

EUROPEAN RESPIRATORY MONOGRAPH

Volume 12
Monograph 40, June 2007



Clinical Exercise Testing

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Preface

The majority of diseases and pathological conditions reduce physical capacity, which may have an influence on every day life. This is particularly the case for individuals suffering from respiratory diseases that frequently lead to symptoms during physical activity. The symptoms that usually reduce physical performance are leg fatigue, pain and dyspnoea; the latter is the most common in respiratory diseases. Dyspnoea is a subjective feeling of not getting enough air and constitutes a disabling symptom, which may severely circumscribe physical activity in patients with pulmonary diseases. As there is no specific available treatment for dyspnoea, it has to be alleviated by treatment of the underlying disease. As dyspnoea is connected with physical activities, it is crucial to understand the mechanisms and the methodology for assessing symptoms associated with exercise; when diagnosing and monitoring patients with respiratory diseases we often have to rely on surrogate markers. The exercise test constitutes a possibility to directly assess the physical capacity, thus providing a good insight into how the disease influences physical performance. Therefore, the exercise test is a valuable tool in diagnosing and staging disease severity, and as a guide for pharmacological and nonpharmacological treatment and action plans. In order to obtain a comprehensive view of the nature of reduced physical capacity the exercise test has to be adjusted to the individual issue with questions relating to the patient.

Exercise tests have been used for a long time as diagnostic tools for cardiac diseases. During recent years they have become more widely recognised as valuable instruments in the diagnosis and monitoring of pulmonary disorders. In the present issue of the *European Respiratory Monograph*, cardiopulmonary exercise testing for cardiac and pulmonary diseases has been presented. Techniques and equipment as well as reference values have been thoroughly described. The specific questions that arise in children have been addressed and exercise testing as a tool for the assessment of prognosis and treatment effects has been exhaustively presented. It is now 10 years since the last *European Respiratory Monograph* on exercise testing was published. This area has developed and there is a lot of new information, in particular regarding physical activity and exercise physiology associated with chronic obstructive pulmonary disease. Therefore, it is timely to update the knowledge in this field and to publish an issue of the *European Respiratory Monograph* that will be helpful to clinicians, physiologists, nurses, physiotherapists and other professionals interested in exercise physiology and testing.

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INTRODUCTION

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Since the publication of the first *European Respiratory Monograph* on "Clinical Exercise Testing" in 1997, the scope of, and clinical insights attendant to, exercise testing has matured to a point where it has become a relatively common element in the elucidation of causes and management of diseases for which exercise intolerance is a cardinal feature. This stems from the recognition that an exercise test which is appropriately designed and executed, with its results perceptively interpreted, allows not only the degree of exercise intolerance to be quantified, but also provides the potential for its mechanism(s) to be elucidated in the context of a patient's integrative physiological system function. This is based on the tenet that the critical source of system failure can be induced while the system(s) (e.g. muscle-energetic, cardiovascular, pulmonary) is under an appropriate exercise stress in a controlled environment. The symptom-limited incremental (or ramp) exercise test remains the "gold standard" in this regard, as it provides a smooth gradational and quantifiable metabolic stress over the patient's entire range of tolerance. In addition, a substantial body of evidence has accrued to demonstrate that the incremental exercise test is central to the optimisation of work-rate intensity for exercise-based rehabilitation and interventional assessment, and can also impact on the prognosis related to outcome from major surgery, post-operative triaging and even life expectancy.

The present, new edition, of the *European Respiratory Monograph* on "Clinical Exercise Testing" is designed to complement and extend the scope of its predecessor. The first two chapters provide a physiological frame of reference for subsequent considerations of the pathophysiology and management of clinical exercise intolerance. The contributions of the muscle-energetic, cardiovascular, pulmonary gas-exchange and ventilatory system responses to the stress of muscular exercise in health are considered, together with their putative limiting factors. This is followed by an assessment of how altered responses may be discriminated and interpreted in relation to key indices of these system functions, as typically discerned from the results of incremental and constant-load exercise tests. In the following two chapters these concepts are extended to considerations of the causes of exercise intolerance in diseases such as chronic obstructive pulmonary disease, interstitial lung disease, pulmonary vascular diseases and chronic heart failure.

Chapters 5, 6 and 7 focus on the technical aspects of contemporary testing procedures. These range from analysis of equipment specifications, breath-by-breath algorithms, calibration techniques and quality control procedures to laboratory- and field-based exercise testing paradigms. The latter aspect, in particular, represents a new addition to the Monograph, reflecting the growing demand for a simpler "alternative"

to the cardiopulmonary exercise test, and one which has already been shown to provide useful value in the context of interventional assessment in chronic lung disease.

In the following four chapters, the emphasis moves on to the testing of two particular populations: patients with lung disease (both children and adult) and heart disease. Central to the interpretation of exercise test results is the availability of robust sets of normative or reference values. Considerations of exercise testing in prognostic evaluation and in the assessment of responses to interventions (*e.g.* exercise training, supplemental oxygen and drug therapies) provide a further addition to the previous Monograph. In the final chapter, the indications for exercise testing in clinical practice are discussed, along with proposals for new directions in the development and application of clinical exercise testing.

CHAPTER 1

Determinants of the physiological systems responses to muscular exercise in healthy subjects

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Background

Exercise intolerance is a consequence of the subject's inability to meet the energy requirements of the chosen or imposed task; its expression is, therefore, task specific. When caused by impaired function of one or more of the physiological systems that link, or support, oxygen transfer from the atmosphere to the energy transduction sites within the contracting muscles, the result is a perception of limb fatigue, breathlessness or even pain, such as the angina of patients with coronary artery disease or the claudication of peripheral vascular disease, which in extreme cases can limit activity to that of a mild domiciliary routine, or worse. In fact, a subject who stops exercising because of unpleasant symptoms may have reached neither maximal oxygen transport capacity nor maximal mitochondrial velocities.

Exercise testing is based on the principle that, as for other systems, physiological systems begin to reach their functional limits under stress. Therefore, the goal of the testing is to stress the organ systems contributing to the exercise intolerance to a level at which abnormality becomes discernible from the magnitude or profile of response of appropriately selected variables, *i.e.* chosen as being reflective of the particular system(s) behaviour. The interpretation of the results is then based on two inter-related considerations, as follows: 1) discriminating a magnitude or pattern of deviation from the normal response of the age-, sex- and, importantly, activity-matched standard subject; and 2) matching the pattern of abnormality with that previously demonstrated to be characteristic of particular impairments of physiological system functioning.

A wide range of exercise test protocols are available to the investigator [reviewed in 1–4], with each being more or less suitable as a stressor of a particular feature of the subject's functional status. However, in the context of clinical exercise testing, the appropriateness of the integrated systemic responses is perhaps best studied, at least initially, utilising an incremental exercise test that provides a smooth gradational stress and which, typically, spans the entire tolerance range. This allows the investigator to establish: 1) the normality, or not, of the pattern of response; 2) the site(s) of any functional failure; 3) the effective operating range of the system(s) of interest; 4) the adequacy of the response for particular purposes, such as occupational, sporting or recreational goals; and 5) an appropriate frame of reference for training and rehabilitative strategies.

However, the crucial shift from simply recognising a response abnormality to discerning its cause and consequence lies in a clear understanding of the normal bio-energetic and associated physiological determinants of the systemic responses.

The bio-energetic basis of work performance

Muscular work requires the chemical energy of ingested food to be transformed into the mechanical force required for tasks involving: 1) shortening of the muscle; 2) increasing muscular tension at constant length; or 3) constraining the rate at which the muscle is being lengthened by an external force. These are all, by convention, termed “contraction”, *i.e.* concentric, isometric and eccentric, respectively.

However, the force-generating sites of skeletal muscles do not directly utilise the energy available from the stored food stuff; rather they require the high free energy of hydrolysis (ΔG) of the terminal phosphate bond(s) of adenosine triphosphate (ATP) as the obligatory currency of skeletal muscle energy exchange:



where ADP and Pi are adenosine diphosphate and inorganic phosphate, respectively; and ΔG_{ATP} has a value, under physiological conditions, of $\sim \geq 10\text{--}12 \text{ Kcal}\cdot\text{mol}^{-1}$, depending on the local ionic concentrations. These processes are shown in figure 1.

The first step involves phosphorylative coupling or the “trapping” of the substrate energy released into a usable form for contraction, *i.e.* as ATP. The second step requires contraction coupling; *i.e.* the utilisation of the phosphate bond energy for the contraction process itself.

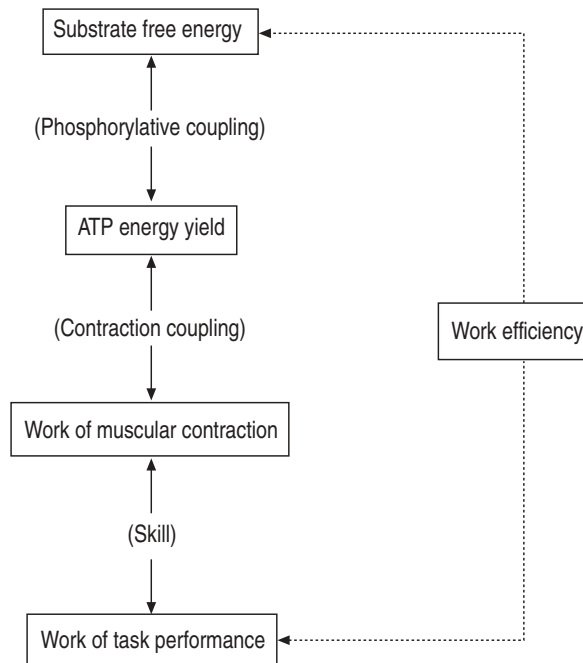


Fig. 1. – Bio-energetic events coupling the energy of ingested food to physical task performance. ATP: adenosine triphosphate.

Efficiency of muscle contraction

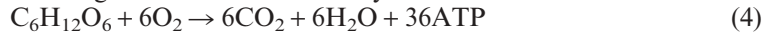
The overall muscular efficiency (η_m) is reflected by the product of the two efficiencies:

$$\eta_m = \eta_p \times \eta_c \quad (2)$$

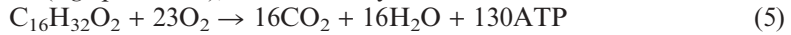
where η_p and η_c are the efficiencies of phosphorylative coupling and contraction coupling, respectively. However, the contracting muscles must be effectively orchestrated to perform the task; *i.e.* a manifestation of the skill (η_s) with which the task is accomplished. Unskilled performance of the task involving, for example, extraneous movements will naturally reduce the overall efficiency of accomplishing the task. The overall efficiency has been termed the work efficiency (η_w):

$$\eta_w = \eta_p \times \eta_c \times \eta_s \quad (3)$$

The phosphorylative coupling can be shown to be accomplished with an efficiency of ~55% (depending on the value chosen for the free energy of ATP hydrolysis), with little difference between different substrates. Consider the stoichiometric relationship with glucose as the substrate being metabolised aerobically:



360 Kcal is usefully conserved from its molar free energy of 686 Kcal, using a value of 10 Kcal·mol⁻¹ for ΔG_{ATP} . This yields an efficiency of ~53%. For a typical fatty acid undergoing oxidation (*e.g.* palmitate), this efficiency is ~56%:



with 1,300 Kcal being usefully conserved from its molar free energy of 2,340 Kcal.

Note, however, that the overall muscular efficiency does not actually depend on the value assigned to ΔG_{ATP} , as it appears in the numerator for the phosphorylative coupling efficiency and in the denominator for the contraction coupling efficiency and is hence “canceled out” in the product.

However, there are other important substrate-linked efficiency relationships. For example, consider what may be termed the storage efficiency. For the carbohydrate, its 686 Kcal are stored in a gram-molecular weight of 180 yielding ~4 Kcal·g⁻¹. For the fatty acid, its 2,340 Kcal are stored in 256 g, providing an appreciably greater storage efficiency of ~9 Kcal·g⁻¹. The substrate mixture being oxidised also plays an important role in the oxygen cost of the task, with more oxygen being required for a given rate of ATP production with fatty acid than for carbohydrate oxidation, as shown in table 1, for a notional body oxygen uptake ($\dot{V}O_2$) cost of 1 L·min⁻¹ [5].

Note that while carbohydrate is the more effective fuel (by ~6%) in terms of oxygen utilisation, fats produce appreciably less carbon dioxide (by ~40%) per unit ATP yield than carbohydrates. Therefore, a high fraction of carbohydrate in the substrate mixture being metabolised minimises the cardiovascular demands of the task (for oxygen delivery), whereas a high fraction of fatty acids tends to reduce the ventilatory demands for a given level of oxygen utilisation (being, as described below, closely linked with the carbon dioxide exchange rate). Of course, this has necessary consequences for arterial oxygenation.

Table 1 – Oxygen and carbon dioxide demands of substrate oxidation

	$\dot{V}O_2$	$\dot{V}CO_2$	RQ	$\sim P:O_2$	$\sim P:CO_2$	$O_2:\sim P$	$CO_2:\sim P$
G	1.0	1.0	1.0	6.00	6.00	0.17	0.17
P	1.0	0.7	0.7	5.65	8.13	0.18	0.12
G/P	1.0	1.43	1.43	1.06	0.74	0.94	1.42

$\dot{V}O_2$: oxygen uptake; $\dot{V}CO_2$: carbon dioxide production; RQ: respiratory quotient; $\sim P:O_2$: rate of adenosine triphosphate (ATP) production for a given $\dot{V}O_2$; $\sim P:CO_2$: rate of ATP production for a given $\dot{V}CO_2$; $O_2:\sim P$: $\dot{V}O_2$ required for a given rate of ATP production; $CO_2:\sim P$: $\dot{V}CO_2$ required for a given rate of ATP production; G: glycogen; P: palmitate.

ATP: the direct energy source for muscle contraction

While ATP is the obligatory energy resource for muscle contraction, its concentration in skeletal muscle is extremely small ($\sim 5 \text{ mM} \cdot \text{kg}^{-1}$); sufficient in itself to sustain a high-intensity activity for only a few seconds. Despite this, its concentration does not decrease during dynamic exercise [e.g. 6, 7], except at extremely high work-rates (WRs) [e.g. 8], and not always then [e.g. 6]. This is because the production rate of ATP is increased through the intensity-dependent contributions from aerobic and anaerobic metabolic reactions (fig. 2).

The major energy source for ATP re-synthesis is oxidative phosphorylation in the mitochondrial electron transport chain.

Oxygen stores and oxygen transport

The oxygen utilised by the muscle for oxidative phosphorylation is derived from both oxygen transported to the muscle from the atmosphere after the start of the exercise and oxygen that is already stored in the body. However, as the arterial oxygen content (CaO_2) does not normally decrease appreciably during exercise (any changes in partial pressure of oxygen (PO_2) that do occur tend to traverse the “flat” upper region of the oxygen dissociation curve) [9–12], the contribution of the blood stores to oxygen utilisation during exercise will increase progressively as (and only as long as) mixed-venous oxygen content (CvO_2) decreases. For example, an adult with a 3 L venous blood volume and a reduction in CvO_2 from $150 \text{ mL} \cdot \text{L}^{-1}$ at rest to $50 \text{ mL} \cdot \text{L}^{-1}$ during high-intensity exercise will have utilised $\sim 300 \text{ mL}$ of blood oxygen stores for those particular conditions: *i.e.* $3 \text{ L} \times 100 \text{ mL} \cdot \text{L}^{-1}$.

Owing to its relatively low concentration, even in red muscle, the contribution from changes in myoglobin saturation [13] will be quantitatively small (although its presence facilitates the diffusion of oxygen through the muscle tissue), as will the contribution from oxygen dissolved in the blood and muscle water. Consequently, for dynamic exercise (but, of course, not isometric exercise) the major source of oxygen utilised is the oxygen transported to the muscle *via* the blood flow distributed to the muscle by the increased cardiac output (Q').

In the steady state, all of the energy demands for ATP re-synthesis will be met by reactions involving oxygen taken up from the atmosphere; $\dot{V}\text{O}_2$ will then remain steady throughout the duration of the exercise as long as the WR and the substrate mixture being metabolised remain constant. However, it takes $\sim 3 \text{ min}$ for $\dot{V}\text{O}_2$ to attain a steady state in a healthy young subject performing moderate intensity exercise [reviewed in 14, 15]. It may be considerably longer in older and/or sedentary subjects [16]. During the period prior to the steady state (fig. 3), energy must naturally be provided from other sources: 1) obligatory reductions in muscle phosphocreatine concentration, with a time course mechanistically linked to that of muscle $\dot{V}\text{O}_2$ [7], and a magnitude proportional to the time constant of the $\dot{V}\text{O}_2$ response; and 2) the intensity-dependent increase in tissue lactate (L^-) concentration.

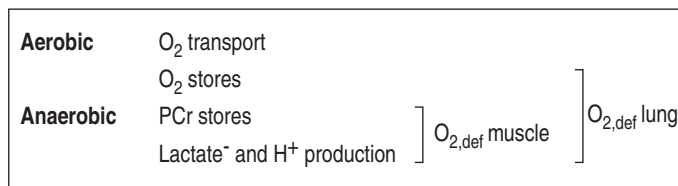


Fig. 2. – Aerobic and anaerobic sources of adenosine triphosphate re-synthesis at different exercise intensities. PCr: phosphocreatine; $\text{O}_{2,\text{def}}$: oxygen deficit.

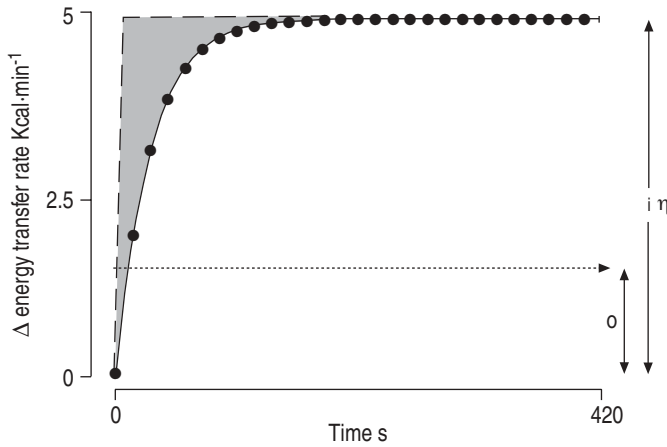


Fig. 3. – Schematic representation of the energy sources utilised during a constant-load (o) test of 100 W. This requires an oxygen uptake increment of $\sim 1 \text{ L} \cdot \text{min}^{-1}$ yielding an energy transfer rate (i) of $\sim 5 \text{ Kcal} \cdot \text{min}^{-1}$. —: total energy input; —: aerobic energy component;: effective energy output. ■: oxygen deficit equivalent of the total energy transfer. η : Efficiency of the energy transfer, $\eta = (o)/(i)$.

$V'O_2$ –WR relationships and efficiency

The actual overall “efficiency” with which the chemical energy of the metabolic substrate is utilised (considered to be the energy “input” to the system) is transformed into the mechanical energy of the task performance (considered to be the energy “output” of the system) and may be calculated from the relationship between the WR being performed, the steady-state $V'O_2$ and its caloric equivalent of the substrate mixture being oxidised (fig. 3), as determined from the steady-state respiratory quotient (RQ).

For example, the steady-state increment in $V'O_2$ ($V'O_{2,ss}$) has been widely demonstrated to be a relatively constant function of increasing WR for moderate-intensity cycle-ergometry at a constant pedalling frequency. The typical slope of this $V'O_2$ –WR relationship ($\Delta V'O_2/\Delta WR$) [2, 5] is easy to remember:

$$\sim 10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1} \text{ or } 1 \text{ L} \cdot \text{min}^{-1} \cdot 100 \text{ W}^{-1} \quad (6)$$

Thus, the $V'O_{2,ss}$ response of the “standard” 70 kg adult pedalling a well-designed ergometer at 60–70 rpm with no braking force applied to the flywheel (*i.e.* “unloaded” cycling or what is termed 0 W) is comprised of: 1) the resting $V'O_2$ ($\sim 250 \text{ mL} \cdot \text{min}^{-1}$); and 2) the “unmeasured” additional $V'O_2$ required to move the mass of the legs at 0 W ($\sim 250 \text{ mL} \cdot \text{min}^{-1}$).

From this $V'O_2$ baseline response of $\sim 500 \text{ mL} \cdot \text{min}^{-1}$, an applied WR of 100 W would result in an increase in $V'O_{2,ss}$ (*i.e.* $\Delta V'O_{2,ss}$) of $\sim 1,000 \text{ mL} \cdot \text{min}^{-1}$, yielding an absolute $V'O_{2,ss}$ of $\sim 1,500 \text{ mL} \cdot \text{min}^{-1}$.

Obesity, or any other “heavy-leg” condition, will therefore increase the overall exercise $V'O_{2,ss}$ as a result of a mass-dependent increase in the $V'O_{2,ss}$ for unloaded cycling, *i.e.* because of an increase in the unmeasured work at 0 W. However, the increment in $V'O_{2,ss}$ associated with the measured increment of WR (*i.e.* the slope $\Delta V'O_{2,ss}/\Delta WR$) will be the same as for the nonobese subject [17–19]. Thus, while the task performance is “inefficient”, in the sense that the total energy and oxygen costs are high, the efficiency of transducing metabolic energy into effective muscular work is not. In both cases the steady-state “efficiency” (η) will be $\sim 30\%$:

$$\eta = \frac{\text{increment of work done} \cdot \text{min}^{-1}}{\text{increment of energy cost} \cdot \text{min}^{-1}} \times 100 \quad (7)$$

For example, for a subject metabolising a carbohydrate-dominated substrate mixture (with an RQ close to 1.0):

$$\eta = \frac{100 \text{ Watts}}{(1.0 \text{ L} \cdot \text{min}^{-1}) \times (5000 \text{ cal} \cdot \text{L}^{-1})} \times 100$$

but as $1 \text{ cal} \cdot \text{s}^{-1} = 4.186 \text{ W}$, then $100 \text{ W} = 1422 \text{ cal} \cdot \text{min}^{-1}$, and:

$$\eta = \frac{1433 \text{ cal} \cdot \text{min}^{-1}}{5000 \text{ cal} \cdot \text{min}^{-1}} \times 100 = 29\% \quad (8)$$

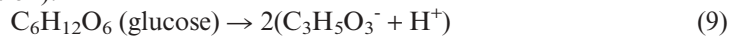
However, in these calculations it is important to stress the use of the increment of $\dot{V}\text{O}_2$ above the “unloaded” cycling value (or some other known reference WR) and its associated equivalent energy utilisation rate, and not the absolute level of $\dot{V}\text{O}_2$ or the increment above the resting value. This is necessary in order to correct for the additional energy cost of the unmeasured work performed when the load on the cycle is ostensibly zero. However, use of the steady state for rigorous efficiency computation should also be stressed, as it is only when there are no additional contributors to the energy transfer that the work efficiency can be appropriately calculated from the measured $\dot{V}\text{O}_2$. It could, naturally, be established if the additional energy utilisation rate from these resources were known, but in practice this is rarely attempted due to the complexities involved.

The computed work efficiency in humans is relatively constant for a given individual in the steady state of exercise, within the moderate-intensity domain, but varies from ~26–32% in individuals with different predominant fibre types in the force-generating muscles [20, 21]; a view, however, recently challenged by BARSTOW *et al.* [22]. It does not vary significantly as a function of the subject’s level of fitness, age or sex.

However, it is also important to introduce a different “efficiency” notion. In this case, instead of the WR or task being considered the effective output of the system, it is considered to be the frame of reference or the system input for the efficiency consideration. The corresponding cost to the physiological system of interest, such as $\dot{V}\text{O}_2$, carbon dioxide output ($\dot{V}\text{CO}_2$), ventilation ($\dot{V}\text{E}$), cardiac frequency ($f\text{C}$), *etc.* is then used as the system output, *i.e.* providing a physiological efficiency (or, more properly, inefficiency). However, in order that the efficiency terms are not confused, many use this system–cost relationship broadly to reflect the effective “gain” of the system with respect to the variable of interest. One should stress ‘broadly’ here as, strictly, gain ought to have no units. Note, however, that the gain for $\dot{V}\text{O}_2$ and the work efficiency are inversely related. The difference is that, in the efficiency computation, $\Delta\dot{V}\text{O}_{2,ss}$ is transformed into its actual energy transfer equivalent, *i.e.* by taking into account the substrate mixture undergoing oxidation.

Generation of ATP from sources not requiring oxygen availability: lactate

Under conditions in which oxygen is not delivered to the electron transport chain at appropriate rates or is not utilised owing, for example, to a low mitochondrial density or an inadequate flux of pairs of hydrogen atoms to it, ATP can then only be formed through the low-yield anaerobic-glycolytic pathway from, for example, glucose to L^- and its associated proton (*i.e.* neither fatty acids nor amino acids can contribute to anaerobic ATP production):



This increase in cellular proton load associated with the accumulation of L^- ions provides greater stress to acid-base regulation, requiring increased levels of $\dot{V}\text{E}$ to compensate for the metabolic acidosis. The benefit to the organism, however, is that the ATP supply can be maintained, with one ATP per L^- molecule formed from glucose or

1.5 ATP per L^- from glycogen. L^- production is, therefore, a vitally important cellular process that allows exercise to continue at high WRs. However, the consequent metabolic acidosis occurs at a cost to the contractile properties of the muscle and to the ventilatory control mechanisms that regulate tissue and blood acid-base status.

As mentioned previously, this anaerobic process yields L^- ions and protons rather than lactic acid (LA) itself. This is because the dissociation reaction has a pK of ~ 3.8 [23]. Consequently, the ratio of L^- plus proton (H^+) ions to LA will be $\sim 1,000:1$ at the pH of muscle during exercise. For example, taking a representative value of 6.8:

$$pH = pK + \log ([L^-] \times [H^+]/[LA]) \quad (10)$$

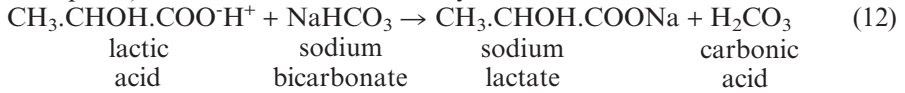
Therefore:

$$([L^-] + [H^+]/[LA]) = \text{antilog } (6.8 - 3.8) = 1000 \quad (11)$$

As a result, there is virtually no actual production of LA *per se* during exercise, even at high WRs. Thus one should refer to production of L^- , rather than of LA.

Consequences of lactate production for acid-base regulation and carbon dioxide removal

Over 90% of the buffering of the protons associated with the L^- production is provided by the bicarbonate (HCO_3^-) system [24–26], and hence the profile of $[L^-]$ change is effectively a mirror image of that of $[HCO_3^-]$; intracellular buffers with pKs close to the intracellular pH, such as the histidine residues of intracellular proteins and intracellular phosphates, subserve an initial buffering of the acid load. However, despite the HCO_3^- system having a less-optimum pK of ~ 6.1 , it is quantitatively the most important contributor to acid-base regulation during exercise. Every proton that does combine with a bicarbonate ion (as sodium bicarbonate in the blood, and potassium into the atmosphere) is hence cleared from the system:



yielding:



As this carbon dioxide is in addition to the continuing component of aerobic carbon dioxide production, it provides an additional load for pulmonary clearance; but not just an additional load, a considerable additional load. For example, consider two muscle fibres (A and B) that each have an ATP production requirement of 37 units $\cdot\text{min}^{-1}$. Furthermore, assume that: 1) fibre A produces ATP aerobically, while fibre B produces ATP anaerobically; and 2) for simplicity, both fibres utilise only glycogen.

Fibre A will, therefore, produce six units of carbon dioxide at a cost of six units of oxygen per glucosyl unit, *i.e.* a 6-carbon subunit of glycogen). In contrast, as fibre B utilises no oxygen, it will produce no carbon dioxide aerobically. However, in order for fibre B to produce 37 units of ATP anaerobically, it must form $\sim 24 L^-$ units from 12 glucosyl units; *i.e.* L^- production provides a considerable drain on the available glycogen stores, as inexperienced marathon runners learn at great cost. If 90% of the $24 L^-$ -linked protons are buffered by HCO_3^- , then this will result in ~ 22 units of carbon dioxide being produced:

$$\Delta CO_2 = \Delta [HCO_3^-] \simeq 0.9 \times \Delta [H^+] = 0.9 \times 24 = 22 \quad (14)$$

That is, the carbon dioxide production rate increases by three-to-four fold over the aerobic rate for those fibres that contract anaerobically [5].

Pulmonary gas exchange

Oxygen uptake

In order to understand the profiles of response of a particular variable of interest during exercise, it is useful to use the “expected” or “normal” kinetic profile as the frame of reference, based upon the known or postulated underlying control mechanism. Consequently, the expected temporal response profile of $\dot{V}O_2$ to a ramp-type incremental exercise test will reflect the fact that the sub-maximal muscle $\dot{V}O_2$ is controlled by the turnover of the high-energy phosphate pool [7, 27–29]. This is known to manifest relatively simple mono-exponential behaviour (at least for moderate exercise). Therefore, in response to a constant WR, $\dot{V}O_2$ in the contracting muscle will change mono-exponentially [30, 31] with $\dot{V}O_2$ at the lung evidencing similar kinetics following a small delay-like phase representing the limb-to-lung transit delay [32, 33], as shown in figure 4.

The time constant (τ) of this response (the time to reach 63% of the steady-state value) is normally 30–45 s, but is faster in fit rather than in unfit subjects [33–35] and in young compared with old subjects [16, 36]. The amplitude of the $\dot{V}O_2$ response in the steady state is not appreciably different in different subjects, with a value, as previously described, of $\sim 10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$ (varying slightly with the substrate mixture being oxidised and the type(s) of muscle fibre being recruited).

The “expected” $\dot{V}O_2$ response during a ramp-type incremental test [37] is shown in figure 5.

Note, that as the ramp can be considered to be the continuous sequential summation of a constant-load WR, then the expected $\dot{V}O_2$ response will also be the continuous sequential summation of the constant-load $\dot{V}O_2$ response. Hence, for a normal subject the linear phase of $\dot{V}O_2$ lags the steady-state $\dot{V}O_2$ response, by the response time constant, or what has also been termed the mean response time, but with the same response gain.

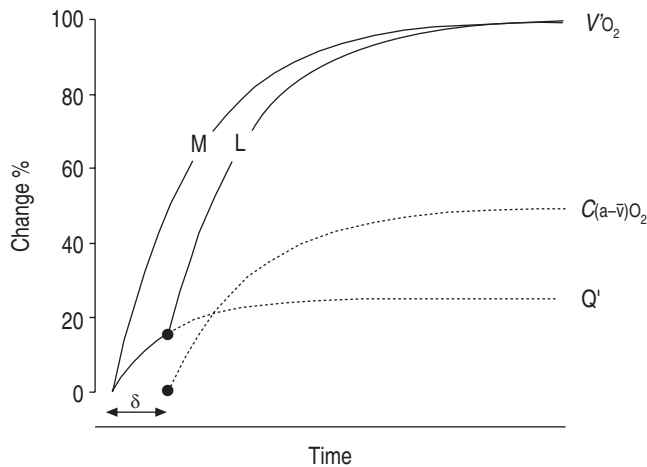


Fig. 4. – Schematic representation of the cardiovascular determinants of the time course of lung (L) oxygen uptake ($\dot{V}O_2$) with respect to that of the contracting muscle (M) units. $C(a-\bar{v})O_2$: arterio-mixed venous oxygen concentration; Q' : cardiac output, equivalent to the pulmonary blood flow. δ : limb-to-lung transit delay. Modified from [15] with permission.

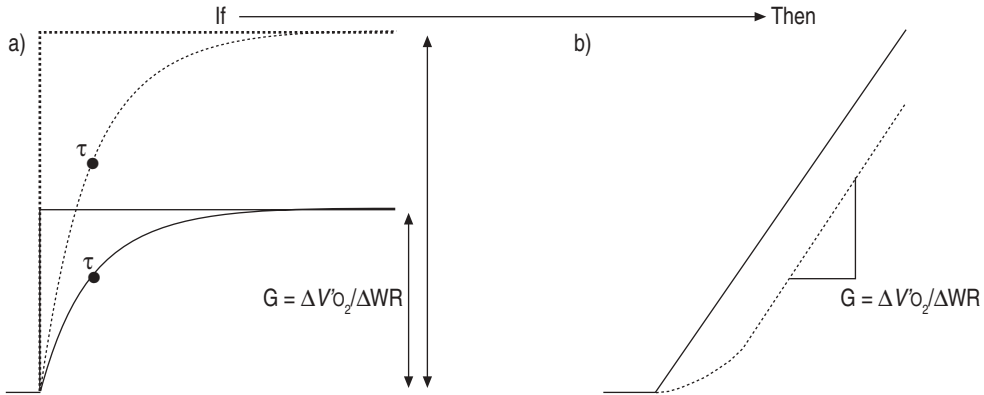


Fig. 5. – Predicted oxygen uptake ($\dot{V}O_2$) response profiles to two constant work rates of a) moderate intensity and b) ramp-incremental exercise, with constant “gain” (G) and time constant (τ). Δ : increment; WR: work rate.

Because steady states are never achieved in such incremental protocols [5], the actual $\dot{V}O_2$ at any instant (t) will always be less than the expected steady-state value for that WR, *i.e.* $\sim 10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$. However, the linearity of the $\dot{V}O_2$ response as a function of WR is only consistently achieved up to the subject’s lactate threshold (θ_L). Above θ_L , the slope has been shown to become less for very rapid WR incrementation rates [38], to be about the same for intermediate rates and to be greater with slow rates of WR change [38, 39]. This is because the $\dot{V}O_2$ kinetics are highly exercise-intensity dependent [*e.g.* 15, 39–43], being only mono-exponential in the moderate WR domain. At higher WRs, a slow component of $\dot{V}O_2$ kinetics, of delayed onset, is superimposed upon the fundamental exponential response (fig. 6), causing $\dot{V}O_2$ during constant-load exercise (or, it has been demonstrated, for slow ramps) to increase to values greater than that predicted from the response in the moderate-intensity domain, *i.e.* below θ_L . During heavy-intensity exercise (*i.e.* between θ_L and what has been termed critical power (CP) [45, 46]), $\dot{V}O_2$ reaches a delayed steady-state only after the excess $\dot{V}O_2$ component has attained its asymptotic value. Very heavy intensity exercise (between CP and maximum

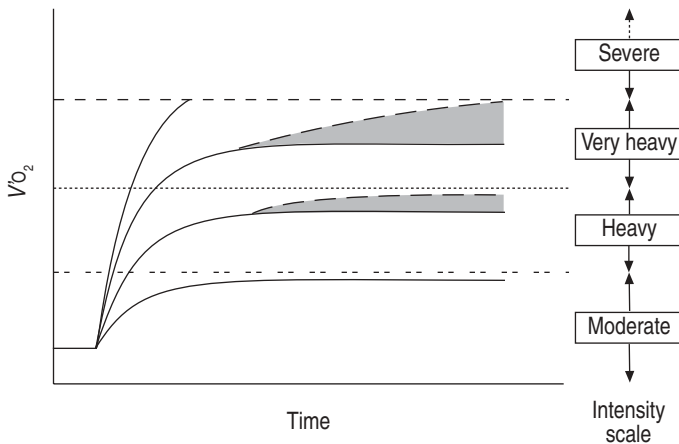


Fig. 6. – Schematic representation of the oxygen uptake ($\dot{V}O_2$) response profiles to constant work-rate exercise in different intensity domains. —: maximum $\dot{V}O_2$;: critical power; - - - -: lactate threshold. ■: “slow phase” of the $\dot{V}O_2$ kinetics. Reproduced from [44] with permission.

$\dot{V}O_2$ ($\dot{V}O_{2,max}$) is characterised by a $\dot{V}O_2$ response that continues to increase inexorably throughout the test to, or towards, $\dot{V}O_{2,max}$ (such that no steady state is achievable for $\dot{V}O_2$). Severe intensity can be characterised as WRs that are supra-maximal with respect to the expected $\dot{V}O_2$ requirement and for which, as they can only be sustained for such a short duration, a slow component of $\dot{V}O_2$ kinetics is commonly not discernible. It should be noted, however, that there is at present no general agreement on how exercise intensity is best characterised.

The mechanisms of this slow component remains to be elucidated [reviewed in 15, 44, 47], but are likely to be a function of a proportionally greater recruitment profile of type IIA or IIX muscle fibres [e.g. 48–51]. Work efficiency estimation from ramp tests should, therefore, be undertaken with care and be restricted to the sub- θL range of the $\dot{V}O_2$ –WR relationship, within which linearity can be reasonably assured. Also, the caloric equivalent of the $\dot{V}O_2$ can only be determined rigorously from the oxygen and carbon dioxide exchange rates during the steady state. The efficiency can, therefore, be measured from constant-load tests but only estimated from ramp tests.

Carbon dioxide output

Pulmonary $\dot{V}CO_2$ also has important implications for the integrated systemic response to exercise. For example, taken with $\dot{V}O_2$ in the steady state, $\dot{V}CO_2$ provides important information regarding the substrate mixture undergoing catabolism. In addition, in the context of arterial blood-gas and acid-base homeostasis, $\dot{V}CO_2$ provides an important frame of reference for establishing the normality of the ventilatory response to exercise. Also, $\dot{V}CO_2$ is an essential determining factor for noninvasive θL estimation [2, 52].

The $\dot{V}CO_2$ ramp response also becomes relatively linear with respect to WR, but only in the sub- θL range. However, because of its slower kinetics relative to those of $\dot{V}O_2$ (longer time constant), the $\dot{V}CO_2$ ramp response is displaced further from that of the steady-state relationship. This reflects the additional component of metabolically produced carbon dioxide retained in the body's carbon dioxide stores. Consequently, carbon dioxide output at the lungs will not properly reflect carbon dioxide production at the tissues [2, 53]. The measured gas exchange ratio at the lungs (R) will, therefore, underestimate the tissue RQ during ramp exercise. The lower slope of the $\dot{V}CO_2$ – $\dot{V}O_2$ relationship (termed the “S1” region [2, 52]) during the moderate-intensity region of ramp exercise, however, has been reported to be similar to that of the steady-state response [54]. At higher WRs, the $\dot{V}CO_2$ profile becomes steeper with respect to WR and $\dot{V}O_2$ (fig. 7), yielding an “S2” region [2, 53] over the isocapnic buffering phase [e.g. 2], prior to the hyperventilatory decrement in end-tidal carbon dioxide tension (P_{ET,CO_2}).

This reflects the generation of additional carbon dioxide from the HCO_3^- component of the buffering of LA in muscle and blood, *i.e.* carbon dioxide is now also being washed out of the stores. The increase in arterial blood L^- concentration has been shown to be essentially mirrored by a decrease in the concentration of HCO_3^- ($[HCO_3^-]$) in arterial blood. The consequence is that $\dot{V}CO_2$ increases faster than $\dot{V}O_2$ with increasing WR. This release of additional carbon dioxide only takes place as the $[HCO_3^-]$ level is actually falling.

The more rapid the WR incrementation rate, the greater the rate of carbon dioxide evolution from these buffering reactions. Consequently, R at maximum exercise may increase to levels of ≥ 1.2 with rapid tests, but only 1.05 or so on slower tests. It is this behaviour that provides the foundation for the “V-slope” approach [5, 52] to estimate θL noninvasively. The $\dot{V}CO_2$ – $\dot{V}O_2$ relationship during rapid-incremental exercise (fig. 7) is characterised by a relatively linear relationship during moderate exercise, which reflects the metabolic and storage components of the gas exchange. However, the

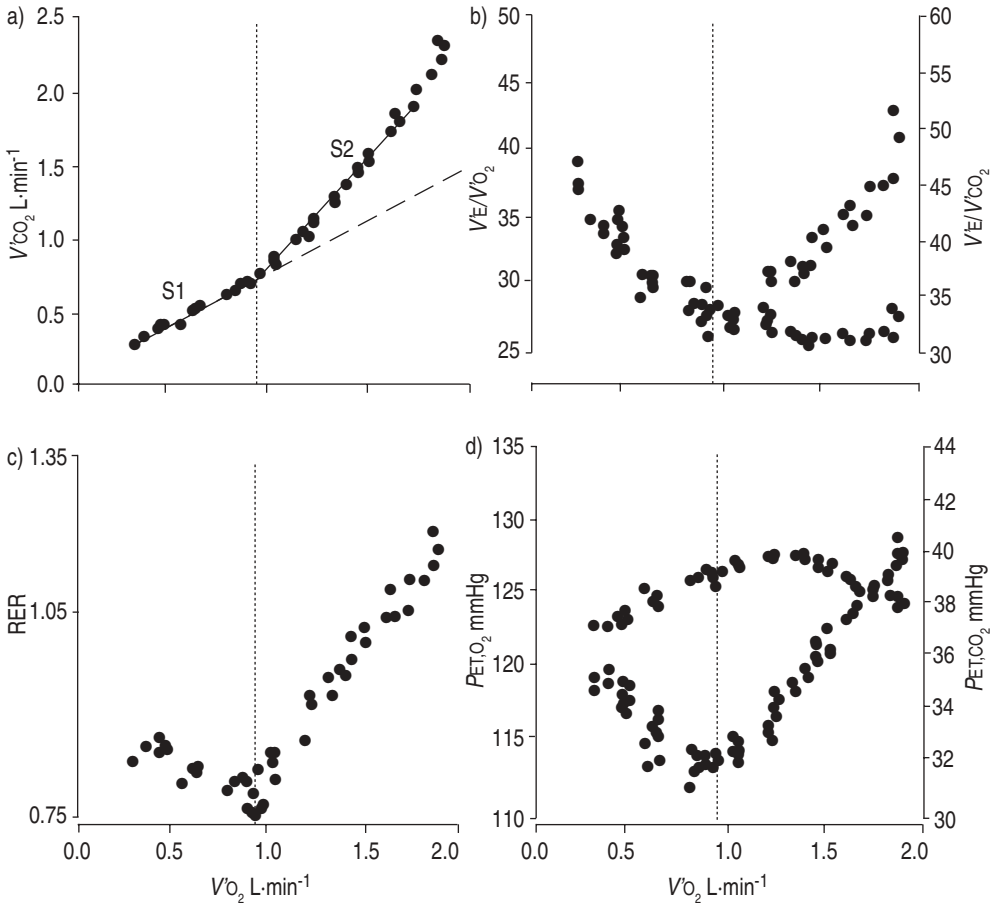


Fig. 7. – Cluster of ventilatory and pulmonary gas exchange indices needed for the estimation of the lactate threshold (·····) in response to a ramp-incremental exercise test expressed relative to oxygen uptake ($\dot{V}O_2$). a) Carbon dioxide output ($\dot{V}CO_2$), b) ventilatory equivalents for carbon dioxide and oxygen ($\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}O_2$, respectively), c) respiratory exchange ratio (RER), and d) end-tidal carbon dioxide and oxygen tensions (P_{ET,CO_2} and P_{ET,O_2} , respectively). —: S1 region; ---: S2 region. Note that $\dot{V}CO_2$ and RER begin to increase more rapidly as a function of $\dot{V}O_2$ at the lactate threshold. $\dot{V}E/\dot{V}O_2$ and P_{ET,O_2} both increase but importantly without a simultaneous increase in $\dot{V}E/\dot{V}CO_2$ or decrease in P_{ET,CO_2} . 1 mmHg=0.133 kPa.

response evidences an increased slope immediately above θ_L , with the change agreeing closely with the beginning of the increase in the concentration of L^- in arterial blood, the arterial $[L^-]/[\text{pyruvate}]$ ratio and the decrease in arterial $[\text{HCO}_3^-]$. However, it is not uncommon for the $\dot{V}CO_2$ – $\dot{V}O_2$ relationship not to be sufficiently bi-linear for this approach to be used with confidence. In this case, the expedient has been proposed of taking the point at which the slope (not necessarily the value) of the relationship becomes 1.0; where the tangent to the relationship is unity [2, 55]. This technique partitions the WR range into a region in which the slope is <1.0 , and one in which the slope is >1.0 which, if hyperventilation can be ruled out, is usually consequent to the lactic acidosis. As such there are three sources of increases in pulmonary carbon dioxide output during exercise: 1) aerobically produced; 2) hyperventilation (reduced carbon

dioxide arterial tension (P_{a,CO_2}) and P_{ET,CO_2}), which releases carbon dioxide stored in the alveolar gas and tissues; and 3) release from $[HCO_3^-]$ in the lactate-related buffering reaction. If the first two can be ruled out, the source of the increase must be the third.

Ventilatory requirements

The ventilatory responses to muscular exercise, including its breathing pattern and airflow profile components, provide important information for interpretation of clinical exercise testing. The appropriateness of the ventilatory response, however, depends not simply on the level of ventilation achieved for a particular WR but also on the extent to which it subserves its pulmonary gas exchange and acid-base regulatory functions. For example, alveolar and arterial blood-gas partial-pressures can only be regulated at, or close to, resting levels if alveolar ventilation ($\dot{V}_A$) increases in proportion to the rates of pulmonary gas exchange:

$$F_{A,CO_2} = \frac{\dot{V}'_{CO_2,STPD}}{\dot{V}'_{A,STPD}} \quad (15)$$

where F_{A,CO_2} is the fractional concentration of alveolar carbon dioxide and $\dot{V}'_{A,STPD}$ is the flow or volume per unit time, both measured under the same conditions (standard temperature and pressure dry; STPD).

However, as the alveolar partial pressure of carbon dioxide (P_{A,CO_2}) is of more interest physiologically, and ventilatory volumes are standardly reported at body temperature and pressure saturated with water vapour (BTPS):

$$P_{A,CO_2} = \frac{863 \times \dot{V}'_{CO_2,STPD}}{\dot{V}'_{A,BTPS}} \quad (16)$$

The 863 in this, and related equations, derives from different frames of reference for the metabolic and ventilatory measurements and reporting carbon dioxide as partial pressure, assuming a body temperature of 37 °C.

Similarly, for oxygen exchange:

$$P_{A,O_2} = \frac{P_{i,O_2} - 863 \times \dot{V}'_{O_2,STPD}}{\dot{V}'_{A,BTPS}} \quad (17)$$

where P_{A,O_2} is the alveolar and P_{i,O_2} is the inspired PO_2 .

However, neither $\dot{V}_A$ nor the alveolar gas partial pressures in equations 16 and 17 are conceptually simple or readily measurable variables in a structure as complex as the lung. This is because it is difficult to establish a single average value for either $\dot{V}_A$ or alveolar gas tensions [56, 57] when there are significant regional variations in alveolar oxygen and carbon dioxide partial pressure and alveolar ventilation to perfusion ratios ($\dot{V}_A/Q'$). Typically this difficulty is overcome by the practical expedient of assuming P_{A,CO_2} to be exactly equal to P_{a,CO_2} ; this can be readily determined by appropriate blood sampling and the equivalent $\dot{V}_A$ can consequently be computed. It is important to recognise that this $\dot{V}_A$ is, in fact, a figment. It is not the actual level of ventilation of the subject's alveoli but the $\dot{V}_A$ that would provide an average P_{A,CO_2} exactly equal to that of P_{a,CO_2} . By the same token, the P_{A,O_2} that is computed in equation 17 is that of the "ideal" lung. This, by definition, yields no difference between the alveolar and arterial oxygen partial pressures. In reality the "real" mean P_{A,O_2} will be systematically higher than the "ideal" P_{A,O_2} .

For P_{A,CO_2} and P_{A,O_2} to be maintained constantly during exercise, $\dot{V}_A$ must change in precise proportion to $\dot{V}'_{CO_2}$ and $\dot{V}'_{O_2}$, respectively, *i.e.* that of pulmonary gas exchange rather than tissue metabolic rates when these rates differ. However, note that $\dot{V}_A$ is common to both relationships in equation 18. Here the effect of the slight difference in inspiratory and expiratory volumes on oxygen partial pressure that occurs

when $R \neq 1$ has been neglected, as the effect is usually relatively small and does not materially affect the argument.

$$\frac{863 \times V'\text{CO}_2}{P_{\text{A},\text{CO}_2}} \leftarrow V'\text{A} \rightarrow \frac{863 \times V'\text{O}_2}{P_{\text{i},\text{O}_2} - P_{\text{A},\text{O}_2}} \quad (18)$$

Note, however, that $V'\text{A}$ cannot meet the regulatory demands of both oxygen and carbon dioxide exchange simultaneously under conditions in which carbon dioxide exchange rate differs from that of oxygen, either as a result of differences in substrate utilisation profiles or because of transient variations in the body gas stores.

It is often stated that ventilation during muscular exercise increases in proportion to metabolic rate. This is imprecise on two accounts. First, the body expresses a metabolic rate both for its $V'\text{O}_2$ and its $V'\text{CO}_2$ and under conditions in which the tissue RQ changes as a result of differences in substrate utilisation, ventilation changes as a close linear function of the $V'\text{CO}_2$ rather than $V'\text{O}_2$. Secondly, the assertion that ventilation during muscular exercise changes as a function of metabolic carbon dioxide production is also imprecise. This is because under conditions in which the changes in body carbon dioxide storage (*e.g.* in muscle and venous blood during exercise transients) dissociates the metabolic production rate from the pulmonary exchange rate, ventilation closely “tracks” the rate of pulmonary $V'\text{CO}_2$, not the rate of muscle metabolic production [58–60]. P_{A,CO_2} is, therefore, the more closely regulated variable for moderate intensity exercise. Any resultant changes of P_{O_2} are normally within the relatively flat region of the oxygen dissociation curve, such that the oxygen content or saturation of the arterial blood will not be affected to any great extent.

Consequently, the demands for ventilation during exercise are usually considered using pulmonary carbon dioxide exchange as the frame of reference. At any set-point level of P_{A,CO_2} , the demand for $V'\text{A}$ increases as a linear function of $V'\text{CO}_2$; the greater the $V'\text{CO}_2$ the greater the ventilation requirement. When P_{a,CO_2} is regulated at a lower level (as is the case in certain subjects with lung disease or normal sea-level subjects sojourning at high altitude), then, for any given level of $V'\text{CO}_2$, $V'\text{A}$ must be appropriately greater. However, it is also necessary to ventilate the dead space of the lung ($V'\text{D}$):

$$V'\text{A} = V'\text{E} - V'\text{D} = V'\text{E} \times (1 - V'\text{D}/V'\text{E})$$

$$\text{or } V'\text{A} = V'\text{E} \times (1 - V'\text{D}/V'\text{T}) \quad (19)$$

where $V'\text{E}$ is the expiratory minute ventilation, $V'\text{T}$ is the tidal volume and $V'\text{D}/V'\text{T}$ is the physiological dead space fraction of the breath and equals $V'\text{D}/V'\text{E}$ because $V'\text{D} = f_R \times V'\text{D}$ and $V'\text{E} = f_R \times V'\text{T}$, where f_R is the breathing frequency.

The ventilatory demand of exercise should, therefore, be considered with respect to its three defining variables: 1) the rate of pulmonary carbon dioxide clearance; 2) the “set-point” at which P_{a,CO_2} is regulated; and 3) the physiological dead space fraction of the breath, which represents an index of the inefficiency of pulmonary gas exchange.

This can be considered in three forms, each providing a slightly different facet of the same inter-relationships:

$$V'\text{E} = \frac{863 \times V'\text{CO}_2}{P_{\text{a},\text{CO}_2} (1 - V'\text{D}/V'\text{T})} \quad (20)$$

$$V'\text{CO}_2 = \frac{863}{P_{\text{a},\text{CO}_2} \times (1 - V'\text{D}/V'\text{T})} \quad (21)$$

$$P_{\text{a},\text{CO}_2} = \frac{863}{(V'\text{E}/V'\text{CO}_2) \times (1 - V'\text{D}/V'\text{T})} \quad (22)$$

Importantly, the regulatory relationship is not, strictly, determined by the slope of the linear region of the plot of $V'\text{E}$ as a function of $V'\text{CO}_2$ (this should not include the hyperventilatory component at high WRs); the intercept on the $V'\text{E}$ axis plays an important contributory role. Rather, P_{a,CO_2} (*i.e.* the functional equivalent of the “ideal”

P_{a,CO_2}) is, therefore, regulated at a particular value only if the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}'CO_2$) changes in precise proportion to the change in $\dot{V}_D/\dot{V}_T$. Or, an abnormally high ventilatory equivalent for carbon dioxide can result from P_{a,CO_2} being low, $\dot{V}_D/\dot{V}_T$ being high or both. However, as it is difficult to estimate P_{a,CO_2} noninvasively in patients with lung dysfunction, one is still left with an uncertainty as to the cause of a high $\dot{V}_E/\dot{V}'CO_2$. For example, it could be high in a patient with normal lung function who regulates P_{a,CO_2} at a lower level (e.g. in a hypoxic subject or one with chronic metabolic acidosis), or P_{a,CO_2} might be normal in a subject with a large $\dot{V}_D/\dot{V}_T$. Attempts to estimate P_{a,CO_2} either from knowing the levels of $\dot{V}_T$ and the P_{ET,CO_2} [61] or from attempts to establish a “mean” P_{a,CO_2} [62, 63], are to be discouraged in patients with lung disease (see the next section for further discussion).

Ventilation and acid-base regulation during exercise

Although P_{a,CO_2} appears to be a regulated variable during moderate exercise in normal subjects, it must be reduced to provide the respiratory compensation that constrains the fall of pH at levels of exercise which induce metabolic acidosis with a consequently reduced arterial $[HCO_3^-]$. This compensatory decrease in P_{a,CO_2} is a result of carbon dioxide being washed-out of the body stores; providing an additional source of expired carbon dioxide at high WRs.

However, the standard Henderson–Hasselbalch equation,

$$pH = pK' + \frac{\log [HCO_3^-]}{\alpha \times P_{a,CO_2}} \quad (23)$$

(where α is the carbon dioxide solubility coefficient which relates P_{a,CO_2} in mmHg to carbon dioxide content in $\text{mmol} \cdot \text{L}^{-1}$) can also profitably be reformulated to focus on the ventilatory processes involved:

$$pH = pK' + \log ([HCO_3^-]/25.9) \times (\dot{V}_E/\dot{V}'CO_2) \times (1 - \dot{V}_D/\dot{V}_T) \quad (24)$$

where the bracketed terms may be considered to represent an metabolic acid-base set point, the “control” component and the ventilatory “efficiency” terms, respectively.

Consequently, over the range of WRs at which the arterial $[HCO_3^-]$ is not reduced, arterial pH is regulated only when the ventilatory equivalent for carbon dioxide and $(1 - \dot{V}_D/\dot{V}_T)$ change in a precisely and hyperbolically reciprocal manner. That is, a reduced $\dot{V}_D/\dot{V}_T$, as occurs with increases in WR because $\dot{V}_T$ increases more than $\dot{V}_D$ (which changes little), requires a matched decrease in $\dot{V}_E/\dot{V}'CO_2$ to regulate P_{a,CO_2} . However, in order to compensate for the metabolic acidosis of high-intensity exercise $\dot{V}_E/\dot{V}'CO_2$ must: 1) increase if $\dot{V}_D/\dot{V}_T$ remains constant; 2) remain the same if $\dot{V}_D/\dot{V}_T$ decreases; or 3) decrease less than $\dot{V}_D/\dot{V}_T$.

Breathing pattern: respiratory frequency and $\dot{V}_T$

The pattern of breathing accompanying the exercise hyperpnoea is highly variable in different subjects, many of whom adjust their respiratory frequency to the locomotor pattern of the activity. The most characteristic pattern of response, however, is for ventilation to be dominated by $\dot{V}_T$ changes over the moderate intensity change, with the hyperpnoea of heavier exercise being achieved largely, or wholly, by increases of f_R , thereby obviating further increases in elastic work of breathing at high lung volumes [reviewed in 64]. Lung size, as reflected by vital or inspiratory capacity for example, plays an important role in the breathing pattern response to exercise [e.g. 65]. Changes of f_R consequently play a more dominant role in patients with restrictive lung disease [e.g. 2, 66, 67], commonly resulting in a $\dot{V}_T$ approaching, or reaching, the subject's

resting inspiratory capacity and respiratory frequencies in excess of 50 breaths·min⁻¹ (see Limitations section).

Further consideration of the ventilatory response pattern to exercise may be undertaken with respect to its inspiratory and expiratory components [68–72]. Typically, in moderate exercise, the increase in $\dot{V}_T$ is accompanied by some shortening of expiratory duration (t_E) with no systematic shortening of inspiratory duration (t_I). However, the marked increase of f_R at higher WRs reflects an appreciable further shortening of t_E with t_I now also starting to shorten. As a result, the “inspiratory duty cycle” (t_I /total time (t_{tot})) typically increases from a resting value of ~0.4 to ~0.5 at maximum WRs in normal subjects; *i.e.* reflecting the greater relative contribution of t_E to the f_R response. The precise characteristics of t_I/t_{tot} will depend on whether or not t_I shortens at low WRs.

Limitations to ventilation

At maximal exercise, there is little evidence of mechanical limitation to ventilation in normal, young moderately fit subjects [72, 73]. Such subjects typically have a considerable breathing reserve (BR), calculated as:

$$BR = \frac{MVV - \dot{V}_{E,max}}{MVV} \times 100 \quad (25)$$

or alternatively:

$$BR = MVV - \dot{V}_{E,max} \quad (26)$$

where MVV is the maximal voluntary ventilation and $\dot{V}_{E,max}$ is the maximum exercise $\dot{V}_E$ [e.g. 1, 2].

The $\dot{V}_{E,max}$ actually attained during exercise is substantially less than the subject's MVV. Furthermore, the spontaneously generated expiratory flow–volume curve does not normally encroach upon the boundaries of the maximum-effort expiratory flow–volume (MEFV) relationship [reviewed in 73–75], usually performed as a vital capacity manoeuvre from total lung capacity (fig. 8).

This provides the maximum airflow that can be attained, at a given lung volume in normal subjects. This, however, is often not the case in patients with chronic obstructive pulmonary disease (COPD) [reviewed in 1, 67, 74, 76, 77] in whom the wide variation of mechanical time constants and the considerable dynamic airway compression during the vital capacity manoeuvre causes maximum airflow at a given lung volume to be attained with: 1) less-than-maximum effort and/or; 2) when the maximum expiration is considered with the inspiratory volume of the spontaneous breath rather than that part-way through the vital capacity manoeuvre.

In elite athletes, however, the high airflow demands of the high levels of $\dot{V}_E$ (required by the supra-normal metabolic rates) can lead to airflow limitation, especially in those who are not genetically gifted with high lung recoil and low airways resistance. In such elite athletes, the spontaneous expiratory flow–volume curve during exercise can impact upon the outer envelope of the MEFV curve [72, 74, 78]. In older athletic subjects this can occur at appreciably lower metabolic rates. For example, BR may approach zero, especially in fitter elderly subjects, and spontaneous expiratory flows may encroach on the MEFV relationship [reviewed in 73, 75]. This reflects the age-related reduction in lung elastic recoil leading to a characteristic “scooping” of the MEFV curve.

Similarly, while the $\dot{V}_T$ range theoretically extends from zero to vital capacity and the f_R extends up to ~5 Hz, the ventilatory system normally operates at a $\dot{V}_T$ of only ~50–60% of the vital capacity and a frequency of ≤ 1 Hz even during maximum exercise. The characteristic decrease in end-expiratory lung volume during exercise in normal, especially young, subjects [reviewed in 67, 72, 74, 78] is of benefit as it increases the

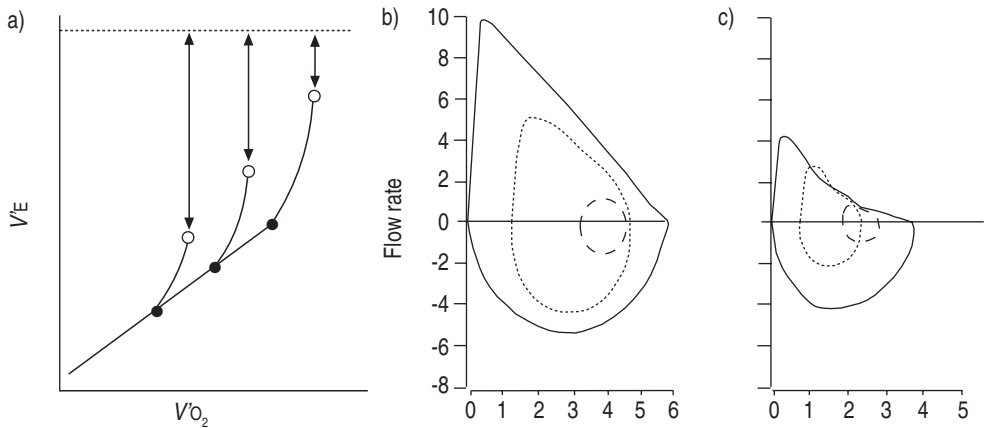


Fig. 8. – a) Schematic diagram of ventilatory response to progressive incremental exercise in three subjects characterised by different levels of maximum attainable oxygen uptake ($\dot{V}O_2$). $\dot{V}E$: minute ventilation.: maximum voluntary ventilation; $\longleftrightarrow$: breathing reserve in each of the three subjects. Modified from [74] with permission. b, c) The flow–volume relationship at rest (– –) and maximum exercise (.....) with respect to a maximum forced exhalation (—) is presented for a normal subject (b) and a subject with chronic obstructive disease (c).

operational inspiratory capacity allowing a greater increase in effective $\dot{V}T$ (any greater $\dot{V}T$ would lead to ineffectively large increases in inspiratory work over the low compliance region of the thoracic volume) and also increases the mechanical advantage of the inspiratory muscles. Normal elderly subjects commonly evidence reduced lung recoil and consequently experience dynamic hyperinflation (increased end-expiratory lung volume) at high WRs [72, 73, 77] in a manner similar to, but of less magnitude than, patients with COPD [reviewed in 1, 67, 74, 77, 78] in whom the effect can be so marked as to create a restrictive-type abnormality acutely superimposed on their chronic condition.

P_{a,O_2} and P_{a,CO_2} and the alveolar–arterial PO_2 difference

In the steady-state of moderate intensity exercise, P_{a,CO_2} is normally regulated at, or close to, resting levels, except if the subject has acutely hyperventilated prior to the exercise, in which case the hyperventilation typically subsides as the exercise develops and the P_{a,CO_2} rises back to the normal control level. During rapid-incremental exercise, however, P_{a,CO_2} does evidence a small but significant increase [2, 79]. This is because the time constant of response is slightly larger for $\dot{V}E$ than for $\dot{V}CO_2$. Above θL , however, there is a developing arterial hypocapnia that provides a component of respiratory compensation for the metabolic (largely lactic) acidemia. Due to the relatively slow time-course of the compensatory hyperpnoea for the acidosis [80], the decrease in P_{a,CO_2} is smaller for rapid-, than for slow-incremental tests.

It is important that the P_{ET,CO_2} should not be used as a direct index of either the level or pattern of change of P_{a,CO_2} . This is because P_{ET,CO_2} is, typically, less than or equal to P_{a,CO_2} at rest; however, it becomes systematically greater than P_{a,CO_2} during incremental exercise, by an amount that depends upon both the metabolic rate and the pattern of breathing [61, 63]. The arterial blood is normally sampled over several, and ideally a whole number of, respiratory cycles; the syringe value, therefore, represents the mean level of P_{a,CO_2} . P_{ET,CO_2} , however, is an index of the peak of the intra-breath

(and intravascular) oscillation of PCO_2 . Consequently, PET,CO_2 exceeds the mean Pa,CO_2 , as shown in figure 9.

Although PET,CO_2 should not be used as a direct estimator of Pa,CO_2 , either for computing the physiological $\dot{V}_D$ or Q' during exercise, it is a component of an equation for estimating Pa,CO_2 developed by JONES *et al.* [61] that has been shown to be reasonable for groups of normal subjects, but is often poorly predictive in individual subjects:

$$Pa,CO_2 = 5.5 + 0.9 \times PET,CO_2 - 0.0021 \times VT \quad (27)$$

Alternatively, mean PA,CO_2 (estimated from the mid-point of the expiratory PA,CO_2 profile (fig. 9)) also provides a more appropriate index of Pa,CO_2 during exercise than does PET,CO_2 in normal subjects [2, 63]. Blood sampled from the dorsum of an appropriately hyperaemic hand, however, (*i.e.* providing a high blood flow through a region of very low metabolic rate) has been shown to provide a value for PCO_2 (and,

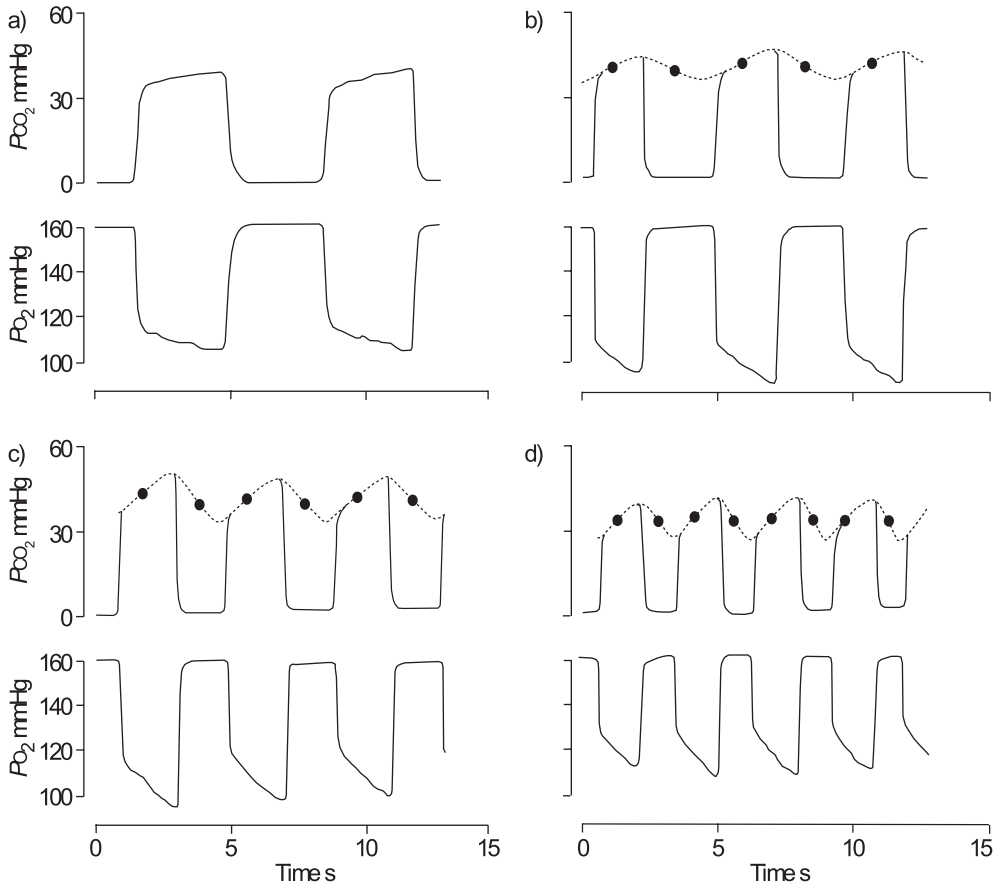


Fig. 9. – On-line recording at the mouth of respired carbon dioxide tension (PCO_2) and oxygen tension (PO_2) at a) rest and work rates of b) 100; c) 200; and d) 300 W in a normal subject.: schematic time-course of arterial carbon dioxide tension, *i.e.* corrected for transit delays to the analyser. Note that the mean alveolar (arterial) PCO_2 (●) differs from the peak expiratory (*i.e.* end-tidal values). 1 mmHg=0.133 kPa. Reproduced from [5] with permission.

incidentally, pH, L^- and other ions such as potassium but, of course, not PO_2) that is to all intents and purposes indistinguishable from that of the arterial value [81, 82].

Although arterial hypocapnia develops in normal subjects above θL during incremental exercise, P_{a,O_2} (at sea level at least), most typically tends to be maintained at, or close to, resting levels. However, as both the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) and the ideal PA_{O_2} (*i.e.* $\approx P_{i,O_2} - (P_{a,CO_2}/R)$) increase systematically at these WRs, why does P_{a,O_2} also not systematically increase? Rather there is a progressive widening of the alveolar–arterial PO_2 difference ($P(A-a)O_2$) from ~ 5 – 10 mmHg to as much as 40 mmHg in athletic subjects [*e.g.* 9–12]. This is usually without arterial hypoxaemia (except in some highly fit athletes) due to the corresponding increase in $\dot{V}E/\dot{V}O_2$ and thus PA_{O_2} . The principal reason for the increased $P(A-a)O_2$ with exercise is considered to be blood-gas oxygen diffusion limitation, with contributions also from $\dot{V}'A/Q'$ mismatching and intra- and post-pulmonary shunts [reviewed in 10–12, 83–85]. However, as P_{a,CO_2} decreases and/or R increases systematically above θL , then the $P(A-a)O_2$ must either begin to widen, or more likely begin to widen more rapidly, at this point.

End-tidal PO_2 and PCO_2

The alveolar gas values determined at the end of an exhalation (the “end-tidal” values) are easy to measure but extremely difficult to interpret. During exhalation, PA_{CO_2} continues to increase (fig. 9) at a rate that is dependent on the mixed venous PCO_2 ($P_{\bar{v},CO_2}$) value and to a level that depends on the duration of the exhalation (tE). PET,CO_2 may, therefore, be considered to be the peak of the intra-breath oscillation of PA_{CO_2} and P_{a,CO_2} during the breathing cycle whereas the measured P_{a,CO_2} , usually sampled over several, and ideally a unit number of, breaths, should be considered to reflect the mean of the oscillation.

The end-tidal value being greater than the mean alveolar and arterial value, as WR increases in normal subjects, therefore, is entirely to be expected. The end-tidal to mean PA_{CO_2} difference continues to increase as WR and, therefore, $\dot{V}'CO_2$ increases, but can then stabilise at WRs at which $\dot{V}T$ ceases to continue to increase and, therefore, fR accelerates progressively, shortening tE (see above). This relative PET,CO_2 constancy above θL (fig. 7) has been termed the phase of “isocapnic buffering” [2, 86].

In the ideal lung, arterial blood will also manifest such an oscillation, but this oscillation is not measured; what is measured is the mean of this oscillation in P_{a,CO_2} , as blood is sampled over several respiratory cycles. Mean P_{a,CO_2} , however, differs from mean PA_{CO_2} as a result of ventilation-to-perfusion inhomogeneities and/or right-to-left shunt, leading to PET,CO_2 being commonly less than P_{a,CO_2} , for example, in patients with COPD [*e.g.* 1, 2]. Consequently, PET,CO_2 being equal to or less than mean P_{a,CO_2} during exercise is reflective of abnormal gas exchange.

PET,CO_2 should not, therefore, be used to represent arterial PCO_2 in computing $\dot{V}D/\dot{V}T$. Doing so overestimates $\dot{V}D/\dot{V}T$ in normal subjects (tending to make abnormal what is normal) and underestimates it in patients with lung disease (tending to make normal what is abnormal). Algorithms for estimating P_{a,CO_2} from PET,CO_2 [61–63] are poor in normal subjects and do not work in subjects with lung disease.

Consequently, the profile of PET,CO_2 with increasing WR is normally such that it increases progressively up to θL , then stabilises in the region of isocapnic buffering, and subsequently decreases as frank compensatory hyperventilation is manifest [2, 5, 86]. In contrast, end-tidal PO_2 (PET,O_2) progressively decreases up to θL , after which it increases systematically (fig. 7), accelerating further with the onset of compensatory hyperventilation.

Cardiovascular responses

Cardiac output

Q' , when measured in the steady- or quasi-steady state, typically increases as a linear function of WR and, therefore, $\dot{V}O_2$ throughout the entire WR range [e.g. 87–91]:

$$Q' = m \times \dot{V}O_2 + c \quad (28)$$

where m is the slope and c is the Q' intercept (fig. 10), with values of approximately five for both m and c , for exercise performed at sea level and in a temperate climate, when Q' and $\dot{V}O_2$ are expressed in units of $L \cdot \min^{-1}$. This relationship is not appreciably affected by training or fitness, although it extends to higher maximal values for both Q' and $\dot{V}O_2$ after training and with increasing fitness.

Arterio-venous oxygen content difference

The increase in Q' that occurs during exercise alone is not sufficient to satisfy the metabolic requirements of the working muscles, even for the lightest WRs. This is, perhaps, better illustrated by a simple rearrangement of the Fick equation:

$$\dot{C}vO_2 = CaO_2 - \dot{V}O_2 / Q' \quad (29)$$

That is, despite Q' increasing by $\sim 5 L \cdot \min^{-1}$ for each $1 L \cdot \min^{-1}$ increase in $\dot{V}O_2$, the proportional increase in Q' is less than that of $\dot{V}O_2$; $\dot{C}vO_2$ must, consequently, fall with a hyperbolic profile.

As a result, the arterio-venous O_2 content difference ($CaO_2 - \dot{C}vO_2$) increases from a resting value of $\sim 5 mL \cdot 100 mL^{-1}$ to ~ 15 – $18 mL \cdot 100 mL^{-1}$ [e.g. 2, 88, 90, 92, 93] at maximum exercise (fig. 10). It may be estimated (in $mL \cdot 100 mL^{-1}$) using the simple rule of thumb as:

$$20 \times \dot{V}O_2 / (1 + \dot{V}O_2), \text{ with } \dot{V}O_2 \text{ in } L \cdot \min^{-1} \quad (30)$$

Higher values of $\dot{V}O_{2,max}$ in highly fit subjects are, therefore, associated with only relatively small further increases in ($CaO_2 - \dot{C}vO_2$); *i.e.* the relationship “flattens out” at high WRs [88, 90]. Even at $\dot{V}O_{2,max}$, the average muscle-venous PO_2 from the exercising region has been estimated to be ~ 2.66 kPa [93–96], although it can be as low ~ 1.33 kPa in highly fit subjects, and average muscle-tissue PO_2 to be ~ 0.4 kPa [97, 98], with little-or-no change over the region for which the metabolic acidosis is manifest despite (or more properly because) the associated concentration of muscle-venous oxygen continuing to decrease progressively over this region to values of 2 – $4 mL \cdot 100 mL^{-1}$. This is a result of a marked rightward shift of the oxygen dissociation curve [2], consequent to the acidaemia, high muscle venous PCO_2 and increased muscle temperature.

The level of CaO_2 does not decrease significantly in normal nonathletic subjects during exercise at sea level. An important consideration in this regard is the diffusive exchange of oxygen. At rest, approximately one third of a second is required for diffusion equilibrium across the alveolar-capillary membrane; during exercise this may be increased chiefly as a result of the mixed venous PO_2 being reduced. The margin of safety is normally considerable, however, the pulmonary capillary transit time (tTR) averages ~ 0.75 s at rest and, although it falls during exercise (consequent to the increased pulmonary blood flow ($Q'P$)), it does not normally approach limiting levels. It is not unusual, however, for arterial hypoxaemia and significant arterial desaturation to develop at high WRs in highly trained athletes (see above). While some of this is likely to be consequent to the increased dispersion of $\dot{V}A/Q'$ and post-pulmonary shunt, a component is also thought to be attributable to a diffusion impairment developing as a result of insufficient time for equilibration of alveolar and capillary PO_2 (see above).

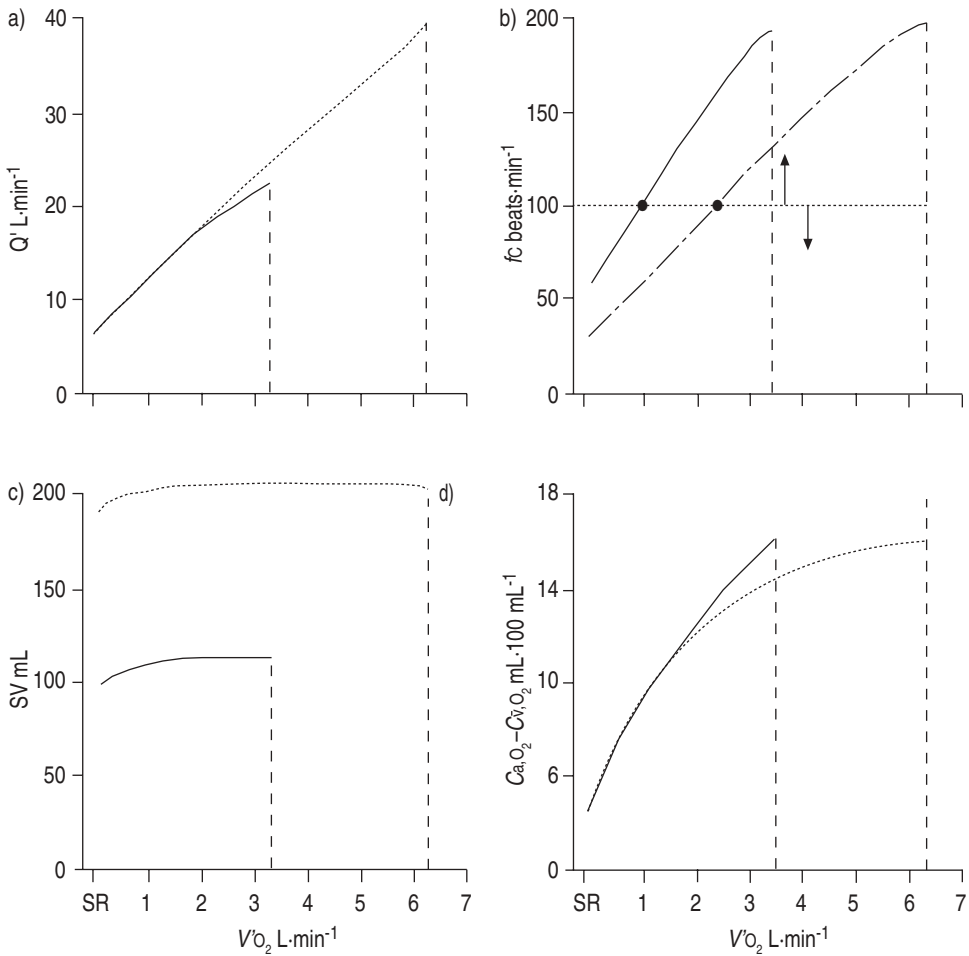


Fig. 10. – Responses of a) cardiac output (Q'); b) cardiac frequency (fc); c) stroke volume (SV); and d) the arterio-venous oxygen difference ($CaO_2 - CvO_2$) for progressive exercise, as a function of oxygen uptake ($\dot{V}O_2$) in elite endurance athletes (---) and normal active subjects (—). — — —: fc value of $100 \text{ beats} \cdot \text{min}^{-1}$ (●) which separates the lower range of parasympathetic withdrawal from the upper range of sympathetic activation. In b) the arrows extending up and down represent sympathetic and vagal responses, respectively. SR: supine rest. Reproduced from [90] with permission.

It should be recognised that t_{TR} is a function of the capacitance-to-conductance ratio of the capillary bed:

$$t_{TR} (s) = V_c (mL) / Q'P (mL \cdot s^{-1}) \quad (31)$$

Therefore, critical reductions of pulmonary capillary residence time at high WRs can only be prevented if an adequate capillary volume (V_c) is recruited as $Q'P$ increases. Consequently, the subjects most prone to developing such diffusion impairment during exercise are those who have an inordinately low capillary blood volume (in patients with pulmonary vascular occlusive disease, for example) and/or those with inordinately high levels of pulmonary blood flow; *i.e.* highly elite endurance athletes, unless they are genetically fortunate enough to have a commensurately large pulmonary-capillary blood volume.

One may use the rule of thumb that the minimum pulmonary Vc (mL) that will maintain a mean transit time of 0.3 s is numerically equivalent to five times the Q'P ($\text{L}\cdot\text{min}^{-1}$). A critical transit time of 0.6 s would require a Vc numerically equivalent to 10 times the Q'P. This, of course, only represents the mean of the distribution of transit times, with the shorter-transit regions tending to be hypoxaemia-inducing but the longer transit times in the distribution not being compensatory.

Cardiac frequency

The increased Q' during exercise depends in large on the increase in f_c . Normally, f_c increases essentially linearly with $\dot{V}\text{O}_2$, although upward deflections in the f_c response at high WRs have also been reported. For modest increases in WR, f_c increases almost entirely as a result of a withdrawal of inhibitory parasympathetic tone to the sinoatrial node [e.g. 87–91]. However, complete suppression of this parasympathetic tone is only able to increase f_c to $\sim 100 \text{ beats}\cdot\text{min}^{-1}$ (fig. 10). The increment in f_c that results from complete parasympathetic suppression will, of course, be larger the lower the resting f_c . This increment is typically $\sim 20\text{--}30 \text{ beats}\cdot\text{min}^{-1}$ in healthy young individuals having a resting f_c of $70\text{--}80 \text{ beats}\cdot\text{min}^{-1}$, but can easily be doubled in endurance athletes whose resting f_c may be $\leq 40 \text{ beats}\cdot\text{min}^{-1}$, reflecting a greater basal vagal tone.

Further increases in f_c depend upon activation of the more slowly developing excitatory sympathetic drive (fig. 10). This is also mediated at the sinoatrial node through: 1) stimulation of β_1 -adrenergic receptors *via* the sympathetic neurotransmitter noradrenaline; and 2) at higher WRs, circulating catecholamines released from the adrenal medulla. The chronotropic drive can elicit an f_c of $\geq 200 \text{ beats}\cdot\text{min}^{-1}$ at maximal exercise in healthy young adults. The maximal f_c , however, decreases progressively with age, on average, by $\sim 10 \text{ beats}\cdot\text{min}^{-1}$ every 10 yrs, resulting in an estimated maximal $f_c = 220 - \text{age (yr)}$. However, the variability of the age-dependent maximum f_c is large with an SD of $\geq 10 \text{ beats}\cdot\text{min}^{-1}$.

Stroke volume

The contribution of stroke volume (SV) to the Q' response depends on the exercise posture. In the supine posture, the resting SV is already close to that normally attained during exercise; i.e. $\sim 90\text{--}120 \text{ mL}$ in healthy young individuals [e.g. 87–91]. Consequently, it is the tachycardia that almost entirely dictates the Q' response under these conditions. However, resting SV is less in the more usual upright posture. This reflects a gravitationally induced pooling of blood in the dependent lower limbs. The increase of SV during upright exercise is largely confined to the lower 30–40% of the $\dot{V}\text{O}_2$ range, remaining almost constant at higher WRs.

Two major mechanisms contribute to increases in SV with exercise. 1) The sympathetic inotropic drive to the myocardium increases with WR and, together with the increased levels of circulating catecholamines at higher WRs, leads to an increase of ventricular contractility, which augments ventricular ejection by encroaching on the end-systolic “reserve”. 2) Ventricular end-diastolic volume also increases because of an augmented venous return (*i.e.* the Frank–Starling effect) brought about by: activation of the “muscle pump”; an increased pressure gradient for venous return, because of the progressive increase in mean arterial blood pressure with increasing WR; and sympathetically mediated constriction of venules and veins, which reduces overall venous compliance and, therefore, translocates a proportion of the “stored” blood (mainly from the splanchnic circulation) towards the right side of the heart.

SV is typically larger in endurance athletes than in untrained individuals, even when allowance is made for body size. Indeed, in elite athletes, it may be twice as large. Consequently, as Q' at a particular $\dot{V}O_2$ is essentially independent of fitness the larger SV accounts for the low fC at rest and during submaximal exercise in athletes: however, as maximum fC is not altered by training *per se*, then the improvement in the maximum Q' in trained subjects results from the increased SV.

Oxygen pulse

Further inferences for cardiovascular function may be drawn from a slight modification of the Fick relationship:

$$\dot{V}O_2/fC = SV \times (Ca_{O_2} - C\bar{v}_{O_2}) \quad (32)$$

The variable $\dot{V}O_2/fC$, termed the “oxygen pulse” (O_2 -P), was defined, by HENDERSON and PRINCE [99] as “the amount of oxygen consumed by the body from the blood of one systolic discharge of the heart”. It is, therefore, determined by the product of SV and $Ca_{O_2} - C\bar{v}_{O_2}$. Consequently, if one is prepared to make the assumption that one or the other variable is constant, then the change in O_2 -P will be a simple function of the other. O_2 -P is higher in fit subjects at a given $\dot{V}O_2$ as a result of the higher SV, the arterio-venous oxygen difference not being significantly different in normal subjects at a given $\dot{V}O_2$. While this is the case for steady-state type increases, it has recently been demonstrated that the $Q' - \dot{V}O_2$ relationship for rapidly incremental exercise of the ramp type is slightly nonlinear (convex upward) over the entire WR range [100]; a likely reflection of the faster kinetics of Q' than of $\dot{V}O_2$ during the continuously nonsteady-state conditions. The arterio-venous oxygen difference is consequently less than in the steady state at a given $\dot{V}O_2$. However, as SV normally becomes constant beyond the moderate WR range, the subsequent time course of O_2 -P will reflect that of the proportional change in tissue oxygen extraction. Similarly, if one assumes that $Ca_{O_2} - C\bar{v}_{O_2}$ is relatively constant for a short duration after the onset of exercise (*i.e.* until $C\bar{v}_{O_2}$ changes as a result of increased tissue oxygen utilisation), then the percentage increase in O_2 -P will directly reflect that of the in SV [2, 101].

Muscle blood flow

At rest, total skeletal muscle blood flow ($Q'M$) is in the region of $1 \text{ L} \cdot \text{min}^{-1}$ (*i.e.* $3\text{--}4 \text{ mL} \cdot 100 \text{ g} \cdot \text{min}^{-1}$) or some 15–20% of Q' [reviewed in 87, 90, 102]. It increases linearly with respect to $\dot{V}O_2$ during progressive exercise. For maximum leg exercise, $Q'M$ may attain values of $\sim 20 \text{ L} \cdot \text{min}^{-1}$ (both legs combined), which is as much as 85% of Q' ; in elite endurance athletes, $Q'M$ can approach $40 \text{ L} \cdot \text{min}^{-1}$ [reviewed in 88, 90, 102].

It is not sufficient simply for Q' to increase as WR increases, the increase must be directed to the contracting muscle units. This is, to a large extent, achieved. That is, the average flow to the remainder of the body does not change appreciably [reviewed in 88, 90], although some regions do have increased flow (skin and coronaries) whereas others (kidney and splanchnic bed) have decreased flow. The reason that blood flow does not increase in most other vascular beds, despite the increased driving pressure for flow (mean systemic blood pressure increases progressively as WR increases), is that local vascular resistance increases as a result of the diffuse sympathetic discharge. As the contracting units are functionally “sympathectomised” by local metabolic vasodilator effects, this allows the increase in Q' to be directed predominantly to the regions with the increased metabolic demands.

Although some initial vasodilatation may result from increased sympathetic-cholinergic stimulation, the predominant local vasodilatation in the contractile units

results from the influence of local metabolites on the vascular smooth muscle [102–105]. Numerous mediators of the vasodilatation have been proposed: potassium, osmolarity, hypoxia, H^+ , adenosine, vasoactive peptides and prostaglandins. However, most recently, attention has focused on nitric oxide, released as a result of elevated shear-stress at the endothelial cell surface as blood flow velocity increases. These agents are thought to impair the ability of noradrenaline to stimulate smooth muscle α -adrenoceptors and/or inhibit the release of noradrenaline from pre-junctional nerve varicosities. Local neurogenic mechanisms may also be contributory; nonadrenergic neurons (possibly *via* release of peptidergic vasodilator transmitters) have been located within the walls of small arteries in skeletal muscle.

Limiting factors

On the basis of the contracting muscles apparently having a greater potential to accommodate blood flow than is actually achieved at maximum exercise, the output of the heart is considered to provide the more important cardiovascular limitation to exercise involving large muscle mass in normal subjects [*e.g.* 90, 92, 106, 107]. However, even in trained athletes during maximal exercise at very high rates of oxygen utilisation, not all oxygen offered to muscles can be extracted. Interestingly, when additional oxygen is offered (transfusion, hyperoxia or increased muscle blood flow), oxygen utilisation can be increased, suggesting that under the control conditions of maximal exercise (without augmenting the oxygen supply) there is something about tissue oxygen utilisation that is being limited.

Tissue oxygen-extraction limitation under these conditions could be due to: 1) limited diffusive conductance for oxygen between the red blood cells and the mitochondria; 2) nonuniformity of perfusion in relation to metabolic rate; and/or 3) shunting of blood between arterioles and venules, bypassing muscle fibres [*e.g.* 15, 90, 92, 108–110]. These mechanisms are quite similar to those seen in the lungs in many different pathological conditions [*e.g.* 111]. Unfortunately, in contrast to the lung, current technology does not provide the tools to distinguish among them appropriately in muscle, particularly in humans. However, there is some evidence which suggests that, among these three potential mechanisms, limited diffusive oxygen conductance is probably the major contributor [92, 110]. For example, when the oxygen dissociation curve is manipulated, at constant convective oxygen delivery, corresponding shifts in $\dot{V}O_{2,max}$ occur, consistent with the concept of diffusion limitation. Also, in healthy subjects exercising maximally, the variation in the inspired fraction of oxygen produces corresponding changes both in $\dot{V}O_{2,max}$ and muscle–venous PO_2 that are also consistent with this concept. Conversely, in normal muscle, blood flow tends to be intrinsically matched to metabolic rate through the production of metabolites during exercise that locally augment blood flow (see above). This makes the hypothesis of significant nonuniformity of perfusion-to-metabolic rate unlikely, at least in healthy subjects exercising maximally. Finally, there is little evidence for the presence of peripheral shunt under these conditions.

If it is accepted that tissue oxygen diffusion limitation is playing a role in limiting oxygen transport to the mitochondria by limiting oxygen extraction, then it is useful to consider the determinants of oxygen extraction in the presence of a finite diffusive conductance. Under these circumstances, oxygen extraction depends upon the ratio of diffusive (D) to perfusive ($\beta Q'M$) conductances, *i.e.* $D/\beta Q'M$ where β is the average slope of the oxygen dissociation curve over that region [108, 109]. As it is this ratio which finally determines the effectiveness of the muscle oxygen extraction [108, 109], it is a necessary consequence that muscle oxygen extraction is not purely a peripheral phenomenon. This is because, although D is largely determined by structural aspects of

the microvasculature and muscle tissue itself (and thus can be considered as peripheral), both β and $Q'M$ represent what would be more properly labelled as central factors, reflecting blood itself and cardiac function [108, 109]. It is, therefore, more appropriate to consider any oxygen extraction limitation in the muscles of maximally exercising healthy subjects as representing the interaction between central and peripheral factors.

Exercise tolerance and exercise intensity

Exercise tolerance is a reflection of how long a subject is able to sustain a particular activity; the closest laboratory equivalent of this is a constant-load test. Although the tolerable duration of a given WR is recognised to be dependent on the intensity of the exercise being performed, there is currently, and surprisingly perhaps, no generally agreed scheme for characterising work intensity. The widely used procedure for assigning work intensity as a percentage of $\dot{V}O_{2,max}$ is, in most cases, not adequate in this regard. For example, while the onset of the metabolic (lactic) acidemia of exercise (θ_L) occurs at $\sim 50\%$ of $\dot{V}O_{2,max}$, on average, the distribution is very large, extending from 35% to at least 80% in normal subjects [112]. Consequently, an assigned work intensity of 70% $\dot{V}O_{2,max}$ could result in one subject exercising at a sub- θ_L WR and being comfortable in a steady state, whereas another subject would be exhausted at $\dot{V}O_{2,max}$ [e.g. 15]. A common exercise intensity should characterise a common degree of physiological stress and systemic response profile, regardless of the subject's state of fitness or training state.

The best noninvasive indicator for assigning domains of exercise intensity, and hence the sustainability of a particular task, is probably the profile of $\dot{V}O_2$ in response to an applied step of WR (fig. 6). This has been demonstrated to be emblematic of the corresponding invasively determined profiles of arterial [L] and pH [reviewed in 15, 46].

If $\dot{V}O_2$ increases mono-exponentially to attain a steady state within ~ 3 min (for healthy young subjects; longer is required for less fit, older individuals or for patients with impaired cardiopulmonary function), then the subject is characteristically below θ_L and the WR is therefore sustainable (moderate-intensity exercise) until glycogen depletion, dehydration, boredom or some other nonspecific limiting factor curtails the performance.

If the attainment of a $\dot{V}O_2$ steady state is delayed as a result of a supplementary slow component of the $\dot{V}O_2$ kinetics [e.g. 15, 40, 41, 43, 46–47], the subject will, by definition, be at or below their maximum sustainable $\dot{V}O_2$ (*i.e.* in the heavy-intensity domain); a parameter shown to correlate highly with the maximum sustainable blood L⁻ and H⁺ concentrations and also with CP (see above) [e.g. 113–115]. However, even though the subject does attain a delayed $\dot{V}O_2$ steady-state (and also one of blood [L] and pH), there will be additional continued stress to both $\dot{V}E$ and the rate of glycogen depletion as a result of the sustained metabolic acidemia.

If, however, $\dot{V}O_2$ continues to climb throughout the exercise with no evidence of a steady state or (nonmaximum) plateau, then the WR is clearly beyond the subject's capacity for sustained performance. Such heavy (supra-CP) WRs are, therefore, those that lead to $\dot{V}O_{2,max}$ being attained with its consequent high levels of metabolic-acidaemic stress to $\dot{V}E$, muscle and pulmonary gas exchange and the perception of the WR itself. In this intensity domain, the tolerable duration of the task declines in a hyperbolic fashion as WR increases [e.g. 45, 113, 115] (see below). The magnitude and time course of $\dot{V}O_2$ (and related ventilatory and pulmonary gas exchange indices) can, therefore, be considered a major index of exercise tolerance, in both health and disease.

The threshold $\dot{V}O_2$ for arterial $[L^-]$ increase or θL , therefore constitutes a partition of exercise intensity with important implications for the ability to sustain a particular WR. However, it should be emphasised that the biochemical and physiological mechanisms underlying the increases in muscle and blood $[L^-]$ that occur above θL remain a highly contentious issue; some investigators even question whether the arterial $[L^-]$ profile actually evidences threshold behaviour [116, 117]. This is reflected in the terminology that is applied to this threshold. For example, the use of the term “anaerobic threshold” is preferred by some. However, until there is convincing evidence that the increased arterial $[L^-]$ above the threshold is caused by lack of oxygen at the cytochrome oxidase terminus of the electron transport chain, in particular, and possibly small, regions of the contracting musculature, this term should be used in only a descriptive sense, *i.e.* to imply only that oxygen was not used in the reactions producing L^- (one is secure that this is not open to challenge), rather than that it was not available to be used. Another commonly encountered term is the “ventilatory threshold”. However, this is a misleading term as it implies that a ventilatory response has to occur, and that when it does it necessarily reflects lactic acidemia; neither, of course, is justifiable.

The resolution would appear to be straightforward: use the simply descriptive term “lactate threshold”. If the threshold “estimator” relates to the discernible increase in certain noninvasive indices of arterial $[L^-]$ increase, then the power of the “estimation” will depend upon assembling an optimal and physiologically robust constellation of variables for identification of the “estimator”. To make any inferences beyond this regarding the cause(s) of the L^- response falls outside the scope of these considerations.

The θL may, therefore, be considered to do the following. 1) Characterise an oxygen-related threshold of metabolic acidemia, of which the chief metabolic acid is lactic. This threshold can be defensibly supported as “oxygen-related” under normal circumstances, as any form of tissue hypoxia (whether hypoxic, stagnant, anaemic or histotoxic) reduces the threshold, while hyperoxia or mild polycythemia increase it. 2) Partition moderate- from heavy-intensity exercise. 3) Reflect the onset of a series of physiological responses that stress ventilation, pulmonary gas exchange and acid-base regulation. 4) Have important implications for the ability to sustain muscular exercise, both in normal individuals and in patients with impaired systemic function.

Maximum $\dot{V}O_{2,max}$ and peak $\dot{V}O_2$

$\dot{V}O_{2,max}$ is traditionally conceded to be the parameter that reflects the upper limit for oxygen conductance and utilisation. Therefore, it is required that a sufficiently large muscle mass be recruited in order to achieve the upper limit for the body rather than, for example, a particular limb. The test to determine $\dot{V}O_{2,max}$ was originally designed to stress the system by means of a series of discrete, constant-load tests of progressively greater power, each conducted on different occasions such that a level would be reached beyond which further increments of power would not result in further increments in $\dot{V}O_2$ or when the $\dot{V}O_2$ increment between the tests was sufficiently small to approximate constancy [118–120]. However, with discontinuous protocols, a high and limiting constant value can be apparent across the numerous tests, meeting the requirements for a $\dot{V}O_{2,max}$, despite no actual plateau on the individual tests themselves. This discontinuous procedure, while necessarily producing an upper limit or “plateau” of $\dot{V}O_2$ with good subject effort, is unrealistic for standard clinically related exercise testing.

Continuous incremental exercise tests, either comprising a series of steps of various durations and power increments or as a continuous ramp protocol, allows the tolerable WR range to be spanned at a single exercise-testing session. While evident in some subjects, plateaux of $\dot{V}O_2$ are not common with such incremental tests (fig. 11) [2, 121].

Consequently, as the $\dot{V}'\text{O}_{2,\text{max}}$ criterion is not met in these circumstances, the test provides what is termed a “peak” $\dot{V}'\text{O}_2$ ($\dot{V}'\text{O}_{2,\text{peak}}$), as shown in figure 11; while the highest $\dot{V}'\text{O}_2$ attained in a well-motivated subject on the incremental ramp protocol is not discernibly different from the $\dot{V}'\text{O}_{2,\text{max}}$ appropriately determined from the discontinuous, constant-load approach, one cannot be certain from the results of the ramp test alone that this was, in fact, the case. Patients, of course, may not be able to attain a $\dot{V}'\text{O}_{2,\text{max}}$ equivalent (or the investigator may not wish to stress them to these levels) because of limitation by some system-related perception (angina, dyspnoea, claudicating pain).

Both $\dot{V}'\text{O}_{2,\text{max}}$ and $\dot{V}'\text{O}_{2,\text{peak}}$ are conventionally expressed in units of $\text{mL}\cdot\text{min}^{-1}$ or $\text{L}\cdot\text{min}^{-1}$ (STPD) or, corrected for body weight (or better, corrected for muscle mass), as $\text{mL}\cdot\text{min}\cdot\text{kg}^{-1}$ or $\text{L}\cdot\text{min}\cdot\text{kg}^{-1}$. It is important to recognise, however, that the added fat mass in an obese subject “distorts” the notion of mass in the context of assessing the adequacy of cardiovascular performance. A more appropriate correction when the fat-free mass is not known is the “ideal” body weight or the subject’s height [2, 112]. The total mass correction is, of course, essential for assessing the appropriateness of the $\dot{V}'\text{O}_2$ for weight-bearing exercise.

The $\dot{V}'\text{O}_{2,\text{peak}}$ achieved during an incremental exercise test is, in normal subjects, largely independent of the rate of WR incrementation, although unusually rapid or prolonged tests can result in a lower $\dot{V}'\text{O}_{2,\text{peak}}$ being attained [122].

Constant load testing

The ramp-incremental exercise protocol [37], while providing an extensive source of relevant information, is highly artificial with respect to any normal activity pattern. Furthermore, establishing a steady-state equivalent of a variable-of-interest at a particular WR from such a test requires certain assumptions, which in many cases have only been verified in normal subjects. These concerns are, to a large extent, obviated by the use of constant-load (or, more properly, constant-WR) tests.

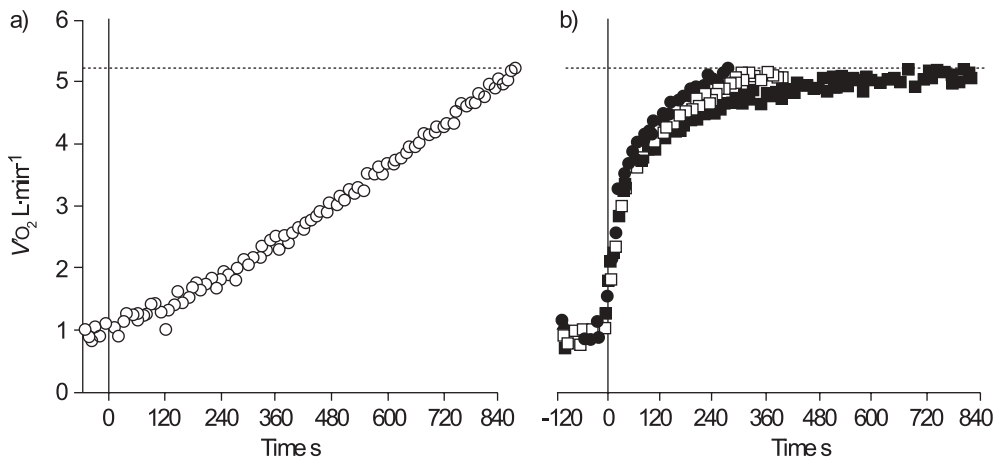


Fig. 11. – An example of the oxygen uptake ($\dot{V}'\text{O}_2$) response to a) a ramp-incremental and b) three very heavy constant-load exercise tests of differing work rates, each performed to the limit of tolerance, in a single subject.: peak $\dot{V}'\text{O}_2$ from the ramp test. ■: 320 W; □: 345 W; ●: 370 W.

In addition to providing a clear characterisation of the steady-state demands of the task, constant-load testing also provides the most convincing demonstration of the response of a particular intervention, such as physical training, rehabilitation, oxygen administration, ameliorating drug therapy, *etc.* It is important at the outset, however, to distinguish between the terms constant-load and steady-state. A constant-load or square-wave change of WR triggers a series of system responses that have a particular trajectory towards the steady state; these, in many instances, such as $\dot{Q}'$, $\dot{V}\text{O}_2$, $\dot{V}\text{CO}_2$, $\dot{V}\text{E}$, *etc.*, can be characterised as exponential. In the simplest form, this means that the instantaneous rate of change of the particular variable will be proportional to the distance from the steady state.

The time to attain a steady state naturally depends upon the rate at which this exponential response develops. This is conventionally characterised with respect to the time constant (τ) of the response. For such an exponential response, this is the time for the variable to attain 63% of the final steady-state change. It is generally accepted that the response has functionally attained a steady state after four time constants have elapsed; *i.e.* the function will have attained 99% of its steady-state value, which is well within current levels of discriminability. However, for those who prefer to use half-times ($t_{0.5}$) of response (the time to attain half of the final steady-state response), the steady state will be functionally attained after six half-times (as $\tau \approx 1.5 \times t_{0.5}$).

As different variables respond to the constant-load challenge with different time constants of response, then the time to attain a steady state will be different for different variables: $\dot{Q}'$, for example, increases faster than $\dot{V}\text{O}_2$ [123, 124], which increases faster than $\dot{V}\text{CO}_2$, which increases slightly faster than $\dot{V}\text{E}$ [reviewed in 2, 60]. Consequently, if steady states are required, the test must be sufficiently long for each variable of interest to attain its steady state. As the effective time constant of the $\dot{V}\text{O}_2$ response during moderate exercise in healthy young subjects is ~ 45 s (or less in fitter subjects), 3 min is the minimum time for the variable to attain a steady state (to within $\sim 1\%$). Steady-state measurements of $\dot{V}\text{O}_2$, therefore, should only begin after 3 min. In patients with heart [125, 126] or lung disease [127, 128] or even older, but sedentary normal subjects [16], this time constant can be appreciably longer, and hence a longer period would be required before the steady state is attained. However, even in normal young subjects, the time constants for $\dot{V}\text{CO}_2$ and $\dot{V}\text{E}$ are closer to 1 min. Consequently, a minimum of 4 min would be required before steady-state measurements should begin.

As discussed earlier, this relatively simple exponential response for $\dot{V}\text{O}_2$, for example, is only demonstrable in the moderate-intensity domain, *i.e.* at WRs that do not yield significant sustained increases of blood [L] (fig. 6). At higher WRs, the response is more complex in that an additional component of $\dot{V}\text{O}_2$ is added to the fundamental exponential response (fig. 6); this has been shown to begin some minutes after the start of the exercise [*e.g.* 15, 40–43, 46–47]. As this results in an increase of $\dot{V}\text{O}_2$ beyond the expected 3-min steady-state value [39], the difference in $\dot{V}\text{O}_2$ between the third and the sixth minute of exercise, which is only manifest at WRs above θL , has been shown to correlate well with the associated increment of arterial blood [L] [2].

This slowly developing component increases the $\dot{V}\text{O}_2$ to levels above those predicted from the pattern of response to moderate exercise; this increment has been termed “excess” $\dot{V}\text{O}_2$. As discussed earlier, over the metabolic rate range of $\sim 50\%$ of the difference between θL and the maximum-attainable $\dot{V}\text{O}_2$ (*i.e.* heavy-intensity exercise), a steady state can be attained but is delayed. CP, the WR equivalent of the maximum-sustainable $\dot{V}\text{O}_2$, occurs on average at $\sim 50\%$ of what is termed “delta” (Δ) [113, 129, 130], defined as the difference between θL and $\dot{V}\text{O}_{2,\text{max}}$; although there is a wide inter-subject variability.

At all WRs above CP, steady states cannot be attained and exercise tolerance becomes progressively reduced the higher the WR. That is, the trajectory of $\dot{V}O_2$ towards the maximum attainable value becomes progressively steeper, as does the rate of rise of blood [L] and the fall of blood pH. The pattern of the reduced tolerable duration (t_{lim}) to constant-WR exercise, not only for large muscle mass exercise such as cycle ergometry [e.g. 45, 113, 115], treadmill running [e.g. 114, 131] and swimming [132] but even for fatiguing contractions of the middle finger flexor muscle [44], as a function of WR above CP is also instructive. This has been shown, in normal subjects and patients with COPD, to be hyperbolic [reviewed in 64] of the form:

$$(WR - CP) \times t_{lim} = W' \quad (33)$$

where W' is the curvature constant, with the mechanistically provocative unit of work.

This has important implications for targeting a particular constant WR with respect to assessing the value of an intervention such as endurance training, breathing increased concentrations of oxygen and/or helium and pharmacological therapy. This is because, as a result of the hyperbolic shape of the WR– t_{lim} relationship, therapies which result in even small increases in CP can translate to an appreciable increase in the tolerable duration of a particular constant-load test, despite only a relatively small percentage increase in $\dot{V}O_{2,peak}$ or maximal WR on an incremental test. This is especially the case for WRs that are only slightly greater than the pre-intervention CP. Naturally, the magnitude of the apparent improvement in such cases will depend on the position of the initial WR on the subject's power–duration relationship [reviewed in 64]. Unfortunately, while CP is an important parameter characterising exercise tolerance in health and disease, it can, at present, only be determined from a series of high-intensity, constant-load tests or estimated “roughly” at 50% Δ from the incremental test.

Whereas the $\dot{V}O_2$ responses to constant WR exercise are characteristically different among the moderate, heavy and very-heavy intensity domains, as shown in figure 6, the $\dot{V}CO_2$ responses in normal subjects are not as evidently different [53, 133], often having a deceptively simple, and apparently exponential, profile in all three domains (fig. 12). However, this is a result of a highly complex combination of carbon dioxide from several sources, each of which has a different time course: 1) carbon dioxide from oxygen-related energy exchange (its aerobic component); 2) additional carbon dioxide from the rate of $[HCO_3^-]$ decrease, secondary to the lactic acidosis; 3) increased carbon dioxide stores in the exercising muscle units and the venous blood (as reflected by the high P_{v,CO_2}); and 4) a wash-out of carbon dioxide from the arterial blood (and, presumably, nonexercising tissues) consequent to arterial hypocapnia. Currently, very little is known about the dynamics of these different components of the pulmonary carbon dioxide response. Caution should, therefore, be exercised in interpreting the carbon dioxide-response profiles.

Since 1913 [32], it has been known that the pulmonary gas-exchange response to constant-load exercise, even to a steady state, is not simply monotonic as depicted in figure 6. Rather, there is an early phase in which pulmonary gas exchange is not influenced by the altered oxygen and carbon dioxide levels in the exercising-muscle venous effluent (fig. 4). Naturally, this can only accelerate pulmonary gas exchange after the limb-to-lung vascular transit delay. However, during this delay, Q' and pulmonary blood flow will have increased and resulted in an increased $\dot{V}O_2$ and $\dot{V}CO_2$. Therefore, the early pulmonary gas exchange is considered to be “cardiodynamic” [2, 33, 46], with the response being subsequently supplemented by the influence of the altered mixed venous gas tensions (fig. 4). It is useful, therefore, to consider pulmonary gas exchange within three temporal domains: 1) phase I being the cardiodynamic phase; 2) phase II the subsequent increase to the steady state; or 3) phase III [2, 33, 46]. Phase I usually lasts ~15–20 s, and the magnitude of the $\dot{V}O_2$ response during this time is, therefore, predominantly consequent to the magnitude of the pulmonary blood-flow changes.

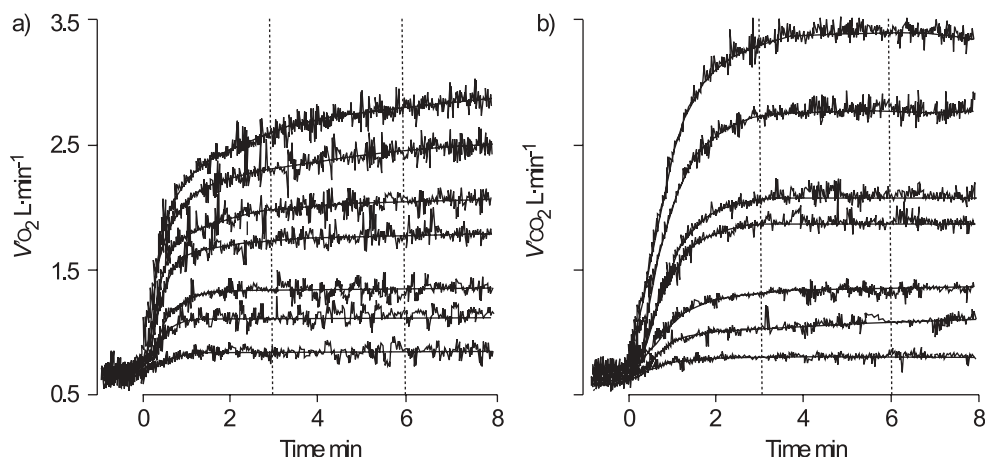


Fig. 12. – Profiles of a) oxygen uptake ($\dot{V}O_2$) and b) carbon dioxide output ($\dot{V}CO_2$) response to a range of constant-load tests spanning the moderate, heavy and severe work-intensity domains.: 3–6 min region of response. Note that, despite the continued increase of $\dot{V}O_2$ at the highest work rates (WRs), $\dot{V}CO_2$ appears to attain a “steady state”. In descending order from the top the lactate (mM) and WRs (W), respectively, were: 8.7, 210; 4.3, 180; 3.2, 150; 1.7, 120; 1.4, 90; 1.4, 60; and 1.2, 30. Reproduced from [133] with permission.

Interestingly, CASABURI *et al.* [134] have shown that, apparently only in rest-to-work transitions in the upright position, an early change in mixed venous gas tensions can be demonstrated within phase I. This is thought to reflect an increased contribution to the mixed venous blood of flow from a region with high resting $\dot{V}O_2/Q'$.

The magnitude of the rapid increase in $\dot{V}O_2$ during phase I has been shown to be markedly reduced in patients with cardiovascular and/or pulmonary disease in whom the magnitude of the early pulmonary blood-flow response is impaired [102]. However, very few data are currently available on the magnitude of the phase I response, so further work is needed before a certain pattern of phase I response can be confidently considered to be either abnormal or to reflect cardiovascular and/or pulmonary disease.

Summary

Maximum exercise in normal subjects is usually limited by perception of limb fatigue and in some cases by breathlessness. This usually results from an oxygen demand above the maximal conductance of the oxygen transport chain. Of the many tests available, an incremental test that provides a smooth gradual stress over the entire tolerance range is most appropriate for, at least initial, clinical investigations. The responses to exercise in patients should be interpreted with reference to the magnitude and pattern of the normal response.

Keywords: Aerobic metabolism, alveolar-to-arterial oxygen difference, anaerobic metabolism, critical power, lactate threshold, ventilatory and cardiovascular responses.

References

1. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
 2. Wasserman K, Hansen JE, Sue DY, Stringer W, Whipp BJ. Principles of Exercise Testing and Interpretation. 4th Edn. Philadelphia, Lea & Febiger, 2005.
 3. Palange P, Ward SA, Carlsen K-H, *et al.* Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; 29: 185–209.
 4. Gosselink R, Troosters T, Langer D. Laboratory tests. In: Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 40: 129–147.
 5. Whipp BJ. The bioenergetic and gas-exchange basis of exercise testing. *Clin Chest Med* 1994; 15: 173–192.
 6. Ivy JL, Chi MM, Hintz CS, Sherman WM, Hellendall RP, Lowry OH. Progressive metabolite changes in individual human muscle fibers with increasing work rates. *Am J Physiol* 1987; 252: C630–C639.
 7. Rossiter HB, Ward SA, Kowalchuk JM, Howe FA, Griffiths JR, Whipp BJ. Dynamic asymmetry of phosphocreatine concentration and O₂ uptake between the on- and off-transients of moderate- and high-intensity exercise in humans. *J Physiol (Lond)* 2002; 541: 991–1002.
 8. Harris RC, Sahlin K, Hultman E. Phosphagen and lactate contents of m. quadriceps femoris of man after exercise. *J Appl Physiol* 1977; 43: 852–857.
 9. Dempsey JA, Hanson P, Hendersen K. Exercise induced arterial hypoxemia in healthy human subjects at sea level. *J Appl Physiol* 1984; 55: 161–175.
 10. Powers SK, Martin D, Dodd S. Exercise-induced hypoxemia in elite endurance athletes. Incidence, causes and impact on V'O₂max. *Sports Med* 1993; 16: 14–22.
 11. Dempsey JA, Wagner PD. Exercise-induced arterial hypoxemia. *J Appl Physiol* 1999; 87: 1997–2006.
 12. Hopkins SR. Exercise induced arterial hypoxemia: the role of ventilation-perfusion inequality and pulmonary diffusion limitation. *Adv Exp Med Biol* 2006; 588: 17–30.
 13. Richardson RS, Leigh JS, Wagner PD, Noyszewski EA. Cellular PO₂ as a determinant of maximal mitochondrial O₂ consumption in trained human skeletal muscle. *J Appl Physiol* 1999; 87: 325–331.
 14. Tschakovsky ME, Hughson RL. Interaction of factors determining oxygen uptake at the onset of exercise. *J Appl Physiol* 1999; 86: 1101–1113.
 15. Whipp BJ, Ward SA, Rossiter HB. Pulmonary O₂ uptake during exercise: conflating muscular and cardiovascular responses. *Med Sci Sports Exerc* 2005; 37: 1574–1585.
 16. Babcock MA, Paterson DH, Cunningham DA, Dickinson JR. Exercise on transient gas exchange kinetics are slowed as a function of age. *Med Sci Sports Exerc* 1994; 26: 440–446.
 17. Dempsey JA, Reddan W, Balke B, Rankin J. Work capacity determinants and physiologic cost of weight-supported work in obesity. *J Appl Physiol* 1966; 21: 1815–1820.
 18. Whipp BJ, Bray GA, Koyal SN, Wasserman K. Exercise energetics and respiratory control in man following acute and chronic elevation of caloric intake. In: Bray GA, ed. Obesity in Perspective. Section II. Washington DC, US Government Printing Office, 1976; pp. 157–163.
 19. Whipp BJ, Davis JA. The ventilatory stress of exercise in obesity. *Am Rev Respir Dis* 1984; 129: S90–S92.
 20. Coyle EF, Sidossis LS, Horowitz JF, Beltz JD. Cycling efficiency is related to the percentage of type I muscle fibers. *Med Sci Sports Exerc* 1992; 24: 782–788.
 21. Mogensen M, Bagger M, Pedersen PK, Fernstrom M, Sahlin K. Cycling efficiency in humans is related to low UCP3 content and to type I fibres but not to mitochondrial efficiency. *J Physiol (Lond)* 2006; 571: 669–681.
 22. Barstow TJ, Jones AM, Nguyen PH, Casaburi R. Influence of muscle fibre type and fitness on the oxygen uptake/power output slope during incremental exercise in humans. *Exp Physiol* 2000; 85: 109–116.
-

23. Holten CH, Muller A, Reh binder D, eds. Lactic Acid: Property and Chemistry of Lactic Acid and Derivatives. Germany, Verlag Chemie, 1971.
24. Visser BF, Kreuknet J, Maas AH. Increase of whole blood lactic acid concentration during exercise as predicted from pH and PCO₂ determinations. *Pflugers Arch* 1964; 281: 300–304.
25. Wasserman K, VanKessel AL, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol* 1967; 22: 71–85.
26. Keul J, Doll E, Keppler D. Oxidative energy supply. In: Energy Metabolism of Human Muscle. Baltimore, University Park Press, 1972; pp. 52–202.
27. Brown GC. Control of respiration and ATP synthesis in mammalian mitochondria and cells. *Biochem J* 1992; 284: 1–13.
28. Meyer RA, Foley JM. Cellular processes integrating the metabolic response to exercise. In: Rowell LB, Shepherd Jt, eds. Handbook of Physiology. Section 12. Exercise: Regulation and Integration of Multiple Systems. Bethesda, Amer Physiol Soc, 1996; pp. 841–869.
29. Kushmerick MJ, Conley KE. Energetics of muscle contraction: the whole is less than the sum of its parts. *Biochem Soc Trans* 2002; 30: 227–231.
30. Mahler M. First-order kinetics of muscle oxygen consumption, and an equivalent proportionality between Q'O₂ and phosphorylcreatine level. *J Gen Physiol* 1985; 86: 35–165.
31. Grassi B, Poole DC, Richardson RS, Knight DR, Erickson BK, Wagner PD. Muscle O₂ uptake kinetics in humans: implications for metabolic control. *J Appl Physiol* 1996; 80: 988–998.
32. Krogh A, Lindhard J. The regulation of respiration and circulation during the initial stages of muscular work. *J Physiol (Lond)* 1913; 47: 112–136.
33. Whipp BJ, Ward SA, Lamarra N, Davis JA, Wasserman K. Parameters of ventilatory and gas exchange dynamics during exercise. *J Appl Physiol* 1982; 52: 1506–1513.
34. Hagberg JM, Hickson RC, Ehsani AA, Holloszy JP. Faster adjustment to and from recovery from submaximal exercise in the trained state. *J Appl Physiol* 1980; 48: 218–222.
35. Powers SK, Dodd S, Beadle RE. Oxygen uptake kinetics in trained athletes differing in V'O₂max. *Eur J Appl Physiol Occup Physiol* 1985; 54: 306–308.
36. Fukuoka Y, Grassi B, Conti M, *et al.* Early effects of exercise training on on- and off-kinetics in 50-year-old subjects. *Pflugers Arch* 2002; 443: 690–697.
37. Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine the parameters of aerobic function during exercise. *J Appl Physiol* 1981; 50: 217–221.
38. Hansen JE, Casaburi R, Cooper DM, Wasserman K. Oxygen uptake as related to work rate increment during cycle ergometer exercise. *Eur J Appl Physiol* 1988; 57: 140–145.
39. Whipp BJ, Mahler M. Dynamics of gas exchange during exercise. In: West JB, ed. Pulmonary Gas Exchange. Vol. II. New York, Academic Press, 1980; pp. 33–96.
40. Linnarsson D. Dynamics of pulmonary gas exchange and heart rate at start and end of exercise. *Acta Physiol Scand Suppl* 1974; 415: 1–68.
41. Barstow TJ. Characterization of V'O₂ kinetics during heavy exercise. *Med Sci Sports Exerc* 1994; 26: 1327–1334.
42. Grassi B. Oxygen uptake kinetics: old and recent lessons from experiments on isolated muscle in situ. *Eur J Appl Physiol* 2003; 90: 242–249.
43. Jones AM, Poole DC. Oxygen uptake dynamics: from muscle to mouth: an introduction to the symposium. *Med Sci Sports Exerc* 2005; 37: 1542–1550.
44. Whipp BJ, Rossiter HB. The kinetics of oxygen uptake: physiological inferences from the parameters. In: Jones AM, Poole DC, eds. Oxygen Uptake Kinetics in Health and Disease. Routledge Publs, London, 2004; pp 64–94.
45. Monod H, Scherrer J. The work capacity of a synergic muscular group. *Ergonomics* 1965; 8: 329–338.
46. Moritani TA, Nagata HA, de Vries HA, Muro M. Critical power as a measure of physical work capacity and anaerobic threshold. *Ergonomics* 1981; 24: 339–350.
47. Jones AM, Poole DC, eds. Oxygen Uptake Kinetics in Health and Disease. Routledge Publs, London, 2004.

48. Shinohara M, Moritani T. Increase in neuromuscular activity and O₂ uptake during heavy exercise. *Ann Physiol Anthropol* 1992; 11: 257–262.
49. Bearden SE, Moffatt RJ. V'O₂ and heart rate kinetics in cycling: transitions from an elevated baseline. *J Appl Physiol* 2001; 90: 2081–2087.
50. Russell A, Wadley G, Snow R, *et al.* Slow component of V'O₂ kinetics: the effect of training status, fibre type, UCP3 mRNA and citrate synthase activity. *Int J Obes Relat Metab Disord* 2002; 26: 157–164.
51. Jones AM, Pringle JSM, Carter H. Influence of muscle fibre type and motor unit recruitment on V'O₂ kinetics. In: Jones AM, Poole DC, eds. *Oxygen Uptake Kinetics in Health and Disease*. Routledge Pubs, London, 2004; pp. 261–293.
52. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting the anaerobic threshold by gas exchange. *J Appl Physiol* 1986; 60: 2020–2027.
53. Whipp BJ. Physiological mechanisms dissociating pulmonary CO₂ and O₂ exchange dynamics during exercise in humans. *Exp Physiol* 2007; 92: 347–355.
54. Cooper CB, Beaver WL, Cooper OM, Wasserman K. Factors affecting the components of the alveolar CO₂ output-O₂ uptake relationship during incremental exercise in man. *Exp Physiol* 1992; 77: 51–64.
55. Sue DY, Wasserman K, Moricca RB, Casaburi R. Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. *Chest* 1988; 94: 931–938.
56. Riley RL, Cournand A. 'Ideal' alveolar air and the analysis of ventilation-perfusion relationships in the lung. *J Appl Physiol* 1949; 1: 825–847.
57. Rahn H, Fenn WO. *A Graphical Analysis of the Respiratory Gas Exchange. The O₂-CO₂ Diagram*. Washington DC, Am Physiol Soc, 1955.
58. Douglas CG. Co-ordination of the respiration and circulation with variations in bodily activity. *Lancet* 1927; 2: 213–218.
59. Casaburi R, Whipp BJ, Wasserman K, Stremel RW. Ventilatory control characteristics of the exercise hyperpnea as discerned from dynamic forcing techniques. *Chest* 1978; 73: Suppl. 2, 280–283.
60. Whipp BJ, Ward SA. The coupling of ventilation to pulmonary gas exchange during exercise. In: Whipp BJ, Wasserman K, eds. *Pulmonary Physiology and Pathophysiology of Exercise*. New York, Dekker, 1991; pp. 271–307.
61. Jones, NL, Robertson DG, Kane, JW. Difference between end-tidal and arterial PCO₂ in exercise. *J Appl Physiol* 1979; 47: 954–960.
62. Robbins PA, Conway J, Cunningham DA, Khamnei S, Paterson DJ. A comparison of indirect methods for continuous estimation of arterial PCO₂ in men. *J Appl Physiol* 1990; 68: 1727–1731.
63. Whipp BJ, Lamarra N, Ward SA, Davis JA, Wasserman K. Estimating arterial PCO₂ from flow-weighted and time-averaged alveolar PCO₂ during exercise. In: Swanson GD, Grodins FS, eds. *Respiratory Control: Modelling Perspective*. New York, Plenum, 1990; pp. 91–99.
64. Ward SA. Discriminating features of responses in cardiopulmonary exercise testing. In: Ward SA, Palange P, eds. *Clinical Exercise Testing*. *Eur Respir Mon* 2007; 40: 36–68.
65. Jones NL, Killian KJ, Stubbing DG. The thorax in exercise. In: Roussos Ch, Macklem PT, eds. *The Thorax. Lung Biology in Health and Disease*. Vol. 29. New York, Dekker, 1988; pp. 627–662.
66. Marciniuk DD, Gallagher CG. Clinical exercise testing in interstitial lung disease. *Clin Chest Med* 1994; 15: 287–303.
67. Younes M. Exercise and breathing in health and disease. In: Bittar EE, ed. *Pulmonary Biology in Health and Disease*. New York, Springer-Verlag, 2002; pp. 289–305.
68. Clark FJ, von Euler C. On the regulation of depth and rate of breathing. *J Physiol (Lond)* 1972; 222: 267–295.
69. Cunningham DJC. Integrative aspects of the regulation of breathing: a personal view. In: Widdicombe JG, ed. *Respiratory Physiology I*. Vol. 2. Baltimore, University Park Press, 1974; pp. 303–369.

70. Gardner WN. The relation between tidal volume and inspiratory and expiratory times during steady-state carbon dioxide inhalation in man. *J Physiol (Lond)* 1977; 272: 591–611.
71. Milic-Emili J, Whitelaw WA, Grassino AE. Measurement and testing of respiratory drive. In: Hornbein T, ed. *The Regulation of Breathing*. New York, Dekker, 1981; pp. 1675–1743.
72. Dempsey JA, Adams L, Ainsworth DM, *et al.* Airway, lung and respiratory muscle function. In: Rowell LB, Shepherd JT, eds. *Handbook of Physiology. Section 12. Exercise: Regulation and Integration of Multiple Systems*. New York, Oxford University Press, 1996; pp 448–514.
73. Johnson BD, Dempsey JA. Demand vs capacity in the aging pulmonary system. *Ex Sports Sci Rev* 1991; 19: 171–210.
74. Whipp BJ, Pardy R. Breathing during exercise. In: Macklem P, Mead J, eds. *Handbook of Physiology, Respiration: Pulmonary Mechanics*. Washington DC, Amer Physiol Soc, 1986; pp. 605–629.
75. Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest* 1999; 116: 488–503.
76. Palange P, Ward SA, Carlsen K-H, *et al.* Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; 29: 185–209.
77. O'Donnell D.E, Ofir D, Laveneziana P. Patterns of cardiopulmonary response to exercise in lung diseases. In: Ward SA, Palange P, eds. *Clinical Exercise Testing. Eur Respir Mon* 2007; 40: 69–92.
78. Beck KC, Staats BA, Hyatt RE. Dynamics of breathing during exercise. In: Whipp BJ, Wasserman K. *Pulmonary Physiology and Pathophysiology of Exercise*. New York, Marcel Dekker Ltd, 1991; pp. 67–97.
79. Ward SA, Whipp BJ. Influence of body CO₂ stores on ventilatory-metabolic coupling during exercise. In: Honda Y, Miyamoto Y, Konno K, Widdicombe JG, eds. *Control of Breathing and its Modeling Perspective*. New York, Plenum Press, 1992; pp. 425–431.
80. Rausch SM, Whipp BJ, Wasserman K, Huszezuk A. Role of the carotid bodies in the respiratory compensation for the metabolic acidosis of exercise in humans. *J Physiol (Lond)* 1991; 444: 567–578.
81. Forster HV, Dempsey JA, Thomson J, Vidruk E, DoPico GA. Estimation of arterial PO₂, PCO₂, pH and lactate from arterialised venous blood. *J Appl Physiol* 1972; 32: 134–137.
82. McLoughlin P, Popham P, Linton RA, Bruce RC, Band DM. Use of arterialized venous blood sampling during incremental exercise tests. *J Appl Physiol* 1992; 73: 937–940.
83. Dempsey JA. Challenges for future research in exercise physiology as applied to the respiratory system. *Exerc Sport Sci Rev* 2006; 34: 92–98.
84. Stickland MK, Lovering AT. Exercise-induced intrapulmonary arteriovenous shunting and pulmonary gas exchange. *Exerc Sport Sci Rev* 2006; 34: 99–106.
85. Wagner PO, Gale GE, Moon RE, Torre-Bueno J, Stolp BW, Saltzman HA. Pulmonary gas exchange in humans exercising at sea level and stimulated altitude. *J Appl Physiol* 1986; 60: 260–270.
86. Whipp BJ, Davis JA, Wasserman K. Ventilatory control of the 'isocapnic buffering' region in rapidly-incremental exercise. *Resp Physiol* 1989; 76: 357–368.
87. Wade OL, Bishop JM. *Cardiac Output and Regional Blood Flow*. Oxford, Blackwell, 1962.
88. Clausen JP. Effect of physical training on cardiovascular adjustments to exercise in man. *Physiol Rev* 1977; 57: 779–815.
89. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res* 1986; 58: 281–291.
90. Rowell LB. *Human Cardiovascular Control*. New York, Oxford University Press, 1993.
91. Janicki JS, Sheriff DD, Robotham JL, Wise RA. Cardiac output during exercise: contributions of the cardiac, circulatory and respiratory systems. In: Rowell LB, Shepherd JT, eds. *Handbook of Physiology. Section 12. Exercise: Regulation and Integration of Multiple Systems*. Bethesda, Amer Physiol Soc, 1996; pp. 649–704.
92. Wagner PD, Hoppeler H, Saltin B. Determinants of maximal oxygen uptake. In: Crystal RG, West JB, eds. *The Lung: Scientific Foundations*. New York, Raven Press, 1991; pp. 1585–1594.

93. Stringer WW, Wasserman K, Casaburi R, Porszasz J, Maehara K, French W. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. *J Appl Physiol* 1994; 76: 1462–1467.
94. Brooks GA. Lactate production under fully aerobic conditions: the lactate shuttle during rest and exercise. *Fed Proc* 1986; 45: 2924–2929.
95. Keul J, Keppeler D, Doll E. Lactate/pyruvate ratio and its relation to oxygen pressure in arterial, coronarvenous and femorolovenous blood. *Arch Int Physiol Biochem* 1967; 75: 573–578.
96. Pirnay F, Lamy M, Dujardin J, Doroanne R, Petit JM. Analysis of femoral venous blood during maximum muscular exercise. *J Appl Physiol* 1972; 33: 289–292.
97. Richardson RS, Leigh JS, Wagner PD, Noyszewski EA. Cellular PO₂ as a determinant of maximal mitochondrial O₂ consumption in trained human skeletal muscle. *J Appl Physiol* 1999; 87: 325–331.
98. Conley KE, Ordway GA, Richardson RS. Deciphering the mysteries of myoglobin in striated muscle. *Acta Physiol Scand* 2000; 168: 623–634.
99. Henderson Y, Prince AL. The oxygen pulse and the systolic discharge. *Am J Physiol* 1914; 35: 106–115.
100. Stringer W, Whipp B, Wasserman K, Christenson P, French W. Non-linear cardiac output dynamics during ramp-incremental cycle ergometry. *Eur J Appl Physiol* 2005; 93: 634–639.
101. Sietsema KE, Cooper DM, Rosove MH, *et al.* Dynamics of oxygen uptake during exercise in adults with cyanotic congenital heart disease. *Circulation* 1986; 73: 1137–1114.
102. Laughlin MH, Korthuis RJ, Duncker DJ, Bache RJ. Control of blood flow to cardiac and skeletal muscle during exercise. In: Rowell LB, Shepherd JT, eds. *Handbook of Physiology*. Section 12. Exercise: Regulation and Integration of Multiple Systems. Bethesda, Amer Physiol Soc, 1996; pp. 705–769.
103. Boushel R. Metabolic control of muscle blood flow during exercise in humans. *Can J Appl Physiol* 2003; 28: 754–773.
104. Chavoshan B, Sander M, Sybert TE, Hansen J, Victor RG, Thomas GD. Nitric oxide-dependent modulation of sympathetic neural control of oxygenation in exercising human skeletal muscle. *J Physiol (Lond)* 2002; 540: 377–386.
105. Radegran G, Hellsten Y. Adenosine and nitric oxide in exercise-induced human skeletal muscle vasodilatation. *Acta Physiol Scand* 2000; 168: 575–591.
106. Andersen P, Saltin B. Maximal perfusion of skeletal muscle in man. *J Physiol (Lond)* 1985; 366: 233–249.
107. Saltin B, Calbet JA. Point: in health and in a normoxic environment, V'O₂ max is limited primarily by cardiac output and locomotor muscle blood flow. *J Appl Physiol* 2006; 100: 744–745.
108. Piiper J. Perfusion, diffusion and their heterogeneities limiting blood-tissue O₂ transfer in muscle. *Acta Physiol Scand* 2000; 168: 603–607.
109. Piiper J, Meyer M, Scheid P. Dual role of diffusion in tissue gas exchange: blood tissue equilibration and diffusion shunt. *Respir Physiol* 1984; 56: 131–144.
110. Wagner PD. Counterpoint: in health and in normoxic environment V'O₂max is limited primarily by cardiac output and locomotor muscle blood flow. *J Appl Physiol* 2006; 100: 745–747.
111. West JB, Wagner PD. Pulmonary gas exchange. In: West JB, ed. *Bioengineering Aspects of the Lung*. New York, Dekker, 1977, pp. 361–394.
112. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; 129: 549–555.
113. Poole DC, Ward SA, Gardner GW, Whipp BJ Metabolic, respiratory profile of the upper limit for prolonged exercise in man, *Ergonomics* 1988; 31: 1265–1279.
114. Smith CG, Jones AM. The relationship between critical velocity, maximal lactate steady-state velocity and lactate turnpoint velocity in runners. *Eur J Appl Physiol* 2001; 85: 19–26.
115. Hill DW, Poole DC, Smith JC. The relationship between power and the time to achieve V'O₂max. *Med Sci Sports Exerc* 2002; 34: 709–714.
116. Hughson RL, Weisiger KH, Swanson GO. Blood lactate concentration increases as a continuous function in progressive exercise. *J Appl Physiol* 1987; 62: 1975–1981.

117. Dennis SC, Noakes TO, Bosch AP. Ventilation and blood lactate increase exponentially during incremental exercise. *J Sports Sci* 1992; 10: 437–449.
118. Hill AV, Lupton H. Muscular exercise, lactic acid and the supply and utilization of oxygen. *Q J Med* 1923; 16: 135–171.
119. Mitchell JH, Sproule BJ, Chapman CB. The physiological meaning of the maximal oxygen intake test. *J Clin Invest* 1957; 37: 538–547.
120. Taylor HL, Buskirk E, Henschel A. Maximal oxygen intake as an objective measure of cardiorespiratory performance. *J Appl Physiol* 1955; 8: 73–80.
121. Day JR, Rossiter HB, Coats EM, Skasick A, Whipp BJ. The maximally attainable $\dot{V}O_2$ during exercise in humans: the peak vs maximum issue. *J Appl Physiol* 2003; 95: 1901–1907.
122. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. *J Appl Physiol* 1983; 55: 1558–1564.
123. De Cort SC, Innes JA, Barstow TJ, Guz A. Cardiac output, oxygen consumption and arteriovenous oxygen difference following a sudden rise in exercise level in humans. *J Physiol (Lond)* 1991; 441: 501–512.
124. Yoshida T, Whipp BJ. Dynamic asymmetries of cardiac output transients in response to muscular exercise in man. *J Physiol (Lond)* 1994; 480: 355–359.
125. Meakins J, Long CN. Oxygen consumption, oxygen debt and lactic acid in circulatory failure. *J Clin Invest* 1927; 4: 273–293.
126. Koike A, Hiroe M, Adachi H, *et al.* Oxygen uptake kinetics are determined by cardiac function at onset of exercise in patients with prior myocardial infarction. *Circulation* 1994; 90: 2324–2332.
127. Nery LE, Wasserman K, Andrews JD, Huntsman OJ, Hansen JE, Whipp BJ. Ventilatory and gas exchange kinetics during exercise in chronic obstructive pulmonary disease. *J Appl Physiol* 1982; 53: 1594–1602.
128. Puente-Maestu L, Sanz ML, Sanz P, Ruiz de Ona JM, Rodriguez-Hermosa JL, Whipp BJ. Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. *Eur Resp J* 2000; 15: 1026–1032.
129. Hill DW. The critical power concept. A review. *Sports Med* 1993; 16: 237–254.
130. Coats EM, Rossiter HB, Day JR, Miura A, Fukuba Y, Whipp BJ. Intensity-dependent tolerance to exercise after attaining $\dot{V}O_{2\max}$ in humans. *J Appl Physiol* 2003; 95: 483–490.
131. Hughson RL, Orok CJ, Staudt LE. A high velocity treadmill running test to assess endurance running potential. *Int J Sports Med* 1984; 5: 23–25.
132. Wakayoshi K, Yoshida T, Udo M, *et al.* Does critical swimming velocity represent exercise intensity at maximal lactate steady state? *Eur J Appl Physiol Occup Physiol* 1993; 66: 90–95.
133. Casaburi R, Barstow TJ, Robinson T, Wasserman K. Influence of work rate on ventilatory and gas exchange kinetics. *J Appl Physiol* 1989; 67: 547–555.
134. Casaburi R, Daly J, Hansen JE, Effros RM. Abrupt changes in mixed venous blood gas composition following the onset of exercise. *J Appl Physiol* 1989; 67: 1106–1112.

CHAPTER 2

Discriminating features of responses in cardiopulmonary exercise testing

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Background

William Harvey's dictum regarding the functioning of the human body, "for that which is normal is right and serves as a criterion both for itself and the abnormal", is particularly apposite to clinical exercise testing when abnormalities and/or limits of system function are discerned from the normal magnitude and profile of response to a defined work-rate (WR) challenge. Consequently, the major goal of clinical exercise testing is to provide a controlled exertional stress to the body to a level that any system dysfunction responsible for, or contributing to, a subject's exercise intolerance becomes apparent. The testing generally involves exercising large muscle groups, usually of the lower extremity although arm or other exercise strategies can be effectively utilised for particular purposes. Cardiopulmonary exercise testing (CPET) allows a rigorous, and largely noninvasive, description of cardio-respiratory and metabolic response profiles to judiciously designed exercise test formats or "forcing functions", in the first instance the ramp (or incremental) test, and often supplemented with step (or constant-load) tests.

Clues to interpretation can derive from: 1) parameters related to exercise capacity, such as peak oxygen uptake ($\dot{V}O_{2,\text{peak}}$) and the lactate threshold (θ_L); 2) values of variables at certain reference points within the tolerable range of the ramp (e.g. the ventilatory equivalent for carbon dioxide (minute ventilation ($\dot{V}E$)/carbon dioxide output ($\dot{V}CO_2$) at θ_L)); and 3) response profiles of variables that span part of or even the full tolerable WR range, expressed against an appropriate dependent variable (e.g. oxygen uptake ($\dot{V}O_2$) *versus* WR or $\dot{V}E$ *versus* $\dot{V}CO_2$). Judgements regarding the normalcy, or otherwise, of such outcomes depend on the availability of suitable population-based "normal" values [reviewed in 1]. This chapter considers the physiological basis of standard (and emerging) measurements using incremental and constant-load (or, more properly, constant-WR) exercise as frames of reference.

Indices of CPET response: incremental exercise

A symptom-limited incremental (or ramp) exercise test [2] can provide information both on the extent to which an individual manifests "exercise intolerance" and whether the intolerance is reflective of abnormal physiological system function, from the response profiles of particular variables of interest. The extent to which these variables exhibit abnormal response profiles allows the cause(s) of any exercise intolerance to be identified. It is thus conventional to employ an incremental test for initial exercise evaluation. A particular merit of the incremental test is that, as it is characterised by a

constant average rate of change of WR with respect to time ($\Delta\text{WR}/\Delta t$), it imposes a relatively smooth gradual stress that spans the subject's full tolerance range [reviewed in 3, 4]. This can be “fine-tuned” when a true ramp profile is used, with the WR being a constant instantaneous rate of change of WR (*i.e.* the WR and time increments becoming disappearingly small).

$\dot{V}\text{O}_2$ –WR relationship

There are several quantifiable features of the $\dot{V}\text{O}_2$ response to incremental exercise that provide important clues to ascertaining why a subject may manifest exercise intolerance. The most obvious of these is the maximum $\dot{V}\text{O}_2$ (most usually inferred from $\dot{V}\text{O}_{2,\text{peak}}$), but additional submaximal indices may also be informative. Interpreting abnormalities in the $\dot{V}\text{O}_2$ response to incremental exercise requires consideration of its determining variables, as characterised by the Fick Principle. For the body as a whole, these are cardiac output (Q'), cardiac frequency (f_c), stroke volume (SV) and the arterio–mixed venous oxygen content difference or “extraction” ($\text{Ca}_{a,\text{O}_2} - \text{C}\bar{\text{v}}_{\text{O}_2}$):

$$\dot{V}\text{O}_2 = Q' \times (\text{Ca}_{a,\text{O}_2} - \text{C}\bar{\text{v}}_{\text{O}_2}) \quad (1)$$

$$\dot{V}\text{O}_2 = f_c \times \text{SV} \times (\text{Ca}_{a,\text{O}_2} - \text{C}\bar{\text{v}}_{\text{O}_2}) \quad (2)$$

and for muscle oxygen consumption ($\dot{Q}'\text{O}_2$), these are muscle blood flow ($Q'M$) and muscle oxygen extraction ($\text{Ca}_{a,\text{O}_2} - \text{C}\bar{\text{v}}_{\text{MO}_2}$):

$$\dot{Q}'\text{O}_2 = Q'M \times (\text{Ca}_{a,\text{O}_2} - \text{C}\bar{\text{v}}_{\text{MO}_2}) \quad (3)$$

Baseline $\dot{V}\text{O}_2$. It is most usual to initiate an incremental test from a background of “unloaded” or very light exercise. This, unlike a test performed from rest, provides a known baseline WR upon which the actual incremental response is superimposed. For cycle ergometry, baseline $\dot{V}\text{O}_2$ ($\dot{V}\text{O}_{2,\text{BL}}$) values in the region of $\sim 500 \text{ mL}\cdot\text{min}^{-1}$ are to be expected in a normal healthy young adult exercising at or close to true unloaded pedalling (*i.e.* 0 W) [5].

$\dot{V}\text{O}_{2,\text{BL}}$ is made up of two components that are required to: 1) support resting metabolism ($\dot{V}\text{O}_{2,\text{rest}}$); and 2) move the legs (for example, in the case of cycling) at the required cadence against no applied load to the flywheel of the cycle ergometer ($\dot{V}\text{O}_{2,0}$). $\dot{V}\text{O}_{2,\text{rest}}$ is influenced by body mass and, more specifically, fat-free mass (FFM) [6] and, therefore, is reduced with muscle wasting (*e.g.* chronic deconditioning). Resting energy expenditure has been widely reported to be increased by 15–20% both in chronic obstructive pulmonary disease (COPD) [*e.g.* 7, 8] and in interstitial lung disease (ILD) [9], a phenomenon attributable to the increased oxygen costs of ventilation.

Accurate measurement of $\dot{V}\text{O}_{2,0}$ requires a steady state to have been achieved following the onset of unloaded pedalling. A 3-min period is typically advocated by many investigators [*e.g.* 4, 10–12]; this is likely to be adequate in most subjects. However, if visual inspection shows $\dot{V}\text{O}_2$ not to have stabilised by this time, clearly the phase should be extended to allow a steady state to be confidently achieved. An additional consideration specific to patients with severe chronic heart failure (CHF) is the high probability of ventilatory and gas exchange oscillations at rest and moderate exercise [12–14]. As these can have an appreciable magnitude and periodicity (fig. 1), it is important to ensure that the measurement period includes an integral number of cycles rather than relying on an arbitrarily fixed period. Naturally, the oscillatory magnitude will be influenced by the particular data-averaging strategy employed.

Alterations in $\dot{V}\text{O}_{2,0}$ influence the position of the $\dot{V}\text{O}_2$ –WR relationship. $\dot{V}\text{O}_{2,0}$ is influenced by the mass of the involved muscles, *i.e.* the legs (largely) for cycle ergometry. As a result, higher-than-normal values of $\dot{V}\text{O}_{2,\text{BL}}$ (*e.g.* $\sim \geq 700 \text{ mL}\cdot\text{min}^{-1}$) result with elevated body, and especially leg, mass, as in obese subjects and in athletes with highly

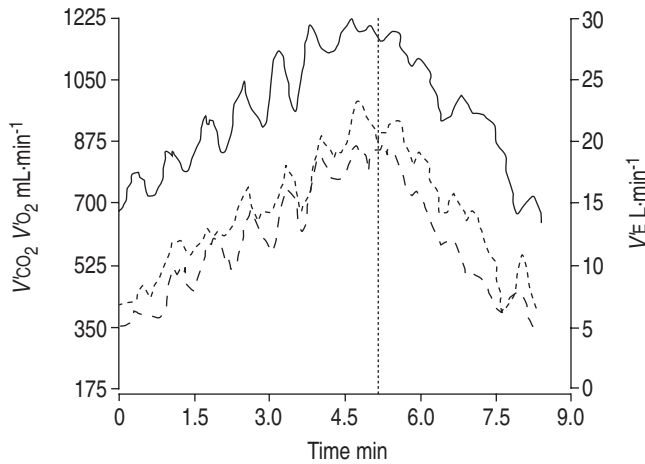


Fig. 1. – Periodic oscillations in carbon dioxide output ($\dot{V}\text{CO}_2$; - - -), oxygen uptake ($\dot{V}\text{O}_2$; - · - · -) and minute ventilation ($\dot{V}\text{E}$; —), during incremental exercise in a patient with heart failure. Reproduced from [14] with permission.

muscle lower limbs (*e.g.* body builders, speed skaters); values increase by $\sim 5.8 \text{ mL}\cdot\text{min}\cdot\text{kg}^{-1}$ body mass at constant pedalling frequency (fig. 2) [5, 15]. This would be expected to impose an upward shift of the $\dot{V}\text{O}_2$ –WR relationship, resulting in an increased oxygen cost at a given WR (fig. 3).

Cycle ergometers with a substantial “unloaded” pedalling setting will also induce higher-than-normal $\dot{V}\text{O}_{2,\text{BL}}$ responses. It is rarely the case that ergometers are truly unloaded; *i.e.* requiring only 0 W [reviewed in 3, 10–12]. Although there are some electromagnetically braked models of cycle ergometer that are loadless (with the resistances provided by the pedals and flywheel being overcome by a driver motor), it is not uncommon to encounter “unloaded” settings as high as 30 W. The baseline conditions associated with treadmill exercise can be even more variable, reflecting differences in baseline grade, speed and body mass, and the mechanical efficiency of

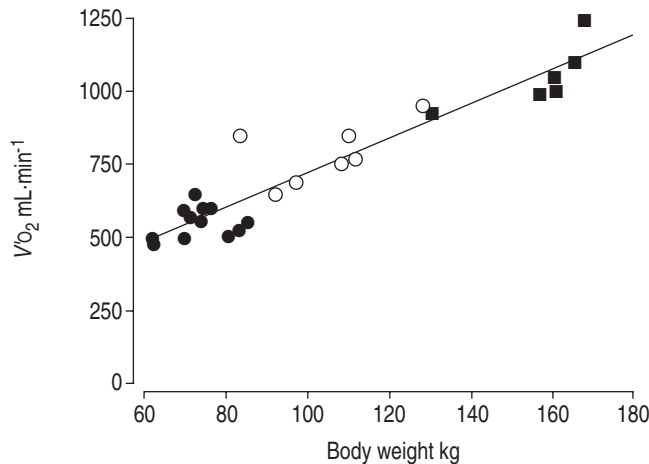


Fig. 2. – Oxygen cost of unloaded pedalling as a function of body mass (pedalling frequency=60 rpm). ●: lean; ○: moderately obese; ■: obese. $\dot{V}\text{O}_2$: oxygen uptake. $y = 5.8x + 151$; $r = 0.94$. Reproduced from [5] with permission.

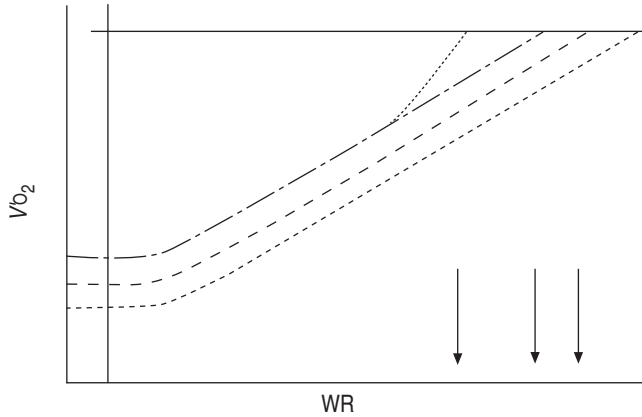


Fig. 3. – Schematic diagram of the oxygen uptake ($\dot{V}O_2$)–work rate (WR) relationship for ramp-incremental exercise showing the influence of altered baseline $\dot{V}O_2$ consequent to increased body mass (e.g. obesity; — — — —), and decreased body mass (e.g. cachexia; ·····) relative to normal (— — — —). Influence of the obese subject pedalling with a progressively increasing cadence ······. Vertical solid line: the start of the ramp phase of the test, from a baseline of unloaded pedalling. Horizontal solid line: peak $\dot{V}O_2$. The arrows represent peak WRs for each condition. See text for further details.

walking (even when the patient does not hold on to the handrail of the treadmill or is partially supported by the investigator) [reviewed in 3, 10–12]. Such factors can elevate $\dot{V}O_{2,BL}$ and by amounts that are not readily predictable. Elevated baseline oxygen costs can impose significant “performance” implications, as they impose a necessarily high oxygen cost at all WRs and, therefore, impose a limitation on the operational WR range that can be accommodated (see below).

In contrast, appreciably lower values of $\dot{V}O_{2,BL}$ (e.g. $\leq 300 \text{ mL} \cdot \text{min}^{-1}$) can be found in conditions where there is a low body mass, FFM and/or leg mass; for example in children, the frail elderly, anorexic subjects and patients with cachexia (e.g. some COPD patients). This would be expected to shift the $\dot{V}O_2$ –WR relationship downwards relative to normal, with the $\dot{V}O_2$ at any particular WR being lower (fig. 3).

Incremental gain ($\Delta\dot{V}O_2/\Delta WR$). As discussed previously [16], for ramp-type cycle ergometry of the kind commonly used in CPET applications, $\dot{V}O_2$ increases as a linear function of time and, therefore, WR (after a small lag-phase, consequent to the system response kinetics; fig. 3). The actual value of $\dot{V}O_2$ at any WR is, therefore, lower for the incremental (or ramp) test than for the steady-state condition, by an amount that reflects the $\dot{V}O_2$ “mean response time” (MRT). This amount will be a close approximation to $\tau\dot{V}O_2$; specifically, the $\dot{V}O_2$ equivalent of the increment in WR that occurs over a period equal to the MRT. However, the slope of the $\dot{V}O_2$ –WR relationship, or “incremental gain” ($\Delta\dot{V}O_2/\Delta WR$), over the linear response range of the incremental test has been shown not to differ from that of the steady state in healthy young adults, being of the order of $\sim 9\text{--}12 \text{ mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$. The incremental gain is often used as an index of the work efficiency (η_w) but, importantly, efficiency cannot be validly estimated unless both $\dot{V}O_2$ and $\dot{V}CO_2$ have achieved their respective steady states; this, of course, is never the case during incremental exercise.

The profile of the $\dot{V}O_2$ –WR relationship has the potential to be influenced by the components of η_w , namely the efficiency of phosphorylative coupling (η_p), the efficiency of contraction coupling (the utilisation of the phosphate bond energy for the contraction process itself) and the motor efficiency (or skill) with which the task is accomplished [e.g. 16]. $\Delta\dot{V}O_2/\Delta WR$ is not appreciably influenced by age [17, 18] or fitness (see below).

The dietary substrate mixture undergoing oxidation has a modest effect on η_p [e.g. 16]. For example, the preferential oxidation of free fatty acids over that of carbohydrate, as occurs in highly fit endurance athletes [e.g. 19] and poorly regulated diabetics [e.g. 20, 21] is associated with a modest reduction in η_p [e.g. 16]. With reference to the former, it is of interest that there are reports of slightly greater $\Delta \dot{V}O_2/\Delta WR$ values in subjects with a high $\dot{V}O_{2,peak}$ [12, 22].

A reduction in η_p consequent to a defect at some point(s) within the energy transduction mechanisms linking adenosine triphosphate production to oxygen utilisation, as might be expected for hyperthyroidism, would predispose towards increased $\Delta \dot{V}O_2/\Delta WR$ values [23]. This has also been reported in patients with a deficiency of muscle succinate dehydrogenase and mitochondrial aconitase [24].

A further factor that has the potential to influence $\Delta \dot{V}O_2/\Delta WR$ is the profile of muscle fibre-type recruitment with increasing WR. Based on single-fibre glycogen depletion profiles, force generation requirements for modest WRs are met from the type I slow-twitch fibre pool, with an involvement of type IIA and type IIX fast-twitch fibres occurring only at relatively high WRs [25, 26]. Type II (fast-twitch) muscle fibres have been reported to have a lower η_p than type I fibres [27–29, for an alternative view see 22, 30, 31]. It has been widely argued that fast-twitch fibre recruitment is a significant contributor to the “slow” and “excess” component of $\dot{V}O_2$ response [reviewed in 32–35], through an increased high-energy phosphate ($\sim P$) cost of force generation rather than an increased oxygen cost of $\sim P$ production [36], which is expressed as a steepening of the $\dot{V}O_2$ –WR relationship in the later stages of longer-duration incremental tests [16, 37–39].

It has also been suggested that fibre type might contribute to the increased oxygen cost of exercise that has been reported in COPD patients, relative to normal [e.g. 5, 40, 41]. Thus, while $\Delta \dot{V}O_2/\Delta WR$ is often within normal limits in patients with COPD [e.g. 10–12, 42], $\dot{V}O_2$ at any particular WR can be elevated above normal (fig. 4). It has been proposed [43] that this might reflect, in part at least, the bio-energetic consequences of selective atrophy of type I (slow-twitch, oxidative) muscle fibres (in m. quadriceps), especially in severe COPD [reviewed in 44, 45]. Whether there is also a similarly increased oxygen cost in other conditions of selective type I fibre atrophy, such as CHF [reviewed in 44, 46], or of reduced type I fibre oxidative capacity consequent to mutations in the β myosin heavy-chain gene in hypertrophic cardiomyopathy [47] is unclear. Neither is it known whether the selective atrophy of type II fibres characteristically found in ageing [48], which has been reported in patients with moderate COPD [reviewed in 45], might have the opposite effect on oxygen cost.

The superimposition of a progressively larger contribution from extraneous “work” on the external work requirements of the task can also lead to a steepening of the $\dot{V}O_2$ –WR relationship. This can occur during cycle ergometry if there is an increasing reliance on the upper-body musculature, as a result of subjects “pulling” forcefully on the handlebars in an attempt to sustain the required power output near the tolerable limit. Likewise, an exacerbated oxygen cost might be expected in clinical conditions characterised by spasms and poor motor coordination. Furthermore, an increased oxygen cost of moving the legs (see above) could also influence $\Delta \dot{V}O_2/\Delta WR$. For example, while $\Delta \dot{V}O_2/\Delta WR$ can be relatively normal in obesity [49, 50], were an obese subject to elect to cycle with a progressively increasing cadence as the exercise test proceeds, the associated increased oxygen cost would cause $\Delta \dot{V}O_2/\Delta WR$ to increase progressively (fig. 3). It would be prudent to ensure that such subjects exercise at a constant cadence throughout the test (fig. 3). Even so, the elevated $\dot{V}O_{2,BL}$ constrains the effective WR range for the obese subject: for example, an obese subject who is physically active with a reasonably normal $\dot{V}O_{2,peak}$ would achieve a lower peak WR (WR_{peak}) than a lean subject with the same $\dot{V}O_{2,peak}$ and WR incrementation rate (fig. 3).

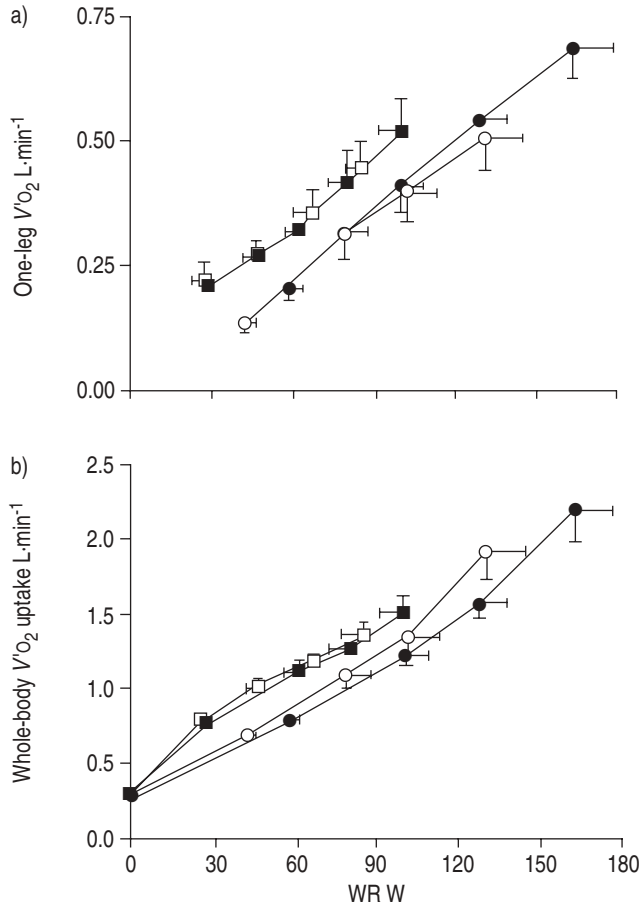


Fig. 4. – Whole-body and one-leg oxygen uptake ($\dot{V}O_2$)–work rate (WR) relationship (mean $\pm$ SE) for ramp-incremental exercise pre-training ($\circ$ and $\square$) and post-training ($\bullet$ and $\blacksquare$) for healthy subjects ($\circ$ and $\bullet$) and patients with chronic obstructive pulmonary disease ($\square$ and $\blacksquare$). Reproduced from [41] with permission.

An increased oxygen cost of breathing consequent to an exacerbated ventilatory response to exercise (caused by an increased physiological dead space fraction of the breath (dead space volume (V_D)/ tidal volume (V_T)) and/or arterial hypoxaemia, for example) in conditions having abnormally high respiratory impedance such as COPD, restrictive disease and obesity [e.g. 42, 51–53] also has the potential to increase $\Delta\dot{V}O_2/\Delta WR$. Despite this, $\Delta\dot{V}O_2/\Delta WR$ is often normal in COPD. It has been suggested [10] that this might reflect the offsetting influence of the abnormally slow $\dot{V}O_2$ kinetics typically found in these patients [54–56]; *i.e.* there is evidence of an increased steady-state oxygen cost at submaximal WRs [5, 12].

In contrast, it is relatively infrequent that an increase in η_p is encountered, which would be expected to lead to a shallower $\dot{V}O_2$ –WR relationship, especially at higher WRs. Some investigators have suggested this occurs for tests having a very fast WR incrementation rate [e.g. 12]. This is certainly the case for exercise-related abnormalities of intramuscular oxygen utilisation, such as have been reported in mitochondrial myopathies [57, 58], CHF [59–61], COPD [e.g. 62–65] and cystic fibrosis [66].

Impaired oxygen delivery to the exercising muscles (*e.g.* inappropriately low muscle perfusion; compromised oxygen carriage by haemoglobin) is the more usual cause of a flatter $\dot{V}O_2$ –WR relationship. A compromised muscle perfusion response to exercise is a major cause of the reduced $\Delta\dot{V}O_2/\Delta WR$ commonly seen in many cardiovascular disease states, either over the entire WR range or over the higher reaches as symptom limitations are approached [reviewed in 11, 12, 67–69]. This latter scenario is exemplified by ischaemic heart disease, for which the $\dot{V}O_2$ –WR relationship initially may be reasonably normal, but becomes flatter as the tolerable limit is approached, often with a rather abrupt transition that coincides with the onset of electrocardiographical abnormalities [12, 69, 70] and with a premature plateau in the oxygen pulse (O_2 -P) response (see below). In such conditions, $\Delta\dot{V}O_2/\Delta WR$ would be expected to be low for a ramp-incremental test, but not for a series of constant-WR tests conducted to steady state.

Sluggish, and even abnormal, $\dot{V}O_2$ response kinetics can also influence the form of the $\dot{V}O_2$ –WR relationship, recognising that the nonsteady-state nature of the incremental (ramp) test format. For example, when $\tau\dot{V}O_2$ is abnormally long (see below), the $\dot{V}O_2$ –WR relationship is shifted to the right (for simplicity, shown here with no change of slope), reflecting the increased prominence of the kinetic phase. When this is accompanied by a reduced $\dot{V}O_{2,peak}$ (as is commonly the case), establishing a linear phase with confidence may be hampered because of the compressed tolerable WR range (fig. 5).

In addition, $\Delta\dot{V}O_2/\Delta WR$ can be lower than normal were there to be a progressive slowing of the $\dot{V}O_2$ kinetics as the WR increases, with $\tau\dot{V}O_2$ lengthening progressively as WR increases during the ramp [16, 33]. Such a scenario could occur were the regional distribution of perfusion to metabolic rate within the exercising muscles to be highly heterogeneous [*c.f.* 33, 71, 72]. This has been suggested to occur in COPD [62] and CHF [69], for example. Again, one would not expect *a priori* the steady-state gain to be low as well, as the effects of these kinetic heterogeneities would have dissipated.

All of these influences will be compounded in patients with severe CHF who exhibit periodic breathing (fig. 1). Particular care is then needed in slope estimation. Whatever the aetiology of these various $\Delta\dot{V}O_2/\Delta WR$ abnormalities, it cannot be emphasised enough that meaningful interpretation of purported changes in $\Delta\dot{V}O_2/\Delta WR$ requires that the slope estimation be conducted over a WR region for which the $\dot{V}O_2$ –WR

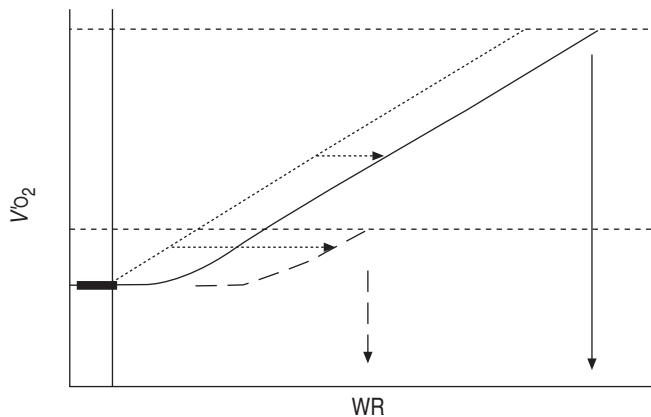


Fig. 5. – Schematic diagram of the oxygen uptake ($\dot{V}O_2$)–work rate (WR) relationship for ramp-incremental exercise showing the response for a subject of poor fitness (slow kinetics, low peak $\dot{V}O_2$; - - -) with a restricted linear phase, relative to normal (—). The solid line represents the steady-state relationship. The dotted horizontal arrows indicate $\dot{V}O_2$ mean response time. Vertical arrows indicate peak WR. - - -: peak $\dot{V}O_2$. See text for further details.

relationship is convincingly linear (fig. 5). This certainly requires exclusion of the initial nonlinear or “kinetic” phase at the beginning of the ramp response. Furthermore, it may not necessarily be the case that a normal $\Delta\dot{V}O_2/\Delta WR$ is indicative of normal function; there is the potential for offsetting influences to disguise underlying abnormality. Finally, in this and subsequent contexts, the manner in which breath-by-breath data are analysed deserves consideration. In particular, the practice of subjecting the data series to a moving- rather than a stationary-average is not to be recommended, especially when departures from linearity are present. This practice predisposes to distortion of the actual response profile and the time-point at which a break-point occurs.

In contrast to cycle ergometry, discriminating abnormalities of $\Delta\dot{V}O_2/\Delta WR$ for treadmill exercise is more problematic. Apart from the considerations raised earlier, there is also the difficulty of providing a metabolic equivalent of the grade and speed profile because of variable and unquantifiable contributions from factors such as technique and vertical displacement of the body [reviewed in 3].

Peak $\dot{V}O_2$. The maximum $\dot{V}O_2$ ($\dot{V}O_{2,max}$) reflects the attainment of a limitation at some point(s) in the oxygen conductance pathway from the lungs to the site of the mitochondrial oxygen consumption at the cytochrome-oxidase terminus of the electron transport chain [reviewed in 73, 74]. Thus, dysfunction in the responses of the convective oxygen flows into the lungs and through the vasculature, and the diffusive oxygen flows across pulmonary and muscle capillary beds will be reflected in abnormally low values of $\dot{V}O_{2,max}$.

The criterion for $\dot{V}O_{2,max}$ is that $\dot{V}O_2$ be demonstrated to no longer increase despite further increases in WR [75]. The classical approach for determining $\dot{V}O_{2,max}$ requires the subject to complete several discrete exhausting constant-WR tests [76, 77]; this is both taxing and time-consuming for the subject and the investigator(s). However, plateauing of the $\dot{V}O_2$ –WR relationship is not commonly seen with rapid incremental tests of the kind used in clinical exercise testing (*i.e.* having a duration of ~10–12 min); although, this may be more likely for tests which are of substantially longer duration because of a relatively low WR incrementation rate and/or because subjects are highly fit. Therefore, it is standard practice to refer to the highest value attained on an incremental test as $\dot{V}O_{2,peak}$; *i.e.* the highest value achieved with good subject effort. This corresponds well with the more traditionally determined $\dot{V}O_{2,max}$ in well-motivated healthy individuals [*e.g.* 78, 79]. However, $\dot{V}O_{2,max}$ cannot be determined in conditions where an exercise test is terminated prematurely because of symptom limiting perceptions, such as dyspnoea, angina or claudicating pain [*e.g.* 10–12].

A recently published useful expedient allows confirmatory evidence for $\dot{V}O_{2,max}$ on the same testing session by imposing a supra-maximal constant-WR test to the limit of tolerance after a short recovery period (*e.g.* ~5 min or so) immediately following the incremental test (fig. 6) [80]. This test is likely to be useful in normal subjects and especially athletes, for whom an accurate measure of $\dot{V}O_{2,peak}$ is important. However, its utility has not yet been demonstrated in patients with cardiac or pulmonary disease. Indeed, whether this test proves to be realistic in such patients is uncertain, given the additional time and compliance demands.

With good subject effort, $\dot{V}O_{2,max}$ is independent of the WR incrementation rate [*e.g.* 37]. Even so, slow incrementation rates are not to be recommended, as there is the risk of underestimating $\dot{V}O_{2,max}$ because of problems with maintaining motivation for prolonged periods. Tests with fast WR incrementation rates also predispose to underestimation of $\dot{V}O_{2,max}$, because the subject may experience difficulties in being able to generate the necessary muscular force to support the high WRs attained. However, reflective of the underlying response kinetics, the WR_{peak} attained is progressively greater the faster the ramp (fig. 7) [*e.g.* 37]. Therefore, WR_{peak} is not a

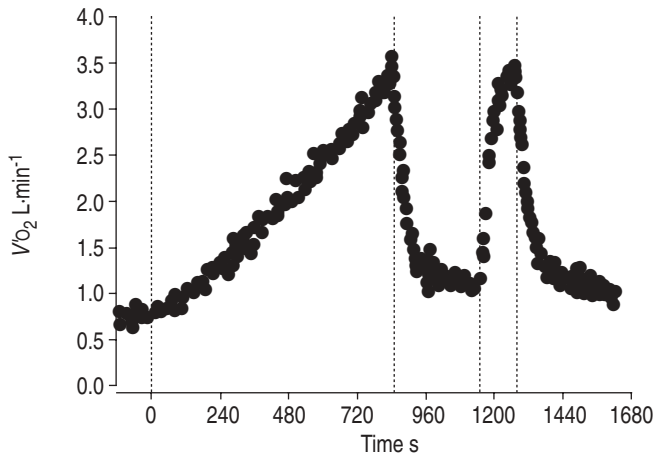


Fig. 6. – Representative response of oxygen uptake ($\dot{V}O_2$) to a rapid incremental test, followed by a 5-min period of 20 W exercise and then step exercise at 95% peak work rate, both performed to the limit of tolerance. Note that peak $\dot{V}O_2$ on the ramp test was similar to maximum $\dot{V}O_2$ on the step test. Reproduced from [80] with permission.

reliable surrogate for $\dot{V}O_{2,\text{peak}}$. This should be borne in mind when interpreting any intervention-related change in WR_{peak} , where an improved exercise tolerance might lead the investigator to impose a slight larger WR incrementation rate post-intervention.

Inadequacies of cardiovascular function, whether the result of chronic inactivity, disease or both, are associated with abnormally low values of $\dot{V}O_{2,\text{peak}}$ (e.g. in the elderly and patients with cardio-circulatory diseases). Discrimination between these two causes requires levels of habitual physical activity between patient and control groups to be matched. The exacerbated exertional dyspnoea resulting from the respiratory mechanical impairments in obstructive and restrictive pulmonary disease, likewise, leads to a low $\dot{V}O_{2,\text{peak}}$. However, the scenario should also be borne in mind that a “normal” $\dot{V}O_{2,\text{peak}}$ could actually represent an abnormality. The case in point being that of the previously “highly fit” subject who became impaired, resulting in a $\dot{V}O_{2,\text{peak}}$ that has plummeted but is still in the normal range for sedentary subjects.

The issue of the period over which $\dot{V}O_{2,\text{peak}}$ is best measured deserves some attention. Due to the typical breath-by-breath variability inherent in $\dot{V}O_2$ (and other gas exchange variables), it is usual practice to select a short interval of time back from the end-exercise point in order to allow the effects of this “noise” to be minimised by breath averaging. However, several considerations should be kept in mind. First, it is preferable that the averaging period is chosen to include an integral number of actual breaths, rather than relying on a fixed interval that would variously truncate the initial breath in the period, *i.e.* depending on breathing frequency (f_R) characteristics. This effect will become less important with the use of longer averaging periods. However, as the duration of the averaging period is increased, so will the resulting average $\dot{V}O_{2,\text{peak}}$ value progressively fall short of the actual value. The magnitude of this shortfall will also depend on the WR incrementation rate being used. For example, assuming an incremental gain of $10 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$, with a $5 \text{ W}\cdot\text{min}^{-1}$ incrementation rate, the $\dot{V}O_2$ increment for a 20-s period would be trivially small (*i.e.* $17 \text{ mL}\cdot\text{min}^{-1}$). However, for a $\Delta WR/\Delta t$ of $30 \text{ W}\cdot\text{min}^{-1}$, which some investigators would advocate for a more highly fit subject, the corresponding $\dot{V}O_2$ increment would be $100 \text{ mL}\cdot\text{min}^{-1}$ and $150 \text{ mL}\cdot\text{min}^{-1}$ for a 20- and 30-s period, respectively. It has recently been stated that errors of the order of 20%

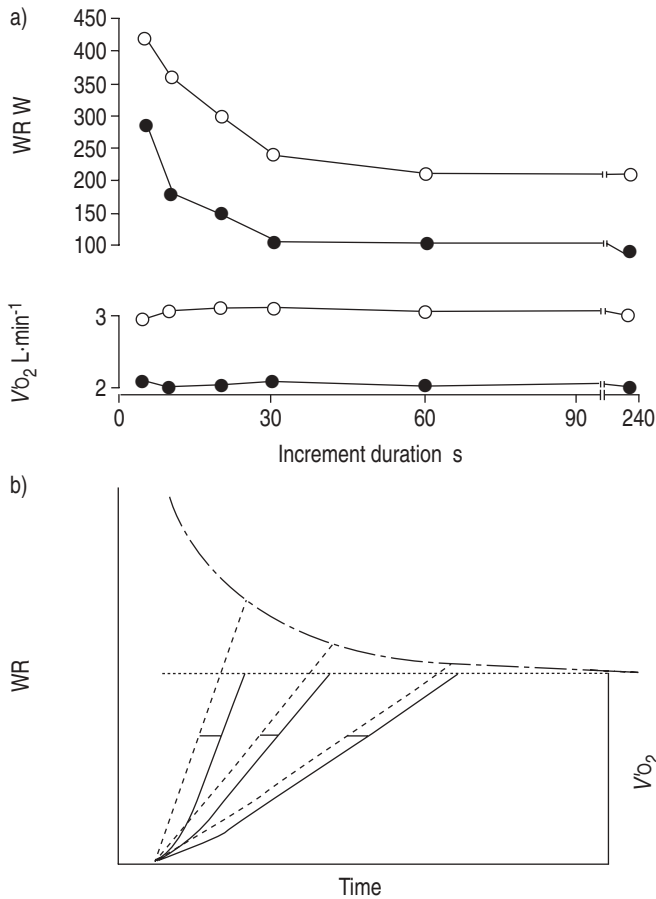


Fig. 7. – a) Influence of work rate (WR) incrementation on oxygen uptake ($\dot{V}O_2$) and WR at peak exercise (○) and at the lactate threshold (●) for a series of incremental tests performed to the limit of tolerance. b) Schematic diagram of the $\dot{V}O_2$ (—) and WR (---) responses to ramp-incremental exercise as a function of time for three different WR incrementation rates. Note the lack of effect on peak $\dot{V}O_2$ (·····) and $\dot{V}O_2$ at the lactate threshold. However, the influence of the $\dot{V}O_2$ mean response time (horizontal solid lines) results in peak WR (— - -) being progressively higher, the faster the incrementation rate. (See text for details). Modified from [37] with permission.

can accrue from this source [81]. There are no formal recommendations in this regard, although an interval of 30 s has been recommended [81].

$\dot{V}O_2$ -fC relationship

fC at any given submaximal metabolic rate is a function of Q' and SV. The close proportionality between Q' and $\dot{V}O_2$ during exercise in normal subjects is essentially uninfluenced by training [74, 82] and also in some disease conditions, such as COPD [42, 83] and ILD [84]. However, as SV is lower the less fit the subject, fC at any WR or $\dot{V}O_2$ will be higher. In patients, however, it is not easy to prove discrimination between lack of conditioning and overt dysfunction as the cause(s) of relative tachycardia during exercise.

Baseline fC. Reliable measurements of resting fC (fC_{rest}) are not always easy to make, as they require the subject to be not only at rest but also in a relaxed state at the time of

measurement. In normal subjects, fC_{rest} is typically higher in subjects who are less fit, this is also the case in many disease states (*e.g.* CHF). fC during unloaded pedalling is similarly higher, an effect which will be more marked in individuals having a high oxygen cost of unloaded pedalling (*e.g.* the obese). Naturally, these values may well be lower in individuals who are taking β -adrenergic blockers (for management of hypertension, for example).

$\Delta fC/\Delta V'O_2$. Normally, fC increases linearly with $V'O_2$ during incremental exercise, although it may start to plateau as $V'O_{2,\text{peak}}$ is approached [*e.g.* 16]. The slope of this relationship ($\Delta fC/\Delta V'O_2$) is steeper in less fit subjects (*fig.* 8a), *i.e.* the increment in Q' required to support a given increment in $V'O_2$ being accomplished with a larger increase in fC because of the smaller SV. This is often the case in cardiac diseases (*e.g.* CHF, hypertrophic cardiomyopathy (HCM)) and pulmonary vascular disease (PVD), where the low SV is also a result of the disease process [*e.g.* 11, 12, 69]. Impaired oxygenation (*e.g.* anaemia, carboxyhaemoglobinaemia) also results in a relatively steep $fC-V'O_2$

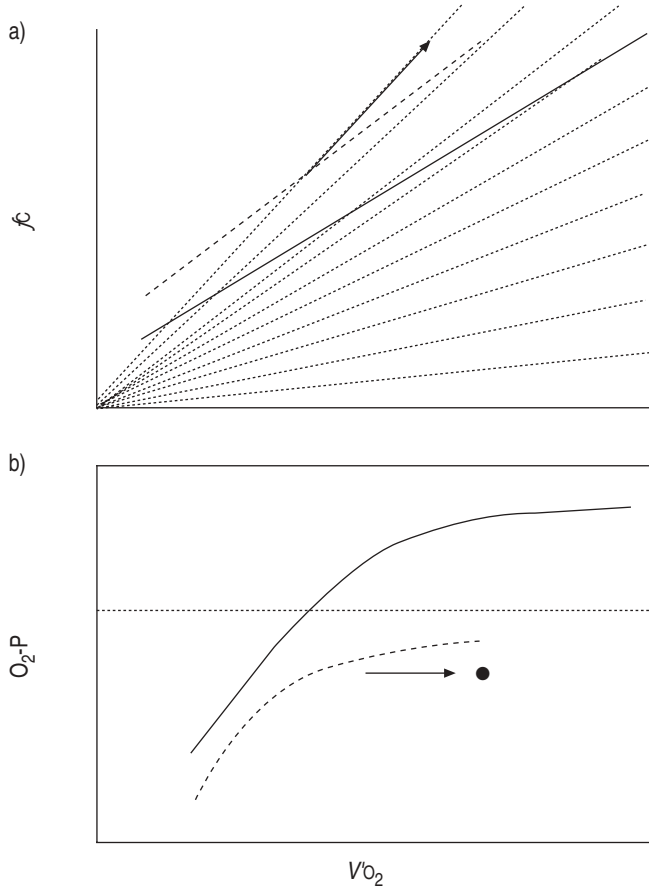


Fig. 8. – Schematic representation of the relationships between a) cardiac frequency (fC) and b) O_2 -pulse (O_2 -P) as a function of oxygen uptake ($V'O_2$). a) - - -: unfit subject; —: fit subject;: $fC-V'O_2$ isopleths. b) —: asymptotic O_2 -P value for the fit subject; - - -: asymptotic O_2 -P value for the unfit subject. Note the scenario in which the O_2 -P response becomes truly flat despite $V'O_2$ continuing to increase (● and arrow), requiring fC to increase at a faster rate and along the $fC-V'O_2$ isopleth corresponding to this limiting O_2 -P value. See text for further details.

relationship [e.g. 11, 12]. However, the $fC-V'O_2$ slope is abnormally low in situations where fC is constrained (e.g. chronotropic insufficiency, β -adrenergic blockade; fig. 8a) [e.g. 11, 12]. The $fC-V'O_2$ relationship can also depart from linearity as the tolerable limit is approached, becoming steeper (e.g. coronary artery disease (CAD)) [e.g. 11, 12, 69]. There may also be nonlinearities at low WRs (e.g. atrial fibrillation) [69]. Thus, it is important to ensure that the range over which the slope is estimated is actually linear, or closely so.

Peak fC and heart rate reserve. The peak fC (fC_{peak}) attained on an incremental test is generally regarded as being independent of fitness, and normally attains values close to the maximal predicted fC ($fC_{max,pred}$), whether the latter is derived as $(220-age(yr))$ [85, 86] or as $(210-0.65 \times age(yr))$ [87]. The heart rate reserve ($fCR = fC_{max,pred} - fC_{peak}$) is thus essentially zero. However, caution should be used when making judgements based solely on fCR to ascertain whether an effort is truly maximal or not [e.g. 12, 88, 89]. For example, the commonly used predictors of fC_{max} have a relatively large SD (~ 10 beats $\cdot$ min $^{-1}$). In addition, subject motivation may be low, which might account, in part at least for reports that fC_{peak} tends to be lower in subjects who are less fit [e.g. 90, 91]. Also, the predicted fC_{max} is not reached in healthy elderly subjects receiving β -blocker medication or, of course, in malingerers. Naturally, a lower than predicted fC_{peak} (and therefore an increased fCR) is characteristic of many clinical situations, e.g. chronotropic insufficiency, or when for example a patient stops exercise prematurely because of dyspnoea, angina or claudication.

Oxygen pulse. The oxygen pulse, or the stroke extraction of oxygen, is readily defined through a simple rearrangement of equation 2:

$$V'O_2/fC = SV \times (C_{a,O_2} - C_{v,O_2}) \quad (4)$$

The initial increase in O_2 -P during incremental exercise is normally reflective of increases in both SV and the arterio-venous oxygen difference. Once SV has reached its peak, however, further increases in O_2 -P are the result of the increasing arterio-venous O_2 difference; it being generally assumed that the flattening off of the O_2 -P response as WR_{peak} is approached is the result of the arterio-venous oxygen difference plateauing.

As the $fC-V'O_2$ relationship normally has a positive intercept on the fC axis (fig. 8a), the increase in O_2 -P will follow a hyperbolic trajectory with respect to $V'O_2$ over the region of an incremental test for which the $fC-V'O_2$ relationship is linear (fig. 8b) [e.g. 5, 12, 37, 92]. This is evident in figure 8a, where the schematic linear $fC-V'O_2$ relationship can be seen to be crossing $fC-V'O_2$ isopleths of progressively decreasing gradient as the incremental test proceeds (i.e. isopleths, by definition, passing through the origin and therefore having a slope equal to $fC/V'O_2$ or the inverse of the O_2 -P). In the limit (i.e. for very high values of $V'O_2$), the O_2 -P response will asymptote towards a value that equals the inverse of the actual $fC-V'O_2$ slope (fig. 8b) [37].

It is important to distinguish between an O_2 -P response that is becoming progressively flatter as it approaches its asymptotic value and one that actually becomes prematurely flat despite WR and $V'O_2$ continuing to increase. The criterion for the latter is that the slope of the $fC-V'O_2$ relationship must manifest not only a discernible increase, but one which constrains the $fC-V'O_2$ relationship to lie along the $fC-V'O_2$ isopleth corresponding to the peak O_2 -P value in question (fig. 8a); i.e. the continued increase in $V'O_2$ is fC dependent [e.g. 12, 93]. An example is shown in figure 9 for a patient with HCM.

Peak O_2 -P is reduced in normal subjects who are less fit (fig. 8b) [e.g. 5, 12, 92], because of the lower than normal SV coupled with fC_{peak} being unaffected in the face of a reduced $V'O_{2,peak}$. As fC is higher at any given submaximal $V'O_2$, O_2 -P will be correspondingly lower. Likewise, diseases in which SV is compromised (e.g. CHF, CAD,

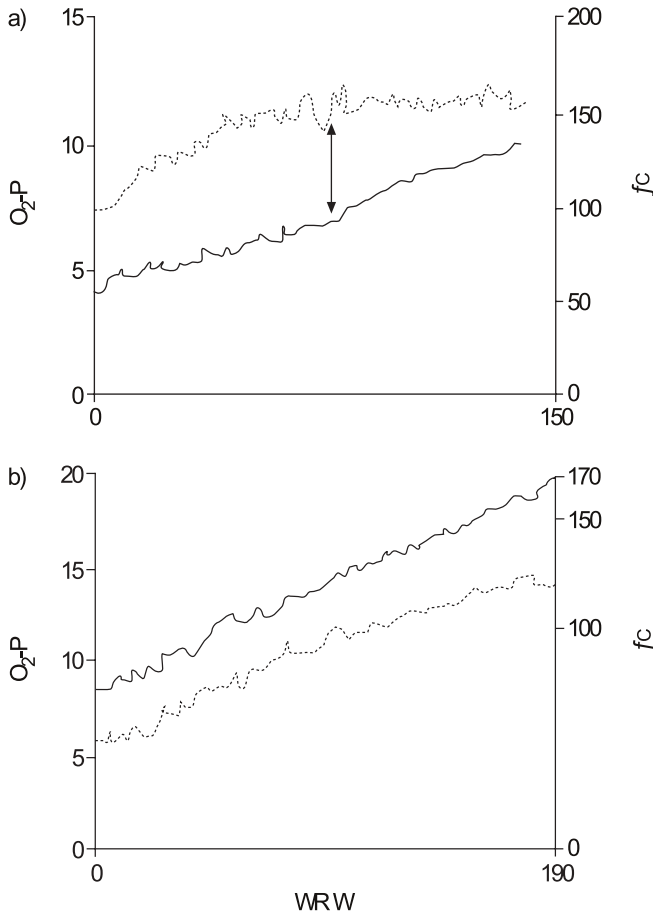


Fig. 9. – Responses of cardiac frequency (f_c :) and oxygen pulse ($O_2\text{-P}$: —) as a function of work rate (WR) during incremental exercise in a) a subject with hypertrophic cardiomyopathy (HCM) and b) an age-matched normal subject. Note the flattening of the $O_2\text{-P}$ profile in the HCM patient (arrow). (See text for further details). Reproduced from [93] with permission.

HCM, PVD) are characterised by an attenuated $O_2\text{-P}$ response [e.g. 5, 11, 12, 68, 69]. Impairments of muscle O_2 extraction that result in a compromised arterio-venous O_2 content difference response (e.g. arterial hypoxaemia, anaemia, carboxyhaemoglobinemia) typically are expressed similarly [e.g. 11, 12, 68, 69].

However, interpretation of the $O_2\text{-P}$ profile should be undertaken with some care. As was first clearly conceived by RADLOFF [94]: “The oxygen-pulse is a somewhat tantalizing function. It is obtainable with precision, since both its factors, the pulse rate and the respiratory oxygen consumption of the body, are readily and accurately determinable. It brings us fairly close to a measurement of the output of the heart per beat, or stroke volume. Yet in the absence of one additional factor it leaves the stroke volume unrevealed. The additional factor needed is the arterio-venous oxygen difference.”

That is, the $O_2\text{-P}$ response should be considered a function only of the product of these two variables, not a function of either. When, for example, the $O_2\text{-P}$ fails to increase despite further increases in WR and $\dot{V}O_2$, then either SV and the arterio-venous O_2 difference variables are both constant or one is increasing while the other decreases in

proportion. Distinguishing between these scenarios requires the accurate measurement of one of the two variables, or at the very least an acceptable approximation to this.

V'E-V'CO₂ relationship

As discussed in detail by WHIPP *et al.* [16], the ventilatory response to exercise is fundamentally related to the regulation of arterial carbon dioxide tension (P_{a,CO_2}) and arterial pH (pH_a). The $V'E$ - $V'CO_2$ relationship for incremental exercise remains linear not only up to θ_L (after an initial kinetic phase, as has been described earlier in the context of $V'O_2$), but also for some way beyond for ramp-type incremental tests. That is, the ventilatory control system operates to clear not only the metabolic carbon dioxide load presented to the lungs during exercise (not, importantly, the actual metabolic production of carbon dioxide [reviewed in 95]), but also any additional load resulting from the buffering of metabolically produced protons (H^+) at supra- θ_L WRs.

Furthermore, the onset of respiratory compensation for the metabolic acidaemia is not expressed at θ_L as is the case for more prolonged constant-load exercise [e.g. 12, 96–98], but rather is delayed with no evidence of P_{a,CO_2} being reduced to provide respiratory compensation. This provides a region of “isocapnic buffering” immediately above θ_L (possible reasons for this unusual behaviour are discussed in [12, 37, 99, 100]). Thus, the linear region of the $V'E$ - $V'CO_2$ relationship typically extends up to the “respiratory compensation point” (RCP). Naturally, therefore, the slope estimation must be confined to the region of the $V'E$ - $V'CO_2$ relationship that is discernibly linear, *i.e.* excluding the initial kinetic phase and also the steeper region above the RCP. It is important that such linearity is demonstrated rather than simply being assumed, especially in diseases characterised by pulmonary gas exchange dysfunction and/or disturbed P_{a,CO_2} regulation (see below).

The $V'E$ - $V'CO_2$ relationship does not normally extrapolate to the origin, but rather evidences a small positive intercept on the $V'E$ axis (~ 3 – 6 L·min⁻¹ in normal subjects):

$$V'E = m \times V'CO_2 + c \quad (5)$$

where m is the slope ($\Delta V'E/\Delta V'CO_2$) and c is the $V'E$ intercept (fig. 10a). Dividing through by $V'CO_2$ and rearranging equation 5 allows $\Delta V'E/\Delta V'CO_2$ to be defined as:

$$\Delta V'E/\Delta V'CO_2 = V'E/V'CO_2 - c/V'CO_2 \quad (6)$$

Recalling earlier considerations of the f_C - $V'CO_2$ relationship and the O_2 -P, the ventilatory equivalent for carbon dioxide ($V'E/V'CO_2$) will, therefore, decline hyperbolically as $V'CO_2$ increases during incremental exercise with an asymptote equal to the $V'E$ - $V'CO_2$ slope (fig. 10b) [e.g. 95, 101]. For this reason, it is important that the $V'CO_2$ at which a particular $V'E/V'CO_2$ value is measured be reported [95]. As long as P_{a,CO_2} remains regulated, then $V'E/V'CO_2$ will change in precise proportion to the change in V_D/V_T [16, 101]:

$$V'E/V'CO_2 = \frac{863}{P_{a,CO_2} \times (1 - V_D/V_T)} \quad (7)$$

In absolute terms, V_D normally increases during exercise consequent to the progressive lung expansion. However, as the compliance of the conducting airways is appreciably less than that of the alveoli, V_D/V_T falls (fig. 11a) [102–105]. However, the linear V_D - V_T relationship has a positive V_D intercept, which dictates that V_D/V_T declines in a hyperbolic fashion not only with respect to V_T but, as equation 6 indicates, with respect to $V'CO_2$, as long as P_{a,CO_2} remains regulated (fig. 11b).

The emerging common clinical practice to report either the “minimum” $V'E/V'CO_2$ (*i.e.* at the RCP: $V'E/V'CO_2$ -min) or $V'E/V'CO_2$ at θ_L ($V'E/V'CO_2$ - θ_L) [12, 106, 107] as indices of “ventilatory efficiency” is, therefore, deserving of comment. In highly fit subjects, for whom the RCP occurs at high absolute values of $V'CO_2$, it is likely that the

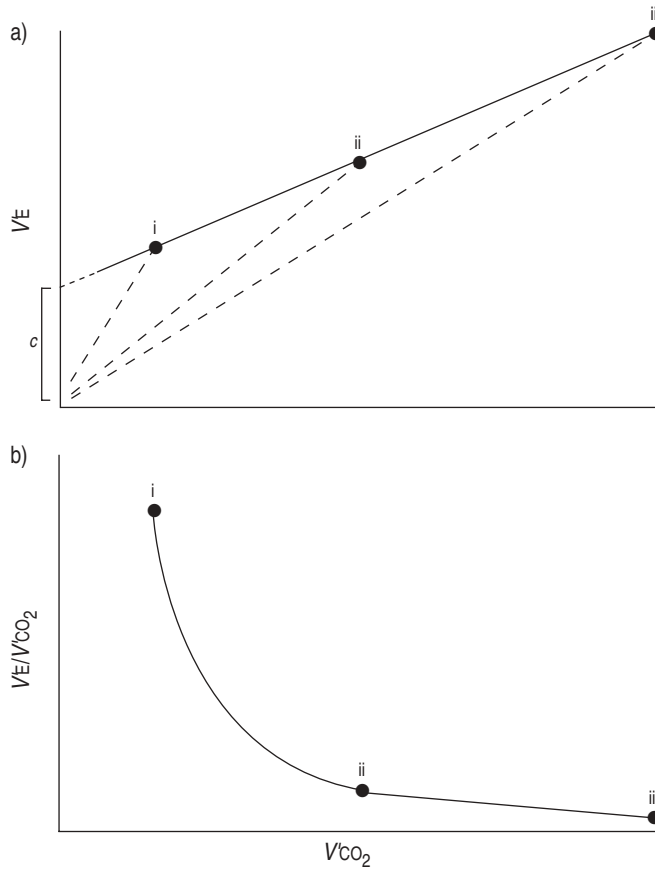


Fig. 10. – Schematic representation of the responses of a) minute ventilation ($V'E$) and b) the ventilatory equivalent for carbon dioxide as a function of carbon dioxide output ($V'CO_2$) under isocapnic conditions. i, ii and iii represent $V'E$ – $V'CO_2$ isopleths. Reproduced from [101] with permission.

assumed minimum $V'E/V'CO_2$ is a close approximation to the true asymptotic value for $V'E/V'CO_2$ (which equals $\Delta V'E/\Delta V'CO_2$). However, in many patients, the compromised $V'O_{2,peak}$ constrains that $V'CO_2$ range within which $V'E/V'CO_2$ is able to decline, such that $V'E/V'CO_2$ may still actually be falling at θL and even approaching the RCP [108].

It is important, however, to avoid being lulled into an overly simple interpretation of the profile of the $V'E/V'CO_2$ response. While it is most commonly the case, $V'E/V'CO_2$ need not increase for there to be respiratory compensation for the metabolic acidaemia. In cases in which subjects reach θL with significant remaining potential for $V'D/V'T$ to continue to decrease (*i.e.* typically in poorly fit subjects), then $V'E/V'CO_2$ need only decrease less than that equivalent for the decrease in $V'D/V'T$ (see equation 7) to result in a hyperventilatory response. A constant or even a falling (but at a slower rate) $V'E/V'CO_2$ can, therefore, be consistent with an RCP.

Abnormally high values for $\Delta V'E/\Delta V'CO_2$ and $V'E/V'CO_2$ (usually $V'E/V'CO_{2-\theta L}$ or $V'E/V'CO_{2-min}$) result when there is a decrease in the Pa,CO_2 set-point (*e.g.* ILD, PVD and even some patients with COPD) or an increased $V'D/V'T$ (*e.g.* COPD, ILD, PVD, CHF). However, as is the case for the O_2-P , measurement (or a plausible estimation) of one of these two variables is needed for the behaviour of the other to be inferred.

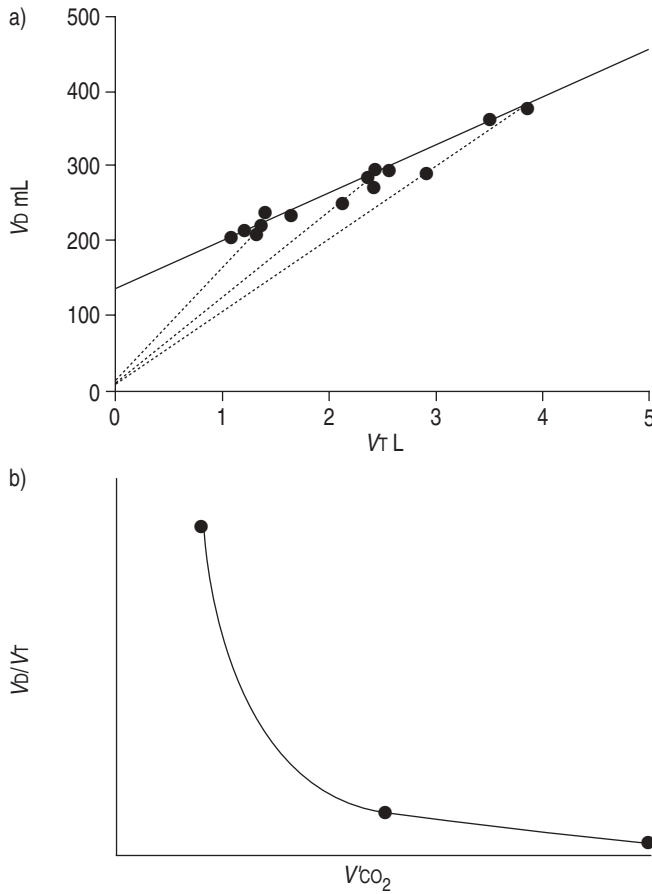


Fig. 11. – a) Physiological dead space (V_D) as a function of tidal volume (V_T) during exercise.: V_D/V_T isopleths. Reproduced from [105] with permission. b) Schematic representation of the predicted hyperbolic decline of the physiological dead space fraction of the breath (V_D/V_T) as a function of carbon dioxide output ($V'CO_2$) under isocapnic conditions. (See text for further details). Reproduced from [101] with permission.

In most patient populations, this requires arterial blood sampling; *i.e.* P_{a,CO_2} cannot validly be predicted from estimators based on the intra-breath alveolar carbon dioxide tension (PCO_2) profile when regional pulmonary gas exchange is highly dispersed. Even in normal subjects, the end-tidal PCO_2 (P_{ET,CO_2}) does not provide a robust estimator of P_{a,CO_2} ; *i.e.* as P_{ET,CO_2} is dictated by the steepness of the alveolar PCO_2 increase during expiration (which is a function of the mixed venous PCO_2) and the time for which it continues (*i.e.* expiratory duration) [reviewed in 16], both metabolic rate and $\dot{f}_R$ will exert a considerable (and complex) influence on the relationship between P_{ET,CO_2} and P_{a,CO_2} [109–111]. However, were P_{ET,CO_2} to be high, it would not be unreasonable to expect P_{a,CO_2} not to be low [112]. In the absence of any V_D/V_T defect (*e.g.* primary alveolar hypoventilation syndromes), $\Delta V'E/\Delta V'CO_2$ and $V'E/V'CO_2 - \theta_L$ and $V'E/V'CO_2 - \min$ will be lower than normal. However, when V_D/V_T is also high, the possibility should be kept in mind that these opposing effects could limit any change in $\Delta V'E/\Delta V'CO_2$ or $V'E/V'CO_2$. Finally, an exception to the above consideration is when V_D/V_T is elevated during exercise in normal subjects who breathe with a tachypnoeic pattern. This can be readily discerned simply from inspection of the breathing pattern responses (see below).

Peak $\dot{V}_E$ and breathing reserve. It is widely acknowledged that peak $\dot{V}_E$ ($\dot{V}_{E,\text{peak}}$) on an incremental exercise test (*i.e.* $\dot{V}_E$ measured at the limit of tolerance) does not encroach on limiting values for healthy subjects who are sedentary or of only average fitness. Thus there is an appreciable breathing (or flow) reserve (BR), whether defined in absolute terms as the difference between the subject's maximum voluntary ventilation (MVV) and $\dot{V}_{E,\text{peak}}$ ($\text{MVV} - \dot{V}_{E,\text{peak}}$) or on a percentage basis as $((\dot{V}_{E,\text{peak}} \times 100)/\text{MVV})$ [*e.g.* 11, 12].

However, some provisos should be noted [see 11, 113, 114 for discussion]. For example, imprecisions could be introduced into the MVV value when it is estimated from the subject's forced expiratory volume in one second (FEV₁; the most commonly used estimators being $40 \times \text{FEV}_1$ [115] or $35 \times \text{FEV}_1$ [116]), rather than measured directly. Also, MVV and $\dot{V}_{E,\text{peak}}$ are measured under quite different conditions. This is well exemplified by the demonstration of negative values for BR in subjects with some ongoing bronchoconstriction, as a result of exercise-induced bronchodilatation associated with increased catecholamine production. Furthermore, because $\dot{V}_{E,\text{peak}}$ in a given subject depends on the particular incremental format being used, this will influence the measured BR, *i.e.* BR should not be viewed as a single constant value [*e.g.* 108]. For example, $\dot{V}_{E,\text{peak}}$ in a given subject is higher on an incremental test having a rapid WR incrementation rate, reflecting the influence the greater rate at which carbon dioxide is evolved from rapidly exchanging body stores through buffering of metabolically produced H^+ . This is reflected in the greater rate of decrease of muscle and blood $[\text{HCO}_3^-]$ [16, 97, 117]. Therefore, BR will be lower than for a test with a slower WR incrementation rate.

A BR that is disappearingly small (or even negative) suggests the presence of ventilatory- or flow-limitation to exercise tolerance. This is characteristic of patients with COPD or asthma [*e.g.* 11, 12, 42, 113]. Also, as MVV is essentially independent of fitness, in healthy subjects BR will become progressively lower (even becoming zero in highly fit subjects) with increasing $\dot{V}_{\text{O}_{2,\text{peak}}}$ as $\dot{V}_{E,\text{peak}}$ is greater.

Breathing pattern

The contributions of $\dot{V}_T$ and f_R to the ventilatory response to incremental exercise can be usefully discerned from the $\dot{V}_E - \dot{V}_T$ relationship [118, 119]; although it has become more recently usual in clinical practice for $\dot{V}_T$ to be plotted as a function of $\dot{V}_E$ [*e.g.* 12]. Additional analysis of the inspiratory–expiratory subdivisions may also be undertaken [*e.g.* 53, 113, 120–122], although this is presently not a common feature of clinical CPET assessment.

Two, and sometimes even three, ranges can normally be discerned in the $\dot{V}_E - \dot{V}_T$ relationship. In normal subjects who do not entrain their breathing rhythm to some constant unit multiple of their locomotor cadence, $\dot{V}_E$ initially increases linearly with respect to $\dot{V}_T$ (range 1) up to a value corresponding to ~ 50 – 60% of vital capacity (VC) [118, 119, 123–125]:

$$\dot{V}_E = m \times \dot{V}_T - c \quad (8)$$

where m and c are the slope ($\Delta \dot{V}_E / \Delta \dot{V}_T$) and $\dot{V}_E$ intercept, respectively; the modest contribution of f_R in this range being evident in the crossing of lower $\dot{V}_E - \dot{V}_T$ isopleths (fig. 12). Indeed, because of the positive $\dot{V}_E$ intercept, f_R in range 1 will increase in a hyperbolic fashion as long as the $\dot{V}_E - \dot{V}_T$ remains linear. When subjects entrain with a constant f_R despite increasing WR, however, the $\dot{V}_E - \dot{V}_T$ relationship intercepts at the origin (*i.e.* $c = 0$), indicating that increases in $\dot{V}_T$ alone contribute to the $\dot{V}_E$ response; the “entrained” f_R value being equal to m (fig. 12).

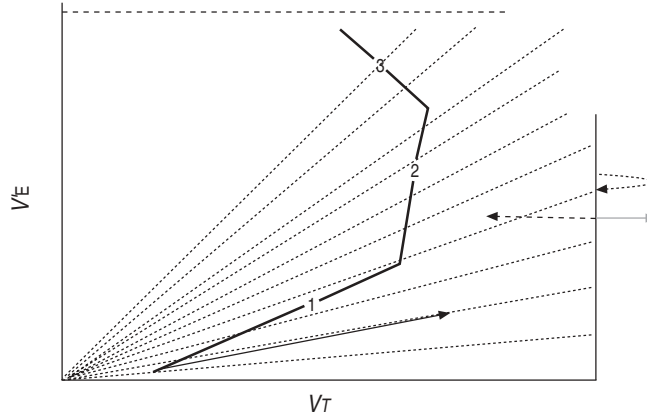


Fig. 12. – Schematic representation of the relationship between minute ventilation ($V'E$) and tidal volume (V_T). The solid arrow represents the response in a subject who entrains at a constant breathing frequency (f_R). 1, 2, 3: ranges 1, 2 and 3, ...: iso- f_R isopleths. - - -: the maximum voluntary ventilation. —: resting inspiratory capacity (IC). The direction of IC change with exercise is shown by the horizontal arrows: increasing in normal young adults (grey arrow); decreasing in patients with chronic obstructive pulmonary disease consequent to dynamic hyperinflation (dashed arrow); and initially increasing and then decreasing in elderly subjects. See text for further details.

The $V'E$ – V_T relationship then typically becomes markedly steeper (range 2); this increase of $V'E$ is achieved largely by progressive increases in f_R [118, 119]. As WR peak is approached, especially in highly fit subjects V_T may be seen to actually decrease (range 3), the increasing $V'E$ being sustained by disproportionately large increases in f_R (fig. 12) [126, 127].

It should be noted that the wide variability in the normal breathing pattern response to exercise has hampered the formulation of normal values for the subcomponents of the $V'E$ – V_T relationship, and how their features are influenced by disease. In addition, the mechanisms that dictate this behaviour can only be speculated upon, even in normal healthy subjects, but may include: the influence of respiratory-mechanical factors related to the disproportionately large increase in the elastic work of breathing as V_T encroaches on the flatter region of the pulmonary compliance curve, especially as respiratory compensation for the metabolic acidosis develops above θL ; and volume-related activation of vagal pulmonary mechanoreceptors [reviewed in 113, 125, 128]. The disproportionately large contribution of f_R to the $V'E$ response that is often seen in more severe COPD [e.g. 42, 53, 129–131] and in restrictive lung disease [e.g. 5, 12, 52–53, 129] is also associated with a disproportionately large increase in f_R during exercise (fig. 13) and coheres with these suggestions.

When V_T at or near peak exercise encroaches upon the inspiratory capacity (IC), this is widely taken to reflect a lack of volume reserve [reviewed in 11, 12, 42, 52, 132]. However, it should be noted that the value used in making such judgements is typically the value obtained under resting conditions. This is not a trivial distinction as (unlike total lung capacity) IC can change with WR to degrees and in directions that can differ widely depending on the particular subject being studied. For example, the progressive decline in end-expiratory lung volume (EELV), which is characteristic of normal healthy subjects [reviewed in 53, 113, 128, 133] will cause IC to increase and thus delay the attainment of any volume-related limit. In contrast, in COPD, the presence of dynamic hyperinflation [reviewed in 53, 113, 132, 133] will lead to a progressive fall in IC and, therefore, predispose to such a limit being attained at lower levels of $V'E$. In the healthy elderly, the age-related loss of lung recoil can reverse the normal decline of EELV with increasing WR to yield dynamic hyperinflation at higher WRs [reviewed in 128, 132, 134].

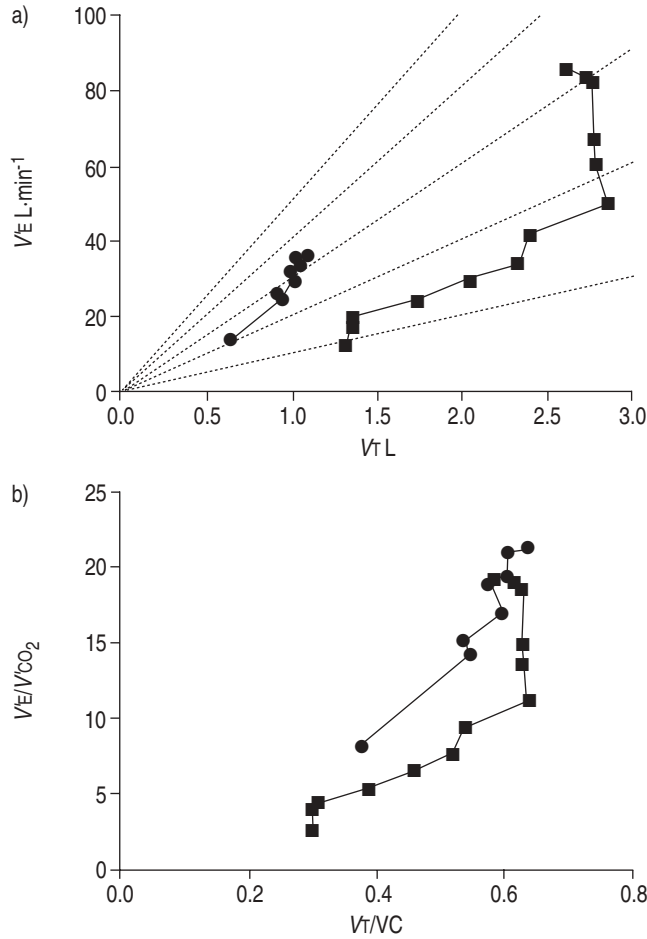


Fig. 13. – a) The minute ventilation-tilde-volume (V_E - V_T) relationship. b) The V_E - V_T relationship normalised to vital capacity (VC).: iso-breathing frequency isopleths. ■: a normal subject; ●: a patient with interstitial lung disease. (See text for further discussion). Reproduced from [125] with permission.

If account is not taken of this, the significance of volume limitation in such individuals could be substantially under-estimated. However, as VC is unlikely to change appreciably during exercise, account might better be taken of changes in lung size and functional operating ranges by expressing V_T as a function of VC when making judgements about volume limitation, although its sensitivity for ILD has been questioned [52].

Lactate threshold

The θ_L is the highest WR (or, more properly, $V\dot{O}_2$) at which arterial $[L^-]$ ($[L^-]_a$) is not systematically increased. Ascribing a mechanistic cause to an abnormally low θ_L value (a cardinal feature of most cardiac and pulmonary diseases [e.g. 10–12, 67, 69, 88]) is challenging. This reflects the considerable debate that continues to surround the processes

that underlie this threshold behaviour. The available evidence demonstrates that the $[L]$ a increase during exercise is oxygen dependent, although intramuscular enzymatic rate limitation and fibre-type recruitment have also been proposed [reviewed in 12, 37, 135–137].

In clinical applications, it is most usual to rely on noninvasive estimation of θL , rather than making a direct estimation based on analysis of arterial, arterialisised-venous or arterialisised-capillary blood [reviewed in 12, 138]. This not only removes the need for blood sampling but, in many cases, may even enhance the discriminability of θL . The recommended approach for noninvasive θL estimation is to identify the intersection of the S1 and S2 regions of the $\dot{V}CO_2$ – $\dot{V}O_2$ relationship (the “V-slope” plot) [139], coupled with additional supporting criteria to establish the presence of hyperventilation relative to oxygen but not carbon dioxide, *i.e.* an increase in the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) and end-tidal oxygen tension (P_{ET,O_2}), with no increase in the $\dot{V}E/\dot{V}CO_2$ or decrease in P_{ET,CO_2} [12, 98, 138, 140, 141].

The S1–S2 break-point is taken as the $\dot{V}O_2$ at which $\dot{V}CO_2$ starts to reflect to influence of additional nonmetabolic carbon dioxide released from bicarbonate [HCO_3^-] buffering of H^+ associated with $[L]$ accumulation, but which is not attributable to hyperventilation [98, 139, 142]. The point of increase in $[L]$ a and $[L]/[\text{pyruvate}]$ ratio and decrease in arterial [HCO_3^-] has been demonstrated to coincide with the S1–S2 break-point (fig. 14) [139]. Below θL , the $\dot{V}CO_2$ – $\dot{V}O_2$ relationship is often linear over all but its very initial stages (reflecting a period of transient carbon dioxide accumulation in the rapidly exchanging body carbon dioxide stores), with a slope (S1) normally below but close to 1 in subjects on a typical western diet. Above θL , the steeper $\dot{V}CO_2$ – $\dot{V}O_2$ relationship can often be linear (or close to linear) up to the RCP (fig. 14). At higher WRs, the $\dot{V}CO_2$ – $\dot{V}CO_2$ slope increases further and progressively, reflecting the influence of compensatory hyperventilation on carbon dioxide clearance.

However, the demonstration of a breakpoint in the $\dot{V}CO_2$ – $\dot{V}O_2$ relationship cannot, on its own, be confidently ascribed to the onset of a lactic acidosis; *i.e.* nonspecific hyperventilation due to factors such as anxiety, pain or hypoxaemia cannot be ruled out [*e.g.* 12, 138]. Therefore, an additional ventilatory-based criterion is required, which derives from the recognition that $\dot{V}E$ during moderate exercise normally responds to clear the carbon dioxide load presented to the lungs rather than to the requirement for pulmonary oxygen exchange [reviewed in 144, 145]. As is the case for $\dot{V}CO_2$, $\dot{V}E$, therefore, also starts to increase at a greater rate at θL ; importantly, however, maintaining its proportionality to $\dot{V}CO_2$ such that the $\dot{V}E$ – $\dot{V}CO_2$ relationship retains its sub- θL slope [*e.g.* 5, 12, 37, 138]. As a result, P_{ET,CO_2} (and P_{a,CO_2} [98]) do not fall and the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) does not increase over this region (fig. 14). In contrast, as $\dot{V}E$ is now of necessity increasing at a greater rate than $\dot{V}O_2$, both $\dot{V}E/\dot{V}O_2$ and P_{ET,O_2} start to increase (fig. 14). That is, there will be the onset of hyperventilation relative to oxygen at θL , but not to carbon dioxide, despite a falling pH_a . It is only above the RCP that hyperventilation relative to carbon dioxide also develops, with $\dot{V}E/\dot{V}CO_2$ starting to increase and P_{ET,CO_2} falling (fig. 14). It is most appropriate that the V-slope approach is used in conjunction with the ventilatory equivalent and end-tidal gas tensions to establish a cluster of variables which cohere with each other to provide the best possible confidence in the estimation [138]. However, this may not always be possible in situations where further increases in $\dot{V}E$ are not possible because of respiratory-mechanical dysfunction (*e.g.* COPD, ILD) [5, 139].

Accurate identification of θL depends on several factors. Identification of the S1–S2 break-point requires that convincingly linear S1 and S2 regions be convincingly identifiable [5, 138, 139]. However, for those instances when the $\dot{V}CO_2$ – $\dot{V}O_2$ relationship cannot validly be partitioned into two clearly linear segments, the point at which a unit tangent (*i.e.* $\Delta\dot{V}CO_2/\Delta\dot{V}O_2 = 1$; the tangent occurs at 45° when the axes have the same scale [12]) impacts on the curve may be used as an alternative [146]. Also, the S1–S2

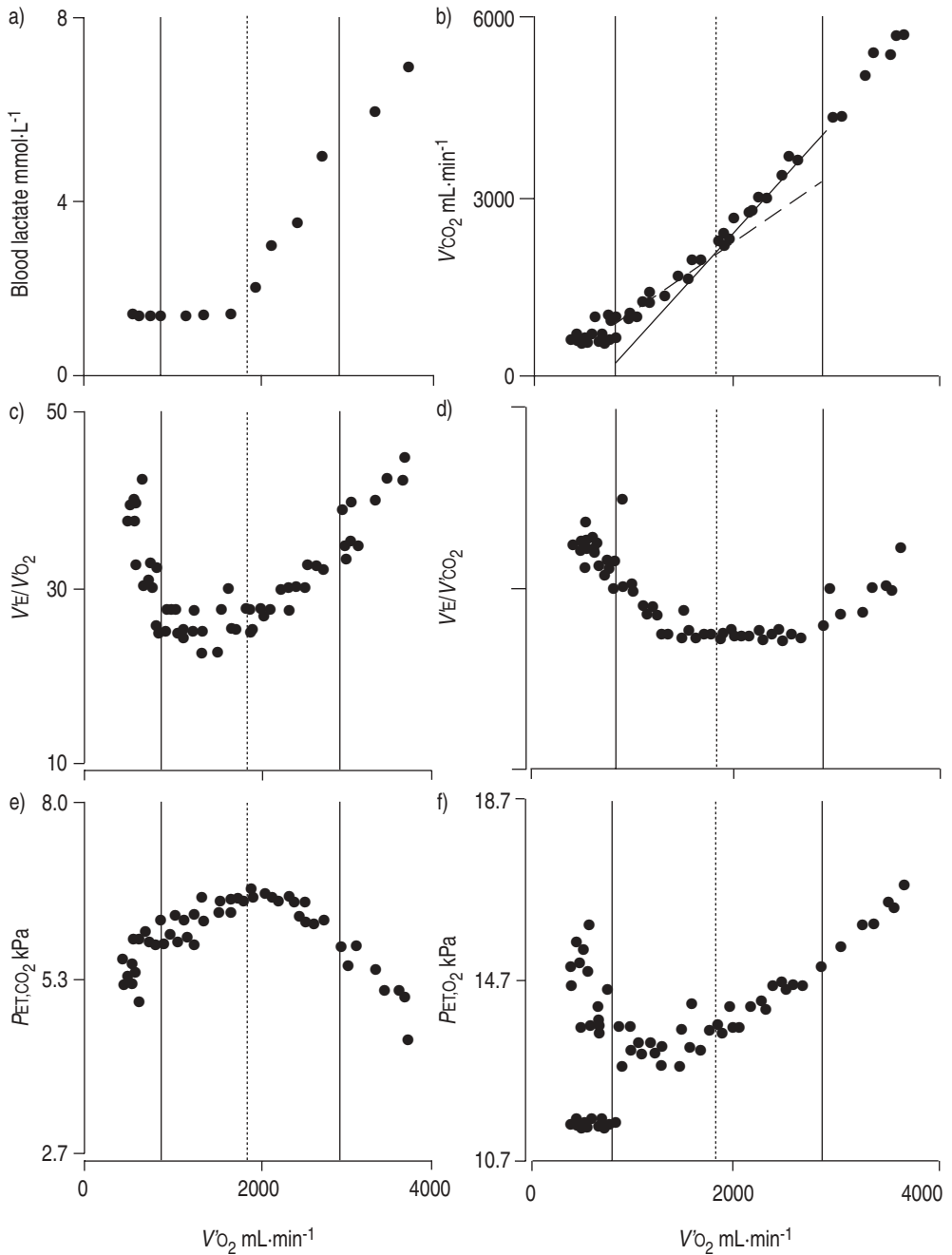


Fig. 14. – Responses in a normal subject of a) blood [lactate]; b) carbon dioxide output ($V'CO_2$); c) ventilatory equivalent for oxygen ($V'E/V'O_2$); d) $V'E/V'CO_2$; e) end-tidal carbon dioxide tension (P_{ET,CO_2}); and f) end-tidal oxygen tension (P_{ET,O_2}) to an exhausting incremental test ($20\text{ W}\cdot\text{min}^{-1}$), as a function of oxygen uptake ($V'O_2$).: lactate threshold (θ_L). —: the “region of interest” for the “V-slope” analysis. The V-slope parameters, S1 and S2, are the slopes of the regressions of the sub- θ_L and supra- θ_L regions of the $V'CO_2$ – $V'O_2$ relationship, respectively. Note that the intersection of these two regressions coincides with the directly-measured θ_L . Reproduced from [143] with permission.

break-point can be difficult to discern in subjects with significant peripheral vascular occlusive disease, as carbon washout from the exercising muscles can be impaired by the poor perfusion [e.g. 12]. Furthermore, mechanisms whose development is unrelated directly to the onset of metabolic acid production, such as arterial hypoxaemia, might also be expected to influence the S1–S2 break-point. However, there is as yet no body of work available on these aspects.

The rate of WR incrementation has an important influence on the resolving power of the V-slope and ventilatory-based noninvasive criteria. Slow WR incrementation rates, in addition to inducing boredom and seat discomfort, also reduce the ability to discriminate θ_L noninvasively. The more slowly the WR is incremented, the more slowly [L]a will increase above θ_L and hence the more slowly arterial $[\text{HCO}_3^-]$ will fall; consequently, the smaller the contribution to $\dot{V}\text{CO}_2$ (i.e. the increase in $\dot{V}\text{CO}_2$ from these buffering reactions is a function of the rate at which arterial $[\text{HCO}_3^-]$ is falling) [16, 96, 117, 147]. As a result, the change of slope between the S1 and S2 segments of the V-slope plot will be small and hence difficult to distinguish. Furthermore, with very slow WR incrementation rates, the onset of respiratory compensation will no longer be delayed relative to θ_L [e.g. 5, 16, 96, 98, 147], with the result that the criterion of isocapnic buffering can no longer be used to rule out nonspecific hyperventilation and, therefore, conclusively establish θ_L .

This raises the question of how “fast” WR should be incremented to secure optimal discrimination of θ_L . The conventional dictum is that the incremental phase of the test should be of the order of 10 min [e.g. 12, 148]; i.e. $\sim 15\text{--}20 \text{ W}\cdot\text{min}^{-1}$ for an “average” healthy individual. As for $\dot{V}\text{O}_{2,\text{peak}}$ (see above), it should be remembered that while θ_L (measured in terms of $\dot{V}\text{O}_2$) is largely independent of the WR incrementation rate, the WR at which θ_L is achieved becomes progressively greater the more rapid the rate of WR increase (fig. 7). The criteria for θ_L identification tend to be easier to discriminate with more rapid rates of WR incrementation, reflecting the more prominent evolution of carbon dioxide from $[\text{HCO}_3^-]$ -buffering, which translates to more marked increases in $\dot{V}\text{CO}_2$, the respiratory exchange ratio (R) and $\dot{V}\text{E}$ above θ_L [16, 96, 117, 147, 149]. It follows from this that the value R attains at end-exercise is highly protocol dependent and, therefore, its use as a valid index of subject “effort” is to be strongly discouraged.

However, too-rapid rates of WR increase have the potential to make θ_L difficult to discern because of an early nonlinearity of the $\dot{V}\text{CO}_2$ response below θ_L . This occurs under conditions in which carbon dioxide is being washed rapidly into the body’s carbon dioxide stores, and is most prominent with rapid and/or large WR increments or with hyperventilation prior to (or in the initial stages of) the exercise test [117, 147, 150]. While the subsequent more rapid carbon dioxide evolution and associated increase in $\dot{V}\text{E}$ reflect an acceleration of $\dot{V}\text{CO}_2$ relative to $\dot{V}\text{O}_2$, this is occurring as a result of the carbon dioxide stores becoming charged up and the rate of carbon dioxide storage, therefore, becoming progressively reduced. As a result, the proportion of the metabolically produced carbon dioxide reaching the lungs starts to increase back towards the new steady-state level. This response can result in a false positive or “pseudo-threshold”; i.e. all the standard noninvasive criteria for θ_L are met, but there is no associated metabolic acidosis. This should not be confused with the acceleration of $\dot{V}\text{CO}_2$ that occurs above θ_L when buffering mechanisms augment $\dot{V}\text{CO}_2$ beyond the new steady state expected on solely metabolic grounds. The clue to pseudo-threshold behaviour is that R is typically falling (or even just reaching its nadir) at the time of the supposed threshold. This means that the profile of R should be included in the cluster of variables used to discriminate θ_L , but as a supporting index and not as one of primary discrimination.

Indices of CPET response: constant-load exercise

Although the appropriateness of the integrated system responses to exercise is best assessed by means of a symptom-limited incremental test, inclusion of other appropriately constructed paradigms provides an additional perspective with regard to the normalcy (or otherwise) of system function. It should be noted that the constant-load test provides a closer approximation to the demands for sustained activities of occupation, daily living, recreation and endurance sport. The value of this testing mode is most evident when the test is designed based on the results of a prior symptom-limited incremental test. That is, the task can then be assigned to the appropriate intensity domain of interest. For example, useful information about cardiac and tissue-metabolic behaviour can be obtained from analysis of the magnitude and rate of change of $\dot{V}O_2$ and the oxygen pulse in the initial stages of a constant-load test (*i.e.* “phase 1”) [e.g. 16] and during the subsequent increasing phase towards the steady state (“phase 2”) [e.g. 5, 33, 95, 144].

Kinetics

The constant-load protocol represents the abrupt imposition of a particular WR from a background, most usually, of unloaded pedalling or of rest (of ≥ 3 min duration). Performance of multiple repeats of a given test provides an improved “signal-to-noise” profile that enhances the discriminability of the associated kinetic parameters [151, 152]. The duration of the increased WR phase will depend on the purpose of the test. For example, for moderate exercise (below θL), it should be sustained sufficiently for the variables of interest to attain a new steady state (*i.e.* ~ 6 min for healthy young subjects, but should be longer in the elderly, the sedentary and patients with cardiopulmonary disease) [153–155]. As discussed previously [16], for WRs above θL but below critical power (CP), steady states may be attained, but require considerably longer periods of time. Above CP, steady states are not attained and fatigue rapidly ensues, the more rapidly the higher the WR (fig. 15).

The model used to “fit” the time course of responses (*e.g.* $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, Q') will depend critically on the intensity domain. For example, for moderate exercise, the “phase 2” response is well fitted by a mono-exponential function [e.g. 16]. However, above θL , the response kinetics become far more complex, reflecting the mechanisms associated with the developing metabolic acidemia [e.g. 16]. More complex models are thus needed to characterise these kinetics. It should be pointed out, however, that there is presently considerable debate as to which particular model structure to use for any of these primary response variables, which reflects the considerable uncertainty surrounding the underlying control mechanisms.

Power–duration relationship

This is deserving of comment in the context of CPET, because of the growing popularity of timed field tests [156] and the high-intensity symptom-limited constant-WR test in interventional and prognostic contexts [reviewed in 68].

The power–duration relationship is well described by a hyperbolic function, both in healthy subjects (fig. 1a) [e.g. 16] and in patients with COPD [157, 158]:

$$(WR - CP) \times t_{lim} = W' \quad (9)$$

where t_{lim} is the tolerable duration, CP is the critical power (*i.e.* the asymptote for this hyperbolic relationship), and W' is the curvature constant (fig. 15a). If, however, WR is plotted as a function of $1/t_{lim}$ rather than t_{lim} , then the relationship becomes linear, with

a slope equivalent to W' and an intercept at CP. This is naturally easier to discriminate than on the curvilinear power–duration plot (fig. 15b):

$$WR = W'/t_{lim} + CP \quad (10)$$

CP is, therefore, the upper limit of sustainable aerobic exercise [e.g. 159, 160] and thus is a crucial determinant of the endurance of a particular task. W' has the interesting property of having the units of work. This suggests that a subject only has access to a certain depletable pool of energy above CP [e.g. 159, 160]. This energy pool may either be utilised rapidly at high WRs or more slowly at lower WRs, until it has been completely depleted. Alternatively, this may reflect the attainment of a critical level of fatigue metabolite build-up (or even of sensation), at a rate related to the increment of WR above CP [161, 162].

In the context of pulmonary and cardiac rehabilitation, it is of interest to note that endurance training increases CP, both in healthy subjects (fig. 16) [163] and in some COPD patients [158], thus making a given supra-CP WR more sustainable. In the context of lung disease with its associated arterial hypoxaemia, it is of interest that acute hypoxia reduces CP (with little or no effect on W') [164]. While the effects of acute

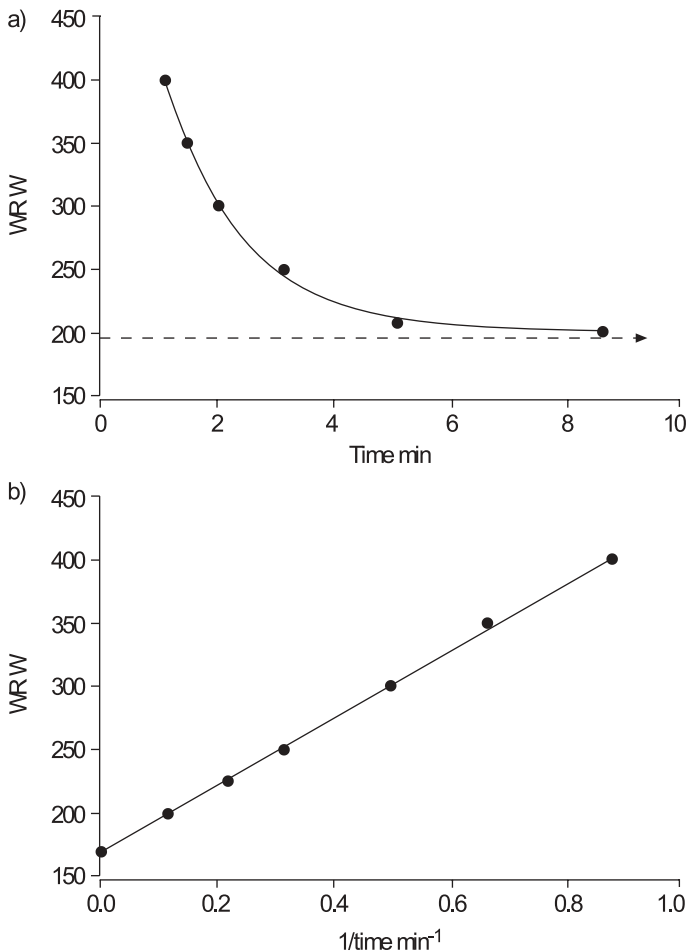


Fig. 15. — a) The power–duration (P–t) relationship for high-intensity exercise. b) Determination of the curvature constant and critical power from the linear P–1/t formulation. WR: work rate.

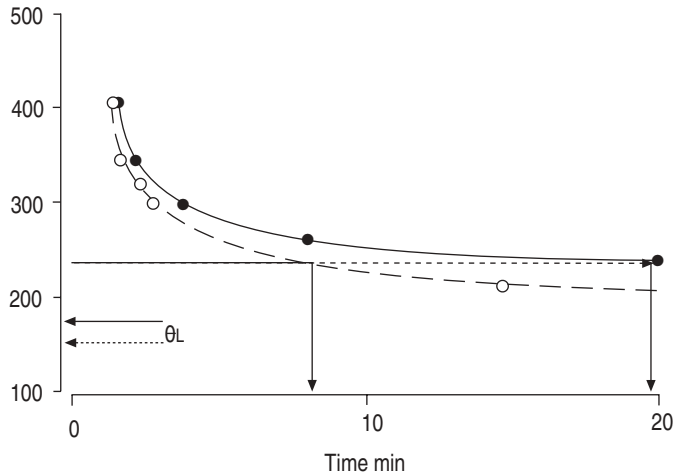


Fig. 16. – The effects of endurance training on the power–duration relationship, resulting in a given work rate being sustainable for a longer period (dotted arrow). – – –: pre-training; —: post-training. Note increase in lactate threshold (θ_L) with training. Modified from [163] with permission.

hypoxia on these parameters of aerobic function have been demonstrated, little or nothing is known about the time course of changes of these parameters during exacerbations of COPD that alter the degree of arterial hypoxaemia. W' is also lower in subjects with COPD [157, 158], presumably as a result of loss of muscle mass (W' having been shown to be a function of muscle mass in healthy subjects [165]). A consequence of the CP and/or W' being reduced is that the tolerable duration at a given WR is reduced or, alternatively, a lower WR must be performed to be sustained for a given time (*i.e.* reduced endurance).

It is evident from figure 16 that the expression of a given functional change (here an increase in CP) is WR dependent. At very high WRs, the absolute magnitude of improvement is small, while it is substantial at lower WRs closer to CP. This effect is a likely contributor to the substantial variability in “improvement” post-intervention that attends the application of an arbitrarily selected high-intensity constant-load test. Ideally, such tests should be designed within the construct of the patient’s power–duration relationship. However, the dilemma facing the experimenter in this context is that it is not possible at present to determine a subject’s CP from a single exercise test. Rather, several tests need to be undertaken in which the subject performs a range of exhausting WRs to the limits of tolerance, each on a separate occasion. The number of tests should be at least the minimum required to ensure a sufficiently confident fit to a hyperbolic model, certainly in normal subjects and (the available evidence indicates) also in COPD patients [157, 158, 166]. However, an *a priori* assumption of hyperbolicity in disease conditions should be made with care. Regardless of the model, the practice of using just two WRs, while apparently expedient, is not to be recommended [166]. When it is not possible to appropriately construct the power–duration relationship, a reasonable compromise is to normalise the applied WR to a given percentage of the WR difference between θ_L and WR_{peak} (termed “ Δ ”), as this strategy goes some way to establish a given degree of metabolic-acidaemic stress across subjects of differing fitness [167]. In the context of setting optimal training strategies in patients with COPD, it has been shown that the difference between CP and $\dot{V}O_{2,peak}$ is proportionally less in COPD patients than matched normal subjects [157]. Such patients might, therefore, be able to tolerate a higher fraction of Δ than one would expect from a normal subject.

Finally, the relevance of tests such as the 6- and 12-min timed walking tests to the power–duration relationship would benefit from investigation. For example, at present, the relationship between the average velocity on the standard (or encouraged) timed walking test and the velocity equivalent of this duration on the power–duration relationship is not known. However, the relationship between the actual power–duration relationship and performance on timed walking tests is poorly understood at present.

Summary

One of the major challenges in clinical exercise testing is to develop a means of distinguishing between the potential contributory mechanisms to the exercise intolerance that characterises most cardiopulmonary diseases, and to establish its dominant cause(s). Appropriately designed clinical exercise tests can: 1) expose abnormalities of physiological system function that contribute to exercise intolerance; and 2) provide a frame of reference for interventions designed to improve performance. Interpreting deviations from an expected response profile (*i.e.* characteristic of a reference population) from such tests requires a clear justification of their underlying physiological determinants.

Keywords: Constant-load exercise test, incremental exercise test, lactate threshold, oxygen pulse, peak oxygen uptake, power–duration relationship.

References

1. Maestu LP. Reference values in adults. *In:* Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 40: 165–185.
2. Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine the parameters of aerobic function during exercise. *J Appl Physiol* 1981; 50: 217–221.
3. Porszasz J, Stringer W, Casaburi R. Equipment, measurements and quality control in clinical exercise testing. *In:* Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 40: 108–128.
4. Gosselink R, Troosters T, Langer D. Laboratory tests. *In:* Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 40: 129–147.
5. Wasserman K, Whipp BJ. Exercise physiology in health and disease. *Am Rev Respir Dis* 1975; 112: 219–249.
6. Owen OE. Resting metabolic requirements of men and women. *Mayo Clin Proc* 1988; 65: 503–510.
7. Creutzberg EC, Schols AMWJ, Bothmer-Quaedvlieg FCM, Wouters EFM. Prevalence of an elevated resting energy expenditure in patients with chronic obstructive pulmonary disease in relation to body composition and lung function. *Eur J Clin Nutr* 1998; 52: 396–401.
8. Hugli O, Fitting JW. Alterations in metabolism and body composition in chronic respiratory diseases. *In:* Nutrition and Metabolism in Chronic Respiratory Disease. *Eur Respir Mon* 2003; 24: 11–22.
9. Fitting JW, Frascarolo P, Jequier E, Leuenberger P. Resting energy expenditure in interstitial lung disease. *Am Rev Respir Dis* 1990; 142: 631–635.
10. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. *Eur Respir J* 1997; 10: 2662–2689.

11. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
12. Wasserman K, Hansen JE, Sue DY, Stringer W, Whipp BJ. Principles of Exercise Testing and Interpretation. 4th Edn. Philadelphia, Lea & Febiger, 2005.
13. Kremser CB, O'Toole MF, Leff AR. Oscillatory hyperventilation in severe congestive heart failure secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy. *Am J Cardiol* 1987; 59: 900–905.
14. Piepoli MF, Ponikowski PP, Volterrani M, Francis D, Coats AJ. Aetiology and pathophysiological implications of oscillatory ventilation at rest and during exercise in chronic heart failure. Do Cheyne and Stokes have an important message for modern-day patients with heart failure? *Eur Heart J* 1999; 20: 946–953.
15. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; 129: S49–S55.
16. Whipp BJ, Wagner PD, Agustí A. Factors determining the response to exercise in healthy subjects. In: Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 1–35.
17. Hansen JE, Sue DY, Oren A, Wasserman K. Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. *Am J Cardiol* 1987; 59: 669–674.
18. Babcock MA, Paterson DH, Cunningham DA. Influence of ageing on aerobic parameters determined from a ramp test. *Eur J Appl Physiol Occup Physiol* 1992; 65: 138–143.
19. Åstrand PO, Rodahl K, Dahl H, Stromme S. Textbook of Work Physiology. 4th Edn. Champaign, Human Kinetics, 2003.
20. Wahren J, Hagenfeldt L, Felig P. Splanchnic and leg exchange of glucose, amino acids, and free fatty acids during exercise in diabetes mellitus. *J Clin Invest* 1975; 55: 1303–1314.
21. Standl E, Janka H-U, Drexel T, Kolb HJ. Muscle metabolism during rest and exercise: influence on the oxygen transport system of blood in normal and diabetic subjects. *Diabetes* 1976; 25: Suppl. 2, 914–919.
22. Barstow TJ, Jones AM, Nguyen PH, Casaburi R. Influence of muscle fibre type and fitness on the oxygen uptake/power output slope during incremental exercise in humans. *Exp Physiol* 2000; 85: 109–116.
23. Kahaly GJ, Nieswandt J, Wagner S, Schlegel J, Mohr-Kahaly S, Hommel G. Ineffective cardiorespiratory function in hyperthyroidism. *J Clin Endocrinol Metab* 1998; 83: 4075–4078.
24. Haller RG, Henriksson KG, Jorfeldt L, *et al.* Deficiency of skeletal muscle succinate dehydrogenase and aconitase. Pathophysiology of exercise in a novel human muscle oxidative defect. *J Clin Invest* 1991; 88: 1197–1206.
25. Gollnick PD, Piehl K, Saltin B. Selective glycogen depletion pattern in human muscle fibres after exercise of varying intensity and at varying pedalling rates. *J Physiol (Lond)* 1974; 241: 45–57.
26. Vøllestad NK, Blom PC. Effect of varying exercise intensity on glycogen depletion in human muscle fibres. *Acta Physiol Scand* 1985; 125: 395–405.
27. Crow MT, Kushmerick MJ. Chemical energetics of slow- and fast-twitch muscles of the mouse. *J Gen Physiol* 1982; 79: 147–166.
28. Kushmerick MJ, Meyer RA, Brown TR. Regulation of oxygen consumption in fast and slow-twitch muscle. *Am J Physiol* 1992; 263: C598–C606.
29. Han Y-S, Proctor DN, Geiger PC, Sieck GC. Reserve capacity for ATP consumption during isometric contraction in human skeletal muscle fibers. *J Appl Physiol* 2001; 90: 657–664.
30. Barclay CJ, Constable JK, Gibbs CL. Energetics of fast- and slow-twitch muscles of the mouse. *J Physiol (Lond)* 1993; 472: 61–80.
31. He Z-H, Bottinelli R, Pellegrino MA, Ferenczi MA, Reggiani C. ATP consumption and efficiency of human single muscle fibers with different myosin isoform composition. *Biophys J* 2000; 79: 945–961.
32. Gaesser GA, Poole DC. The slow component of oxygen-uptake kinetics in humans. *Exerc Sport Sci Rev* 1996; 24: 35–70.

33. Whipp BJ, Ward SA, Rossiter HB. Pulmonary O₂ uptake during exercise: conflating muscular and cardiovascular responses. *Med Sci Sports Exerc* 2005; 37: 1574–1585.
34. Jones AM, Pringle JSM, Carter H. Influence of muscle fibre type and motor unit recruitment on V'O₂ kinetics. In: Jones AM, Poole DC, eds. *Oxygen Uptake Kinetics in Health and Disease*. London, Routledge Publs, 2004; pp. 261–293.
35. Rossiter HB, Howe FA, Ward SA. Intramuscular [PCr] and pulmonary V'O₂ kinetics: implications for control of muscle oxygen consumption. In: Jones AM, Poole DC, eds. *Oxygen Uptake Kinetics in Health and Disease*. Routledge Publs, London, 2004; pp. 154–184.
36. Rossiter HB, Ward SA, Kowalchuk JM, Howe FA, Griffiths JR, Whipp BJ. Dynamic asymmetry of phosphocreatine concentration and O₂ uptake between the on- and off-transients of moderate- and high-intensity exercise in humans. *J Physiol (Lond)* 2002; 541: 991–1002.
37. Whipp BJ. The bioenergetic and gas-exchange basis of exercise testing. *Clin Chest Med* 1994; 15: 173–192.
38. Hansen JE, Casaburi R, Cooper DM, Wasserman K. Oxygen uptake as related to work rate increment during cycle ergometer exercise. *Eur J Appl Physiol* 1988; 57: 140–145.
39. Zoladz JA, Rademaker AC, Sargeant AJ. Nonlinear relationship between O₂ uptake and power output at high intensities of exercise in humans. *J Physiol (Lond)* 1995; 488: 211–217.
40. Baarends EM, Schols AM, Akkermans MA, Wouters EF. Decreased mechanical efficiency in clinically stable patients with COPD. *Thorax* 1997; 52: 981–986.
41. Sala E, Roca J, Marrades RM, *et al.* Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 1726–1734.
42. Gallagher CG. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. *Clin Chest Med* 1994; 15: 305–326.
43. Gosker HR, Schrauwen P, Hesselink MK, *et al.* Uncoupling protein-3 content is decreased in peripheral skeletal muscle of patients with COPD. *Eur Respir J* 2003; 22: 88–93.
44. Gosker HR, Wouters EF, van der Vusse GJ, Schols AM. Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: underlying mechanisms and therapy perspectives. *Am J Clin Nutr* 2000; 71: 1033–1047.
45. Gayan-Ramirez G, Koulouris N, Roca J, Decramer M. Respiratory and skeletal muscles in chronic obstructive pulmonary disease. In: *Management of Chronic Obstructive Pulmonary Disease*. *Eur Respir Mon* 2006; 38: 201–223.
46. Stassijns G, Lysens R, Decramer M. Peripheral and respiratory muscles in chronic heart failure. *Eur Respir J* 1996; 9: 2161–2167.
47. Cuda G, Fananapazir L, Zhu W-S, Sellers J, Epstein ND. Skeletal muscle expression and abnormal function of β myosin in hypertrophic cardiomyopathy. *J Clin Invest* 1993; 91: 2861–2865.
48. Brooks SV, Faulkner JA. Effect of aging on the structure and function of skeletal muscle. In: Roussos C. ed. *The Thorax*. New York, Marcel Dekker, 1995; pp. 295–312.
49. Dempsey JA, Reddan W, Balke B, Rankin J. Work capacity determinants and physiologic cost of weight-supported work in obesity. *J Appl Physiol* 1966; 21: 1815–1820.
50. Whipp BJ, Davis JA. The ventilatory stress of exercise in obesity. *Am Rev Respir Dis* 1984; 129: S90–S92.
51. Charniack RM. Respiratory effects of obesity. *Can Med Assoc J* 1959; 80: 613–616.
52. Marciniuk DD, Gallagher CG. Clinical exercise testing in interstitial lung disease. *Clin Chest Med* 1994; 15: 287–303.
53. Younes M. Determinants of thoracic excursions during exercise. In: Whipp BJ, Wasserman K, eds. *Lung Biology in Health and Disease*. Vol. 42. Exercise, Pulmonary Physiology and Pathophysiology. New York, Marcel Dekker, 1991; pp. 1–65.
54. Nery LE, Wasserman K, Andrews JD, Huntsman OJ, Hansen JE, Whipp BJ. Ventilatory and gas exchange kinetics during exercise in chronic obstructive pulmonary disease. *J Appl Physiol* 1982; 53: 1594–1602.

55. Palange P, Galassetti P, Mannix ET, *et al.* Oxygen effect on O₂ deficit and V'O₂ kinetics during exercise in obstructive pulmonary disease. *J Appl Physiol* 1995; 78: 2228–2234.
56. Somfay A, Porszasz J, Lee SM, Casaburi R. Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients. *Chest* 2002; 121: 393–400.
57. Flaherty KE, Wald J, Weisman IM, *et al.* Unexplained exertional limitation: characterization in a large cohort discovered to have mitochondrial endurance performance of patients with interstitial lung disease myopathy. *Am J Respir Crit Care Med* 2001; 164: 425–432.
58. Taivassalo T, Dysgaard Jensen T, Kennaway N, *et al.* The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. *Brain* 2003; 126: 413–423.
59. Harrington D, Coats AJ. Skeletal muscle abnormalities and evidence for their role in symptom generation in chronic heart failure. *Eur Heart J* 1997; 18: 1865–1872.
60. Nicoletti I, Cicoira M, Zanolla L, *et al.* Skeletal muscle abnormalities in chronic heart failure patients: relation to exercise capacity and therapeutic implications. *Congest Heart Fail* 2003; 9: 148–154.
61. Brassard P, Maltais F, Noel M, *et al.* Skeletal muscle endurance and muscle metabolism in patients with chronic heart failure. *Can J Cardiol* 2006; 22: 387–392.
62. American Thoracic Society and European Respiratory Society statement. Skeletal muscle dysfunction in obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 2S–40S.
63. Palange P, Wagner PD. The skeletal muscle in chronic respiratory diseases, summary of the ERS research seminar in Rome, Italy, February 11–12 1999. *Eur Respir J* 2000; 15: 807–815.
64. Casaburi R. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Med Sci Sport Exerc* 2001; 33: Suppl. 7, S662–S670.
65. Maltais F, Leblanc P, Jobin J, Casaburi R. Peripheral muscle dysfunction in chronic obstructive pulmonary disease. *Rev Mal Respir* 2002; 19: 444–453.
66. Moser C, Tirakitsoontorn P, Nussbaum E, Newcomb R, Cooper DM. Muscle size and cardiorespiratory response to exercise in cystic fibrosis. *Am J Respir Crit Care Med* 2000; 162: 1823–1827.
67. Task Force of the Italian Working Group on Cardiac Rehabilitation Prevention, Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology; Piepoli MF, Corra U, Agostoni PG, *et al.* Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation. Part I: definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006; 13: 150–164.
68. Palange P, Ward SA, Carlsen K-H, *et al.* Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; 29: 185–209.
69. Agostoni P, Cattadori G. Patterns of response diagnostic for cardiac disease. In: Ward SA, Palange P, eds. *Clinical Exercise Testing*. *Eur Respir Mon* 2007; 40: 93–107.
70. Belardinelli R, Lacalaprice F, Carle F, *et al.* Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J* 2003; 24: 1304–1313.
71. Prior BM, Foley JM, Jayaraman RC, Meyer RA. Pixel T2 distribution in functional magnetic resonance images of muscle. *J Appl Physiol* 1999; 87: 2107–2114.
72. Richardson RS, Haseler LJ, Nygren AT, Bluml S, Frank LR. Local perfusion and metabolic demand during exercise: a noninvasive MRI method of assessment. *J Appl Physiol* 2001; 91: 845–853.
73. Wagner PD. Determinants of maximal oxygen transport and utilization. *Ann Rev Physiol* 1996; 58: 21–50.
74. Rowell LB. Limitations to oxygen uptake during dynamic exercise. In: Rowell LB, ed. *Human Cardiovascular Control*. New York, Oxford University Press, 1993; pp. 326–340.
75. Hill AV, Lupton H. Muscular exercise, lactic acid and the supply and utilization of oxygen. *Q J Med* 1923; 16: 135–171.
76. Taylor HL, Buskirk E, Henschel A. Maximal oxygen intake as an objective measure of cardiorespiratory performance. *J Appl Physiol* 1955; 8: 73–80.

77. Mitchell JH, Sproule BJ, Chapman CB. The physiological meaning of the maximal oxygen intake test. *J Clin Invest* 1957; 37: 538–547.
78. Day JR, Rossiter HB, Coats EM, Skasick A, Whipp BJ. The maximally attainable $\dot{V}O_2$ during exercise in humans: the peak vs maximum issue. *J Appl Physiol* 2003; 95: 1901–1907.
79. Hawkins MN, Raven PB, Snell PG, Stray-Gundersen J, Levine BD. Maximal oxygen uptake as a parametric measure of cardiorespiratory capacity. *Med Sci Sports Exer* 2007; 39: 103–107.
80. Rossiter HB, Kowalchuk JM, Whipp BJ. A test to establish maximum O_2 uptake despite no plateau in the O_2 uptake response to ramp incremental exercise. *J Appl Physiol* 2006; 100: 764–770.
81. Task Force of the Italian Working Group on Cardiac Rehabilitation Prevention, Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology; Piepoli MF, Corra U, Agostoni PG, *et al.* Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation. Part III: interpretation of cardiopulmonary exercise testing in chronic heart failure and future applications. *Eur J Cardiovasc Prev Rehabil* 2006; 13: 485–494.
82. Clausen JP. Effect of physical training on cardiovascular adjustments to exercise in man. *Physiol Rev* 1977; 57: 779–815.
83. Light RW, Mintz HM, Linden GS, Brown SE. Hemodynamics of patients with severe chronic obstructive pulmonary disease during progressive upright exercise. *Am Rev Respir Dis* 1984; 130: 391–395.
84. Roca J, Rabinovich R. Clinical exercise testing. In: Lung Function Testing. *Eur Respir Mon* 2005; 31: 146–165.
85. Fox SM, Haskell WL. The exercise stress test: needs for standardization. In: Eliakim M, Neufeld HN, eds. Cardiology: Current Topics and Progress. 6th Edn. New York, Academic Press, 1970; pp. 149–154.
86. Fox SM, Naughton JP, Haskell WL. Physical activity and the prevention of coronary heart disease. *Ann Clin Res.* 1971; 3: 404–432.
87. Jones NL. Clinical Exercise Testing. 3rd Ed. Philadelphia, W.B. Saunders, 1988.
88. Gibbons RJ, Balady GJ, Beasley JW, *et al.* ACC/AHA Guidelines for Exercise Testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 1997; 30: 260–311.
89. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription, 6th Edn. Baltimore, Williams & Wilkins, 2000.
90. Cooper KH, Purdy J, White S, Pollack M, Linnerud AC. Age-fitness adjusted maximal heart rates. *Med Sci Sports* 1977; 10: 78–86.
91. Sheffield LT, Maloof JA, Sawyer JA, Roitman D. Maximal heart rate and treadmill performance of healthy women in relation to age. *Circulation* 1978; 57: 79–84.
92. Henderson Y, Prince AL. The oxygen pulse and the systolic discharge. *Am J Physiol* 1914; 35: 106–116.
93. Jones S, Elliot PM, Sharma S, McKenna WJ, Whipp BJ. Cardiopulmonary response to exercise in patients with hypertrophic cardiomyopathy. *Heart* 1998; 80: 60–67.
94. Radloff EM. The oxygen pulse in athletic girls during rest and exercise. *Am J Physiol* 1931; 96: 126–131.
95. Whipp BJ. The control of exercise hyperpnea. In: Hornbein T, ed. The Regulation of Breathing. New York, Marcel Dekker, 1981; pp. 1069–1139.
96. Whipp BJ, Mahler M. Dynamics of gas exchange during exercise. In: West JB, ed. Pulmonary Gas Exchange. Vol. II. New York, Academic Press, 1980; pp. 33–96.
97. Whipp BJ. Dynamics of pulmonary gas exchange during exercise in man. *Circulation* 1987; 76: VI18–VI28.
98. Whipp BJ, Davis JA, Wasserman K. Ventilatory control of the 'isocapnic buffering' region in rapidly-incremental exercise. *Resp Physiol* 1989; 76: 357–368.
99. Whipp BJ. Peripheral chemoreceptor control of the exercise hyperpnea in humans. *Med Sci Sports Ex* 1994; 26: 337–347.

100. Ward SA. Models of ventilatory control during exercise: peripheral chemoreflex considerations. *Int J Computer Sci* 2003; 2: 52–65.
101. Whipp BJ, Ward SA. Cardiopulmonary coupling during exercise. *J Exp Biol* 1982; 100: 175–193.
102. Jones NL, McHardy GJ, Naimark A, Campbell EJ. Physiological dead space and alveolar-arterial gas pressure differences during exercise. *Clin Sci* 1966; 31: 19–29.
103. Wasserman K, VanKessel AL, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol* 1967; 22: 71–85.
104. Whipp BJ, Wasserman K. Alveolar-arterial gas tension differences during graded exercise. *J Appl Physiol* 1969; 27: 361–366.
105. Lamarra N, Whipp BJ, Ward SA. Physiological inferences from intra-breath measurement of pulmonary gas exchange. New Orleans, Proc Ann. Internat Conf IEEE Eng Med Biol Soc, 1988; pp. 825–826.
106. Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001; 104: 429–435.
107. Sun X-G, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med* 2002; 166: 1443–1448.
108. Palange P, Ward SA, Carlsen K-H, *et al.* Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; 29: 185–209.
109. DuBois AB, Britt AG, Fenn WO. Alveolar CO₂ during the respiratory cycle. *J Appl Physiol* 1952; 4: 535–548.
110. Jones NL, Robertson DG, Kane JW. Difference between end-tidal and arterial PCO₂ in exercise. *J Appl Physiol* 1979; 47: 954–960.
111. Whipp BJ, Lamarra N, Ward SA, Davis JA, Wasserman K. Estimating arterial PCO₂ from flow-weighted and time-averaged alveolar PCO₂ during exercise. In: Swanson GD, Grodins FS, eds. *Respiratory Control: Modelling Perspective*. New York, Plenum, 1990; pp. 91–99.
112. Casaburi R, Carithers E, Casaburi JD. Noninvasive assessment of normality of VD/VT in clinical cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 1996; 153: A650.
113. Whipp BJ, Pardy R. Breathing during exercise. In: Macklem P, Mead J, eds. *Handbook of Physiology, Respiration (Pulmonary Mechanics)*. Washington D.C., American Physiological Society, 1986; pp. 605–629.
114. Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow–volume loop. *Chest* 1999; 116: 488–503.
115. Campbell SC. A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation. *J Occup Med* 1982; 24: 531–533.
116. Clark TJ, Freedman S, Campbell EJ, Winn RR. The ventilatory capacity of patients with chronic airways obstruction. *Clin Sci* 1969; 36: 307–316.
117. Whipp BJ. Physiological mechanisms dissociating pulmonary CO₂ and O₂ exchange dynamics during exercise in humans. *Exp Physiol* 2007; 92: 347–355.
118. Milic-Emili G, Cajani F. La frequenza dei respiri in funzione della ventilazione plomonare durante la marcia. [Breathing frequency and pulmonary ventilation during walking.] *Bol Soc Ital Biol Sper* 1957; 33: 825–827.
119. Hey EN, Lloyd BB, Cunningham DJC, Jukes MGM, Bolton DPG. Effects of various respiratory stimuli on the depth and frequency of breathing in man. *Respir Physiol* 1966; 1: 193–205.
120. Clark FJ, von Euler C. On the regulation of depth and rate of breathing. *J Physiol (Lond)* 1972; 222: 267–295.
121. Cunningham DJC. Integrative aspects of the regulation of breathing: a personal view. In: Widdicombe JG, ed. *Respiratory Physiology I*. Vol. 2. Baltimore, University Park Press, 1974; pp. 303–369.
122. Milic-Emili J, Whitelaw WA, Grassino AE. Measurement and testing of respiratory drive. In: Hornbein T, ed. *The Regulation of Breathing*. New York, Marcel Dekker, 1981; pp. 1675–1743.
123. Bechbache RR, Chow HHK, Duffin J, Orsini EC. The effects of hypercapnia, hypoxia, exercise, and anxiety on the pattern of breathing in man. *J Physiol (Lond)* 1979; 293: 285–300.

124. Folinsbee LJ, Wallace ES, Bedi JF, Horvath SM. Respiratory patterns and control during unrestrained human running. *In: Whipp BJ, Wiberg, DM. Modelling and Control of Breathing.* New York, Elsevier, 1983; pp. 205–212.
125. Gallagher CG, Brown E, Younes M. Breathing pattern during maximal exercise and during submaximal exercise with hypercapnia. *J Appl Physiol* 1987; 63: 238–244.
126. Whipp BJ, Wasserman K. The effects of work intensities on the transient respiratory responses immediately following exercise. *Med Sci Sports* 1973; 5: 14–17.
127. Jensen JI, Lyager S, Pedersen OF. The relationship between maximal ventilation, breathing pattern and mechanical limitation of ventilation. *J Physiol* 1980; 309: 521–532.
128. Dempsey JA, Adams L, Ainsworth DM, *et al.*, Airway, lung and respiratory muscle function. *In: Rowell LB, Shepherd JT. Handbook of Physiology. Section 12. Exercise: Regulation and Integration of Multiple Systems.* New York, Oxford University Press, 1996; pp. 448–514.
129. Bradley GW, Crawford R. Regulation of breathing during exercise in normal subjects and in chronic lung disease. *Clin Sci Mol Med* 1967; 51: 575–582.
130. Schanning J. Respiratory cycle time duration during exercise in patients with chronic obstructive lung disease. *Scand J Respir Dis* 1978; 59: 313–318.
131. Sergysels RS, Degree P, Garcia-Herreros R, Willeput R, De Coster A. Le profil ventilatoire a l'exercice dans les bronchopathies chroniques obstructive. [The profile of ventilation during exercise in chronic obstructive pulmonary disease.] *Bull Eur Physiopathol Respir* 1979; 15: 57–73.
132. O'Donnell D, Ofir D, Laveneziana P. Patterns of cardiopulmonary response to exercise in lung diseases. *In: Ward SA, Palange P, eds. Clinical Exercise Testing. Eur Respir Mon* 2007; 40: 69–92.
133. Beck KC, Staats BA, Hyatt RE. Dynamics of breathing during exercise. *In: Whipp BJ, Wasserman K. Pulmonary Physiology and Pathophysiology of Exercise.* New York, Marcel Dekker, 1991; pp. 67–97.
134. Johnson BD, Dempsey JA. Demand vs capacity in the aging pulmonary system. *Ex Sports Sci Rev* 1991; 19: 171–210.
135. Brooks GA. Anaerobic threshold: review of the concept and directions for future research. *Med Sci Sports Ex* 1985; 17: 22–34.
136. Gladden LB. Lactate metabolism: a new paradigm for the third millennium. *J Physiol* 2006; 558: 5–30.
137. Philp A, Macdonald AL, Watt PW. Lactate: a signal coordinating cell and systemic function. *J Exp Biol* 2005; 208: 4561–4575.
138. Whipp BJ, Ward SA, Wasserman K. Respiratory markers of the anaerobic threshold. *Adv Cardiol* 1986; 35: 47–64.
139. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting the anaerobic threshold by gas exchange. *J Appl Physiol* 1986; 60: 2020–2027.
140. Wasserman K, Whipp BJ, Koyal SN, Beaver WL. The anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol* 1973; 35: 236–242.
141. Reinhard U, Muller PH, Schmulling RM. Determination of anaerobic threshold by the ventilation equivalent in normal individuals. *Respiration* 1979; 38: 36–42.
142. Beaver WL, Wasserman K, Whipp BJ. Bicarbonate buffering of lactic acid generated during exercise. *J Appl Physiol* 1986; 60: 472–478.
143. Henson LC, Poole DC, Whipp BJ. Fitness as a determinant of oxygen uptake response to constant-load exercise. *Euro J Appl Physiol* 1989; 59: 21–28.
144. Whipp BJ, Ward SA. The coupling of ventilation to pulmonary gas exchange during exercise. *In: Whipp BJ, Wasserman K, eds. Pulmonary Physiology and Pathophysiology of Exercise,* New York, Marcel Dekker, 1991; pp. 271–307.
145. Ward SA, Whipp BJ. Coordination of circulation and respiration during exercise. *In: Greger R, Windhorst U, eds. Comprehensive Human Physiology.* Heidelberg, Springer-Verlag, 1996; pp. 2145–2173.

146. Sue DY, Wasserman K, Moricca RB, Casaburi R. Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. *Chest* 1988; 94: 931–938.
147. Ward SA, Whipp BJ. Influence of body CO₂ stores on ventilatory-metabolic coupling during exercise. In: Honda Y, Miyamoto Y, Konno K, Widdicombe JG, eds. *Control of Breathing and its Modeling Perspective*. New York, Plenum Press, 1992; pp. 425–431.
148. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. *J Appl Physiol* 1983; 55: 1558–1564.
149. Scheuermann BW, Kowalchuk JM. Attenuated respiratory compensation during rapidly incremented ramp exercise. *Respir Physiol* 1998; 114: 227–238.
150. Ozcelik O, Ward SA, Whipp BJ. Effect of altered body CO₂ stores on pulmonary gas exchange dynamics during incremental exercise in humans. *Exp Physiol* 1999; 84: 999–1011.
151. Lamarra N, Whipp BJ, Ward SA, Wasserman K. Effect of interbreath fluctuations on characterizing exercise gas exchange kinetics. *J Appl Physiol* 1987; 62: 2003–2012.
152. Puente-Maestu L, Sanz ML, Sanz P, Nunez A, Gonzalez F, Whipp BJ. Reproducibility of the parameters of the on-transient cardiopulmonary responses during moderate exercise in patients with chronic obstructive pulmonary disease. *Eur J Appl Physiol* 2001; 85: 434–441.
153. Babcock MA, Paterson DH, Cunningham DA, Dickinson JR. Exercise on transient gas exchange kinetics are slowed as a function of age. *Med Sci Sports Ex* 1994; 26: 440–446.
154. Nery LE, Wasserman K, Andrews JD, Huntsman OJ, Hansen JE, Whipp BJ. Ventilatory and gas exchange kinetics during exercise in chronic obstructive pulmonary disease. *J Appl Physiol* 1982; 53: 1594–1602.
155. Koike A, Hiroe M, Adachi H, *et al.* Oxygen uptake kinetics are determined by cardiac function at onset of exercise in patients with prior myocardial infarction. *Circulation* 1994; 90: 2324–2332.
156. Singh S. Walking for the assessment of patients with chronic obstructive pulmonary disease. In: Ward SA, Palange P, eds. *Clinical Exercise Testing*. *Eur Respir Mon* 2007; 40: 148–164.
157. Neder JA, Jones PW, Nery LE, Whipp BJ. Determinants of the exercise endurance capacity in patients with chronic obstructive pulmonary disease. The power-duration relationship. *Am J Respir Crit Care Med* 2000; 162: 497–504.
158. Puente-Maestu L, SantaCruz A, Vargas T, Martinez-Abad Y, Whipp BJ. Effects of training on the tolerance to high-intensity exercise in patients with severe COPD. *Respiration* 2003; 70: 367–370.
159. Moritani TA, Nagata HA, Vries HA de, Muro M. Critical power as a measure of physical work capacity and anaerobic threshold. *Ergonomics* 1981; 24: 339–350.
160. Poole DC, Ward SA, Gardner GW, Whipp BJ. Metabolic and respiratory profile of the upper limit for prolonged exercise in man. *Ergonomics* 1988; 31: 1265–1279.
161. Coats EM, Rossiter HB, Day JR, Miura A, Fukuba Y, Whipp BJ. Intensity-dependent tolerance to exercise after attaining V_O₂max in humans. *J Appl Physiol* 2003; 95: 483–490.
162. Fukuba Y, Miura A, Endo M, Kan A, Yanagawa K, Whipp BJ. The curvature constant parameter of the power-duration curve for varied-power exercise. *Med Sci Sports Exerc* 2003; 35: 1413–1418.
163. Poole DC, Ward SA, Whipp BJ. Effect of training on the metabolic and respiratory profile of heavy and severe exercise. *Eur J Appl Physiol* 1990; 59: 421–429.
164. Whipp BJ, Huntsman DJ, Storer T, Lamarra N, Wasserman K. A constant which determines the duration of tolerance to high-intensity work. *Fed Proc* 1982; 41: 1591.
165. Miura A, Endo M, Sato H, Sato H, Barstow TJ, Fukuba Y. Relationship between the curvature constant parameter of the power-duration curve and muscle cross-sectional area of the thigh for cycle ergometry in humans. *Eur J Appl Physiol* 2002; 87: 238–244.
166. Malaguti C, Nery LE, Dal Corso S, *et al.* Alternative strategies for exercise critical power estimation in patients with COPD. *Eur J Appl Physiol* 2006; 96: 59–65.
167. Rausch SM, Whipp BJ, Wasserman K, Huszezuk A. Role of the carotid bodies in the respiratory compensation for the metabolic acidosis of exercise in humans. *J Physiol (Lond)* 1991; 444: 567–578.

Patterns of cardiopulmonary response to exercise in lung diseases

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Cardiopulmonary exercise testing (CPET) is increasingly being used for the clinical evaluation of patients with respiratory diseases. Exercise performance cannot reliably be predicted by tests of resting pulmonary function. Exercise testing alone, therefore, provides an accurate assessment of functional capacity on an individual basis. CPET can uncover abnormalities in the integrated functions of the cardiovascular, respiratory, metabolic, peripheral muscle and neurosensory systems. CPET uniquely permits an evaluation of the interface between impairment and disability under measured physiological stress.

The ventilatory (minute ventilation ($\dot{V}_E$)) response to exercise is usually abnormal across the spectrum of more advanced pulmonary disorders. The response patterns in early disease are less well characterised, but appear to be more variable. As a result of numerous small pathophysiological studies in various respiratory disease subtypes, a number of typical abnormalities in ventilatory response patterns to exercise have been identified.

Conventionally, assessment of ventilatory limitation or of the prevailing ventilatory constraints involves calculation of the ventilatory index, *i.e.* the ratio of peak $\dot{V}_E$ to the estimated maximal ventilatory capacity (MVC; (peak $\dot{V}_E$ /MVC) $\times$ 100) [1, 2]. $\dot{V}_E$ /MVC is generally increased in respiratory disorders, reflecting either increased ventilatory demand, reduced ventilatory capacity or both. Preliminary information suggests that quantitative exercise flow–volume loop analysis may permit greater refinement in the assessment of dynamic ventilatory constraints than the ventilatory index, particularly in patients with earlier disease [3]. Flow–volume loop analysis is emerging as an important component of clinical exercise test interpretation, and can provide valuable insights into the nature and extent of abnormalities of ventilatory mechanics and their contribution to exercise limitation.

Exercise is often limited by intolerable symptoms of dyspnoea, leg discomfort or a combination of both of these well before the physiological boundaries of the respiratory and cardiovascular systems are reached [4–7]. The measurement of exertional symptoms using validated scales is, therefore, an integral component of CPET and strengthens clinical interpretation [8, 9].

The present chapter begins with a brief overview of exercise physiology in the elderly, since this population is the appropriate reference for patients with most chronic respiratory conditions. It then compares and contrasts the ventilatory patterns during incremental cycle-ergometer exercise testing in patients with common obstructive, restrictive and pulmonary vascular disorders. Finally, it examines the role of exercise flow–volume loop analysis in the evaluation of abnormal dynamic ventilatory mechanics and comments on their potential clinical utility.

Ventilatory constraints associated with ageing

Precise control of $\dot{V}_E$ ensures that alveolar oxygen and carbon dioxide tension, and thus arterial oxygen and carbon dioxide tension (P_{a,CO_2}), are maintained near resting values throughout exercise despite large increases in metabolic demand by the exercising muscles. The respiratory system is normally highly efficient during maximal exercise. Young untrained adults can accomplish very high peak $\dot{V}_E$, in the order of $120 \text{ L} \cdot \text{min}^{-1}$, while requiring only 5–7% of their total body oxygen uptake ($\dot{V}O_2$) [10]. Ventilatory work and the oxygen cost of breathing during exercise are minimised through several acute physiological adjustments: 1) operating lung volumes are controlled in order to minimise the elastic loading of the inspiratory muscles [11]; 2) resistive work is minimised during the high respired flows of exercise by intra- and extrathoracic airway dilatation [12, 13]; and 3) $\dot{V}_E$ is maintained close to alveolar ventilation because enhanced ventilation/perfusion relationships during exercise reduce wasted ventilation (physiological dead space) [14].

These adaptations are attenuated to various degrees in the elderly. Changes in the connective tissue matrix of the lung reduce the elastic recoil pressure, and thus the driving pressure for expired flow [15–19]. The attendant reduced airway tethering, together with changes in the autonomic balance of airway smooth muscle tone (as a result of increased cholinergic influences), predisposes the elderly to expiratory flow limitation [18–20]. During resting breathing, closing volume is increased, the ratio of residual volume (RV) to total lung capacity (TLC) is increased, and the resting inspiratory capacity (IC) may be diminished [16]. These mechanical derangements are further amplified during exercise under conditions of increased ventilation (fig. 1). Thus air trapping has been reported, particularly during high ventilation in fitter elderly individuals [19, 20, 22]. In young adults, reduction of end-expiratory lung volume (EELV) during exercise by expiratory muscle recruitment permits tidal volume (V_T) expansion to ~50–60% of the vital capacity (VC) by encroachment into both the expiratory and inspiratory reserve volume (ERV and IRV, respectively) [11]. This means that the increased elastic work associated with breathing close to TLC is avoided. The inability to reduce EELV in the elderly means that the elastic work of breathing is increased and work-sharing with the inspiratory muscles is diminished compared with young individuals. The oxygen cost of breathing in the elderly may represent as much as 13% of total $\dot{V}O_2$ [23].

The alveolocapillary surface area for gas exchange is reduced with advancing age [24]. Moreover, worsening ventilation/perfusion relationships during exercise in the elderly mean that physiological dead space cannot decline as normal, and submaximal ventilation is, therefore, increased at any given $\dot{V}O_2$ or work-rate [24]. The higher ventilatory demand in the setting of significant restrictive mechanical constraints on V_T expansion (as a result of the diminished resting IC) contribute to higher levels of exertional breathlessness in the elderly compared with young individuals [25].

Chronic obstructive pulmonary disease

Practical considerations in CPET interpretation

CPET should be considered an integral part of a more complete clinical characterisation of the symptomatic patient. Thus CPET is of limited value unless it is undertaken in the context of a comprehensive evaluation of resting physiological and functional data. Enquiry concerning the level of chronic activity-related dyspnoea and

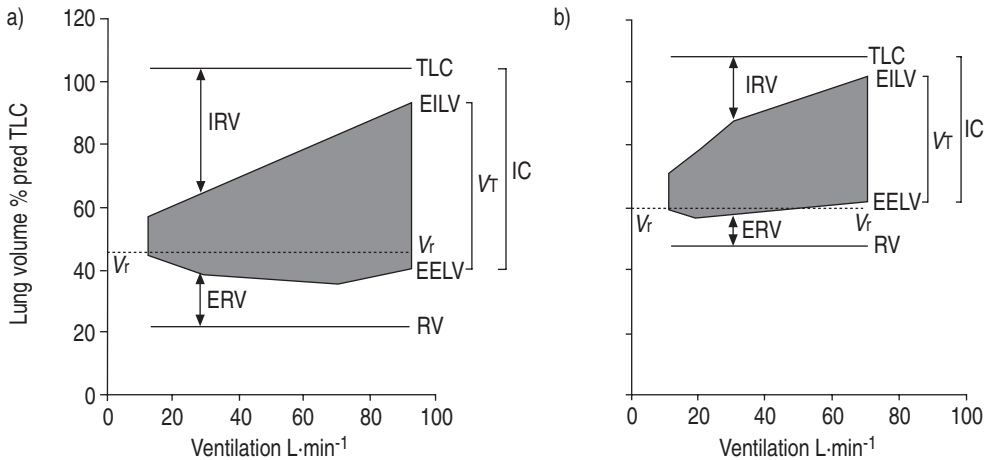


Fig. 1. – Relationship of lung volume to ventilation during exercise in a) a healthy younger male; and b) an older male subject. There are greater volume constraints on tidal volume (V_T) expansion (■) during exercise in the older subject, i.e. increased residual volume (RV) and dynamic end-expiratory lung volume (EELV), and a relatively reduced inspiratory reserve volume (IRV; $IRV = \text{total lung capacity (TLC)} - V_T$) at similar submaximal levels of ventilation. EILV: end-inspiratory lung volume; IC: inspiratory capacity; ERV: expiratory reserve volume; V_r : relaxation volume of the respiratory system; % pred: % predicted. Reproduced from [21] with permission.

functional disability (as assessed by the UK Medical Research Council scale, for example) [26] provides important information about an individual's exercise capacity, and, of itself, has been shown to provide prognostic information in chronic obstructive pulmonary disease (COPD) [27]. Important confounders in CPET include the patient's age (see above), the presence of obesity or kyphosis, and significant comorbid conditions, each of which have obvious implications for clinical interpretation. The operating limits of V_T expansion during exercise can be assessed from the resting IC as a percentage of the predicted value [28, 29]. Resting diffusing capacity of the lung for carbon monoxide (DL_{CO}) provides information regarding the surface area available for pulmonary gas exchange, and has been shown to predict arterial oxygen desaturation during exercise in respiratory diseases [30]. The measurement of static inspiratory and expiratory muscle strength may also be relevant to the assessment of MVC.

Ventilatory response patterns

Exercise intolerance in COPD is multifactorial. Recognised contributory factors include: 1) intolerable exertional symptoms; 2) ventilatory factors (abnormalities of mechanics, muscle pump or gas exchange); 3) peripheral muscle dysfunction; 4) cardiovascular factors; 5) metabolic abnormalities; and 6) any combination of the above. These factors are highly interdependent and occur in variable combinations that differ from patient to patient. As the disease advances, more of these factors come into play in a complex integrative fashion. For a more comprehensive review see [21, 31].

Peak symptom-limited $\dot{V}O_2$ has been shown to predict survival in a COPD population, independent of age and forced expiratory volume in one second (FEV₁) [32]. Moreover, tests of exercise capacity correlate well with measures of health status in COPD [33]. Peak $\dot{V}O_2$ cannot be reliably predicted by spirometric measurements of FEV₁ [27, 32]. There is new information that, in patients with COPD who have demonstrable resting expiratory flow limitation, resting and peak exercise IC (% predicted) correlate strongly with peak V_T and peak symptom-limited $\dot{V}O_2$ [28, 29].

Patients with a low resting IC have reduced ability to expand V_T with the increasing respiratory drive of exercise and, therefore, reach early mechanical limitation to ventilation [29].

In more advanced COPD, dyspnoea is the predominant exercise-limiting symptom [6, 7]. Leg discomfort is also a frequent exertional symptom, at least during cycle ergometry in COPD patients, as is the case in sedentary healthy subjects [4, 5]. It is important to ascertain the predominant exercise-limiting symptom in each individual by simply asking this question at the end of exercise.

Abnormal ventilatory patterns

Numerous studies have consistently reported the following ventilatory abnormalities in COPD: 1) low peak ventilation, reflecting the prevailing mechanical constraints; 2) high submaximal ventilation for a given work-rate or $\dot{V}O_2$; 3) increased ventilatory inefficiency (*i.e.* increased ventilatory equivalent for carbon dioxide ($\dot{V}E/\text{carbon dioxide production } (\dot{V}CO_2)$), certainly below the lactate threshold); and 4) decreased ventilatory reserve (*i.e.* increased peak $\dot{V}E/MVC$; fig. 2) [7, 34–37]. Significant ventilatory constraints may be detected on exercise flow–volume loop analysis, even in patients with mild COPD who have an apparently normal ventilatory reserve at peak exercise, as ascertained by the peak $\dot{V}E/MVC$ method [38]. Contributory factors to increased submaximal ventilation in COPD include: 1) increased physiological dead space; 2) early metabolic acidosis; 3) feed-forward efferent activation of the medullary respiratory centre in association with increased motor command output to the exercising muscles; 4) critical arterial hypoxaemia or hypercapnia; 5) increased activation of peripheral muscle metaboreceptors and mechanoreceptors; 6) anxiety; and 7) increased sympathetic nervous system activation [21, 31].

Abnormal pattern of dynamic ventilatory mechanics

Expiratory flow limitation is the pathophysiological hallmark of COPD [39]. The time constant for lung emptying (*i.e.* product of lung compliance and resistance) is slower in COPD than in health, and the expiratory time available is often insufficient to permit the EELV to decline to its predicted relaxation volume. This leads to lung hyperinflation during spontaneous resting breathing (fig. 3) [39]. During exercise, increased ventilatory demand often gives rise to further air trapping in flow-limited patients as inspired V_T increases and expiratory time decreases (figs 3 and 4) [21, 28–42]. This temporary and variable increase in EELV above its baseline value, already elevated, is termed dynamic hyperinflation (DH). The extent of DH depends upon the degree of expiratory flow limitation, the prevailing ventilation and the breathing pattern for a given ventilation, and is inversely related to the level of resting lung hyperinflation [29].

Change in EELV during exercise can be reliably tracked using serial IC measurements since TLC remains unaltered [37, 42, 43]. Regardless of the behaviour of TLC, a progressive reduction in IC and IRV indicates increasing proximity of the V_T to TLC and the upper stiff noncompliant portion of the respiratory system pressure–volume relationship, where there is increased elastic and inspiratory threshold loading (secondary to an intrinsic positive end-expiratory pressure effect) of the inspiratory muscles (fig. 5) [40, 41]. Exercise IC measurements are reproducible, provided care is taken with their measurement [44–46]. In recent multicentre studies involving 463 patients with moderate-to-severe COPD, the intraclass correlation coefficient for exercise IC measurements during serial exercise tests was >0.85 , indicating excellent reproducibility [47]. The extent of reduction in IC with exercise is variable in COPD; in a

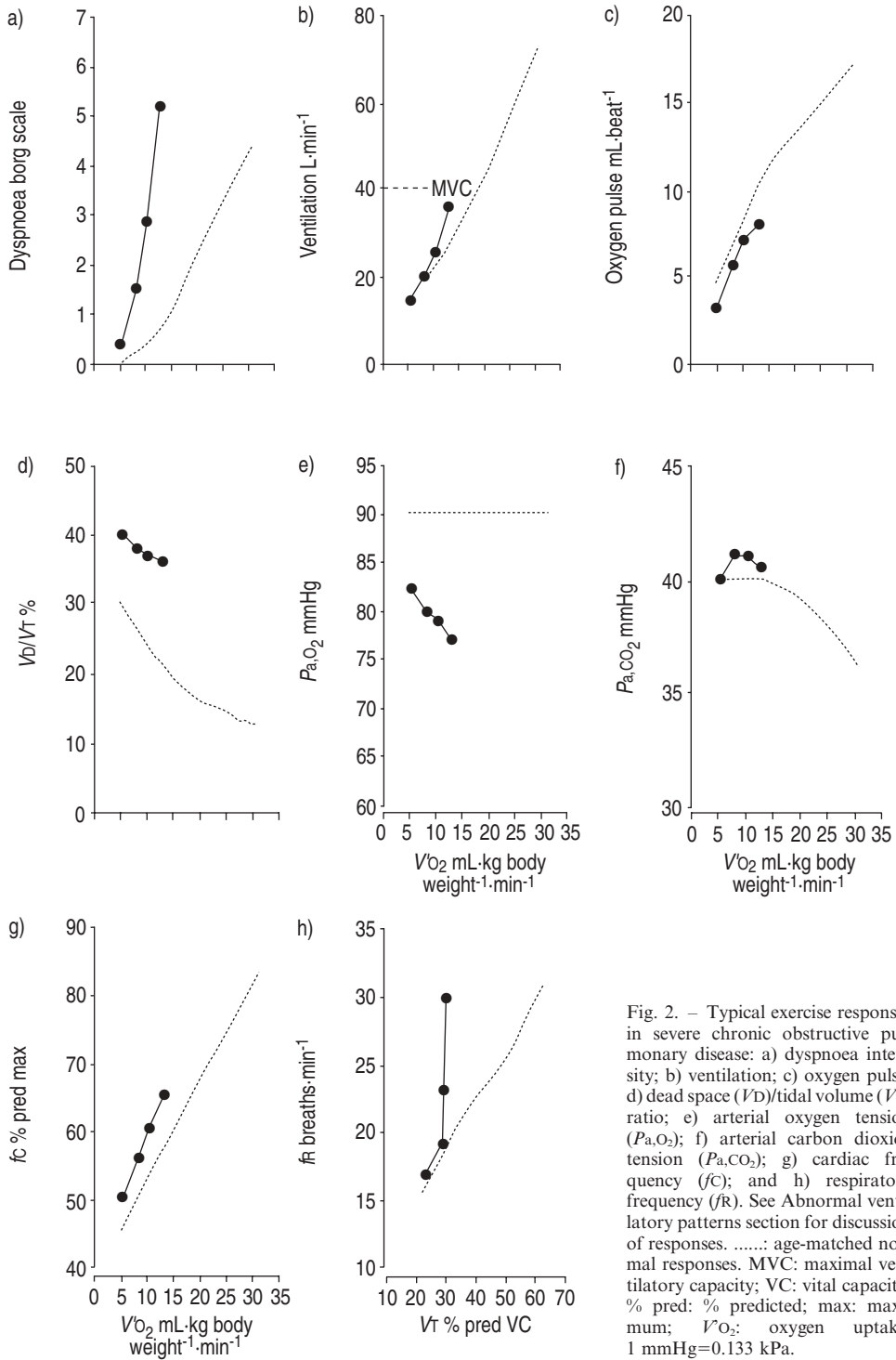


Fig. 2. – Typical exercise responses in severe chronic obstructive pulmonary disease: a) dyspnoea intensity; b) ventilation; c) oxygen pulse; d) dead space (V_D)/tidal volume (V_T) ratio; e) arterial oxygen tension (P_{a,O_2}); f) arterial carbon dioxide tension (P_{a,CO_2}); g) cardiac frequency (f_c); and h) respiratory frequency (f_R). See Abnormal ventilatory patterns section for discussion of responses.: age-matched normal responses. MVC: maximal ventilatory capacity; VC: vital capacity; % pred: % predicted; max: maximum; $\dot{V}O_2$: oxygen uptake. 1 mmHg=0.133 kPa.

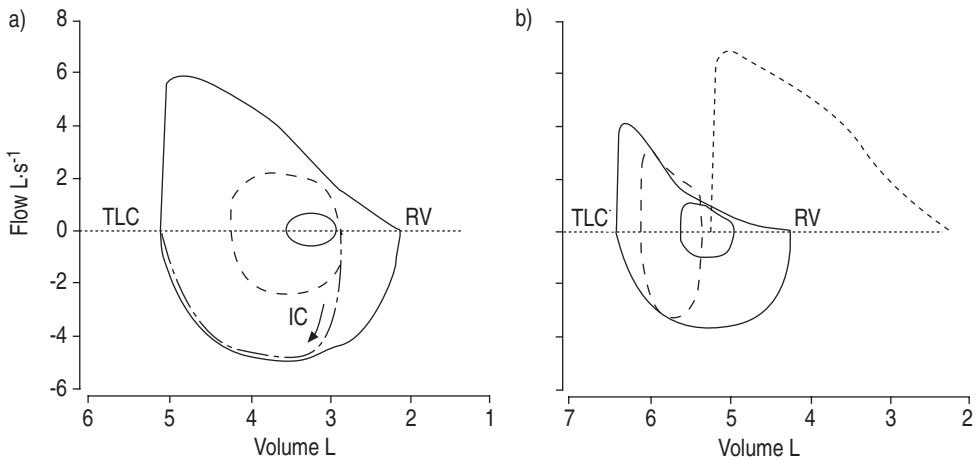


Fig. 3. – Flow–volume loops showing the effects of exercise on tidal volume (V_T) in a) healthy control subjects >40 yrs of age; and b) patients with chronic obstructive pulmonary disease (COPD); —: outer maximal limits of flow and volume and inner resting V_T ; - - -: increased V_T and flows seen with exercise; — - -: inspiratory capacity (IC) manoeuvre to total lung capacity (TLC) used to anchor tidal flow–volume loops within the respective maximal loops; ----: predicted normal maximal expiratory loop. RV: residual volume. Healthy subjects are able to increase both their V_T and inspiratory and expiratory flows. In COPD, expiratory flow is already maximal during resting ventilation. In order to increase expiratory flow further, these patients must hyperinflate.

population of 105 patients with moderate-to-severe COPD, IC at end-exercise was reduced by a mean of 18% of its already reduced resting value [29].

The reduction in IC during exercise correlates well with oesophageal balloon-derived measurements of dynamic elastance; therefore, IC measurement is a useful noninvasive

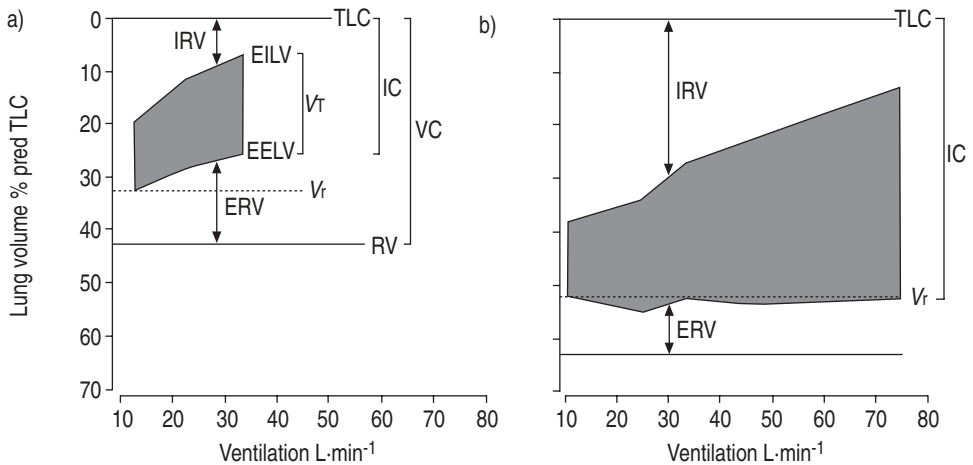


Fig. 4. – Changes in operating lung volumes as ventilation increases with exercise in a) chronic obstructive pulmonary disease (COPD); and b) age-matched healthy subjects. End-expiratory lung volume (EELV) increases above the relaxation volume of the respiratory system (V_r) in COPD, as reflected by a decrease in inspiratory capacity (IC), whereas EELV in health either remains unchanged or decreases. Restrictive constraints on tidal volume (V_T) expansion (■) during exercise are significantly greater in the COPD group from both below (increased EELV) and above (reduced inspiratory reserve volume (IRV) as end-inspiratory lung volume (EILV) approaches total lung capacity (TLC)). ERV: expiratory reserve volume; RV: residual volume; VC: vital capacity; % pred: % predicted. Adapted from [29] with permission.

surrogate for more invasive mechanical measurements [44]. At any given work-rate, $\dot{V}O_2$ or $\dot{V}E$, $\dot{V}T/IC$ ratios are increased and IRV is diminished in COPD compared with health [29, 44]. When dynamic IRV diminishes to ~ 0.5 L, further increases in $\dot{V}T$ are not possible, and exercise soon stops [29, 44, 48]. The relatively rapid shallow breathing pattern in COPD compared with health reflects these mechanical constraints on $\dot{V}T$ expansion. The greater the resting hyperinflation and DH in COPD patients, the lower the ventilation (and work-rate) during incremental cycle exercise at which $\dot{V}T$ reaches a plateau and respiratory frequency accelerates. Greater reliance on increasing respiratory frequency to increase ventilation rebounds to cause further DH and decreased dynamic lung compliance, which shows an exaggerated frequency dependency in COPD [40]. Thus DH during exercise leads to an early mechanical limitation of ventilation. Reduction in IC during exercise correlates well with the changes in dyspnoea intensity, suggesting that restrictive mechanics and the consequent neuromechanical uncoupling contribute to the genesis of this symptom [44–46].

Cardiac dysfunction

The effect of COPD on cardiac performance during exercise is complex and multifactorial. Severe lung hyperinflation and excessive expiratory muscle recruitment can impair venous return and reduce right ventricular pre-load in COPD. Moreover, large intrathoracic pressure swings generated during exercise to overcome the increased elastic and resistive loads may result in left ventricular dysfunction (increased left ventricular afterload), especially in patients with cardiac comorbid conditions. Several studies have demonstrated increased pulmonary vascular resistance (PVR) during exercise in COPD [49–52]. This results from emphysematous vascular destruction with reduced volume or compliance of the pulmonary vascular bed, and, in some cases, from critical hypoxaemia as a result of alveolar hypoventilation [49–53].

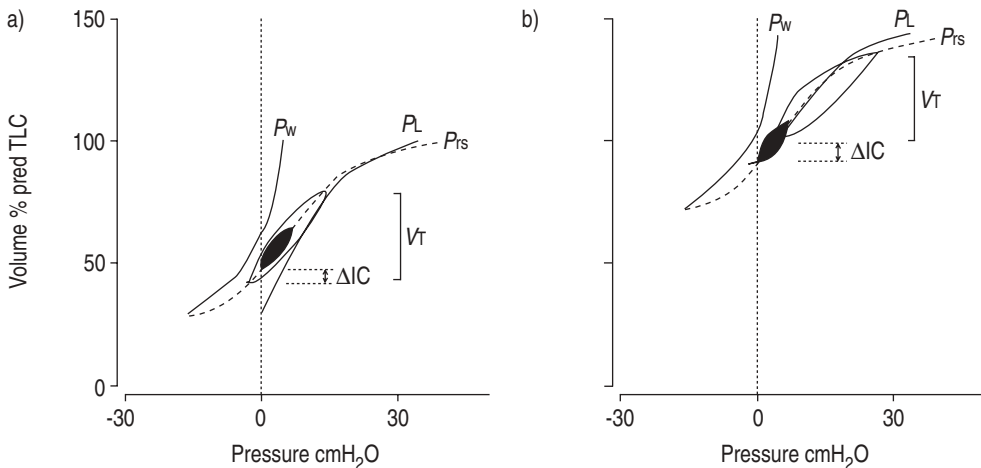


Fig. 5. – Pressure (P)–volume (V) relationships of the lung (P_L), chest wall (P_W) and total respiratory system (P_{RS}) in a) health; and b) chronic obstructive pulmonary disease (COPD) during rest (■) and exercise (□). In COPD, because of resting and dynamic hyperinflation (a further decreased inspiratory capacity (IC)), exercise tidal volume (V_T) encroaches on the upper alinear extreme of the respiratory system P – V curve, where there is increased elastic loading. TLC: total lung capacity; Δ : change; % pred: % predicted. Reproduced from [21] with permission.

Pulmonary arterial pressure (P_{pa}) and right ventricular afterload are generally much higher than in health at a given cardiac output in COPD [53, 54]. Right ventricular afterload during exercise is also increased because of the increased PVR associated with breathing at lung volumes close to TLC (*i.e.* DH) [52–55]. Earlier studies showed that the right ventricular ejection fraction failed to increase despite a rise in right ventricular end-diastolic pressure in COPD during exercise [51]. Left ventricular ejection fraction is generally preserved in COPD in the absence of concomitant ischaemic heart disease or hypertension [55, 56]. Left ventricular diastolic function may be impaired because of ventricular interdependence; increased tension or displacement of the right ventricle, as a result of increased PVR, may impede left diastolic filling [55, 56]. Cardiac output has been found to increase normally with $\dot{V}O_2$ during submaximal exercise in COPD, despite the increased PVR, but peak cardiac output (and $\dot{V}O_2$) reaches a lower value than in health [50, 57]. Stroke volume is generally smaller and cardiac frequency (f_c) correspondingly higher at a given $\dot{V}O_2$ in COPD compared with health [50].

Gas exchange abnormalities

The degree of arterial oxygen desaturation during exercise cannot consistently be predicted from resting pulmonary function test results or arterial blood gas levels. The mechanisms of hypoxaemia during exercise have been studied extensively and shown to reflect the impact of a fall in mixed venous oxygen content on low ventilation/perfusion areas of the lung and intrapulmonary shunting [58, 59]. Exercise hypercapnia, which reflects overt ventilatory insufficiency during exercise, is relatively rare and cannot be predicted from resting P_a,CO_2 or the results of pulmonary function tests or tests of resting ventilatory chemosensitivity [60–63]. Mechanical factors may seriously constrain the ventilatory response to metabolic acidosis in COPD such that P_a,CO_2 may not decrease as normal during high work-rates (*i.e.* compromised respiratory compensation). Severe mechanical restriction secondary to DH in a setting of an increased physiological dead space has been recognised as a contributory factor to hypercapnia in COPD as $\dot{V}CO_2$ increases with work-rate [64]. Other potential factors contributing to exercise hypercapnia include an increased load/capacity ratio (*i.e.* inspiratory muscle fatigue) and breathing pattern alterations (*i.e.* shallow breathing) to minimise discomfort [60–67]. Several studies have found that central neural efferent drive is preserved, or amplified, in hypercapnic COPD, making this a less likely explanation for exercise hypercapnia [62, 65–67].

Early metabolic acidosis has been described during exercise in COPD, and this represents a powerful additional stimulus to ventilation [68, 69]. Contributory factors include deconditioning, peripheral muscle dysfunction with abnormalities of oxidative capacity and vasoregulatory control, and the presence of concomitant heart disease [68–73]. However, ventilatory based methods for detection of the anaerobic (or lactate or ventilatory) threshold [74] are unreliable, particularly in patients with more severe COPD, who show a low peak symptom-limited $\dot{V}O_2$ and significant mechanical limitation to ventilation; arterial or arterialised venous blood (lactate) and standard (bicarbonate) measurements are, therefore, preferable.

Physiological events at peak or symptom-limited oxygen uptake

The combined mechanical and gas exchange abnormalities described above result in an increased work and oxygen cost of breathing at any given ventilation, compared with age-matched healthy controls. In one study, it was estimated that the oxygen cost of breathing in patients with severe COPD represented as much as 40% of their total $\dot{V}O_2$ [75].

Before exercise termination, central respiratory efferent drive reaches almost maximal values, but the respiratory muscle pump, which is overloaded and functionally weakened, responds inadequately to the increased electrical activation [76]. Thus, despite near maximal inspiratory efforts, very little air enters the lungs with each breath. This neuromechanical uncoupling may be consciously perceived as the distressing sensation of unsatisfied inspiration (*e.g.* “I cannot get enough air in”), an important qualitative dimension of the intolerable dyspnoea that limits exercise in patients with moderate-to-severe COPD [44].

Restrictive lung diseases

Restrictive lung disorders are also characterised by the inability to expand V_T appropriately during the increased metabolic demand of exercise. Lung parenchymal diseases, neuromuscular disorders, chest wall restriction and pulmonary resection represent the most common restrictive disorders. The present chapter focuses on the interstitial lung diseases (ILDs). These represent a broad and heterogeneous group of disorders that display common patterns of ventilatory response to exercise. As in other pulmonary conditions, exercise intolerance is multifactorial, but intolerable exertional symptoms, restrictive mechanics and severe pulmonary gas exchange derangements are often the proximate causes [77]. Concomitant cardiovascular abnormalities (pulmonary hypertension) and peripheral muscle dysfunction may also contribute importantly to reduced exercise capacity in ILD [78].

Abnormal ventilatory patterns

Typical ventilatory response patterns in ILD have been well described: low peak $\dot{V}_E$, high peak $\dot{V}_E/\text{MVC}$ ratio, and high submaximal $\dot{V}_E$ (increased slopes of the $\dot{V}_E$ – $\dot{V}_{O_2}$ and $\dot{V}_E$ – $\dot{V}_{CO_2}$ relationships), with a high respiratory frequency and low V_T at any given ventilation (*fig. 6*) [79–82]. The breathing pattern is usually more rapid and shallow throughout exercise than in health. Indeed, it is not uncommon to record respiratory frequencies of >50 breaths·min⁻¹ at peak exercise in patients with ILD. Increases in submaximal ventilation in ILD reflect ventilatory inefficiency due to high physiological dead space, critical arterial hypoxaemia and early metabolic acidosis [83–86]. Other possible, but less well studied, contributors include increased sympathetic nervous system activation, increased pulmonary vascular pressures, increased peripheral muscle mechanoreceptor/metaboreceptor activation and altered vagal afferent activity [87–90].

There is limited information from smaller studies that severe dyspnoea is the main locus of sensory limitation in patients with ILD. The prevalence of leg discomfort as the limiting factor is unknown, but is likely to be significant.

Ventilatory mechanics

The static pressure–volume curve of the lung is shifted down, indicating an increased static recoil pressure of the lung at any given lung volume [91, 92]. In ILD, the pressure–volume relationship of the entire respiratory system is contracted along its volume axis, but maintains its sigmoidal shape (*fig. 7*). The resting IC and IRV are usually diminished in ILD. With exercise, the end-inspiratory lung volume encroaches further on the upper alinear extreme of the pressure–volume relationship, where there is significant elastic loading. V_T saturates at 50–60% of the reduced VC early in exercise when the minimal dynamic IRV is reached and there is resultant tachypnoea.

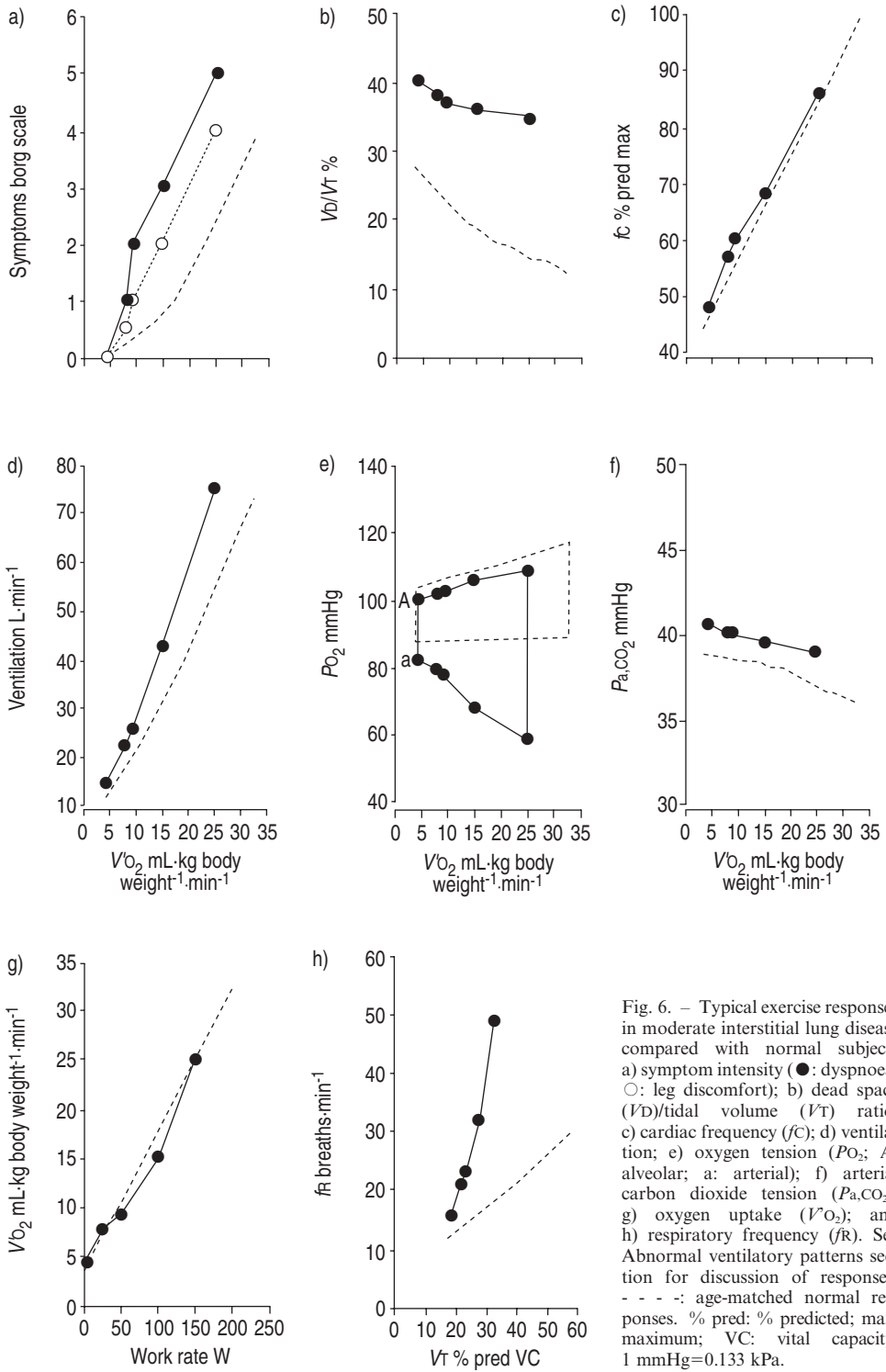


Fig. 6. — Typical exercise responses in moderate interstitial lung disease compared with normal subjects a) symptom intensity (●: dyspnoea; ○: leg discomfort); b) dead space (V_D)/tidal volume (V_T) ratio; c) cardiac frequency (f_c); d) ventilation; e) oxygen tension (P_{O_2} ; A: alveolar; a: arterial); f) arterial carbon dioxide tension (P_{a,CO_2}); g) oxygen uptake ($V\dot{O}_2$); and h) respiratory frequency (f_R). See Abnormal ventilatory patterns section for discussion of responses. - - -: age-matched normal responses. % pred: % predicted; max: maximum; VC: vital capacity. 1 mmHg=0.133 kPa.

During exercise, tidal expiratory flows may exceed those of healthy individuals at a given lung volume, reflecting the increased driving pressure for flow (fig. 8). A few small studies have indicated that IC remains largely unaltered throughout exercise [93, 94]. Avoidance of further encroachment of the V_T on the ERV would be expected to attenuate expiratory flow limitation over the lower lung volumes. However, as has been seen, failure to reduce EELV may have negative consequences with respect to work sharing between the inspiratory and expiratory muscles.

Expiratory flow limitation has been described in some patients with ILD, and may reflect airway obstruction as a result of smoking or airway involvement in the disease process [82]. The lack of DH during exercise in these patients with concomitant airway obstruction may reflect the already diminished IC at rest; patients may reach a critically reduced IRV and terminate exercise before air trapping can occur (fig. 9). In ILD, dyspnoea intensity has been shown to correlate well with the increasing V_T/IC during exercise [94]. Inspiratory muscle function is often relatively preserved in patients with ILD, reflecting the mechanical advantage of the inspiratory muscles at the lower operating lung volumes [94, 95]. However, in some individuals, involvement of the ventilatory muscles in the underlying systemic inflammatory disease process, effects of high-dose oral steroids, malnutrition and electrolytic disturbances may have a deleterious impact on muscle function [96].

Gas exchange abnormalities

Significant widening of the alveolar–arterial oxygen tension gradient (P_{A-a,O_2}) with arterial hypoxaemia can occur in early ILD, even before resting pulmonary function tests show overt impairment (fig. 6) [97–99]. Relative alveolar hyperventilation is not uncommon during exercise. In more severe disease, profound arterial oxygen desaturation during rest and exercise is the rule [100–103]. The mechanisms of arterial oxygen desaturation have been clearly defined, and include inter- and intraregional ventilation/perfusion inequalities in the lungs, low mixed venous oxygen concentration

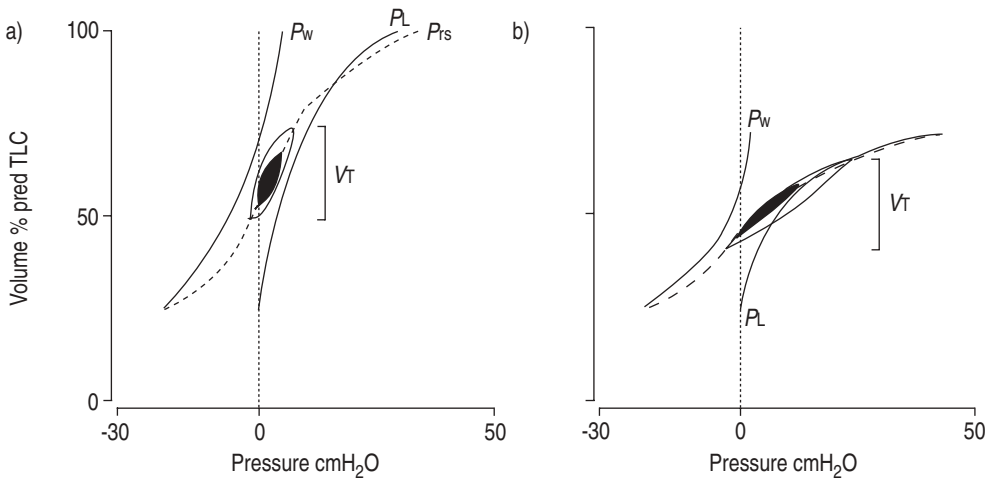


Fig. 7. — Pressure (P)–volume (V) relationships of the lung (P_L), chest wall (P_w) and total respiratory system (P_{rs}) in a) health; and b) interstitial lung disease (ILD) during rest (■) and exercise (□). In ILD, greater P is required to generate tidal volume (V_T) during exercise. TLC: total lung capacity; % pred: % predicted. Reproduced from [77] with permission.

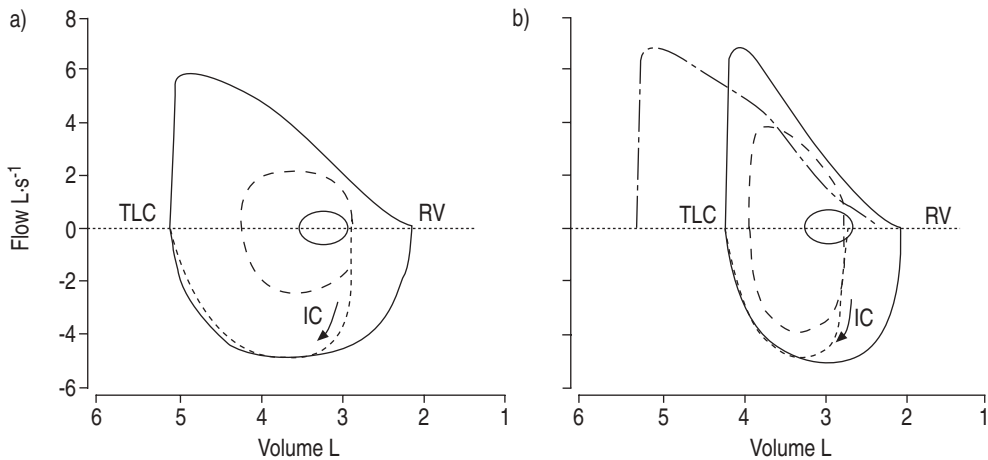


Fig. 8. – Typical flow–volume loops in a) a normal subject; and b) a patient with interstitial lung disease (ILD). —: maximal and tidal loops at rest; ---: tidal loops at peak exercise in ILD and at a similar work rate in the normal subject; - - -: inspiratory capacity (IC) manoeuvre to total lung capacity (TLC) used to anchor tidal flow–volume loops within the respective maximal loops; - - -: predicted normal maximal expiratory loop. In ILD, tidal flows at peak exercise approach the maximal envelope. The inspiratory reserve volume (IRV; $IRV = TLC - \text{end-inspiratory lung volume}$) is markedly reduced in ILD compared to normal. RV: residual volume.

in the setting of low ventilation/perfusion ratios, diffusion disequilibrium with decreased pulmonary capillary transit time and, in some individuals, increased intracardiac and intrapulmonary shunting [100–103]. Alveolar hypoventilation is not commonly reported during exercise, even in advanced ILD, but severe V_T restriction in the setting of a fixed high physiological dead space can potentially cause carbon dioxide retention. Correlations have been found between the low resting DL_{CO} and arterial hypoxaemia

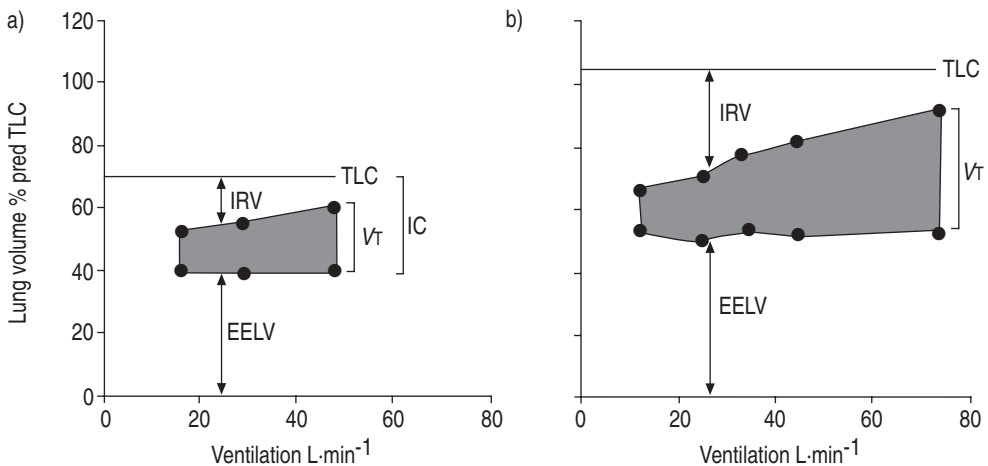


Fig. 9. – Change in operating lung volume as ventilation increases with exercise in a) interstitial lung disease (ILD); and b) age-matched healthy subjects. Restrictive constraints on tidal volume (V_T) expansion (■) during exercise are significantly greater in the ILD group from above (reduced inspiratory reserve volume (IRV) as end-inspiratory lung volume approaches total lung capacity (TLC)). EELV: end-expiratory lung volume; IC: inspiratory capacity; % pred: % predicted. Data reproduced from [94] with permission.

during exercise [100], but there is considerable overlap in this relationship, particularly in patients with mild-to-moderate disease.

Cardiovascular responses

The characteristic cardiac abnormality in ILD is increased PVR, with consequent right ventricular hypertrophy, which ultimately leads to the development of cor pulmonale during the terminal phase of the illness [103, 104]. Left ventricular ejection fraction and pressures are usually preserved, as are pulmonary artery occlusion pressures [105, 106]. Cardiac output is usually normal at rest and during low levels of exercise in ILD, but the rate of increase in cardiac output is diminished at higher work-rates [105, 106], due, in part, to increased PVR. In several studies, P_{pa} has been shown to be high at rest and to further increase during exercise in the majority of patients with ILD [103, 107, 108]. P_{pa} in the 40 mmHg range is not unusual in patients with even moderate disease during minimal activity. High P_{pa} is required during exercise in order to maintain cardiac output when PVR is increased; P_{pa} is often at least twice the normal value [103, 104]. Obliteration of the vascular bed by progressive parenchymal fibrosis is the main explanation for the reduced vascular bed and increased PVR in ILD [109, 110]. Other factors contributing to the increased PVR are: 1) hypoxic vasoconstriction; and 2) reduced lung volume.

f_c responses to incremental exercise in ILD are variable. f_c is often higher than normal at submaximal work-rates [78, 111], reflecting the relatively reduced stroke volume (fig. 6). Maximal f_c , however, is generally diminished, and there is adequate cardiac reserve (predicted maximal f_c minus peak f_c) at exercise termination. Diminished cardiac reserve may become evident in patients with cardiac involvement in the disease process (e.g. sarcoidosis) [112], and in patients with additional extensive pulmonary vascular disease (e.g. scleroderma) [113].

Comparison of ventilatory responses in COPD and ILD

Clearly, ventilatory patterns during conventional CPET are remarkably similar in obstructive and restrictive disorders (table 1). However, a comparison of the operating lung volumes during exercise permits easy diagnostic differentiation. In COPD, V_T is restricted from below by the effects of hyperinflation, whereas, in ILD, the restriction is from above, reflecting the reduced TLC and IRV (figs 4 and 9). Regardless of the mechanism of restriction, the inability to expand V_T in response to the increasing respiratory drive (or inspired effort) of exercise contributes importantly to low ventilatory capacity (fig. 10).

Patients with ILD often exhibit better preservation of inspiratory muscle force-generating capacity, reflecting the mechanical advantage of lower operating lung volumes. Furthermore, patients with ILD, unlike those with COPD, do not usually have to contend with inspiratory threshold and resistive loading. However, clinically stable ILD patients generally show relatively greater tachypnoea and attendant dynamic muscle dysfunction, and often more severe gas exchange abnormalities during exercise. These latter abnormalities generally occur earlier in ILD than in COPD and may precede other pulmonary function abnormalities. Remarkably, despite these differences, exertional dyspnoea is qualitatively similar in COPD and ILD patients at peak exercise [44, 94]. The present authors postulate that these dominant qualitative respiratory sensations, which allude to unsatisfied inspiration, ultimately have their neurophysiological basis in the conscious awareness of a disparity between the increased drive to breathe and the restricted mechanical response of the respiratory system.

Table 1. – Typical exercise responses in chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and pulmonary vascular disease (PVD)

	COPD	ILD	PVD
Reduced peak oxygen uptake and work rate	+	+	+
Increased dyspnoeic intensity at submaximal exercise	+	+	+
Diminished ventilatory reserve [#]	+	+	±
High submaximal ventilation [‡]	+	+	+
High-frequency/low tidal volume breathing pattern	+	+	+
Increased mechanical restriction ⁺	+	+	±
Arterial oxygen desaturation	±	+	+
Adequate cardiac reserve [†]	+	+	+
Reduced submaximal and peak oxygen pulse	±	±	+

+: present; ±: either present or normal. [#]: high minute ventilation ($\dot{V}_E$)/maximum voluntary ventilation ratio; [‡]: high resting and exercise physiological dead space and increased $\dot{V}_E$ /carbon dioxide production ratios; ⁺: high ratio of tidal volume to inspiratory capacity (reduced submaximal inspiratory reserve volume); [†]: low peak cardiac frequency ± high submaximal cardiac frequencies.

Pulmonary vascular diseases

Pulmonary hypertension is defined as a mean P_{pa} of >25 mmHg at rest or >30 mmHg during exercise [114]. Pulmonary hypertension is consistently associated with reduced exercise capacity [115–117]. It has recently been shown that peak $\dot{V}O_2$ correlates significantly with New York Heart Association symptom class in patients with primary pulmonary hypertension [117]. Typical abnormalities in the cardiopulmonary responses to exercise in this condition are well described [118]. Pulmonary hypertension can be primary (*i.e.* idiopathic) or secondary to a variety of respiratory conditions associated with increased PVR [119]. These include obstructive and restrictive lung diseases, chronic thromboembolic disease and sleep-disordered breathing. Secondary pulmonary hypertension also occurs in patients with left ventricular dysfunction, high cardiac output states, connective tissue disorders, HIV infection [120] and portopulmonary hypertension [121], and as an adverse reaction to certain drugs [122–124].

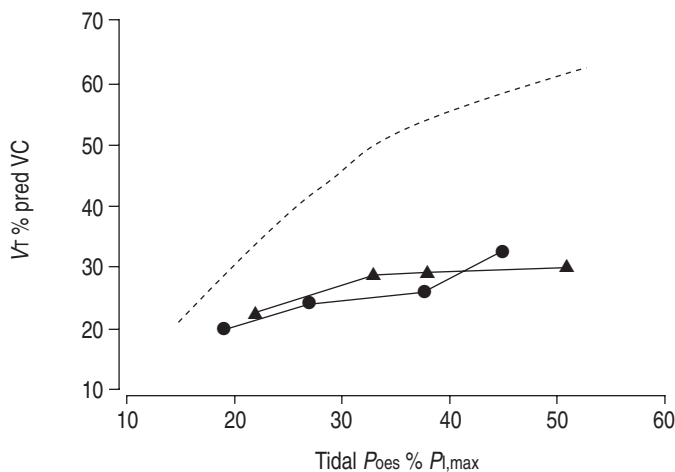


Fig. 10. – During exercise, tidal volume ($\dot{V}_T$) responses are reduced for a given inspiratory effort (oesophageal pressure (P_{oes})/maximal inspiratory pressure ($P_{I,max}$)) in both interstitial lung disease (●) and chronic obstructive pulmonary disease (▲) compared with normal (---), *i.e.* neuromechanical dissociation.

The present chapter focuses primarily on cardiopulmonary response patterns in patients with increased PVR whose dynamic ventilatory mechanics are largely preserved during exercise (*e.g.* primary pulmonary hypertension and thromboembolic disease). Therefore, consideration of patients with pulmonary hypertension secondary to COPD, restrictive lung diseases or primary cardiac diseases is excluded.

Abnormal ventilatory patterns

Pulmonary hypertension should be suspected when ventilatory responses to exercise are abnormally elevated in the presence of relatively preserved spirometric parameters. Studies have indicated that some patients with primary pulmonary hypertension may show a mild restrictive spirometric pattern, as indicated by a small reduction in TLC with preservation of the FEV₁/forced VC ratio. The underlying mechanism(s) remain unclear, but reduced lung compliance and inspiratory muscle weakness have been suggested as potential contributors [125–132].

Exertional dyspnoea and fatigue may be quite pronounced, even during moderate exercise, and are often the proximate limiting factors to exercise performance (fig. 11) [127, 133]. Similarly, peak $\dot{V}_E$ is diminished, reflecting the reduced peak symptom-limited $\dot{V}O_2$, whereas the $\dot{V}_E/\dot{V}O_2$ ratio is relatively preserved at peak exercise [115, 117, 118, 131]. $\dot{V}_E$, at any given submaximal $\dot{V}O_2$, is increased, reflecting poor pulmonary perfusion and resultant wasted ventilation [115, 117, 118, 131]. The slope of $\dot{V}_E/\dot{V}CO_2$ is consistently elevated (*e.g.* >25–30) compared to health, as is the ventilatory equivalent (in absolute terms) at the ventilatory threshold (*e.g.* >34) [115, 117]. Studies have indicated that the $\dot{V}_E/\dot{V}CO_2$ ratio correlates well with haemodynamic indices of pulmonary hypertension [117, 134], and that effective vasodilator therapy results in a reduction in this variable [135]. Ventilatory thresholds are lower in pulmonary hypertension than in health, reflecting reduced oxygen delivery to the active peripheral muscles and a greater reliance on anaerobic glycolysis [117]. Significant skeletal muscle deconditioning can arise as a result of dyspnoea-related inactivity in patients with pulmonary hypertension, which again may be associated with an earlier metabolic acidosis and increased ventilatory stimulation. Breathing pattern responses to exercise are usually more rapid and shallow than in health. The reduced $\dot{V}_T$ expansion is not explained by restrictive mechanics as IRV is generally preserved or increased at peak exercise compared with health. Relative tachypnoea may be related to activation of unmyelinated pulmonary C fibres and/or altered mechanosensor inputs from the right heart and pulmonary vasculature in a manner that remains incompletely understood [136].

Dynamic ventilatory mechanics during exercise should not be abnormal in patients with pulmonary hypertension in the absence of concomitant COPD or restrictive thoracic diseases. However, it is conceivable that, in some such patients with high ventilatory demand, air-trapping and DH may occur, particularly towards the end of exercise in elderly individuals with expiratory flow-limitation (fig. 12).

Gas exchange abnormalities

Arterial oxygen desaturation with widening of the $P_{A-a}O_2$ typically occurs in patients with established pulmonary hypertension [115, 117, 131]. The widened $P_{A-a}O_2$ reflects critical ventilation/perfusion inequalities and a diffusion defect as a result of reduced red cell transit times through the abnormal pulmonary vasculature [115, 117, 131]. End-tidal carbon dioxide tensions are often diminished at higher levels of exercise compared with health, reflecting relative alveolar hyperventilation. It has been suggested that pulmonary hypertension should be suspected in patients who present with unexplained

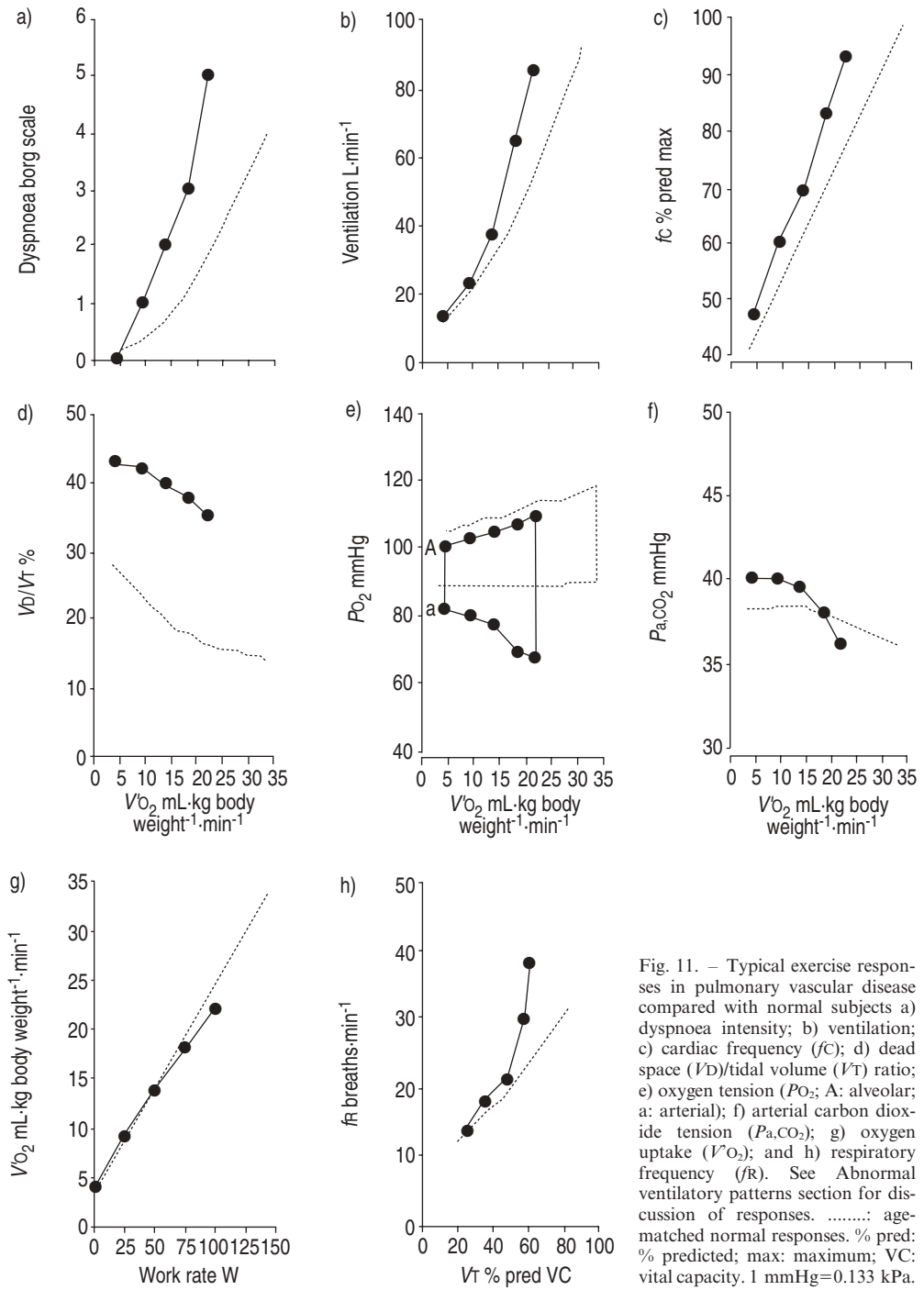


Fig. 11. – Typical exercise responses in pulmonary vascular disease compared with normal subjects a) dyspnoea intensity; b) ventilation; c) cardiac frequency (f_c); d) dead space (V_D)/tidal volume (V_T) ratio; e) oxygen tension (P_{O_2} ; A: alveolar; a: arterial); f) arterial carbon dioxide tension (P_{a,CO_2}); g) oxygen uptake ($V\dot{O}_2$); and h) respiratory frequency (f_R). See Abnormal ventilatory patterns section for discussion of responses.: age-matched normal responses. % pred: % predicted; max: maximum; VC: vital capacity. 1 mmHg=0.133 kPa.

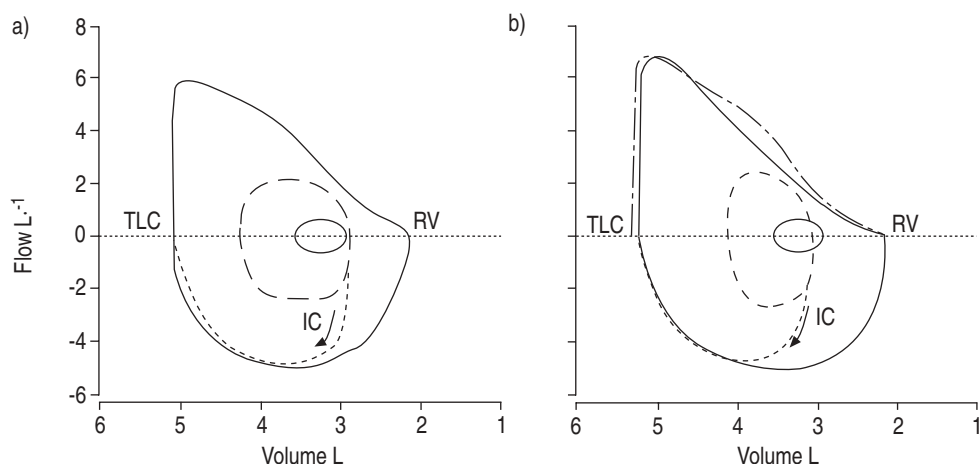


Fig. 12. – Typical flow–volume loops in a) a normal subject; and b) a patient with pulmonary vascular disease (PVD). —: maximal and tidal loops at rest; ---: tidal loops at peak exercise in PVD and at a similar work rate in the normal subject; - - - -: inspiratory capacity (IC) manoeuvre to total lung capacity (TLC) used to anchor tidal flow–volume loops within the respective maximal loops; — - - -: predicted normal maximal expiratory loop. RV: residual volume.

dyspnoea and exercise limitation, and whose end-tidal carbon dioxide tension at the ventilatory threshold is <4.0 kPa [134]. These gas exchange abnormalities, which typify pulmonary arterial hypertension, are usually not found in patients with pulmonary venous hypertension secondary to cardiac diseases [137].

Cardiac responses

Increased PVR increases right ventricular afterload, which can limit the normal increase in stroke volume and cardiac output responses to increasing exercise [138]. Critical right ventricular decompensation may be associated with concomitant left ventricular dysfunction [138] through the well-described effect of ventricular interdependence [139]. Relatively increased f_c with low peak oxygen pulse is not unusual, but these indirect indices of cardiac function are often quite variable and nonspecific for pulmonary hypertension [131, 137]. These cardiac responses are similar to those described in patients with reduced cardiac output due to other causes and in those with significant skeletal muscle deconditioning [137].

Summary

Abnormalities in cardiopulmonary responses to incremental cycle ergometer exercise are often similar in obstructive, restrictive and pulmonary vascular disorders. All are characterised by an accelerated ventilatory response, primarily as a result of the effects of a high fixed physiological dead space, combined, in many cases, with attendant arterial oxygen desaturation. Skeletal muscle deconditioning, with earlier metabolic acidosis, is also a common feature of all chronic respiratory disorders and can further amplify ventilatory stimulation during exercise. The breathing pattern is more rapid and shallow in both obstructive and restrictive lung disorders compared to health, and reflects the dynamic mechanical constraints on tidal volume (V_T)

expansion. In general, respiratory frequency responses to exercise are most pronounced in patients with restrictive lung disease. In chronic obstructive pulmonary disease, a V_T plateau with concomitant tachypnoea early in exercise at relatively low ventilation generally indicates the presence of significant resting and additional dynamic lung hyperinflation. Cardiac frequency responses to exercise are variably abnormal, but are broadly similar across these disease groups and, therefore, nonspecific. Resting pulmonary function test results, in association with quantitative exercise flow–volume loop analysis, can accurately delineate abnormalities in resting and dynamic ventilatory mechanics that characterise obstructive and restrictive lung disease and permit easy differentiation from primary pulmonary vascular disorders. Such noninvasive assessments of ventilatory mechanics during exercise, together with the quantification of exertional symptoms, permit comprehensive clinical characterisation of the individual presenting with reduced exercise capacity.

Keywords: Chronic obstructive pulmonary disease, dyspnoea, exercise, interstitial lung disease, pulmonary mechanics, pulmonary vascular diseases.

References

1. Gandevia B, Hugh-Jones P. Terminology of measurements of ventilatory capacity. *Thorax* 1957; 12: 290–293.
2. Dillard TA, Piantadosi S, Rajagopal KR. Prediction of ventilation at maximal exercise in chronic airflow obstruction. *Am Rev Respir Dis* 1985; 132: 230–235.
3. Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow–volume loop. *Chest* 1999; 116: 488–503.
4. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJM. Exercise capacity and ventilatory, circulatory and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992; 146: 935–940.
5. Hamilton AL, Killian KJ, Summers E, Jones NL. Symptom intensity and subjective limitation to exercise in patients with cardiorespiratory disorders. *Chest* 1996; 110: 1255–1263.
6. O'Donnell DE, Webb KA. Exercise reconditioning in patients with chronic airflow limitation. In: Torg JS, Shepherd RJ, eds. *Current Therapy in Sports Medicine*. 3rd Edn. St. Louis, MO, Mosby Year Book, Inc., 1995; pp. 678–684.
7. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation: the role of hyperinflation. *Am Rev Respir Dis* 1993; 148: 1351–1357.
8. Borg GAV. Psychophysical basis of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377–381.
9. Gift AG. Validation of vertical visual analogue scale as a measure of clinical dyspnea. *Rehabil Nurs* 1989; 14: 313–325.
10. Aaron EA, Johnson BD, Seow KC, Dempsey JA. Oxygen cost of exercise hyperpnea: implications for performance. *J Appl Physiol* 1992; 72: 1818–1825.
11. Henke KG, Sharratt M, Pegelow DF, Dempsey JA. Regulation of end-expiratory lung volume during exercise. *J Appl Physiol* 1988; 64: 135–146.
12. Warren JB, Jennings SJ, Clark TJH. Effect of adrenergic and vagal blockade on the normal human airway response to exercise. *Clin Sci* 1984; 66: 79–85.
13. England SJ, Bartlett DJ. Changes in respiratory movements of the human vocal cords during hyperpnea. *J Appl Physiol* 1982; 52: 780–785.
14. Dempsey JA, Adams L, Ainsworth DM, *et al.*, Airway, lung and respiratory muscle function during exercise. In: Rowell LB, Shepard JT, eds. *Handbook of Physiology. Exercise. Regulation and Integration of Multiple Systems*. New York, Oxford University Press, 1996; pp. 448–514.

15. Olafsson S, Hyatt RE. Ventilatory mechanics and expiratory flow limitation during exercise in normal subjects. *J Clin Invest* 1969; 48: 564–573.
16. Anthonisen NR, Danson J, Robertson PC, Ross WR. Airway closure as a function of age. *Respir Physiol* 1969; 8: 58–65.
17. Frank NR, Mead J, Ferris BG Jr. The mechanical behaviour of the lungs in healthy elderly persons. *J Clin Invest* 1957; 36: 1680–1687.
18. D’Errico A, Scarani P, Colosimo E, Spina M, Grigioni WF, Mancini AM. Changes in the alveolar connective tissue of the aging lung. *Virch Arch A Pathol Pathol Anat* 1989; 415: 137–144.
19. Johnson BD, Badr MS, Dempsey JA. Impact of the aging pulmonary system on the response to exercise. *Clin Chest Med* 1994; 15: 229–246.
20. Johnson BD, Reddan DF, Pegelow KC, Seow KC, Dempsey JA. Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. *Am Rev Respir Dis* 1991; 143: 960–967.
21. O’Donnell DE, Webb KA. Exercise. In: Calverley P, MacNee W, Rennard S, Pride N, eds. *Chronic Obstructive Lung Disease*. 2nd Edn. London, Edward Arnold (Publishers), 2003; pp. 243–265.
22. Johnson BD, Reddan WG, Seow KC, Dempsey JA. Mechanical constraints on exercise hyperpnea in a fit aging population. *Am Rev Respir Dis* 1991; 143: 968–977.
23. Harms CA, Babcock MA, McClaran SR, *et al.* Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol* 1997; 82: 1573–1583.
24. Tenney SM, Miller RM. Dead space ventilation in old age. *J Appl Physiol* 1956; 9: 321–327.
25. Ofir D, McBride I, Peters MM, Webb KA, O’Donnell DE. Age-related evolution of ventilatory constraints and dyspnea during exercise in health. *Am J Respir Crit Care Med* 2005; 171: A494.
26. Fletcher M, Elmes PC, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ* 1959; 1: 257–266.
27. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002; 121: 1434–1440.
28. Diaz O, Villafranco C, Ghezzi H, *et al.* Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. *Eur Respir J* 2000; 16: 269–275.
29. O’Donnell DE, Revill S, Webb KA. Dynamic hyperinflation and exercise intolerance in COPD. *Am J Respir Crit Care Med* 2001; 164: 770–777.
30. Mohsenifar Z, Lee SM, Diaz P, *et al.* Single-breath diffusing capacity of the lung for carbon monoxide: a predictor of PaO₂, maximum work rate, and walking distance in patients with emphysema. *Chest* 2003; 123: 1394–1400.
31. O’Donnell DE. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. In: Weisman IM, Zeballos RJ, eds. *Clinical Exercise Testing*. Basle, Karger, 2002; pp. 138–158.
32. Oga T, Nishimura K, Tsukino M, Sato S, Hajiuro T. Analysis of factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003; 167: 544–549.
33. Oga T, Nissimura K, Tsukino M, Hajiuro T, Ikeda A, Mishima M. Relationship between different indices of exercise capacity and clinical measures in patients with chronic obstructive pulmonary disease. *Heart Lung* 2002; 31: 374–381.
34. Grimby G, Bunn J, Mead J. Relative contribution of rib cage and abdomen to ventilation during exercise. *J Appl Physiol* 1968; 24: 159–166.
35. Potter WA, Olafsson S, Hyatt RE. Ventilatory mechanics and expiratory flow limitation during exercise in patients with obstructive lung disease. *J Clin Invest* 1971; 50: 910–919.
36. Dodd DS, Brancatisano T, Engel LA. Chest wall mechanics during exercise in patients with severe chronic airway obstruction. *Am Rev Respir Dis* 1984; 129: 33–38.
37. Stubbing DG, Pengelly LD, Morse JLC, Jones NL. Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. *J Appl Physiol* 1980; 49: 511–515.

38. Babb TG, Viggiano R, Hurley B, Staats B, Rodarte JR. Effect of mild-to-moderate airflow limitation on exercise capacity. *J Appl Physiol* 1991; 70: 223–230.
39. Hyatt RE. Expiratory flow limitation. *J Appl Physiol* 1983; 55: 1–8.
40. Pride NB, Macklem PT. Lung mechanics in disease. In: Fishman AP, ed. *Handbook of Physiology*. Section 3. Vol. III. Part 2: The Respiratory System. Bethesda, MD, American Physiological Society, 1986; pp. 659–692.
41. Younes M. Determinants of thoracic excursions during exercise. In: Whipp BJ, Wasserman K, eds. *Lung Biology in Health and Disease*. Vol. 42. Exercise, Pulmonary Physiology and Pathophysiology. New York, Marcel Dekker, 1991; pp. 1–65.
42. Yan S, Kaminski D, Sliwinski P. Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 156: 55–59.
43. Vogiatzis I, Georgiadou O, Golemati S, *et al.* Patterns of dynamic hyperinflation during exercise and recovery in patients with severe chronic obstructive pulmonary disease. *Thorax* 2005; 60: 723–729.
44. O'Donnell DE, Chau LKL, Bertley JC, Webb KA. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med* 1997; 155: 109–115.
45. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158: 1557–1565.
46. Marin JM, Carrizo SJ, Gascon M, Sanchez A, Gallego BA, Celli BR. Inspiratory capacity, dynamic hyperinflation, breathlessness and exercise performance during the 6-minute-walk test in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1395–1399.
47. O'Donnell DE, He Z, Lam M, Webb KA, Hamilton A. Reproducibility of measurements of inspiratory capacity, dyspnea intensity and exercise endurance in multicentre trials in COPD. *Eur Respir J* 2004; 24: Suppl. 48, 323s.
48. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J* 2004; 24: 86–94.
49. Light RW, Mintz WM, Linden GS, Brown SE. Hemodynamics of patients with severe chronic obstructive pulmonary disease during progressive upright exercise. *Am Rev Respir Dis* 1984; 130: 391–395.
50. Mahler DA, Brent BN, Loke J, Zaret BL, Matthay RA. Right ventricular performance and central hemodynamics during upright exercise in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1984; 130: 722–729.
51. Oswald-Mammosser M, Apprill M, Bachez P, Ehrhart M, Weitzenblum E. Pulmonary hemodynamics in chronic obstructive pulmonary disease of the emphysematous type. *Respiration* 1991; 58: 304–310.
52. Magee F, Wright JL, Wiggs BR, Pare PD, Hogg JC. Pulmonary vascular structure and function in chronic obstructive pulmonary disease. *Thorax* 1988; 43: 183–189.
53. Agusti AGN, Barbera JA, Roca J, Wagner PD, Guitart R, Rodriguez-Roisin R. Hypoxic pulmonary vasoconstriction and gas exchange during exercise in chronic obstructive pulmonary disease. *Chest* 1990; 97: 268–275.
54. Matthay RA, Berger HJ, Davies RA, *et al.* Right and left ventricular exercise performance in chronic obstructive pulmonary disease: radionuclide assessment. *Ann Int Med* 1980; 93: 234–239.
55. Vizza CD, Lynch JP, Ochoa LL, Richardson G, Trulock EP. Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998; 113: 576–583.
56. Morrison DA, Adcock K, Collins CM, Goldman S, Caldwell JH, Schwartz MI. Right ventricular dysfunction and the exercise limitation of chronic obstructive pulmonary disease. *J Am Coll Cardiol* 1987; 9: 1219–1229.
57. Montes de Oca M, Rassulo J, Celli BR. Respiratory muscle and cardiopulmonary function during exercise in very severe COPD. *Am J Respir Crit Care Med* 1996; 154: 1284–1289.

58. Barbera JA, Roca J, Ramirez J, Wagner PD, Usetti P, Rodriquez-Roisin R. Gas exchange during exercise in mild chronic obstructive pulmonary disease: correlation with lung structure. *Am Rev Respir Dis* 1991; 144: 520–525.
59. Dantzker DR, D'Alonzo GE. The effect of exercise on pulmonary gas exchange in patients with severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 134: 1135–1139.
60. Begin P, Grassino A. Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 143: 905–912.
61. Light RW, Mahutte CK, Brown SE. Etiology of carbon dioxide retention at rest and during exercise in chronic airflow obstruction. *Chest* 1988; 94: 61–67.
62. DeTroyer A, Leeper JB, McKenzie D, Gandevia S. Neural drive to the diaphragm in patients with severe COPD. *Am J Respir Crit Care Med* 1993; 155: 1335–1340.
63. Moutain R, Zwillich C, Weil J. Hypoventilation in obstructive lung disease. The role of familial factors. *N Engl J Med* 1978; 298: 521–525.
64. O'Donnell DE, D'Arsigny C, Fitzpatrick M, Webb KA. Exercise hypercapnia in advanced chronic obstructive pulmonary disease: the role of lung hyperinflation. *Am J Respir Crit Care Med* 2002; 166: 663–668.
65. Montes de Oca M, Celli BR. Mouth occlusion pressure, CO₂ response and hypercapnia in severe obstructive pulmonary disease. *Eur Respir J* 1998; 12: 666–671.
66. Scano G, Spinelli A, Duranti R, *et al.* Carbon dioxide responsiveness in COPD patients with and without hypercapnia. *Eur Respir J* 1995; 8: 78–85.
67. Montes de Oca M, Celli B. Respiratory muscle recruitment and exercise performance in eucapnic and hypercapnic severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 880–885.
68. Casaburi R. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2001; 33: Suppl. 7, S662–S670.
69. Bernard S, Leblanc P, Whittom F, *et al.* Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158: 629–634.
70. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996; 153: 976–980.
71. Whittom F, Jobin J, Simard PM, *et al.* Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 1998; 30: 1467–1474.
72. Jakobsson P, Jorfeldt L, Henriksson J. Metabolic enzyme activity in the quadriceps femoris muscle in patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 151: 374–377.
73. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reduction in exercise lactic acidosis and ventilation as a result of exercise training in obstructive lung disease. *Am Rev Respir Dis* 1991; 143: 9–18.
74. Ward SA. Discriminating features of responses in cardiopulmonary exercise testing. In: Ward SA, Palange P, eds. *Clinical Exercise Testing*. *Eur Respir Mon* 2007; 40: 36–68.
75. Levison H, Cherniack RM. Ventilatory cost of exercise in chronic obstructive pulmonary disease. *J Appl Physiol* 1968; 25: 21–27.
76. Sinderby C, Spahija J, Beck J, *et al.* Diaphragm activation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 1637–1641.
77. O'Donnell DE, Fitzpatrick MF. Physiology of interstitial lung disease. In: Schwartz MI, King TE Jr, eds. *Interstitial Lung Disease*. 4th Edn. Hamilton, Decker, 2003; pp. 54–74.
78. Widimsky J, Riedel M, Stonek V. Central hemodynamics during exercise in patients with restrictive pulmonary disease. *Bull Eur Physiopathol Respir* 1977; 13: 369–379.
79. Spiro SG, Dowdeswell IRG, Clark TJH. An analysis of submaximal exercise responses in patients with sarcoidosis and fibrosing alveolitis. *Br J Dis Chest* 1981; 75: 169–180.
80. Kaltreider NL, McCann WS. Respiratory response during exercise in pulmonary fibrosis and emphysema. *J Clin Invest* 1937; 16: 23–40.

81. Burdon JGW, Killian KJ, Jones NL. Pattern of breathing during exercise in patients with interstitial lung disease. *Thorax* 1983; 38: 778–784.
82. Jones NL, Rebuck AS. Tidal volume during exercise in patients with diffuse fibrosing alveolitis. *Bull Eur Physiopathol Respir* 1979; 15: 321–327.
83. Georges R, Saumon G, Lafosse JE, Turiaf J. Membrane-diffusing capacity and pulmonary capillary blood volume. *Prog Respir Res* 1975; 8: 198–212.
84. Wagner PD, Dantzker DR, Dueck R. Distribution of ventilation–perfusion ratios in patients with interstitial lung disease. *Chest* 1976; 69: 256–257.
85. Austrian R, McClement JH, Renzetti AD Jr, Donald KW, Riley RL, Cournand A. Clinical and physiologic features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion; the syndrome of “alveolar-capillary block”. *Am J Med* 1951; 2: 267–285.
86. Jernudd-Wilhelmsson T, Hornblad Y, Hedenstierna G. Ventilation–perfusion relationships in interstitial lung disease. *Eur J Respir Dis* 1986; 68: 39–49.
87. Lourenco RV, Turino GM, Davidson LAG, Fishman AP. The regulation of ventilation in diffuse pulmonary fibrosis. *Am J Med* 1965; 38: 199–216.
88. Turino GM, Lourenco RV, Davidson LAG, Fishman AP. The control of ventilation in patients with reduced pulmonary distensibility. *Ann N Y Acad Sci* 1963; 109: 932–941.
89. Widdicombe JG. Nervous receptors in the respiratory tract and lung. In: Hornbein TD, ed. *Regulation of Breathing. Lung Biology in Health and Disease. Vol. I.* 17th Edn. New York, Marcel Dekker, 1981; pp. 429–472.
90. Paintal AS. Vagal sensory receptors and their reflex effects. *Physiol Rev* 1973; 53: 159–227.
91. Yernault JC, de Jonghe M, de Coster A, Englert M. Pulmonary mechanics in diffuse fibrosing alveolitis. *Bull Eur Physiopathol Respir* 1975; 22: 231–244.
92. Gibson GJ, Pride NB. Pulmonary mechanics in fibrosing alveolitis: the effects of lung shrinkage. *Am Rev Respir Dis* 1977; 116: 637–647.
93. Marciniuk DD, Sridhar G, Clemens RE, Zintel TA, Gallagher CG. Lung volumes and expiratory flow limitation during exercise in interstitial lung disease. *J Appl Physiol* 1994; 77: 963–973.
94. O'Donnell DE, Chau LKL, Webb KA. Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. *J Appl Physiol* 1998; 84: 2000–2009.
95. DeTroyer A, Yernault JC. Inspiratory muscle force in normal subjects and patients with interstitial lung disease. *Thorax* 1980; 35: 92–100.
96. Baydur A, Alsalek M, Louie SG, Sharma OP. Respiratory muscle strength, lung function and dyspnea in patients with sarcoidosis. *Chest* 2001; 210: 102–108.
97. Keogh BA, Lakatos E, Price D, Crystal RG. Importance of the lower respiratory tract in oxygen transfer. Exercise testing in patients with interstitial and destructive lung disease. *Am Rev Respir Dis* 1984; 129: S76–S80.
98. Risk C, Epler GR, Gaensler EA. Exercise alveolar–arterial oxygen pressure difference in interstitial lung disease. *Chest* 1984; 5: 69–74.
99. Johnson RL Jr, Spice WS, Bishop JM, Forster RE. Pulmonary capillary blood volume, flow and diffusing capacity during exercise. *J Appl Physiol* 1960; 15: 893–902.
100. Agusti AGN, Roca J, Gea J, Wagner PD, Zaubet A, Rodriguez-Roisin R. Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1991; 143: 219–225.
101. Hughes JMB, Lockwood DNA, Jones HA, Clark RJ. DLCO/Q and diffusion limitation at rest and on exercise in patients with interstitial fibrosis. *Respir Physiol* 1991; 83: 155–166.
102. Hamer J. Cause of low arterial oxygen saturation in pulmonary fibrosis. *Thorax* 1964; 19: 507–514.
103. Weitzenblum E, Ehrhart M, Rasaholinjanahary I, Hirth C. Pulmonary hemodynamics in idiopathic pulmonary fibrosis and other interstitial pulmonary diseases. *Respiration* 1983; 44: 118–127.
104. Sturani C, Papiris S, Galavotti V, Gunella G. Pulmonary vascular responsiveness at rest and during exercise in idiopathic pulmonary fibrosis: effects of oxygen and nifedipine. *Respiration* 1986; 50: 117–129.

-
105. Lupi-Herrera E, Seoane M, Verdejo J, *et al.* Hemodynamic effects of hydralazine in interstitial lung disease patients with cor pulmonale. *Chest* 1985; 87: 564–573.
 106. Bush A, Busst CM. Cardiovascular function at rest and on exercise in patients with cryptogenic fibrosing alveolitis. *Thorax* 1988; 43: 276–283.
 107. Jezek V, Michalnanik A, Fucik J, Ramaisl R. Long-term development of pulmonary arterial pressure in diffuse interstitial lung fibrosis. *Prog Respir Res* 1985; 20: 170–175.
 108. Hawrylkiewicz I, Izdebska-Makosa Z, Grebska E, Zielinski J. Pulmonary haemodynamics at rest and on exercise in patients with idiopathic pulmonary fibrosis. *Bull Eur Physiopathol Respir* 1982; 18: 403–410.
 109. Enson Y, Thomas HM, Bosken CH, *et al.* Pulmonary hypertension in interstitial lung disease: relation of vascular resistance to abnormal lung structure. *Trans Assoc Am Physicians* 1975; 88: 248–255.
 110. McLees B, Fulmer J, Adair N, *et al.* Correlative studies of pulmonary hypertension in idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1977; 115: 354A.
 111. Baughman PR, Gerson M, Bosken CH. Right and left ventricular function at rest and with exercise in patients with sarcoidosis. *Chest* 1984; 85: 301–306.
 112. Eklund A, Broman L, Broman M, Holmgren A. *V/Q* and alveolar gas exchange in pulmonary sarcoidosis. *Eur Respir J* 1989; 2: 135–144.
 113. Guttadauria M, Ellman H, Kaplan D. Progressive systemic sclerosis: pulmonary involvement. *Clin Rheum Dis* 1979; 5: 151–166.
 114. Hatano S, Strasser T, eds. Primary Pulmonary Hypertension: Report on a World Health Organization Meeting. Geneva, World Health Organization, 1975.
 115. Markowitz DH, Systrom DM. Diagnosis of pulmonary vascular limit to exercise by cardiopulmonary exercise testing. *J Heart Lung Transplant* 2004; 23: 88–95.
 116. Wensel R, Opitz CF, Anker SD, *et al.* Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation* 2002; 106: 319–324.
 117. Sun XG, Hansen JR, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001; 104: 429–435.
 118. Systrom DM, Cockrill BA, Hales CA. Role of cardiopulmonary exercise testing in patients with pulmonary vascular disease. In: Weisman IM, Zeballos RJ, eds. *Clinical Exercise Testing*. Basle, Karger, 2002, pp. 200–204.
 119. Galie N, Torbicki A, Barst R, *et al.* Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; 25: 2243–2278.
 120. Petitpretz P, Brenot F, Azarian R, *et al.* Pulmonary hypertension in patients with human immunodeficiency virus infection: comparison with primary pulmonary hypertension. *Circulation* 1994; 89: 2722–2727.
 121. Edwards BS, Weir EK, Edwards WD, Ludwig J, Dykoski RK, Edwards JE. Coexistent pulmonary and portal hypertension: morphologic and clinical features. *J Am Coll Cardiol* 1987; 10: 1233–1238.
 122. Schaiberger PH, Kennedy TC, Miller FC, Gal J, Petty TL. Pulmonary hypertension associated with long-term inhalation of “crank” methamphetamine. *Chest* 1993; 104: 614–616.
 123. Brenot F, Herve P, Petitpretz P, Parent F, Duroux P, Simonneau G. Primary pulmonary hypertension and fenfluramine use. *Br Heart J* 1993; 70: 537–541.
 124. Abenhaim L, Moride Y, Brenot F, *et al.* Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996; 335: 609–616.
 125. Escribano PM, Sanchez MA, de Atauri MJ, Frade JP, Garcia IM. Lung function testing in patients with pulmonary arterial hypertension. *Arch Bronconeumol* 2005; 41: 380–384.
 126. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Pulmonary function in primary pulmonary hypertension. *J Am Coll Cardiol* 2003; 41: 1028–1035.
 127. Rich S, Dantzker DR, Ayres SM, *et al.* Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987; 107: 216–223.
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128. Riley MS, Pórszász J, Engelen MPK, Wasserman K. Gas exchange response to continuous incremental cycle ergometry exercise in primary pulmonary hypertension in humans. *Eur J Appl Physiol* 2000; 83: 63–70.
 129. Phipps B, Wang G, Chang CHJ, Dunn M. Unexplained severe pulmonary hypertension in the old age group. *Chest* 1983; 84: 399–402.
 130. Meyer FJ, Lossnitzer D, Kristen AV, *et al.* Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2005; 25: 125–130.
 131. Deboeck G, Niset G, Lamotte M, Vachiery JL, Naeije R. Exercise testing in pulmonary arterial hypertension and in chronic heart failure. *Eur Respir J* 2004; 23: 747–751.
 132. Polkey MI, Green M, Moxham J. Measurement of respiratory muscle strength. *Thorax* 1995; 50: 1131–1135.
 133. Rubin LJ. Clinical diagnosis of pulmonary vascular disease. In: Cagle PT, ed. *Diagnostic Pulmonary Pathology*. New York, Marcel Dekker, 2000; pp. 429–436.
 134. Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal PCO_2 abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest* 2005; 127: 1637–1646.
 135. Ting H, Sun XG, Chuang ML, Lewis DA, Hansen JE. A noninvasive assessment of pulmonary perfusion abnormality in patients with primary pulmonary hypertension. *Chest* 2001; 119: 824–832.
 136. Aguggini G, Clement MG, Widdicombe JG. Lung reflexes affecting the larynx in the pig, and the effect of pulmonary microembolism. *Q J Exp Physiol* 1987; 72: 95–104.
 137. Wasserman K, Hansen J, Sue DY, Casaburi R, Whipp B, eds. *Principles of Exercise Testing and Interpretation*. 3rd Edn. Baltimore, MD, Lippincott, Williams and Wilkins, 1999.
 138. Holverda S, Gan CT, Marcus JT, Postmus PE, Boonstra A, Vonk-Noordegraaf A. Impaired stroke volume response to exercise in pulmonary arterial hypertension. *J Am Coll Cardiol* 2006; 47: 1732–1733.
 139. Janicki JS. Influence of the pericardium and ventricular interdependence on left ventricular diastolic and systolic function in patients with heart failure. *Circulation* 1990; 81: Suppl. 2, III15–III20.
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CHAPTER 4

Patterns of response diagnostic for cardiac disease

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Background

As the data from current literature clearly show, the vast majority of cardiopulmonary exercise tests (CPETs) in cardiac diseases are performed in patients with chronic heart failure (CHF). The present chapter will largely focus on this patient group. Cycle ergometry and treadmill exercise are the most frequently used modalities. As discussed in Chapter 5, a higher oxygen uptake ($\dot{V}O_2$) is achieved at peak exercise ($\dot{V}O_{2,\text{peak}}$) with treadmill exercise than with cycle ergometry (~10% greater) due to the larger muscle mass involved, albeit with the same maximal cardiac frequency (f_C) [1]. In addition, as the work performed can only be approximately estimated, it is not possible to accurately characterise the linearity (or otherwise) of the relationship between $\dot{V}O_2$ and work rate (WR) or to estimate work efficiency. It should also be noted that, when the subject is running rather than walking on the treadmill, it is almost impossible to obtain reliable invasive haemodynamic measurements.

Two CPET protocols are usually utilised when testing cardiac patients: the maximal (or symptom-limited) incremental test and the constant-WR test (see Chapter 5).

Exercise pathophysiology in cardiac diseases

Incremental exercise

The incremental exercise test (see Chapter 5 for details) is considered the “gold standard” when studying the cardiovascular, pulmonary and metabolic adaptations to exercise in cardiac patients. This protocol allows the identification of indices of particular prognostic or interventional significance in cardiac disease, such as the lactate threshold (θ_L) and $\dot{V}O_{2,\text{peak}}$, as well as indices derived from particular physiological system responses, such as the slope of the $\dot{V}O_2$ -WR relationship and that of the relationship between minute ventilation ($\dot{V}E$) and carbon dioxide production ($\dot{V}CO_2$).

As discussed previously in Chapter 1, the $\dot{V}O_2$ response in exercise is determined by the product of cardiac output (CO) and the arterio-venous oxygen content difference ($C_{(a-vDO_2)}$) [2]. During incremental exercise, directly measured CO in normal subjects has been shown to increase as a curvilinear function of $\dot{V}O_2$ [3], which contrasts with the linear characteristic seen for steady-state exercise (refer to Chapter 1). This effect is ascribed to CO dynamics which are faster than those of $\dot{V}O_2$ [3]. It is of note that

$C_{(a-vDO_2)}$ increases linearly (rather than hyperbolically; refer to Chapter 1) with $\dot{V}O_2$ when normalised to $\dot{V}O_{2,peak}$ both in normal subjects [2] and in CHF patients [4]. Finally, a linear correlation between peak CO and $\dot{V}O_{2,peak}$ has been reported in CHF patients [5].

As in normal subjects, arterial oxygen content (C_{a,O_2}) increases at higher WRs in CHF patients, because of an increase in haemoglobin (Hb) concentration [4], which promotes oxygen delivery to the exercising muscles. This certainly reflects exercise-induced haemoconcentration, due to an oncotic effect of increased intracellular metabolite levels in muscle, which accounts for ~20% of the increase in $C_{(a-vDO_2)}$ at peak exercise for CHF patients [4]. However, a contribution from splenic contraction cannot be excluded [6]. Indeed, a reduction of spleen size has been documented after exercise in healthy humans [6], and thalassaemic patients who have undergone splenectomy demonstrate less exercise-induced haemoconcentration than nonsplenectomised patients [7]. However, as arterial oxygen tension (P_{a,O_2}) typically operates over the upper flat region of the oxygen dissociation curve during exercise in normal subjects (at least those of average fitness) and CHF patients, any increase in P_{a,O_2} will have little influence on C_{a,O_2} [4].

Therefore, femoral venous and mixed venous oxygen contents fall progressively throughout incremental exercise. This reflects the falling partial pressure of oxygen (PO_2) that occurs with increasing WR, certainly up to θL , with an additional contribution from the rightward shift in the oxygen dissociation curve (Bohr effect) at higher WRs [4, 6, 8]. However, while mixed venous PO_2 continues to decline above θL , any further fall in femoral venous PO_2 becomes insignificant not only in normal subjects [9] but also in CHF patients [8] (fig. 1). This discrepant behaviour reflects a progressively greater contribution to the venous return from blood draining the exercising muscle at higher WRs. In CHF patients, the overall reduction in femoral venous PO_2 and the Bohr effect account for 60 and 20%, respectively, of the $C_{(a-vDO_2)}$ increase at peak exercise [4].

The nadir in the femoral venous PO_2 response appears to be relatively fixed at around 2.39 kPa in normal subjects [10, 11], and has led to the concept of the “critical capillary PO_2 ” [10, 11]. This states that a PO_2 gradient of 2.39 kPa is the lowest gradient able to guarantee oxygen flow from the capillary bed to the mitochondria. However, it should

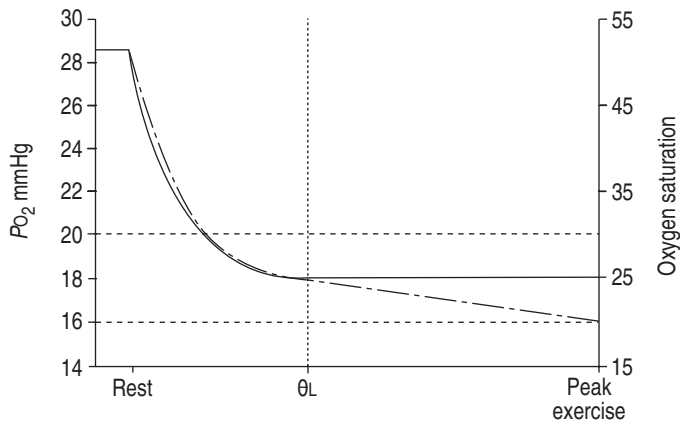


Fig. 1. – Schematic diagram of femoral venous partial pressure of oxygen (PO_2 ; —) and oxygen saturation changes (---) during progressive exercise. θL : lactate threshold.: critical capillary PO_2 (2.39 kPa); -----: upper (2.66 kPa) and lower (2.12 kPa) limits. 1 mmHg=0.133 kPa.

be recognised that, according to the laws of diffusion, there must be, and there is, some oxygen flow below the value of 2.39 kPa. However, in an incremental exercise test, this flow is not enough to guarantee sufficient oxygen delivery for the increasing metabolic rate over the entire WR range. It should also be recognised that the measured femoral venous PO_2 represents a mean value of a large number of muscle fibres whose local ratio of blood flow to metabolic rate vary significantly. Indeed, lower values of femoral venous PO_2 have been reported during submaximal exercise performed with inhalational hypoxia [12]. Furthermore, the nadir in femoral venous PO_2 is more variable in CHF [11]. In some heart failure patients, femoral venous PO_2 actually increases with further increases in WR up to peak exercise, which is suggestive of an intramuscular mismatching of perfusion to metabolic rate. In the current authors' experience, this happens in at least 20% of patients and, more frequently in patients with severe heart failure.

The $C(a-vDO_2)$ at θL is deserving of comment, especially in cardiac patients. At θL , the $C(a-vDO_2)$ is relatively fixed, as both $[Hb]$ and the fall in mixed venous PO_2 are known and the metabolic acidosis has not yet begun. In a large CHF population, $C(a-vDO_2)$ at θL is $12.3 \pm 1.3 \text{ mL} \cdot 100 \text{ mL}^{-1}$ in Class A patients ($\dot{V}O_{2,\text{peak}} > 20 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$), 13.1 ± 2.7 in Class B patients ($\dot{V}O_{2,\text{peak}} 15\text{--}20 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) and 13.4 ± 2.6 in Class C patients ($\dot{V}O_{2,\text{peak}} < 15 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$; Class A = $p < 0.05$ versus Class B and C) [13]. Accordingly, it is possible to estimate CO at θL in CHF patients if simultaneous $\dot{V}O_2$ measurements are made [13].

Finally, when making judgements on the incremental exercise protocol that is most appropriate for a specific CHF patient, several points should be kept in mind. The first is the need for a familiarisation test. This is underscored by a difference of up to 25% in $\dot{V}O_{2,\text{peak}}$ between the first and second test, simply because of a lack of patient confidence with the technique on the first test [14]. Secondly, the WR incrementation rate and hence time needed to reach peak exercise can influence outcome (refer to Chapter 1) [15]. However, these can be particularly difficult to predict in CHF. Recently, the current authors have shown that in a CHF population tested with different incremental protocols aimed at achieving peak exercise in 5, 10 and 15 min while, as expected, exercise time was longer and peak WR lower with the lowest WR incrementation rate (refer to Chapter 1), only peak exercise oxygen pulse, $\dot{V}O_2$ at θL and the $\dot{V}E\text{--}\dot{V}CO_2$ slope were independent of the WR incrementation rate (table 1) [16]. In contrast, $\dot{V}O_{2,\text{peak}}$ and peak f_c , as well as the $\dot{V}O_2\text{--}WR$ slope, were all influenced by the WR incrementation rate. Therefore, for comparison purposes, it is recommended that all tests should reach peak exercise in ~ 10 min and that the test duration should be reported. An additional point to be kept in mind relates to the conventional practice of reporting $\dot{V}O_{2,\text{peak}}$ as the mean over the final 20–30 s of the incremental phase of the test. In CHF, however, because of the presence of a low CO, $\dot{V}O_{2,\text{peak}}$ might be measured at the very beginning of the recovery phase. Finally, in cases of exercise-induced periodic breathing, which may persist until the end of the test, a mean value of $\dot{V}O_{2,\text{peak}}$ needs to be calculated over a longer interval (e.g. 1 min).

Constant WR exercise

Although constant WR protocols can provide valuable additional information to that obtained with an incremental test, with the exception of walking tests, they are not widely utilised in the clinical setting. Patients with CHF, like those with chronic obstructive pulmonary disease, have an impaired ability to utilise oxygen which, at the onset of exercise, depends in part on the kinetics of CO increase. Thus, in cardiac patients, $\dot{V}O_2$ kinetics for constant WR exercise are slower the more severe the exercise impairment [17]. Several kinetic parameters have been used to evaluate $\dot{V}O_2$ kinetics in

TABLE 1 – Cardiopulmonary exercise test responses for the three different endurance tests in heart failure patients

Test min	Peak WR W	Exercise time s	$\dot{V}O_{2,peak}$ $mL \cdot min^{-1} \cdot kg^{-1}$	Peak fc bpm	$\dot{V}O_{2,peak}$ -WR slope $mL \cdot min^{-1} \cdot W^{-1}$	Peak O_2 pulse $mL \cdot min^{-1} \cdot beat^{-1}$	$\dot{V}E_{peak}$ $L \cdot min^{-1}$	$\dot{V}E-\dot{V}CO_2$ slope	θL $mL \cdot min^{-1} \cdot kg^{-1}$
Class C[#]									
5	77±26	323±35	11.8±2.0**	124±24***	7.28±1.12	7.2±1.4	42±12**	38.8±7.0	8.0±2.9
10	76±24	565±39	12.5±1.7	131±26	7.63±1.55	7.3±1.4	46±13	38.0±7.1	9.1±1.9
15	65±20***	899±96	12.3±2.0	126±23*	8.63±1.24***	7.5±1.5	42±13**	37.4±7	8.4±2.1
Class B[*]									
5	111±28**	311±24	16.4±1.7***	125±23***	8.18±0.97***	10.0±3.0	47±10***	32.4±5.8	12.1±2.1
10	106±24	583±43	17.4±1.3	134±20	9.14±1.22	10.0±2.9	54±10	32.3±4.7	11.7±1.5
15	97±27***	860±62	17.6±1.7	132±23	9.81±1.04***	10.1±2.7	54±12	32.7±5.6	12.0±2.0
Class A[†]									
5	154±41	318±31	21.9±2.3***	136±24***	8.96±0.84***	12.6±2.8	54±12***	28.9±4.2	16.2±2.7
10	154±30	600±58	23.2±2.0	146±24	9.74±1.19	12.6±3.0	61±13	28.9±3.5	16.4±2.0
15	150±32*	868±58	23.4±2.4*	151±23*	9.94±0.79	12.3±3.5	66±16**	28.9±5.5	16.3±2.7

Data are presented as mean±sd. WR: work rate; $\dot{V}O_2$: oxygen uptake; fc : cardiac frequency; $\dot{V}E$: minute ventilation; $\dot{V}CO_2$: carbon dioxide production; θL : lactate threshold. Class A: $\dot{V}O_{2,peak} > 20 mL \cdot min^{-1} \cdot kg^{-1}$; Class B: $\dot{V}O_{2,peak} 15-20 mL \cdot min^{-1} \cdot kg^{-1}$; Class C: $\dot{V}O_{2,peak} < 15 mL \cdot min^{-1} \cdot kg^{-1}$. [#]: n=23; [†]: n=39; *: n=28. *: p<0.05 versus 10-min test; **: p<0.01 versus 10-min test; ***: p<0.001 versus 10-min test. Modified from [16] with permission.

CHF, including the $\dot{V}O_2$ time constant (τ) and, as long as the response is a close approximation to exponential, the $\dot{V}O_2$ half time ($t_{1/2}$; refer to Chapter 1). BELARDINELLI *et al.* [18] have shown a good correlation between these kinetic parameters and $\dot{V}O_{2,peak}$ in CHF patients. It is also possible to characterise $\dot{V}O_2$ kinetics in the recovery phase of the test [19]. Above θL , $\dot{V}O_2$ kinetics become more complex because of the additional and delayed “slow component” (refer to Chapter 1). A useful index of the prominence of the $\dot{V}O_2$ slow component, and one which has been used in CHF, is the $\dot{V}O_2$ increment between the 3rd and the 6th min of the test [20]. As each of these indices correlates with exercise performance in CHF, this can remove the need for patients to undergo a symptom-limited incremental test [21].

The distance walked on the 6-min walking test (6MWT; refer to Chapter 7) allows the prediction of prognosis in patients with CHF, New York Heart Association functional class and left ventricular ejection fraction [22, 23]. The correlation between the distance walked on the 6MWT and $\dot{V}O_{2,peak}$ measured on a maximal incremental test ranges 0.54–0.90 [24]. ZUGCK *et al.* [25] have shown that the repeatability of the 6MWT in CHF is high. Changes in the distance walked on the 6MWT have also been utilised in CHF to assess the efficacy of interventions, such as cardiac rehabilitation [26].

CPET indices of relevance for cardiac patients

Several indices of response to incremental tests, either singly or in combination, are relevant in cardiac patients.

$\dot{V}O_{2,peak}$

$\dot{V}O_{2,peak}$ is the most well-known and widely used variable obtained from a CPET. Indeed, as it is often the only test variable that clinicians ask for, this does not help in

promoting the popularity of CPET. In 1985, WEBER and JANICKI [27] reported a still frequently utilised classification of heart failure severity, based on $\dot{V}O_{2,\text{peak}}$. The value of $\dot{V}O_{2,\text{peak}}$ is reported as normalised for body weight, but does not take age, sex or fitness into account. Fitness is an important determinant of exercise capacity in CHF patients. Furthermore, although the study by WEBER and JANICKI [27] reports $\dot{V}O_2$ normalised for body weight, it does not take obese subjects into account. By recognising that fat has a very low metabolic rate, $\dot{V}O_2 \cdot \text{kg}^{-1}$ will, therefore, underestimate the true $\dot{V}O_2$; a better strategy would be to normalise to fat-free mass. This is an important issue for CHF, as obesity is frequently a comorbidity of CHF patients and also CHF can be misdiagnosed in obese subjects.

$\dot{V}O_{2,\text{peak}} < 10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ is associated with a very poor prognosis, while $\dot{V}O_{2,\text{peak}} > 16 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ is associated with a good prognosis. However, there is a wide range of values between these two extremes, making comparisons among such patients difficult. Recognising that $\dot{V}O_{2,\text{peak}}$ is dependent on a range of factors such as body mass, muscle mass, age, sex and degree of training, it is perhaps not surprising that $\dot{V}O_{2,\text{peak}}$ expressed as a percentage of predicted $\dot{V}O_{2,\text{peak}}$ (refer to Chapter 8) provides better prognostic power than the absolute value [28–30]. Unfortunately, performance classifications based on a percentage of $\dot{V}O_{2,\text{peak}}$ are not very popular.

$\dot{V}O_{2,\text{peak}}$ is useful for evaluating the efficacy of treatment if (and sometimes this is not the case) the effects of treatment are reflected in peak exercise performance. A typical example in which peak exercise performance is not a good indicator of treatment efficacy is β -blocker therapy for heart failure. Indeed, although β -blockers are among the most effective treatments for heart failure with respect, for example, to improving quality of life and prognosis, they do not improve peak exercise performance [31–35]. Also, it is likely that CHF patients treated with biventricular pacemakers do not significantly improve $\dot{V}O_{2,\text{peak}}$ as much as other clinical and echocardiographic parameters due to the fixed and low f_C at peak exercise.

Lactate threshold

This is defined as the $\dot{V}O_2$ at which the criteria for θ_L discrimination are met (refer to Chapters 1 and 2). θ_L is a good indicator of exercise capacity in CHF patients, for whom its estimation is independent of exercise duration, at least in the range 5–15 min [16]. As described in Chapters 1 and 2, the recommended approach for noninvasive estimation of θ_L is to identify the intersection of the S1 and S2 regions of the $\dot{V}CO_2$ – $\dot{V}O_2$ relationship (the “V-slope” plot) [36, 37], coupled with additional supporting criteria to establish the presence of hyperventilation relative to oxygen but not carbon dioxide, *i.e.* an increase in the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) and end-tidal PO_2 , with no increase in the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) or decrease in end-tidal (PCO_2) [38]. It is important to note that the response profiles early in the test may be influenced by psychologically induced hyperventilation, particularly in patients with a severe exercise limitation, which can predispose to the generation of a “false positive” or “pseudo-threshold” [39]. In CHF patients, θ_L can be difficult to identify in some cases. For example, a gradual adjustment of peripheral muscle metabolism may occur, making θ_L more of a zone rather than more of a true threshold. Furthermore, the presence of exercise-induced periodic breathing (*i.e.* a cyclic variation of $\dot{V}E$ with a period of ~ 60 s), often evident in patients with severe heart failure, can make the V-slope break-point difficult to discern. Therefore, it is strongly recommended that, in CHF patients, the θ_L value estimated from the V-slope criterion is confirmed by the other recommended supporting criteria. However, θ_L is rarely utilised by itself to quantify exercise capacity in CHF, but more often is used as an accessory tool.

$\dot{V}O_2$ –WR relationship

The slope of the $\dot{V}O_2$ –WR relationship for incremental exercise is often used to make inferences about cardiovascular performance. The lower the $\dot{V}O_2$ –WR slope, the worse the performance is likely to be, as less energy is produced aerobically. However, the $\dot{V}O_2$ –WR slope is normally relatively invariant, for example, being unaffected by high levels of fitness. In CHF, the $\dot{V}O_2$ –WR relationship may flatten at higher WRs [40], which is to be expected in conditions in which the CO and/or muscle/blood flow response during exercise is abnormally low. In some patients, the $\dot{V}O_2$ –WR relationship shows two distinct regions, with the lower region having a slope in the normal range ($\sim 10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{W}^{-1}$) and the upper region having a reduced slope. This is suggestive of effort-induced cardiac ischaemia or mitral regurgitation, which result in inadequate oxygen availability to the exercising muscle [40]. Figure 2c is an example of an asymptomatic patient with effort-induced ischaemia; above the ischemic threshold, the $\dot{V}O_2$ –WR relationship is flatter. Figure 2b presents a case of a so called “false-positive” test for cardiac ischaemia in a subject with normal coronary angiography; note the normal $\dot{V}O_2$ –WR relationship. An upward shift of the $\dot{V}O_2$ –WR relationship with a normal slope is found in obese subjects who do not have a cardiovascular deficit, reflective of the increased oxygen cost of moving the abnormally large mass of the lower limbs.

$\dot{V}O_2$ –fC relationship and oxygen pulse

The profiles of the $\dot{V}O_2$ –fC relationship and the oxygen pulse (*i.e.* $\dot{V}O_2$ –fC) are considered indices of cardiac performance in exercise [41–43]. Indeed, the oxygen pulse is stroke volume multiplied by the $C_{(a-vDO_2)}$, and it is often used as a surrogate measurement of stroke volume; although this is only justified when either $C_{(a-vDO_2)}$ can reasonably be assumed not to be changing or when it is actually known (refer to Chapter 1). The normal oxygen pulse response for incremental exercise is hyperbolic as a function of $\dot{V}O_2$ with the slope becoming progressively shallower as WR increases. This is predictable from the fact that the linear $\dot{V}O_2$ –fC relationship has a positive intercept on the fC axis (refer to Chapter 2). Therefore, for all but the initial portion of the incremental test, it is tachycardia that supports the CO increment. This is not the case in the presence of atrial fibrillation, however, for which fC increases at the beginning of exercise (and mainly in the first minute or so). The finding of a $\dot{V}O_2$ –fC relationship (or of its last portion) that extrapolates to the origin means that it is fC and not stroke volume that contributes to the $\dot{V}O_2$ increase.

Peak exercise oxygen pulse is typically low in CHF patients. However, therapy such as β -blockers, digitalis, amiodarone and biventricular pacemakers, because of their actions on peak exercise fC, tend to normalise the oxygen pulse; this does not, of course, imply a normalisation of CO. Another surrogate of left ventricular performance is the cardiac power which is calculated as the product of $\dot{V}O_2$ and systolic blood pressure [43, 44].

Cardiac output

In CHF patients, measurement of CO during exercise is important in defining the severity of the disease [27, 45–47] and its prognosis [48–52], and to tailor the most efficient therapy for each patient [51, 53]. Indeed, exercise haemodynamics have a better prognostic value than $\dot{V}O_{2,\text{peak}}$ and other noninvasive exercise variables [48–51]. In particular, CHOMSKY *et al.* [50] and METRA *et al.* [51] showed that a number of patients have a good prognosis, despite a low $\dot{V}O_{2,\text{peak}}$, if the CO increase during exercise is preserved. It is likely that those patients with low $\dot{V}O_{2,\text{peak}}$ and a preserved CO increase

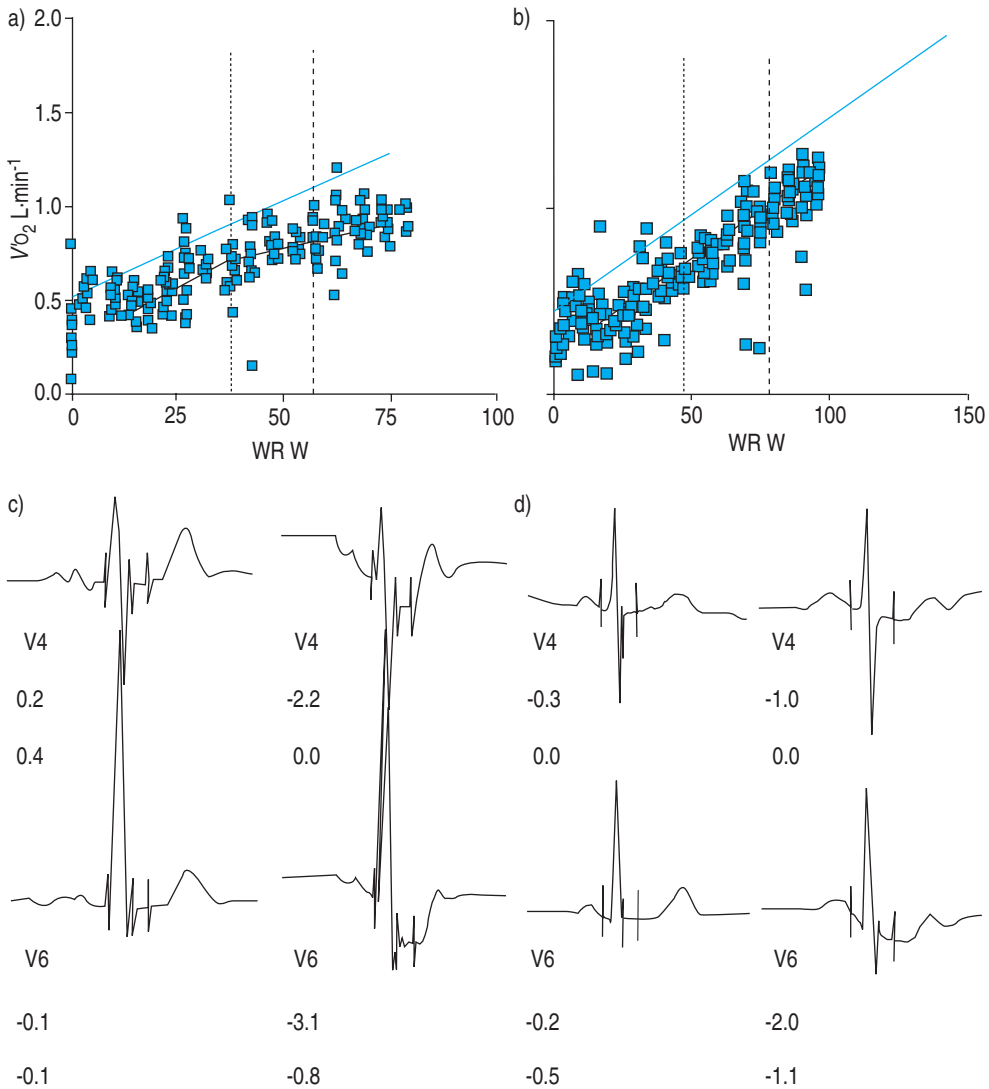


Fig. 2. – Oxygen uptake ($\dot{V}O_2$)–work rate (WR) relationship in a patient with exercise-induced a, c) silent cardiac ischaemia and three-vessel coronary artery disease, and b, d) ST changes resembling silent cardiac ischaemia (false-positive test). Above the lactate threshold (-----) and the ischemic threshold (·····) the $\dot{V}O_2$ –WR relationship flattens. c, d) ECGs at rest (left-hand panels) and peak exercise (right-hand panels). c) ECG shows ST depression at peak exercise. d) This subject has a normal coronary artery anatomy at angiography. The $\dot{V}O_2$ –WR relationship remains in the normal range throughout the test.

during exercise are those with more severe muscular deconditioning [50]. At present, however, no data regarding the use of the CO response to exercise as a tool to assess therapeutic efficacy are available. This is due to the invasive nature of CO determination during exercise, which severely limits the capability of repeating the measurements. As reported previously, it is not possible to estimate CO from $\dot{V}O_2$ kinetics during exercise in CHF, except possibly at 0L [13]. Therefore, in CHF patients, the actual measurement of CO is needed during exercise.

The ideal method for determining CO during an exercise test should be safe, reliable, repeatable and preferably cheap. Unfortunately, at present, reliable CO measurement techniques are invasive and therefore potentially dangerous, difficult to repeat and expensive. Among the invasive techniques for CO determination, the direct Fick method is considered the gold standard, while thermodilution is probably the most frequently used [54, 55]. To date, CO is not routinely measured in exercise testing laboratories. Indeed, the noninvasive techniques for CO determination, such as the single-breath acetylene method [56, 57], the carbon dioxide rebreathing methods [58–61], methods based on impedance cardiography [62] and pulse contour analysis [63] have all been proven to be less reliable during exercise. In contrast, the inert-gas rebreathing technique with continuous analysis of expired gas concentrations is a reliable, safe and inexpensive method to obtain noninvasive measurements of pulmonary blood flow; *i.e.* corresponding to CO in the absence of any vascular shunt [64]. This method seems promising and might open a new era of CO measurements during exercise and extend CPET interpretation.

Simultaneous measurements of $\dot{V}O_2$ and CO during exercise are useful because they allow the calculation of $C_{(a-vDO_2)}$ and, therefore, the construction of the $CO-C_{(a-vDO_2)}$ relationship against the frame of reference of superimposed $\dot{V}O_2$ isopleths [2]. This plot is important for CHF patients because it helps to discriminate between exercise limitation due to altered left ventricular pump function and from other causes (mainly muscle deconditioning) [65]. Indeed, in the former case, the CO increase at a particular level of $\dot{V}O_2$ is limited by the maximal possible widening of $C_{(a-vDO_2)}$ while, in the latter, the CO increase is greater with a less prominent widening of the $C_{(a-vDO_2)}$. STRINGER *et al.* [2] presented the $CO-C_{(a-vDO_2)}-\dot{V}O_2$ characteristic for both healthy subjects and CHF patients pooled from different studies (fig. 3) [5, 27, 66]. For a given $\dot{V}O_2$, CHF patients are expected to have a lower CO and therefore a greater $C_{(a-vDO_2)}$ when compared with normal subjects. This pattern is progressive as heart failure severity increases [4]. The $CO-C_{(a-vDO_2)}-\dot{V}O_2$ plot should be able to distinguish deconditioned heart failure patients from those with a better degree of fitness [4]. This is important when selecting the most appropriate patients for intensive cardiac rehabilitation programmes. Indeed, although muscle deconditioning is extremely frequent in CHF, so far it has been difficult to both diagnose and quantify. Therefore, it is appropriate to note that a new noninvasive inert-gas rebreathing technique for measuring CO during exercise has recently been developed and proved to be reliable for heart failure patients [67]. However, albeit the clinical application of the $CO-C_{(a-vDO_2)}-\dot{V}O_2$ graphical analysis has potential, assessment of its usefulness in evaluating the effects of exercise training and other heart failure therapies is still lacking.

Ventilatory response

The progressive increase of $\dot{V}E$ during incremental exercise is largely due to tidal volume ($\dot{V}_T$) increase at low WRs, with respiratory frequency (f_R) contributions becoming more important at higher WRs (refer to Chapter 1). In patients with atrial fibrillation but without other cardiac disease, the so-called “lone fibrillation”, the increase in $\dot{V}E$ during exercise is a little higher than in normal subjects, is shown by an increased slope of the $\dot{V}E-\dot{V}'CO_2$ relationship and an increased $\dot{V}E/\dot{V}'CO_2$ value at θ_L . Indeed, abnormal hyperventilation is a striking characteristic of the integrated response to exercise in CHF patients [68–70]. At a given WR, CHF patients evidence a higher $\dot{V}E$ than normal subjects [68], the result of an exaggerated f_R response and a truncated $\dot{V}_T$ response (fig. 4). Several observations relate heart failure severity to hyperventilation: 1) hyperventilation is associated with dyspnoea, one of the most common symptoms of

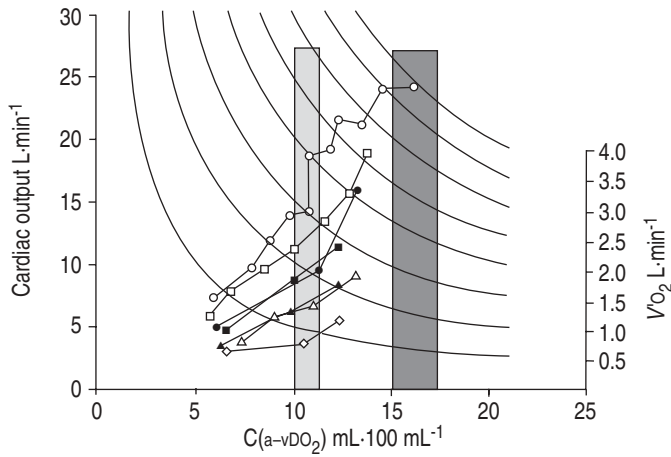


Fig. 3. – Cardiac output *versus* arterio–venous oxygen content difference ($C(a-vDO_2)$)/oxygen uptake ($\dot{V}O_2$) in normal and chronic heart failure (CHF) patients. ■: lactic anaerobic threshold; ■: peak $\dot{V}O_2$. ○: normal subjects ($\dot{V}O_{2,peak}$ 3.91 ± 0.68 L·min⁻¹); □: normal subjects, Sullivan Study ($\dot{V}O_{2,peak}$ 2.41 ± 0.61 L·min⁻¹); △: CHF, Sullivan Study ($\dot{V}O_{2,peak}$ 1.06 ± 0.36 L·min⁻¹); ●: CHF Class A, Weber Study; ■: CHF Class B, Weber Study; ▲: CHF Class C, Weber Study; ◇: CHF Class D, Weber Study. The sloping solid lines are iso $\dot{V}O_2$. Reproduced from [2] with permission.

CHF patients [69, 71]; 2) an abnormally increased $\dot{V}E$ requirement is one of the limiting factors of exercise capacity [72–74]; and 3) a low ventilatory efficiency, defined as a high $\dot{V}E$ relative to $\dot{V}'CO_2$, is a strong negative prognostic predictor, independent of peak $\dot{V}'O_2$ [75, 76].

Hyperventilation during exercise in CHF may be due to several causes including: 1) alteration of lung mechanics; 2) reduced lung diffusion; and 3) increased ventilatory requirements, *e.g.* resulting from an increased $\dot{V}'CO_2$ and/or increased dead space volume (V_D)/ V_T or decreased ventilatory efficiency. A further cause may arise from exacerbated sensitivity of reflexes from muscle metaboreceptors, baroreceptors and chemoreceptors [77–80], all of which are part of the widespread derangement of cardiovascular reflex control in CHF [76]. As discussed in Chapter 1, $\dot{V}E$ at sea-level increases in direct proportion to $\dot{V}'CO_2$ with a slope that is inversely proportional to arterial PCO_2 (P_{a,CO_2}) and directly proportional to V_D/V_T :

$$\dot{V}E = \dot{V}'CO_2 \times 863 / (P_{a,CO_2} \times (1 - V_D/V_T)) \quad (1)$$

In CHF, hyperventilation is associated with an increased V_D/V_T and $\dot{V}'CO_2$ and a lower P_{a,CO_2} , when compared with similar normal subjects at a similar per cent of $\dot{V}'O_{2,peak}$ [68].

The $\dot{V}E$ – $\dot{V}'CO_2$ relationship for incremental exercise is normally linear up to and beyond θ_L , specifically up to the “respiratory compensation point” (refer to Chapter 1). Respiratory compensation becomes evident as an increase in the $\dot{V}E$ – $\dot{V}'CO_2$ slope as P_{a,CO_2} is driven down largely, if not exclusively, by the stimulatory effects of the metabolic acidosis [81]. Over the linear phase of the $\dot{V}E$ – $\dot{V}'CO_2$ relationship, for which P_{a,CO_2} is normally stable, the profile of $\dot{V}E/\dot{V}'CO_2$ closely reflects that of V_D/V_T , *i.e.* providing information on ventilatory efficiency. This is not the case at higher WRs.

More detailed information about ventilatory abnormalities during exercise in CHF is provided by analysis of the spontaneous expiratory flow–volume loop relative to the maximal forced curve (refer to Chapter 3). JOHNSON *et al.* [82] showed that the expiratory flow reserve in CHF patients was dramatically reduced in exercise, with increases in end-expiratory lung volume (EELV) being the only means of supporting

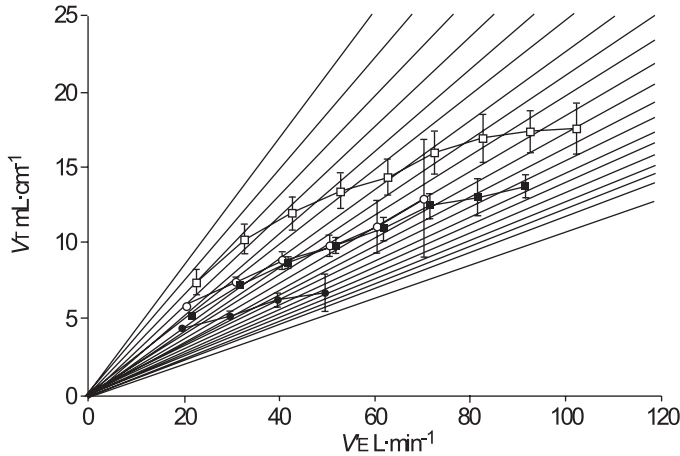


Fig. 4. – Tidal volume (V_t) normalised for height as a function of minute ventilation ($\dot{V}_E$) during exercise in normal subjects ($\square$) and in heart failure patients with severe ($\bullet$: peak oxygen uptake ($\dot{V}O_{2,\text{peak}}$) $<12 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$), moderate-to-severe ($\circ$: $\dot{V}O_{2,\text{peak}}$ $12\text{--}16 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) and moderate ($\blacksquare$: $\dot{V}O_{2,\text{peak}}$ $<16 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) exercise limitation. Individual lines represent respiratory rate. Reproduced from [68] with permission.

further increases in flow and hence $\dot{V}_E$ (*i.e.* “dynamic hyperinflation”; refer to Chapter 3). This is illustrated in figure 5a, where the responses of a normal subject during progressive exercise show a progressive reduction in EELV as WR increases, with no evidence of the spontaneous flow–volume loop impacting on the maximal expiratory curve (*i.e.* no flow limitation). In contrast, in a patient with CHF (fig. 5b), the spontaneous flow–volume loop quickly reached the maximal flow–volume, exhausting the expiratory flow reserve and, therefore, requiring an increase in EELV.

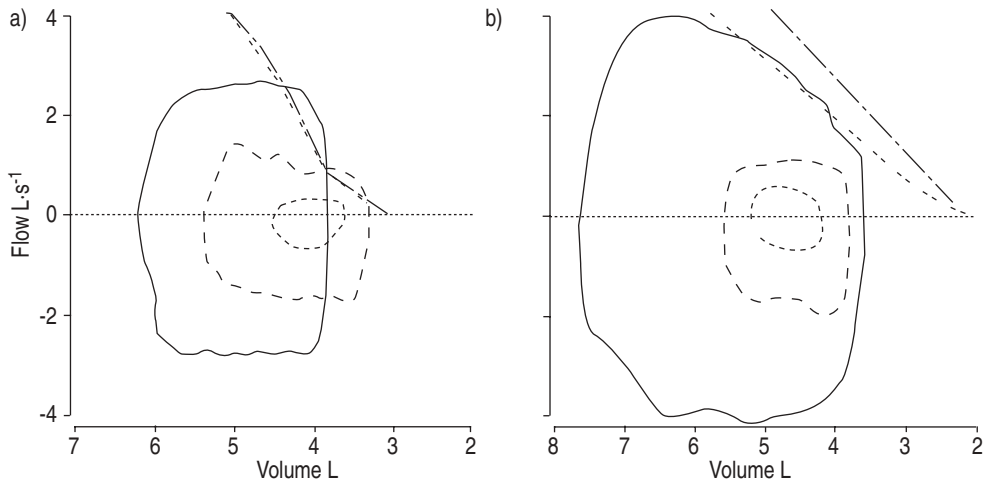


Fig. 5. – Flow–volume loops during exercise in a) a heart failure patient and b) a normal subject. -----: Rest; ----: 40% of peak exercise; —: peak exercise. Partial forced expiratory flows recorded at rest before ($\cdots \cdots$) and immediately after ($- \cdot -$) peak exercise. Reproduced from [74] with permission.

Furthermore, post-exercise in the normal subject, the maximal flow–volume loop is increased due to airway expansion; this was not the case in heart failure [74].

Several therapeutic interventions affect the ventilatory response to exercise in CHF patients. Angiotensin-converting enzyme (ACE) inhibitors, but not angiotensin (AT)1 receptor blockers, improve lung diffusion due to an increase in bradykinin levels [83–86]. However, both ACE inhibitors and AT1 blocking agents improve exercise performance, but most likely through different mechanisms [85]. Without affecting exercise performance, β -blockers reduce exercise-induced hyperventilation, as shown by a lower $\dot{V}_E$ – $\dot{V}_{CO_2}$ slope, consequent to an increase in the carbon dioxide set-point [86]. This would be consistent with a reduction of previously hypersensitive reflex responses (see above). Anti-aldosterone drugs improve lung diffusion as well as exercise performance [87]. Ultra-filtration, a dialysis technique used to reduce the body fluid content, improves lung mechanics but not lung diffusion, and increases exercise tolerance [73, 88, 89].

Conclusion

In CHF patients, compared with age-matched healthy individuals, CPET typically reveals reductions in peak WR, $\dot{V}_{O_{2,peak}}$, θ_L , $\dot{V}_{O_2}$ –WR slope, oxygen pulse at any given WR and the increment in $\dot{f}C$ between rest to peak exercise. Importantly, changes in ventilatory efficiency, an increased $\dot{V}_E$ – $\dot{V}_{CO_2}$ slope and dynamic hyperinflation (increased EELV) at peak exercise can be observed. In the presence of atrial fibrillation, the exercise-induced increase of $\dot{f}C$ mainly occurs at the beginning of exercise while in the case of transient cardiac ischaemia the slope of the $\dot{V}_{O_2}$ –WR relationship shows an abrupt reduction. In clinical practice, the detection of the magnitude of changes from normal is very useful for correct functional and prognostic evaluation of patients with CHF.

Summary

A cardiopulmonary exercise test (CPET) is often used in the functional and prognostic evaluation of patients with heart disease. As exercise tolerance cannot be predicted from resting cardiac and pulmonary function tests (*e.g.* echocardiography, spirometry), a CPET is particularly useful to properly evaluate the degree of exercise limitation and to identify its underlying causes. Furthermore, CPET is a very important tool in assessing the prognosis of cardiac patients, choosing the most effective treatment and evaluating the response to treatment.

Keywords: Cardiac output, chronic heart failure, oxygen uptake, prognosis, ventilatory equivalents.

References

1. Myers J, Buchanan N, Walsh D, *et al.* Comparison of the ramp *versus* standard exercise protocols. *J Am Coll Cardiol* 1991; 17: 1334–1342.
2. Stringer WW, Hansen JE, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. *J Appl Physiol* 1997; 82: 908–912.

3. Stringer W, Whipp B, Wasserman K, Christenson P, French W. Non-linear cardiac output dynamics during ramp-incremental cycle ergometry. *Eur J Appl Physiol* 2005; 93: 634–639.
4. Perego GB, Marenzi M, Guazzi M, *et al.* Contribution of PO₂, P₅₀, and Hb to changes in arteriovenous O₂ content during exercise in heart failure. *J Appl Physiol* 1996; 80: 623–631.
5. Lang C, Katlin P, Haythe J, Tsao L, Mancini D. Ease of non invasive measurements of cardiac output coupled with peak VO₂ determination at rest and during exercise in patients with heart failure. *Am J Cardiol* 2007; 99: 404–405.
6. Agostoni PG, Wasserman K, Guazzi M, *et al.* Exercise-induced hemoconcentration in heart failure due to dilated cardiomyopathy. *Am J Cardiol* 1999; 83: 278–280.
7. Agostoni P, Cerino M, Palermo P, *et al.* Exercise capacity in patients with β -thalassaemia intermedia. *Br J Haem* 2005; 131: 278–281.
8. Stringer WW, Wasserman K, Casaburi R, *et al.* Lactic acidosis as a facilitator of oxyhaemoglobin dissociation during exercise. *J Appl Physiol* 1994; 76: 1462–1467.
9. Agostoni PG, Wasserman K, Perego GB, *et al.* Oxygen transport to muscle during exercise in chronic congestive heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; 79: 29–33.
10. Wittenberg BA, Wittenberg JB. Transport of oxygen in muscle. *Annu Rev Physiol* 1989; 51: 857–878.
11. Koike A, Wasserman K, Taniguchi K, Hiroe M, Marumo F. Critical capillary oxygen partial pressure and lactate threshold in patients with cardiovascular disease. *J Am Coll Cardiol* 1994; 23: 1644–1650.
12. Richardson RS, Knight DR, Poole DC, *et al.* Determinants of maximal exercise VO₂ during single leg knee-extensor exercise in humans. *Am J Physiol* 1995; 268: H1453–H1461.
13. Agostoni PG, Wasserman K, Perego GB, *et al.* Non-invasive measurement of stroke volume during exercise in heart failure patients. *Clin Sci* 2000; 98: 545–551.
14. Elborn JS, Stanford CF, Nicholls DP. Reproducibility of cardiopulmonary parameters during exercise in patients with chronic cardiac failure. The need for a preliminary test. *Eur Heart J* 1990; 11: 75–81.
15. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. *J Appl Physiol* 1983; 55: 1558–1564.
16. Agostoni PG, Bianchi M, Moraschi A, *et al.* Work rate affects cardiopulmonary exercise test results in heart failure. *Eur J Heart Fail* 2005; 7: 498–504.
17. Koike A, Yajima T, Adachi H, *et al.* Evaluation of exercise capacity using submaximal exercise at a constant work rate in patients with cardiovascular disease. *Circulation* 1995; 81: 1719–1724.
18. Belardinelli R, Zhang YY, Wasserman K, Purcaro A, Agostoni PG. A four-minute submaximal constant work rate exercise test to assess cardiovascular functional class in chronic heart failure. *Am J Cardiol* 1998; 81: 1210–1214.
19. Tanabe Y, Takahashi M, Hosaka Y, Ito M, Ito E, Suzuki H. Prolonged recovery of cardiac output after maximal exercise in patients with chronic heart failure. *J Am Coll Cardiol* 2000; 35: 1228–1236.
20. Zhang YY, Wasserman K, Sietsema KE, *et al.* O₂ uptake kinetics in response to exercise. A measure of tissue anaerobiosis in heart failure. *Chest* 1993; 103: 735–741.
21. Sietsema KE, Daly JA, Wasserman K. Early dynamics of O₂ uptake and heart rate as affected by exercise work rate. *J Appl Physiol* 1989; 67: 2535–2541.
22. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: Guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
23. Bitter V, Weiner DH, Yusuf S, *et al.* Predictors of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. *JAMA* 1993; 270: 1702–1707.
24. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests in the cardiorespiratory domain. *Chest* 2001; 119: 256–270.
25. Zugck C, Kruger C, Durr S, *et al.* Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? *Eur Heart J* 2000; 21: 540–549.
26. Shepard R. Exercise for patients with congestive heart failure. *Sports Med* 1997; 23: 75–92.

-
27. Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. *Am J Cardiol* 1985; 55: 22A–31A.
 28. Stelken AM, Younis LT, Jennison SH, *et al*. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. *J Am Coll Cardiol* 1996; 27: 345–352.
 29. Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *Am J Cardiol* 1987; 59: 634–638.
 30. Aaronson KD, Mancini DM. Is percentage of predicted maximal exercise oxygen consumption a better predictor of survival than peak exercise oxygen consumption for patients with severe heart failure? *J Heart Lung Transplant* 1995; 14: 981–989.
 31. Packer M, Bristow MR, Cohn JN, *et al*. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996; 334: 1349–1355.
 32. Colucci WS, Packer M, Bristow MR, *et al*. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. *Circulation* 1996; 94: 2800–2806.
 33. Packer M, Fowler MB, Roecker EB, *et al*. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002; 106: 2194–2199.
 34. Lechat P, Hulot JS, Escolano S, *et al*. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. *Circulation* 2001; 103: 1428–1433.
 35. Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1997; 30: 27–34.
 36. Sullivan MJ, Cobb FR. The anaerobic threshold in chronic heart failure. Relation to blood lactate, ventilatory basis, reproducibility, and response to exercise training. *Circulation* 1990; 81: 47–58.
 37. Beaver WL, Wasserman K, Whipp BJ. Improved detection of lactate threshold during exercise using a log-log transformation. *J Appl Physiol* 1985; 59: 1936–1940.
 38. Whipp BJ, Ward SA, Wasserman K. Respiratory markers of the anaerobic threshold. *Adv Cardiol* 1986; 35: 47–64.
 39. Whipp BJ. Physiological mechanisms dissociating pulmonary CO₂ and O₂ exchange dynamics during exercise. *Exp Physiol* 2007; 92: 347–355.
 40. Berardinelli R, Lacalaprice F, Carle F, *et al*. Exercise-induced myocardial ischemia detected by cardiopulmonary exercise testing. *Eur Heart J* 2003; 24: 1304–1313.
 41. Goerg R, Reinicke H, Daum S. The oxygen pulse coefficient: an index of physical working capacity. *Bull Eur Physiopathol Respir* 1979; 15: 135–142.
 42. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Clinical applications of cardiopulmonary exercise testing. In: Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ, eds. *Principle of Exercise Testing and Interpretation*. 3rd Edn. Philadelphia, Lippincott Williams, 1999; pp. 77–78.
 43. Williams SG, Cooke GA, Wright DJ, *et al*. Peak exercise cardiac power output. A direct indicator of cardiac function strongly predictive of prognosis in chronic heart failure. *Eur Heart J* 2001; 22: 1496–1503.
 44. Cotter G, Williams SG, Vered Z, Tan LB. Role of cardiac power in heart failure. *Curr Opin Cardiol* 2003; 18: 215–222.
 45. Franciosa JA, Ziesche S, Wilen M. Functional capacity of patients with chronic left ventricular failure. Relationship of bicycle exercise performance to clinical and hemodynamic characterization. *Am J Med* 1979; 67: 460–466.
 46. Weber KT, Kinasewitz GT, Janicki JS, Fishman AF. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982; 65: 1213–1223.
 47. Gelber HJ, Rubin SA, Ports TA, Brundage BH, Parmley WW, Chatterjee K. Detection of left ventricular functional reserve by supine exercise hemodynamics in patients with severe, chronic heart failure. *Am J Cardiol* 1979; 44: 1062–1067.
-

48. Griffin BP, Shah PK, Ferguson J, Rubin SA. Incremental prognostic value of exercise hemodynamic variables in chronic congestive heart failure secondary to coronary artery disease or to dilated cardiomyopathy. *Am J Cardiol* 1991; 67: 848–853.
49. Roul G, Moulichon ME, Bareiss P, *et al.* Prognostic factors of chronic heart failure in NYHA class II or III: value of invasive exercise haemodynamic data. *Eur Heart J* 1995; 16: 1387–1398.
50. Chomsky DB, Lang CC, Rayos GH, *et al.* Haemodynamic exercise testing. A valuable tool in the selection of cardiac transplantation candidates. *Circulation* 1996; 94: 3176–3183.
51. Metra M, Faggiano P, D'Aloia A, *et al.* Use of cardiopulmonary exercise testing with haemodynamic monitoring in the prognostic assessment of ambulatorial patients with chronic heart failure. *J Am Coll Cardiol* 1999; 33: 943–950.
52. Myers J, Gullestad L, Vagelos R, *et al.* Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med* 1998; 129: 286–293.
53. Leier CV, Patrick TJ, Hermiller J, *et al.* Nifedipine in congestive heart failure: effects on resting and exercise hemodynamics and regional blood flow. *Am Heart J* 1984; 108: 1461–1468.
54. Lipkin DP, Poole-Wilson PA. Measurement of cardiac output during exercise by the thermodilution and direct Fick techniques in patients with chronic congestive heart failure. *Am J Cardiol* 1985; 56: 321–324.
55. Nakanishi N, Yoshioka T, Okano Y, Nishimura T. Continuous Fick cardiac output measurement during exercise by monitoring of mixed venous oxygen saturation and oxygen uptake. *Chest* 1993; 104: 419–426.
56. Elkayam U, Wilson AF, Morrison J, *et al.* Noninvasive measurement of cardiac output by single breath constant expiratory technique. *Thorax* 1984; 39: 107–113.
57. Zenger MR, Brenner M, Haruno M, Mahon D, Wilson AF. Measurement of cardiac output by automated single-breath technique, and comparison with thermodilution and Fick methods in patients with cardiac disease. *Am J Cardiol* 1993; 71: 105–109.
58. Jones NL, Campbell EJM, McHardy GJR, Higgs BE, Clode M. The estimation of carbon dioxide pressure of mixed venous blood during exercise. *Clin Sci* 1967; 32: 311–327.
59. Van Herwaarden A, Binkhorst RA, Fennis JFM, Laar A. Reliability of the cardiac output measurement. The indirect Fick-principle for CO₂ during exercise. *Pflugers Arch* 1980; 385: 21–23.
60. Klausen K. Comparison of CO₂ rebreathing and acetylene methods for cardiac output. *J Appl Physiol* 1965; 20: 763–766.
61. Farhi LE, Nesarajah MS, Olszowka AJ, Metildi LA, Ellis AK. Cardiac output determination by simple one-step rebreathing technique. *Respir Physiol* 1976; 28: 141–159.
62. Sramek BB. Thoracic electrical bioimpedance measurement of cardiac output. *Crit Care Med* 1994; 22: 1337–1339.
63. Stok WJ, Baisch F, Hillebrecht A, Schulz H, Meyer M, Karemaker J. Noninvasive cardiac output measurement by arterial pulse analysis compared with inert gas rebreathing. *J Appl Physiol* 1993; 74: 2687–2693.
64. Sackner MA, Greeneltch D, Heiman MS, Epstein S, Atkins N. Diffusing capacity, membrane diffusing capacity, capillary blood volume, pulmonary tissue volume, and cardiac output measurement by a rebreathing technique. *Am Rev Respir Dis* 1975; 111: 157–165.
65. Cohn JN, Johnson GR, Shabetai R, *et al.* Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993; 87: VI5–VI6.
66. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. *Circulation* 1989; 80: 769–781.
67. Agostoni P, Cattadori G, Apostolo A, *et al.* Noninvasive measurements of cardiac output during exercise by inert gas rebreathing technique: a new tool for heart failure evaluation. *Am J Coll Cardiol* 2005; 46: 1779–1781.

-
68. Wasserman K, Zhang Y, Gitt A, *et al.* Lung function and exercise gas exchange in chronic heart failure. *Circulation* 1997; 96: 2221–2227.
 69. Sullivan MJ, Higginbotham MB, Cobb FR. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation* 1988; 77: 552–559.
 70. Metra M, Dei Cas L, Panina G, Visioli O. Exercise hyperventilation chronic congestive heart failure, and its relation to functional capacity and hemodynamics. *Am J Cardiol* 1992; 70: 622–628.
 71. Lipkin DP, Poole-Wilson PA. Symptoms limiting exercise in chronic heart failure. *Br Med J Clin Res* 1986; 292: 1030–1031.
 72. Myers J, Salleh A, Buchanan N, *et al.* Ventilatory mechanisms of exercise intolerance in chronic heart failure. *Am Heart J* 1992; 124: 710–719.
 73. Agostoni PG, Marenzi GC, Pepi M, *et al.* Isolated ultrafiltration for moderate heart failure. *J Am Coll Cardiol* 1993; 21: 424–431.
 74. Agostoni P, Pellegrino R, Conca C, Rodarte J, Brusasco V. Exercise hyperpnea in chronic heart failure: relation to lung stiffness and exercise flow limitation. *J Appl Physiol* 2002; 92: 1409–1416.
 75. Kleber FX, Vietzke G, Wernecke KD, *et al.* Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation* 2000; 101: 2803–2809.
 76. Ponikowski P, Chua TP, Piepoli M, *et al.* Augmented peripheral chemosensitivity as a potential input to baroreflex impairment and autonomic imbalance in chronic heart failure. *Circulation* 1997; 96: 2586–2594.
 77. Chua TP, Clark AL, Amadi AA, Coats AJ. Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1996; 27: 650–657.
 78. Chua TP, Harrington D, Ponikowski P, Webb-Peploe K, Poole-Wilson PA, Coats AJ. Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol* 1997; 29: 147–152.
 79. Ponikowski P, Francis DP, Piepoli MF, *et al.* Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation* 2001; 103: 967–972.
 80. Scott AC, Francis DP, Coats AJS, Piepoli MF. Reproducibility of the measurement of the muscle ergoreflex activity in chronic heart failure. *Eur J Heart Fail* 2003; 5: 453–461.
 81. Wasserman K, Whipp BJ, Koyal SN, Cleary M. Effect of carotid body resection on ventilatory and acid-base control during exercise. *J Appl Physiol* 1975; 39: 354–358.
 82. Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation during exercise. The exercise tidal flow-volume loop. *Chest* 1999; 116: 488–503.
 83. Wilson IR, Ferraro N. Effect of the renin-angiotensin system on limb circulation and metabolism during exercise in patients with chronic heart failure. *J Am Coll Cardiol* 1985; 6: 556–563.
 84. Hamroff G, Katz SD, Mancini D, *et al.* Addition of angiotensin II receptor blockade to maximal angiotensin-converting enzyme inhibition improves exercise capacity in patients with severe congestive heart failure. *Circulation* 1999; 99: 990–992.
 85. Guazzi M, Marenzi GC, Alimento M, Contini M, Agostoni PG. Improvement of alveolar-capillary membrane diffusing capacity with enalapril in chronic heart failure and counteracting effect of aspirin. *Circulation* 1997; 95: 1930–1936.
 86. Agostoni P, Guazzi M, Bussotti M, De Vita S, Palermo P. Carvedilol reduces the inappropriate increase of ventilation during exercise in heart failure patients. *Chest* 2002; 122: 2062–2067.
 87. Agostoni P, Magini A, Andreini D, *et al.* Spironolactone improves lung diffusion in chronic heart failure. *Eur Heart J* 2005; 26: 159–164.
 88. Agostoni PG, Marenzi GC, Sganzerla P, *et al.* Lung-heart interaction as a substrate for the improvement in exercise capacity following body fluid volume depletion in moderate congestive heart failure. *Am J Cardiol* 1995; 76: 793–798.
 89. Agostoni PG, Guazzi M, Bussotti M, Grazi M, Palermo P, Marenzi G. Lack of improvement of lung diffusing capacity following fluid withdrawal by ultrafiltration in chronic heart failure. *J Am Coll Cardiol* 2000; 36: 1600–1604.
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CHAPTER 5

Equipment, measurements and quality control in clinical exercise testing

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Background

The goal of cardiopulmonary exercise testing (CPET) protocols is to impose substantial stress on all the organ systems involved in the exercise response. For this reason exercise testing generally involves large muscle groups, usually the lower extremity muscles. An important requirement is that the exercise stimulus is quantifiable in terms of the rate of external work performed. Simpler tests, such as stepping tests or timed distance walk tests (*e.g.* 6 or 12 min) can provide measures of exercise tolerance but cannot contribute to diagnosis [1]. Furthermore, it is most efficient to employ a progressively increasing work-rate (WR) protocol so that a range of exercise intensities can be studied in a short period of time. Technological advances have made it possible for sufficient density of data to be acquired in a test lasting <20 min from start to finish.

Equipment and measurements

Choice of ergometer

Two modes of exercise are commonly employed in cardiopulmonary exercise tests: cycle ergometer and treadmill.

Cycle ergometer. For laboratory exercise testing, there are several advantages to using a cycle ergometer. The cycle ergometer is generally cheaper and requires less space. It is also less prone to introducing movement or noise artefacts into measurements; blood pressure auscultation, for example, is generally easier. An important advantage is that the rate at which external work is performed is determined much more easily. The major confounding factor is the metabolic cost of moving the legs. There is a moderately greater metabolic requirement for moving heavier legs [2–5] but as long as the pedalling cadence is kept constant, this represents a constant offset. The predictability of the relationship between the imposed cycle ergometer WR and metabolic energy expenditure is important for the diagnosis of cardiovascular disease; in most circumstances it makes the cycle ergometer the preferable mode of exercise in CPET.

The electromagnetically braked cycle ergometer [6] is generally used for CPET. Friction-braked cycle ergometers [7] do not usually offer sufficiently precise WR settings.

In contrast, the electromagnetically braked cycle ergometer allows direct quantification of the WR performed and can be computer controlled. This allows WR to be incremented continuously ("ramp pattern") [8–13]. These ergometers are often constructed so that moderate changes in pedalling rate do not influence the WR performed, although major changes in pedalling rate lead to detectable changes in the physiological responses at the same WR setting [14]. Recently, cycle ergometers have become available that allow true unloaded pedalling. This capability means that patients do not have to overcome flywheel inertia as exercise begins and, for the most debilitated patients, a lower starting WR can be selected.

Treadmill. The motor-driven treadmill imposes progressively increasing exercise stress through a combination of speed and grade (slope) increases. Treadmill exercise testing has several advantages. For most individuals, treadmill walking is a more familiar activity than cycling. Furthermore, a larger muscle mass can be brought to endurance during treadmill exercise, leading to a greater stress on the organ systems mediating the exercise response. On average, maximal oxygen uptake ($\dot{V}O_2$) is reported to be 5–10% higher on a treadmill than a cycle ergometer [15–18]. This may help in detecting abnormalities (*e.g.* cardiac ischaemia), which only occur with the highest metabolic demand. If exercise testing is being used to provide a prescription for subsequent exercise training, then it may be advantageous to use the same exercise modality in testing as for training. For example, in a walking exercise programme in pulmonary rehabilitation, use of a treadmill in testing will provide a more direct translation of the exercise prescription for the training programme. It should be noted, however, that factors such as walking efficiency (influenced by factors such as footwear, length of the lower limb and familiarisation with treadmill exercise) and the use of arm support may have unpredictable influences on metabolic rate.

Several incremental protocols are popular [19–25]. However, most have disadvantages when used in CPET as follows. 1) The speed and grade increment profile is fixed so that test duration will vary widely with subjects of varying exercise tolerance. This constrains the diagnostic value [22]. A correlate of this problem is that, for individuals of low exercise tolerance, the initial speed and grade setting is often a large fraction of their peak capacity, and occasionally it may even exceed the achievable peak WR and/or the maximum tolerable walking speed. This often leads to tests with unsatisfactory characteristics, *e.g.* short duration. 2) The combination of linear speed and linear grade increase does not generally elicit a linear increase in WR and metabolic rate. The assumption of a linear increase in metabolic rate underlies some CPET measurements, *e.g.* detection of lactate threshold (LT) [26]. 3) Lack of precision in determining the quantity of WR is generally considered a major problem, as the characteristic abnormalities of the $\dot{V}O_2$ WR relationship in cardiovascular disease may be missed. 4) Unlike cycle ergometry, the weight of the subject is a major determinant of WR.

A treadmill exercise test has recently been described that provides a low initial metabolic rate and then increasing WR linearly to reach the subject's limits of tolerance in ~10 min [27]. The imposed WR is calculated as that required to move the body up the treadmill slope against gravity. A linear increase in treadmill speed, combined with a curvilinear time course of grade, results in a linear WR increase. Using the individual's body weight, height, age and sex, the subject's predicted peak WR is determined. This target can then be moved up or down, depending on the pre-test assessment of likely exercise tolerance. Specifying the desired target peak WR, as well as the initial and maximal walking speeds, enables the speed and grade time course to be calculated. The protocol has been validated in a study of 22 healthy subjects of varying fitness who performed this treadmill protocol as well as ramp cycle ergometry. As for the cycle

ergometer protocol, the $\dot{V}O_2$ time course was found to be linear for the treadmill test and the test duration was in the region of 10 min, irrespective of fitness. This treadmill protocol appears to have major advantages over older protocols and seems to be especially well suited to the requirements of CPET of patients with severely limited exercise tolerance. This protocol enables higher speeds (>3–3.5 mph) to be avoided as the slope of the linear $\dot{V}O_2$ –WR relationship gets steeper beyond the walking speed range. This suggests that the actual WR is underestimated as soon as the gait pattern changes from walking to jogging and running.

An additional consideration favouring treadmill testing over cycle ergometer testing has recently been reported. A systematic comparison utilising the same ramp-incremental slope on the treadmill and on the cycle ergometer in chronic obstructive pulmonary disease (COPD) patients showed that the majority demonstrated arterial oxyhaemoglobin desaturation (assessed by pulse oximeter) during treadmill exercise but not with cycle ergometry, even when identical WRs were compared [28]. Other investigators have reported similar findings [29, 30]. This suggests that exercise testing carried out for the purpose of exercise oxygen prescription should not be performed on the cycle ergometer.

Other devices. Occasionally, patients are encountered who are unable to perform lower-extremity exercise. For such patients, arm-crank ergometers can be adapted for incremental exercise testing. However, the metabolic stress that can be induced during arm cranking is limited. In healthy subjects, peak $\dot{V}O_2$ averages ~70% of that achievable during lower-extremity exercise [31–33] and lactic acidosis begins at very low WRs [31]. Furthermore, the muscles that contribute to arm exercise include some of the accessory muscles of respiration, making arm exercise poorly tolerated in patients with lung disease [34–36].

Gas exchange measurement

A central focus of comprehensive CPET is the interpretation of gas exchange responses, so the methods used to measure $\dot{V}O_2$ and carbon dioxide output ($\dot{V}CO_2$) are of great importance. These measurements are not trivially easy to make and a clear understanding of the methods involved and of the quality-control procedures required are necessary prerequisites. These techniques require validation studies in which the actual measuring technique is compared with an independent gold standard method.

Timed gas collection. The conceptually simplest technique involves directing the expired air (by use of a suitable breathing valve) into a collection bag. A timed collection is made and the concentrations of CO_2 and O_2 in the bag and the volume of the bag are subsequently measured for calculation of $\dot{V}O_2$ and $\dot{V}CO_2$. Note that $\dot{V}CO_2$ and $\dot{V}O_2$ are expressed at STPD (standard temperature and pressure dry) while ventilation is expressed at body temperature and pressure saturated. Use of highly accurate, independent gas analysis is required. Only a few laboratories are capable of performing Scholander analysis of gas concentrations [37]. Mass spectrometry is a reasonable alternative for the gold standard gas concentration measurement modality. Although careful attention to technique is essential, the bag collection method is capable of very precise measurements even at high metabolic rates. However, it is limited to the measurement of steady-state responses and cannot be easily adapted to rapid-incremental exercise protocols. Bag collection systems are now mainly used as a validation technique for more complex gas exchange systems. However, care must be

applied when using the timed gas collection method in validation studies, as follows. 1) The exact temperature at which the volume measurement is made must be estimated but is often not known precisely. 2) After completion of the bag collection, the gas concentrations in the bag change as most bags allow diffusion of the gases of interest and cooling of the exhalate yields water condensation on the walls of the bag. In the condensate, CO_2 will be absorbed leading to changes in the CO_2 concentration in the air compartment. Although this change is likely to be small, it is nevertheless variable depending on the extent of condensation. 3) The valves used to direct gas flow in and out of the bag during gas collection and the gas volume measurement may leak, leading to errors in the gas volume measurement. 4) In most laboratories, the Scholander apparatus [38] is not available and the use of similarly accurate methodology [39] or the use of mass spectrometry is not feasible. The use of the same gas analysers to make and validate gas exchange calculations is clearly not acceptable.

Mixing chamber systems. Systems featuring mixing chambers allow continuous measurement of $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ [2, 40, 41]. The subject respire through a breathing valve and expired air is directed through a baffled chamber. The concentrations of CO_2 and O_2 are measured continuously at the distal end of the mixing chamber. Expired volume is measured, usually breath-by-breath. By utilising the gas concentration signals, $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ can be calculated. In the steady state of exercise or with slowly incremental protocols, mixing chamber systems are capable of accurate metabolic rate measurements. However, since the washout of the mixing chamber requires a finite time, which depends on the level of exhaled ventilation, the volume and gas concentration signals will be “misaligned” in the nonsteady state, leading to inaccurate calculations. For incremental protocols commonly used in clinical CPET, ventilation and mixed expired gas concentrations do not change rapidly and the accuracy of a well-designed mixing chamber system may be quite acceptable. However, care must be taken to recognise that slurring may occur when variables change direction.

In recent years, the development of systems featuring a miniature mixing chamber, which samples the exhalate at a rate proportional to exhaled airflow [42–44], seek to avoid misalignment of gas concentrations with the flow signal. The measured gas concentrations are intended to approximate the mixed expired values for the breath for which the volume has just been measured. Theoretically, as systems based on intra-breath gas mixing are less prone to noise originating from uneven tidal volumes, the breath-by-breath signal-to-noise ratio is usually better than systems utilising the classic breath-by-breath method (see later). A drawback of mixing chamber systems is that end-tidal O_2 and CO_2 concentrations are not readily available, hindering some of the diagnostic evaluations in clinical practice. In addition, some commercial systems (usually mobile systems) do not measure $\dot{V}\text{CO}_2$ and assume that the respiratory exchange ratio (R) is 1.0, which hinders interpretation of exercise responses [42]. This assumption may also lead to significant measurement errors with deviation of R from 1.0, and this error is greater when the inspired O_2 fraction (F_{I,O_2}) is >0.21 [45].

Breath-by-breath systems. With the readily available online digital computers to analyse physiological transducer signals, it has become practical to compute $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ breath by breath [46–51]. By utilising algorithms first reported in 1973 [47], a signal proportional to expired airflow and signals proportional to fractional concentrations of CO_2 and O_2 measured near the mouth are typically sampled 50–125 $\text{times}\cdot\text{s}^{-1}$. Therefore, breath is broken down into a large number of parts and the CO_2 output and O_2 uptake are calculated for each interval as the product of the expired gas

fraction and the volume of gas exhaled during the time interval. These measurements are summed over the entire expiration in order to calculate the total volume of $V'\text{CO}_2$ and $V'\text{O}_2$, as follows:

$$V'\text{CO}_2 = \sum F_{\text{E},\text{CO}_2} \times V'\text{E} \times \Delta t \quad (1)$$

$$V'\text{O}_2 = \sum (F_{\text{I},\text{O}_2} - F_{\text{E},\text{O}_2}) \times V'\text{E} \times \Delta t \quad (2)$$

where minute ventilation ($V'\text{E}$) is the instantaneous expired airflow, Δt is the sampling interval and fractional concentration of oxygen and carbon dioxide in expired gas are F_{E,O_2} and F_{E,CO_2} , respectively. These calculations must accommodate water vapour, barometric pressure and ambient temperature variations in order to obtain STPD values [47]. In the respiratory volume calculation, the gas temperature at the point of measurement is needed and not the ambient temperature.

Importantly, compensation is necessary for the delay between the time at which gas is sampled at the mouth and the time at which the gas concentration is measured within the gas analysers (usually in the order of 0.25–0.5 s). The time alignment of the flow and gas concentration signals is carried out before the calculation of $V'\text{O}_2$ and $V'\text{CO}_2$ using the time delays measured at the time of calibration (fig. 1). In this example, the concentration and flow signals were sampled at 125 Hz (8-ms sampling interval) but for purposes of illustration only every third point is plotted. This detection scheme might be a source of error if the flow towards the end of exhalation “resides” in this threshold area for an appreciable period of time. In severe COPD patients, as the expiratory flow rate is slow and might approach zero towards the end of exhalation, it may fall within the threshold region at a time when exhalation is still proceeding. At the start of exhalation, the gas concentrations do not change until after air from the anatomical portion of the dead space is exhaled (~300 ms in this example). The length of time before gas concentrations change depends on the gas sampling flow rate and the size of the dead space. At the end of exhalation, as the flow drops and changes direction as inspiration begins, the gas concentration signals change rapidly. Generally, the time delays for the two gas analysers are not the same since gas is directed through the two analysers sequentially. This difference must be considered when aligning these signals. If water vapour condensation occurs in the sampling line or a mucus droplet is trapped in the sampling line during a test, the time delays may change unpredictably, resulting in calculation errors. The effect of this error in delay times is shown in figure 2. It can be seen that modest estimation error of delay times leads to appreciable errors in $V'\text{O}_2$ and/or $V'\text{CO}_2$ [48]. Checking the system’s performance with a metabolic simulator across the range of respiratory rates often identifies this problem.

Another characteristic of gas analysers in current use is that they do not respond instantaneously to an abrupt change in gas concentration, but rather demonstrate an exponential rise in signal with a time constant often in the range 50–100 ms (rise time). It is difficult to compensate for the rise time, especially if the analyser response characteristics are not mono-exponential but rather take on a sigmoid shape. The rise time also depends on the viscosity of the gas sampled and, therefore, it changes with increasing F_{I,O_2} [48]. Often the time constant of response is added to the sampling transport delay to yield a delay time that at least partly compensates for the rise time.

Therefore, breath-by-breath analysis requires precise knowledge of, and computerised compensation for, gas analyser delays and rise times [48]. Thus, the increased temporal resolution of breath-by-breath analysis comes at a price of more exacting calibration requirements.

Gas exchange measurement at elevated inspired oxygen concentration. Measurement of $V'\text{O}_2$ when F_{I,O_2} is high presents particular problems. The source of inspired gas must have a constant O_2 fraction, e.g. from large gas bags with sufficient continuous gas

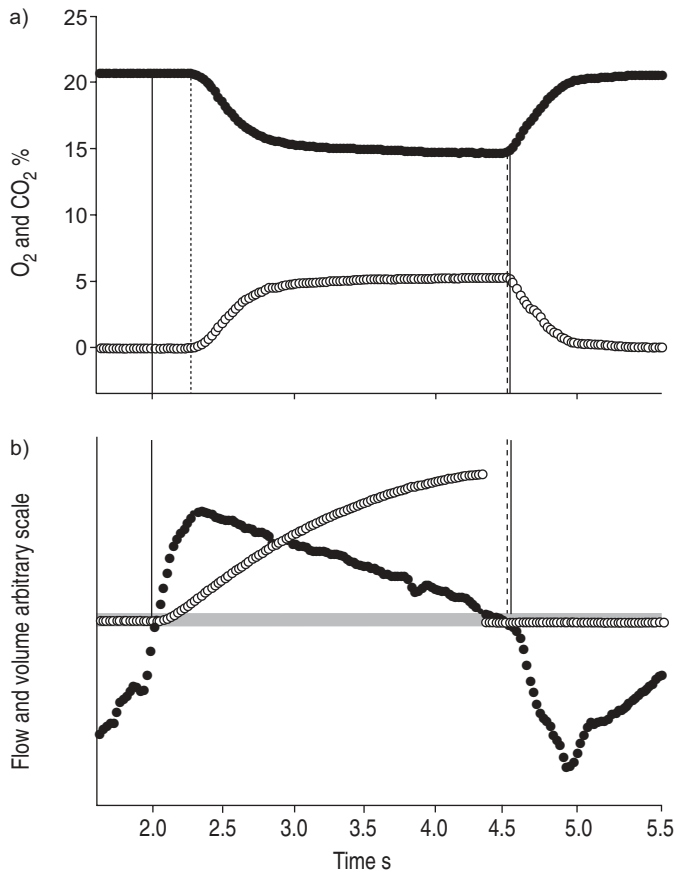


Fig. 1. – Digitised signals after holding the flow signal for the delay time caused by gas analyser transport delay in a) O_2 and CO_2 concentrations and b) flow and volume signals. There is still an ~ 300 ms time-lag between the start of expiratory flow and the start of change in the gas concentration signals due to the volume exhaled from the anatomical dead space (phase 1 of delay). With perfect time alignment for the transport delay, at the end of exhalation, sudden changes in the concentration signals occur at the same time as flow crosses zero. a and b) —: start and end of expiratory flow;: end of Phase 1 of transport delay; - - -: aligned end of exhalation. a) ●: O_2 concentration; ○: CO_2 concentration. b) ●: air flow; ○: integrated volume. The “threshold” area for flow detection is represented by the thick grey line. Digitising frequency: 125 Hz; plotting interval: 24 ms. Note that the sudden drops in the flow during mid-exhalation are the result of changes in flow due to cardiac contraction (60 bpm).

supply. Furthermore, when F_{I,O_2} approaches 1, nitrogen balance corrections become more subject to error [48]. Depending on the methodology employed and the accuracy required, F_{I,O_2} in the range 0.6–0.8 should be regarded as the practical upper limit for achievable measurement. For measurements during room-air breathing, the calibration curve of the oxygen analyser is typically constructed from measurements of two concentrations (usually between 12 and 26% O_2), assuming that the gas analyser is linear, or can be linearised, in the calibration range. Unless calibration gases at higher oxygen concentrations are employed, measurements at high inspired oxygen concentrations require substantial extrapolation of the two-point calibration line. Therefore, small deviations in accuracy of the calibration gas concentrations or any small nonlinearities in the analyser’s response can cause large errors in measurement when hyperoxic inspirates are used.

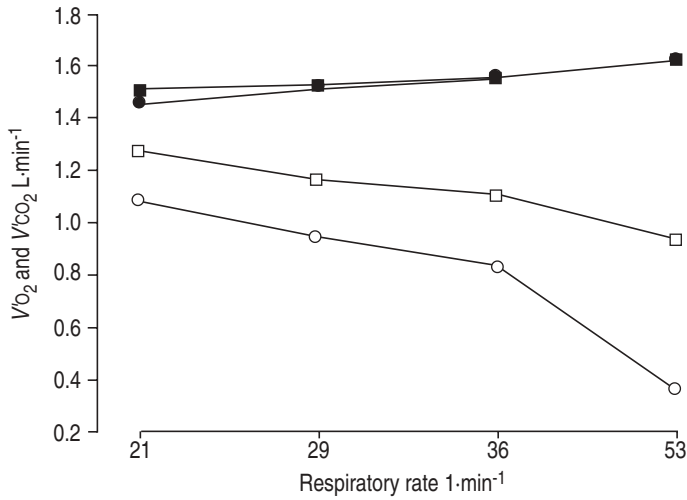


Fig. 2. – Respiratory-rate dependent change in oxygen uptake ($V'O_2$) and carbon dioxide production ($V'CO_2$) calculations produced by an exercise system when a metabolic simulator was used. True gas analyser time delay is 0.6 and 0.48 s for the oxygen analyser and the carbon dioxide analyser, respectively. Note that, using these values, changes in piston “respiratory rate” yields only modest changes in calculated metabolic rate. When incorrect values for delay time are inserted, considerably different metabolic rates are calculated and these values change substantially with simulated respiratory rate. ●: $V'O_2$ at 6-s delay time; ○: O_2 analyser delay time increase to 0.85 s; ■: $V'CO_2$ at 0.48-s delay time; □: CO_2 analyser delay time increased to 0.73 s.

In most systems, only $V'E$ is measured, although both the inspired and expired flow signals are available. Because, over a period of time, the body maintains constant nitrogen content, the inspired and expired volumes of nitrogen are equal:

$$VI \times FI,N_2 = V'E \times FE,N_2 \quad (3)$$

Therefore, inspired volume (VI) can be calculated as:

$$VI = V'E \times (FE,N_2 / FI,N_2) \quad (4)$$

Nitrogen concentrations are, however, not generally measured. If it is assumed that the respired gas is composed only of nitrogen, oxygen and carbon dioxide, both fractional concentration of nitrogen in expired air (FE,N_2) and fractional concentration of nitrogen in inspired gas (FI,N_2) can be calculated as:

$$FE,N_2 = 1 - FE,O_2 - FE,CO_2 \quad (5)$$

and:

$$FI,N_2 = 1 - FI,O_2 - FI,CO_2 \quad (6)$$

Therefore:

$$VI = V'E \times (1 - FE,O_2 - FE,CO_2) / (1 - FI,O_2 - FI,CO_2) \text{ (Haldane transformation)}$$

It can be seen that any errors in determining gas concentrations accurately lead to errors in the Haldane transformation and, consequently, in determining the VI . As a result, inaccurate gas concentrations are multiplied with inaccurate VI in determining the inspired volume of oxygen (VI,O_2) and carbon dioxide (VI,CO_2), leading to amplification of errors in calculation of $V'O_2$ and $V'CO_2$.

Random fluctuations in FI,O_2 due to leakage occurring either at the nose-clip or mouthpiece lead to rapid and unpredictable changes in $FI,O_2 - FE,O_2$, and consequently an unpredictable error in $V'O_2$ calculation. Due to dilution in the alveolar volume, any transient change in FI,O_2 will have a long-lasting effect on FE,O_2 (up to and over 1 min, depending on the equilibration time), causing a long-lasting error in $V'O_2$ calculation. Therefore, particular care should be assured when using elevated FI,O_2 in exercise tests.

Additionally, it should be noted that only systems continuously measuring $\dot{V}I_{O_2}$ can yield accurate $\dot{V}'O_2$ measurements when hyperoxic gases are inhaled.

Most modern exercise systems do not require a valve to separate the inspire from the expire. However, respiring high O_2 concentrations require such a breathing valve. The valve assembly imposes an additional source of potential error. These “non-rebreathing” valves can leak [46] and usually do at low flow rates. Furthermore, at the start of inspiration, a volume of end expiratory (end-tidal; ET) gas that resides in the valve is re-inhaled. This results in lower $\dot{V}I_{O_2}$ and elevated $\dot{V}I_{CO_2}$ in proportion to the volume dilution imposed by the volume of the valve in use. Therefore, a correction must be introduced into the gas exchange calculation as follows:

$$\dot{V}'O_2 = \dot{V}'O_2 \text{ measured} - (V_{\text{valve dead space}} \times f \times (\dot{V}I_{O_2} - \dot{V}ET_{O_2})) \quad (7)$$

Assuming that $\dot{V}I_{CO_2}$ is zero:

$$\dot{V}'CO_2 = \dot{V}'CO_2 \text{ measured} - (V_{\text{valve dead space}} \times f \times \dot{V}ET_{CO_2}) \quad (8)$$

where $V_{\text{valve dead space}}$ (in STPD) and f is respiratory rate. The effect of valve assembly on the tidal volume and gas exchange calculations without the above correction is presented in figure 3.

A final potential source of error when hyperoxic gas mixtures are inhaled is that 100% O_2 is ~11% more dense than room air. For airflow sensors that are sensitive to changes in gas density, appropriate corrections are needed. Using physiological calibration studies, it is possible to check the system's accuracy in calculating metabolic rate under different $\dot{V}I_{O_2}$ conditions. Such a comparison is demonstrated in figure 4, where the standard physiological validation protocol was used (see below) while breathing room air and 50% O_2 . It is also important to allow a sufficient wash-in period, usually breathing the high $\dot{V}I_{O_2}$ gas mixture for 7–10 min (or longer if severe ventilation/perfusion inequalities are present) until stable values of $\dot{V}'O_2$ (and R) are achieved, before starting the exercise test. Otherwise a significant error will be incurred in the $\dot{V}'O_2$ calculation as discussed previously.

Highly developed systems. With the advent of flow and volume transducers that measure both the inspiratory and expiratory phases of respiration, it has become possible to measure pulmonary gas exchange without employing the Haldane transformation [52]. However, to date, few (if any) commercial systems use both phases of respiration to determine the exact volume of inspired and expired air.

Furthermore, algorithms enabling breath-by-breath correction for both changes in lung volumes and in alveolar gas concentrations have been developed and implemented [46, 53], allowing calculations of the true “alveolar” gas exchange. To the authors' current knowledge, this strategy is not used in any of the available commercial systems. The alveolar gas exchange method allows approximation of the rate of gas transfer across the alveolar-capillary barrier and has the practical advantage of eliminating the effect of breath-to-breath changes in lung volume in gas exchange calculations, therefore yielding a less “noisy” $\dot{V}'O_2$ and $\dot{V}'CO_2$ time course.

Exercise testing measurement system components

There are a host of transducers and analytic devices that constitute the measurement system for CPET. The following components are usually present.

Digital computer. For an adequate reconstruction of an analogue signal with a rise time of flow or concentration signal of ~40 ms [46], a sampling rate of ≥ 50 Hz is required. Calculations are performed during each sampling interval. A key function is breath detection (discussed further later), often signalled by the detection of the onset of

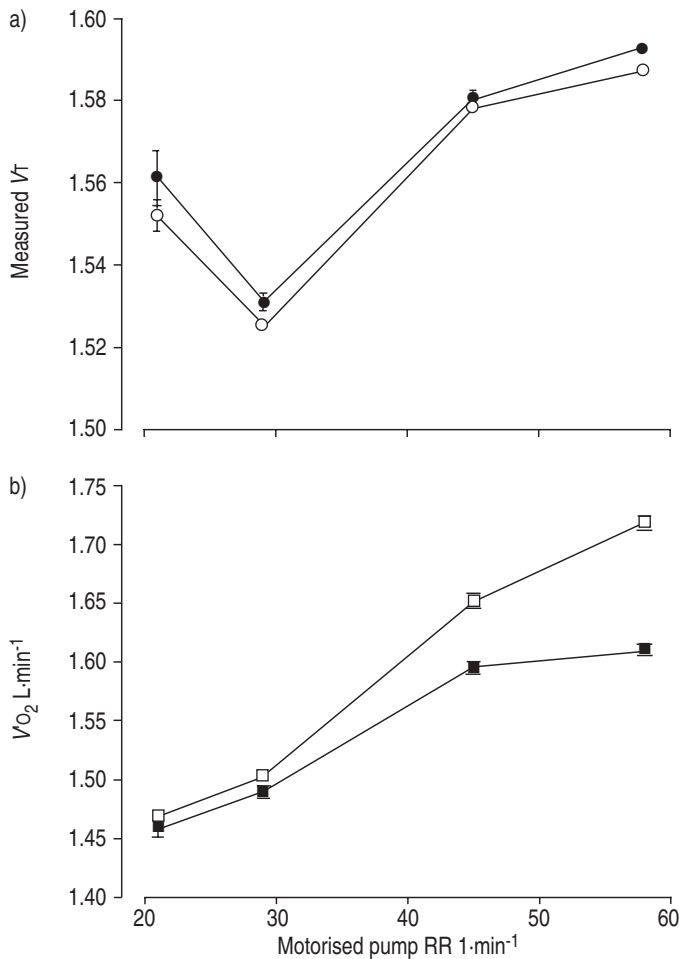


Fig. 3. – Exercise system performance tested by a metabolic simulator. The influence of respiratory rate (RR) changes and the addition of a breathing valve on a) tidal volume (V_T) and b) oxygen uptake ($V'O_2$) calculations. Note that V_T varies only a ~4% range despite a three-fold change in respiratory rate (RR). The valve assembly introduces minimal error in V_T measurement. However, especially at high RR, the breathing valve yields inappropriately high $V'O_2$ values, unless explicit corrections are made. ●: RR versus V_T no valve; ○: RR versus V_T with valve; ■: RR versus $V'O_2$ no valve; □: RR versus $V'O_2$ with valve.

expiratory airflow. The values of a number of variables are calculated for each breath. These values are available for online graphical or tabular display and are stored for later analysis.

In many applications, the digital computer is divided into two components. A pre-processing unit samples signals and performs breath-by-breath calculation. This information is then passed to the computer, which performs the display and storage functions and acts as the user interface.

During the 1970s and 1980s, the early days of CPET, the computing power necessary for breath-by-breath analysis required specialised equipment. However, today's routinely available computers can generally be adapted to this task.

Flow or volume of respired air. A number of transducers have been used for measurement of respired flow or volume during exercise. In part, the expansion of the

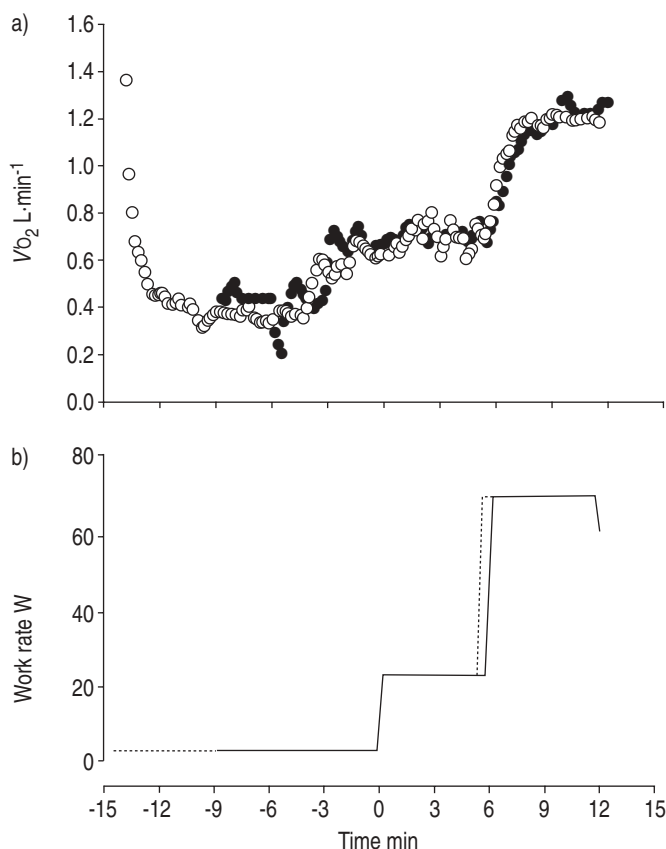


Fig. 4. – Physiological validation study of respiring room air and elevated oxygen concentration gas mixture. a) Oxygen uptake ($\dot{V}O_2$) and b) work rate. Protocol: rest, equilibration/wash-in period, 3-min unloaded cycling (6 min at 20 W and 6 min at 70 W constant work rate exercise). The two tests were aligned at the start of 20-W exercise periods. Data points are at 10-s intervals with three-point moving averages. $\bullet$: inspiratory oxygen fraction (F_{I,O_2}) 0.21; $\circ$: F_{I,O_2} 0.50; —: work rate in test F_{I,O_2} 0.21;: work rate in test F_{I,O_2} 0.50. Note that due to the initially high fractional concentration of nitrogen in expired air, the initial $\dot{V}O_2$ calculation is in error.

choice of transducers has resulted from the use of computerised data analysis. Digital computer processing can accommodate a nonlinear relationship between flow or volume and transducer output, as long as the nonlinearity is static (the relationship does not vary with time). Furthermore, the choice of a flow *versus* a volume transducer is no longer crucial since numerical integration or differentiation can be employed to calculate one quantity from the knowledge of the other. A key consideration is whether the transducer can be positioned near the mouth. Such transducers are capable of sensing flow or volume bidirectionally. They also eliminate the need for a non-rebreathing valve, which means that the apparatus dead space can be lower. All of the following transducers, with the exception of the pneumotachograph, have been used in a bidirectional configuration.

The American Thoracic Society (ATS) and European Respiratory Society (ERS) have established standards for flow and volume measurement in the context of spirometry [54]. The transducers used in exercise testing should also meet these standards.

Transducers currently commonly employed for measuring flow or volume in CPET are as follows.

Pneumotachograph. This flow transducer measures the pressure drop across a low resistance screen or bundle of capillary tubes [55–58]. Since laminar flow is required and sputum impaction on the transducer screen can degrade performance, pneumotachographs have generally been positioned well downstream (or upstream) from the mouth. In order to eliminate condensation from the exhaled air, the pneumotachograph is typically heated to body temperature.

Pitot tube flow meter. This device is an impact flow sensor, which measures the difference between pressure at orifices facing the flow stream and those that are perpendicular to the flow stream. Turbulent, rather than laminar, airflow is involved and the pressure difference is proportional to the square of the flow rate [2, 59]. This requires an extensive linearisation algorithm, which involves corrections for the density differences of relevant gas concentrations and for the measurement of temperature in order to achieve a sufficient linearity [59]. In addition, in order to cover the more than 10-fold flow rate difference usually found in the respired airflow, there is a need to use more than one differential pressure transducer to cover the very low and very high flow rate ranges adequately. The Pitot tube flow sensor has usually been produced for single use, therefore helping to eliminate cross-infection between patients.

Mass flow meter. This device is related to the older hot-wire anemometer in which the current required to heat a wire to a certain temperature increases (nonlinearly) as airflow increases [60, 61]. In one presently used configuration, two wires heated to different temperatures are utilised. Flow detection depends on the fact that the hotter wire loses heat more rapidly than the cooler wire. Compensation is made electronically for changes in gas temperature. The signal generated is (nonlinearly) proportional to the number of molecules passing the sensor rather than the volume of gas the molecules occupy.

Turbine volume transducer. A lightweight impeller is placed in the flow stream and the number of interruptions of a light beam produced by the rotating impeller blades is counted by a computerised system [58]. Although small, the mass of the impeller causes the impeller speed to lag behind changes in flow rate, *i.e.* dynamic nonlinearities, which can lead to errors in gas exchange calculations [62].

Ultrasonic Doppler flow sensor. The ultrasonic Doppler flow-sensor technology detects a frequency shift (Doppler effect) in an ultrasonic signal when a moving stream of air is placed between the generator and sensor; the frequency shift is in proportion to the airflow velocity [63].

Variable orifice flow sensor. This flow sensor is based on flow-dependent generation of differential pressure across a plastic flap orifice. While this type of flow sensor is widely used in some mechanical ventilators, very few systems exist for measuring exercise gas exchange. The advantage of this flow sensor is that, because of its relatively low price, it can be produced for single use.

Some flow sensors cannot be used when low-density, highly viscous gases and those with high heat capacitance and conductance are respired, *e.g.* xenon, helium. For example, in a comparative study of three flow sensors (Pitot-tube, turbine volume transducer and variable orifice), when xenon-containing gas mixtures were respired only the turbine volume transducer gave acceptable results [64].

Breath detection. Regardless of what type of flow sensor is used to record respiratory flow, a highly sophisticated computer algorithm decides when the exhalation and

inhalation starts and ends. Expiratory flow integration is usually triggered when the flow rate exceeds a specified threshold level and continues until the flow drops below the threshold level at the end of exhalation (fig. 1). However, typically the flow signal is not smooth and the transitions between breathing phases may not be distinct. There is always a certain level of irregularity that might be considered noise. There are breaths in which flow ceases during exhalation but is not followed by an inhalation; the exhalation continues after a short pause, *e.g.* after swallowing. Sometimes a prolonged exhalation is observed during which the expiratory flow is very low for several seconds. An abrupt flow signal disturbance is observed during cough. It should also be considered that errors in the integration will occur when too high a threshold level is selected and the flow does not exceed the threshold level for an appreciable period of time. In all of these instances, the expiratory (or inspiratory) flow signal presents special problems for the breath-detection algorithm.

The onset of breath phase is only part of the breath detection algorithm. A secondary (logical) decision is performed after all calculations have been made with regard to the “validity” of the calculated tidal volume (V_T), $V'O_2$, $V'CO_2$ and R values. Commercial systems often have error-checking routines incorporated that reject breaths with “unfeasible” values for any of these variables, *e.g.*, $V_T < 100$ mL or $R < 0.5$. After rejection of such a “bad breath”, the next breath interval should be started from the time of the end of the rejected breath [65], otherwise a calculation error will lead to erroneously high or low values in calculated gas exchange.

Gas concentrations. Two different strategies have been employed to measure the gas concentrations necessary for breath-by-breath analysis. The first is to use an analyser capable of measuring all the relevant gases (CO_2 , O_2 and, for some purposes, N_2). Mass spectrometry has most often been used for this purpose. The second approach utilises separate analysers for each gas species. Key requirements are stability and rapidity of response. The dynamics of analyser response has two separable components: 1) transport delay, the time required for gas to traverse the distance from the sampling site to the analyser; and 2) analyser response, the kinetics of response to a change in gas composition introduced into the analyser. Transport delay can be compensated for, generally in the order of 0.2–0.5 s, depending on the length of the gas sampling tube and the gas sampling rate. The analyser response, often taking the form of an exponential response to a stepwise change in gas composition cannot be fully compensated [48, 49, 51] and must be kept as short as possible (as previously discussed). An additional concern is sensitivity of the analyser to water vapour partial pressure in the sampled gas. Since the water vapour concentration in the sampled gas can be difficult to assess (principally because the gas temperature at the sampling point is difficult to assess), this can introduce substantial errors in $V'O_2$ and $V'CO_2$ calculations [66].

The mass spectrometer ionises gas molecules in a high vacuum environment and then separates them (by one of several mechanisms) on the basis of mass-to-charge ratio. This enables the time courses of a number of gas species to be measured essentially simultaneously. These analysers are linear, usually highly stable and have rapid response characteristics (analyser time constants of ~25–50 ms). They are usually configured to ignore water vapour, yielding “dry gas fractions”. However, the high cost of mass spectrometers has inhibited their use in most commercial cardiopulmonary exercise systems.

Discrete O_2 and CO_2 analysers have been designed specifically for the demands of CPET. CO_2 analysers based on absorption of infrared light by CO_2 [67] are commonly used. Oxygen analysers based on two principles have been employed. In paramagnetic analysers, the effect of oxygen molecules on a magnetic field is utilised. In the electrochemical (“fuel cell”) analyser, high temperature reactions between O_2 and

substrate are measured. These analysers have potential disadvantages. The analyser output is not usually a linear function of gas concentration; however, computerised correction can be made for these nonlinearities. Also, analyser measurements are influenced by water vapour concentration of the sampled gas. Use of sampling tubing composed of the co-polymer Nafion has largely circumvented this problem. This polymer (co-polymer of Teflon and perfluoro-3,6-dioxo-4-methyl-7-octene-sulfonic acid) is highly hydrophilic with each sulphonic acid group binding to 13 molecules of water, resulting in an absorption rate of 22% by weight of water. The reaction is a first-order chemical reaction that typically takes places within milliseconds. The water moves through the wall of the tubing and evaporates into the environment. This process is driven by the humidity gradient between the inside and the outside of the tubing. Since the reaction is specific to water, the concentrations of other gases are left entirely unaffected.

Heart rate. Heart rate is derived from measuring the R-R interval through ECG leads. Sweat-resistant adhesive patches are applied to the cleaned skin surface. A key requirement is that the electrodes and the detection electronics are specially designed for movement-artefact rejection.

ECG. Continuous ECG monitoring is a necessity in most exercise tests. For optimal detection of myocardial ischaemia during exercise and definition of arrhythmias, serial 12-lead ECGs should be obtained in clinical exercise tests [7, 68]. However, in some cases, a smaller number of leads may be used to monitor for arrhythmias and screen for ischaemia. In this regard, a bipolar monitoring lead (CM5) seems to be sufficient [24]. Again, artefact suppression is of concern. Computerised systems enabling continuous display on the computer screen contribute to test safety. Averaging of ECG complexes and trend analysis of ST segment changes during exercise can improve sensitivity and also specificity in detecting ischemic changes during exercise [69].

Noninvasive blood pressure. Auscultation of blood pressure becomes more difficult during exercise because of the increase in ambient noise. Yet detection of exercise-induced hypertension (or, less commonly, hypotension) is an important goal in many circumstances [7]. Automated blood pressure measurement systems have been specifically developed for use during exercise. Many operate on the oscillometric method in which, as the cuff is automatically deflated in stages, pressure oscillations induced within the cuff by pulsations in the arm are detected [70]. Despite algorithms designed to decrease the effects of artefacts, blood pressure measurements may be inaccurate when, for example, the arm is flexed during the measurement cycle. There are anecdotal reports of intermittent unreliability of automated blood pressure cuffs; periodic checks against manual determinations are important. It should be noted that measuring blood pressure by sphygmomanometry in patients with a large amount of subcutaneous fat requires an appropriately wide cuff [71].

Intra-arterial blood pressure. For studies in which an arterial catheter is inserted to facilitate blood sampling, it may be useful to measure blood pressure directly. It should be appreciated that there are (modest) systematic differences between auscultated and intra-arterial blood pressure measurements, particularly in systolic pressure measurements [72, 73]. Miniature transducers are available that can be attached to the arm while the subject exercises. Meticulous attention to technique (*e.g.* exclusion of air bubbles) is necessary to assure good frequency response. Sterility concerns have led some laboratories to employ the use of single-use disposable blood pressure transducers.

Noninvasive oximetry. The current generation of pulse oximeters detects the variation in transmission of light of two different wavelengths that occur with arterial pulsations in an extremity (usually the finger or ear lobe). As oxygenated and reduced haemoglobin transmit certain light wavelengths differently, this information can be used to estimate arterial O_2 saturation (S_{a,O_2}) [74]. While useful and convenient for continuous monitoring [75, 76], several concerns in the context of exercise testing need to be kept in mind. Pulse oximeters have limited accuracy (95% confidence interval ± 4 –5% as compared with directly measured S_{a,O_2} [77]). Some authors have reported that pulse oximeters tend to overestimate true S_{a,O_2} [78–80], a particular problem when test results are being used to prescribe oxygen therapy. Conversely, poor perfusion of the extremity (yielding decreased pulsatility), which may occur in cardiovascular disease, may yield falsely low readings [81, 82]. Movement and stray light can yield artefacts. Dark skin colour can also interfere with signal detection [83, 84]. Furthermore, the inherent limitations of pulse oximetry must be appreciated. These devices cannot detect the effects of increased carboxyhaemoglobin (or methaemoglobin), the calculations of which approximate the oxygenated fraction of available haemoglobin. An additional disadvantage of pulse oximetry is that S_{a,O_2} rather than partial pressure of oxygen (PO_2) is measured. Arterial oxygen tension (P_{a,O_2}) is more relevant in assessing the effects of lung disease on pulmonary gas exchange. As the oxyhaemoglobin dissociation curve is relatively flat over the range of PO_2 , generally found in the arterial blood, large changes in P_{a,O_2} (3.32 or 3.99 kPa) may be necessary to obtain an appreciable change in O_2 saturation (4–5%). Therefore, noninvasive oximetry is not a sensitive method for detecting changes in P_{a,O_2} over the range seen in healthy subjects.

Quality control

It has been observed that variation of results between laboratories in gas exchange measurements can be as high as 25% [85, 86]. Both the ERS [85] and ATS [86] have recognised the need for standardisation and quality control of exercise gas-exchange systems. The importance of quality control is especially important in multicentre clinical trials in which the accuracy among laboratories is crucial for assuring a successful trial. There are three levels of quality control, as follows.

Manufacturer-suggested calibration procedure

This consists of entering the daily environmental standards, such as ambient temperature, humidity and barometric pressure, as well as performing standard volume and gas analyser calibrations. Most systems' calibration routines do not prompt entry of environmental characteristics; therefore, the technician should pay attention that these values are accurate and up-to-date. The flow range encountered during exercise varies over a 10–15-fold range in most cases; therefore, special attention should be paid to the proper flow sensor calibration over the full operating range. Verification of calibration of the air flow or volume transducer is typically performed with a precision 3-L syringe. A range of flow rates should be introduced to simulate the wide range of flow rates occurring from rest to heavy exercise. Syringe strokes varying from 1–15 s in duration cover most of this range. Agreement in calculated volumes to within $\pm 3\%$ signifies adequate performance.

The gas analyser calibration routine involves measurement of gas concentrations at two points: one is usually in the range of ambient concentrations and the other is in the range of exhaled concentrations. The gas analyser delay and rise times are also measured

by the system automatically and these are considered in the flow and concentration signal alignment (fig. 1). On occasion, certified tanks with other relevant compositions should be used to verify linearity. It is good practice to maintain a single precision gas cylinder for occasional use (grandfather tank); such a tank can last a number of years and provide a long-term validation of calibration accuracy.

Both flow sensors and gas analysers tend to drift (gradual baseline offset); therefore it is good practice to perform standard calibration procedures immediately preceding each test.

Devices are available to calibrate electromagnetically braked cycle ergometers [87–89]. Calibration should be performed every 6 months or whenever the cycle ergometer is moved, as jarring often disturbs the calibration. For treadmills, belt speed should be verified by timing revolutions of the belt with a subject on the treadmill; accuracy of the grade indication should also be validated [7].

Use of metabolic simulator for routine quality control

After following the manufacturers' suggested calibration procedures, it is often assumed that the system gives precise and accurate unbiased results. This is not always the case, as has been shown in the past [90–92]. With the help of a metabolic simulator [93] it is possible to perform an overall system check to assure correct ventilatory and gas exchange calculations. Metabolic simulator calibrations are preferably performed daily, but may be performed less frequently, in some settings. A metabolic calibrator has a reciprocating piston and allows frequency and $\dot{V}_T$ to be changed to generate a wide range of $\dot{V}'E$. A precision gas mixture (usually 21% CO_2 , balance N_2) is bled into the piston chamber where it mixes with the “inhaled” gas so that the “expire” simulates metabolic rates with a respiratory quotient of ~ 1 [93]. This combination of a reciprocating piston with variable rate and $\dot{V}_T$, along with variable rates of precision gas flow creates the potential for a wide range of metabolic rate simulations. Note that the simulated metabolic rate ($\dot{V}'\text{O}_2$ and $\dot{V}'\text{CO}_2$) is entirely determined by the flow rate of the precision gas mixture; therefore, at a given precision gas flow rate, a constant $\dot{V}'\text{O}_2$ and $\dot{V}'\text{CO}_2$ should be observed despite changes in piston simulations of $\dot{V}_T$ volume and respiratory rate. The measured values can be directly compared to the predicted value and the error can be reported in percentages. Patterns of error suggest specific device malfunctions. For example, if both $\dot{V}'\text{O}_2$ and $\dot{V}'\text{CO}_2$ are below target values by similar percentages and the respiratory quotient is near its target, malfunction of the flow sensor is likely. If only one of the two gas exchange variables differs from target (with consequent deviation of the respiratory quotient from its target), dysfunction of the analyser for that gas or estimation error of the associated time delay is implicated. Day-to-day variation of these calculations should roughly be in the range of $\pm 3\%$; wider deviations should warrant a thorough system check. It should be noted that the current generation of gas exchange simulator does not simulate moist, room temperature exhalate. Thus, assumptions about temperature and humidity corrections are not tested.

Physiological calibration in validation of gas exchange systems

Physiological calibration, consisting of testing a “standard” subject at regular intervals, can assist in quality control, especially when a gas exchange simulator is not available [94]. Physiological calibration should occur regularly; once a week is a good target. It requires that a healthy subject with a good exercise tolerance (specifically, the LT should be higher than the highest WR utilised) be identified who is likely to be available to the laboratory for an extended period. A typical protocol would have the subject perform constant WR exercise at two or three levels after a warm-up period, all

of which should be below the individual's LT to avoid the slow rise in $\dot{V}'\text{O}_2$ characteristic of tests above the LT. Tests conducted at regular intervals are highly reproducible and are suitable to check the system's accuracy. The physiological responses ($\dot{V}'\text{O}_2$, $\dot{V}'\text{CO}_2$ and $\dot{V}'\text{E}$) of a standard subject have little variability (fig. 5). The average of the last 2–3 min at each WR (during which the subject is in steady state) is calculated. This allows the precise calculation of $\dot{V}'\text{O}_2$, $\dot{V}'\text{CO}_2$ and $\dot{V}'\text{E}$ at the three WRs. For the $\dot{V}'\text{O}_2$ measurements, the $\dot{V}'\text{O}_2$ difference between each of the two 50-W increments should be $\sim 500 \text{ mL}\cdot\text{min}^{-1}$ (corresponding to $10 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$); if this value is not observed, troubleshooting is indicated. It should be noted that with physiological calibration, all exercise system components are tested, including the ergometer. In a systematic validation study on three sub-threshold WRs (20 W, 50% LT and LT) [95], it was found that the coefficient of variation for $\dot{V}'\text{O}_2$, $\dot{V}'\text{CO}_2$ and $\dot{V}'\text{E}$ averaged 6.0% for the three variables at the lowest WR and 3.0, 4.0 and 3.9%, respectively, at the two higher WRs.

This technique of physiological calibration has been used to improve the quality control of CPET systems involved in multicentre trials that had exercise physiology outcomes. Between 2003 and 2005, the current authors' research laboratory served as the coordinating centre for CPET validation from 42 sites in two different industry sponsored studies. Physiological calibration was used to identify participant laboratories with results outside the $9.2\text{--}10.8 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$ range, *i.e.* $\pm 8\%$. After troubleshooting, re-testing was performed for laboratories performing outside this range. As a result, the average $\dot{V}'\text{O}_2$ –WR relationship for the 42 sites averaged $10.23 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$.

Conclusion

Clinical exercise physiology is a method of assessing the limitation of exercise tolerance. This complicated procedure requires complex and sound methodology, the knowledge of which is not taught in the curricula of most universities around the world. Today's highly developed and sophisticated computerised systems provide ample capabilities for clinical exercise testing and for research in exercise and respiration physiology.

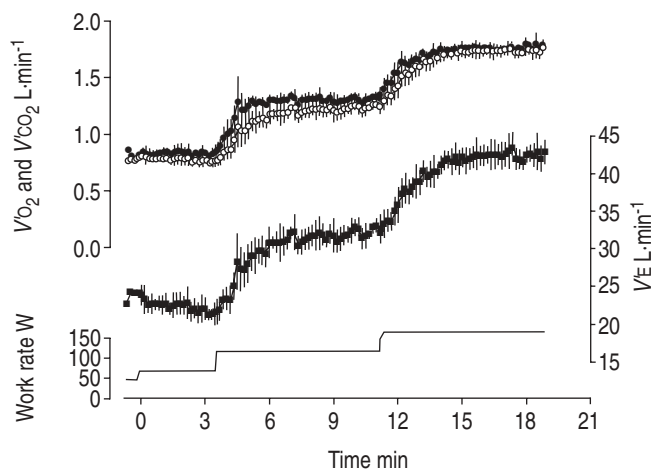


Fig. 5. – Average response of a healthy subject performing physiological calibration studies. The tracings are averages from six consecutive tests on different days in which the subject exercised at 70 and 120 W after a warm-up period of 3 min at 20 W. ●: oxygen uptake ($\dot{V}'\text{O}_2$) $\pm$ SD; ○: carbon dioxide production ($\dot{V}'\text{CO}_2$) $\pm$ SD; ■: minute ventilation ($\dot{V}'\text{E}$) $\pm$ SD. —: work rate. The $\Delta\dot{V}'\text{O}_2/\Delta\text{work rate}$ was evaluated between 70 and 120 W.

It is highly desirable that the laboratory staff, as well as the physician and/or the researcher, is aware of the principles of the operation of these systems. This is important not only in order to be able to operate these complicated devices but it is necessary to be able to conduct adequate quality control and trouble-shooting. Only in possession of this information is it possible to make decisive and correct clinical diagnostic conclusions.

Summary

Cardiopulmonary exercise testing (CPET) allows a comprehensive assessment of the mechanisms of exercise intolerance using a test that can generally be performed within 20 min. However, the test relies on a number of devices and sensors, and assessment will only be valid if all function correctly. It is the user's responsibility to understand the equipment and measurements involved in the testing modality. Performance of the test on a cycle ergometer or a treadmill is an important choice, as each has advantages and disadvantages.

A central focus of the test measurements is calculation of the time course of pulmonary gas exchange. Although breath-by-breath analysis of oxygen uptake and carbon dioxide output is generally performed, this is a complex measurement technique requiring precise knowledge of the oxygen and carbon dioxide sensors and of the flow or volume sensors being used. Advances in the ability of digital computer analysis has led to the successful use of sensors with a number of operating principles and the ability to interpret breathing patterns with less than ideal characteristics. Tests involving elevated inspired oxygen levels present special measurement challenges. Consideration must also be given to heart rate measurement, ECG, blood pressure and pulse oximetry, which are all integral parts of the testing paradigm. A major focus in CPET is quality control, which should include both regular analysis of the performance of individual sensors and the assessment of overall system performance. This overall analysis may include expired gas collection, use of a metabolic simulator and use of a "standard" human subject. The accuracy of the diagnostic conclusions of CPET will only be assured if the user is confident in the accuracy of the measurements.

Keywords: Cardiopulmonary exercise testing equipment, gas exchange measurement, quality control, troubleshooting.

References

1. Ries AL. The role of exercise testing in pulmonary diagnosis. *Clin Chest Med* 1987; 8: 81–89.
2. Physiology of exercise. In: Wasserman K, Hansen JE, Sue DY, Whipp BJ, Stringer WW, eds. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. 4th Edn. Philadelphia, Lippincott Williams & Wilkins, 2005; pp. 10–65.
3. Wasserman K, Whipp BJ. Exercise physiology in health and disease. *Am Rev Respir Dis* 1975; 112: 219–249.
4. Whipp BJ. The physiological and energetic basis of work efficiency. In: Bray GA, ed. *Obesity in Perspective*. Washington DC, Government Printing Office, 1976; pp. 121–126.

-
5. Whipp BJ, Bray GA, Koyal SN, Wasserman K. Exercise energetics and respiratory control in man following acute and chronic elevation of calorie intake. *In*: Bray GA, ed. *Obesity in Perspective*. Washington DC, Government Printing Office, 1976; pp. 157–163.
 6. Bonjer FH, Lanooy C. A hyperbolic ergometer for cycling and cranking. *J Appl Physiol* 1956; 9: 499–500.
 7. Hellerstein HK. Specifications for exercise testing equipment. American Heart Association subcommittee on rehabilitation target activity group. *Circulation* 1979; 59: 849A–854A.
 8. Zhang YY, Johnson MC 2nd, Chow N, Wasserman K.. Effect of exercise testing protocol on parameters of aerobic function. *Med Sci Sports Exerc* 1991; 23: 625–630.
 9. Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine parameters of aerobic function during exercise. *J Appl Physiol* 1981; 50: 217–221.
 10. Tanner CS, Heise CT, Barber G. Correlation of the physiologic parameters of a continuous ramp *versus* an incremental James exercise protocol in normal children. *Am J Cardiol* 1991; 67: 309–312.
 11. Myers J, Buchanan N, Walsh D, *et al.* Comparison of the ramp *versus* standard exercise protocols. *J Am Coll Cardiol* 1991; 17: 1334–1342.
 12. Hansen JE, Casaburi R, Cooper DM, Wasserman K. Oxygen uptake as related to work rate increment during cycle ergometer exercise. *Eur J Appl Physiol Occup Physiol* 1988; 57: 140–145.
 13. Davis JA, Whipp BJ, Lamarra N, Huntsman DJ, Frank MH, Wasserman K. Effect of ramp slope on determination of aerobic parameters from the ramp exercise test. *Med Sci Sports Exerc* 1982; 14: 339–343.
 14. Casaburi R, Whipp BJ, Wasserman K, Koyal SN. Ventilatory and gas exchange responses to cycling with sinusoidally varying pedal rate. *J Appl Physiol* 1978; 44: 97–103.
 15. Hermansen L, Saltin B. Oxygen uptake during maximal treadmill and bicycle exercise. *J Appl Physiol* 1969; 26: 31–37.
 16. Koyal SN, Whipp BJ, Huntsman D, Bray GA, Wasserman K. Ventilatory responses to the metabolic acidosis of treadmill and cycle ergometry. *J Appl Physiol* 1976; 40: 864–867.
 17. McArdle WD, Katch FI, Pechar GS. Comparison of continuous and discontinuous treadmill and bicycle tests for max Vo₂. *Med Sci Sports* 1973; 5: 156–160.
 18. McKay GA, Banister EW. A comparison of maximum oxygen uptake determination by bicycle ergometry at various pedaling frequencies and by treadmill running at various speeds. *Eur J Appl Physiol Occup Physiol* 1976; 35: 191–200.
 19. Astrand PO, Rodahl K. *Textbook of Work Physiology: Physiological Bases of Exercise*. New York, McGraw Hill, 1986.
 20. Balke B, Ware RW. An experimental study of physical fitness of Air Force personnel. *U S Armed Forces Med J* 1959; 10: 875–888.
 21. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. *Ann Clin Res* 1971; 3: 323–332.
 22. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. *J Appl Physiol* 1983; 55: 1558–1564.
 23. Cotes JE. *Lung Function: Assessment and Application in Medicine*. Oxford, Blackwell Scientific Publications, 1993.
 24. Ellestad MH. *Stress Testing: Principles and Practice*. Oxford, Oxford University Press, 2003.
 25. Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. *Am J Cardiol* 1972; 30: 757–762.
 26. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; 60: 2020–2027.
 27. Porszasz J, Casaburi R, Somfay A, Woodhouse LJ, Whipp BJ. A treadmill ramp protocol using simultaneous changes in speed and grade. *Med Sci Sports Exerc* 2003; 35: 1596–1603.
 28. Hsia D, Casaburi R, Torres E, Porszasz J. Comparison of responses to a new linearized treadmill protocol to incremental cycle ergometer and standard treadmill protocols in COPD patients. *Proc Am Thorac Soc* 2006; 3: A210.
-

29. Palange P, Forte S, Onorati P, Manfredi F, Serra P, Carlone S. Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. *J Appl Physiol* 2000; 88: 1715–1720.
30. Poulain M, Durand F, Palomba B, *et al.* 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. *Chest* 2003; 123: 1401–1407.
31. Casaburi R, Barstow TJ, Robinson T, Wasserman K. Dynamic and steady-state ventilatory and gas exchange responses to arm exercise. *Med Sci Sports Exerc* 1992; 24: 1365–1374.
32. Franklin B, Vander L, Wrisley D, Rubenfire M. Aerobic requirements of arm ergometry: implications for exercise testing and training. *Physician Sportsmed* 1983; 11: 81–90.
33. Sawka MN. Physiology of upper body exercise. *Exerc Sport Sci Rev* 1986; 14: 175–211.
34. Casaburi R. Exercise training in chronic obstructive lung disease. In: Casaburi R, Petty T, eds. *Principles and Practice of Pulmonary Rehabilitation*. Philadelphia, Saunders, 1993; pp. 204–224.
35. Celli BR, Rassulo J, Make BJ. Dyssynchronous breathing during arm but not leg exercise in patients with chronic airflow obstruction. *N Engl J Med* 1986; 314: 1485–1490.
36. Criner GJ, Celli BR. Effect of unsupported arm exercise on ventilatory muscle recruitment in patients with severe chronic airflow obstruction. *Am Rev Respir Dis* 1988; 138: 856–861.
37. Astrup P, Severinghaus J. *The History of Blood Gases, Acids and Bases*. Copenhagen, Munksgaard, 1986.
38. Erikson H, Scholander PF, Irving L. Apparatus for complete volumetric recording of the respiratory gaseous exchange in man. *Scand J Clin Lab Invest* 1951; 3: 228–233.
39. Johansson UB. Determination of respiratory gases (CO₂, O₂, Ar and N₂) with gas solid chromatography. *Scand J Clin Lab Invest* 1983; 43: 91–94.
40. Poole GW, Maskell RC. Validation of continuous determination of respired gases during steady-state exercise. *J Appl Physiol* 1975; 38: 736–738.
41. Spiro SG, Juniper E, Bowman P, Edwards RH. An increasing work rate test for assessing the physiological strain of submaximal exercise. *Clin Sci Mol Med* 1974; 46: 191–206.
42. Patton JF. Measurement of oxygen uptake with portable equipment. In: Carlson-Newberry SJ, Costello RB, eds. *Emerging Technologies for Nutrition Research: Potential for Assessing Military Performance Capability*. Washington, National Academy Press, 1997; pp. 297–314.
43. Sanjo Y, Ikeda K. A small bypass mixing chamber for monitoring metabolic rate and anesthetic uptake: the bymixer. *J Clin Monit* 1987; 3: 235–243.
44. Wideman L, Stoudemire NM, Pass KA, McGinnes CL, Gaesser GA, Weltman A. Assessment of the aerosport TEEM 100 portable metabolic measurement system. *Med Sci Sports Exerc* 1996; 28: 509–515.
45. Otis AB. Quantitative relationships in steady-state gas exchange. In: Fenn WO, Rahn H, eds. *Handbook of Physiology*. Washington DC, American Physiological Society, 1964; pp. 681–698.
46. Beaver WL, Lamarra N, Wasserman K. Breath-by-breath measurement of true alveolar gas exchange. *J Appl Physiol* 1981; 51: 1662–1675.
47. Beaver WL, Wasserman K, Whipp BJ. On-line computer analysis and breath-by-breath graphical display of exercise function tests. *J Appl Physiol* 1973; 34: 128–132.
48. Lamarra N, Whipp BJ. Measurement of pulmonary gas exchange. In: Maud PJ, Foster C, eds. *Physiological Assessment of Human Fitness*. Champaign, Human Kinetics, 1995; pp. 19–35.
49. Noguchi H, Ogushi Y, Yoshiya I, Itakura N, Yamabayashi H. Breath-by-breath VCO₂ and VO₂ required compensation for transport delay and dynamic response. *J Appl Physiol* 1982; 52: 79–84.
50. Sue DY, Hansen JE, Blais M, Wasserman K. Measurement and analysis of gas exchange during exercise using a programmable calculator. *J Appl Physiol* 1980; 49: 456–461.
51. Yamamoto Y, Takei Y, Mokushi K, Morita H, Mutoh Y, Miyashita M. Breath-by-breath measurement of alveolar gas exchange with a slow-response gas analyser. *Med Biol Eng Comput* 1987; 25: 141–146.
52. Wilmore JH, Costill DL. Adequacy of the Haldane transformation in the computation of exercise VO₂ in man. *J Appl Physiol* 1973; 35: 85–89.

-
53. Swanson G. Breath-by-breath considerations for gas exchange kinetics. In: Cerretelli P, Whipp BJ, eds. *Exercise Bioenergetics and Gas Exchange*. Amsterdam, Elsevier, 1980; pp. 211–222.
 54. Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
 55. Standardization of spirometry--1987 update. Statement of the American Thoracic Society. *Am Rev Respir Dis* 1987; 136: 1285–1298.
 56. Finucane KE, Egan BA, Dawson SV. Linearity and frequency response of pneumotachographs. *J Appl Physiol* 1972; 32: 121–126.
 57. Miller MR, Pincock AC. Linearity and temperature control of the Fleisch pneumotachograph. *J Appl Physiol* 1986; 60: 710–715.
 58. Yeh MP, Adams TD, Gardner RM, Yanowitz FG. Turbine flowmeter vs. Fleisch pneumotachometer: a comparative study for exercise testing. *J Appl Physiol* 1987; 63: 1289–1295.
 59. Porszasz J, Barstow TJ, Wasserman K. Evaluation of a symmetrically disposed Pitot tube flowmeter for measuring gas flow during exercise. *J Appl Physiol* 1994; 77: 2659–2665.
 60. Yoshiya I, Nakajima T, Nagai I, Jitsukawa S. A bidirectional respiratory flowmeter using the hot-wire principle. *J Appl Physiol* 1975; 38: 360–365.
 61. Yoshiya I, Shimada Y, Tanaka K. Evaluation of a hot-wire respiratory flowmeter for clinical applicability. *J Appl Physiol* 1979; 47: 1131–1135.
 62. Cooper CB, Harris ND, Howard P. Evaluation of a turbine flow meter (Ventilometer Mark 2) in the measurement of ventilation. *Respiration* 1990; 57: 243–247.
 63. Gardner RM. Monitoring of physiological data in a clinical environment. *Annu Rev Biophys Bioeng* 1972; 1: 211–224.
 64. Goto T, Saito H, Nakata Y, *et al.* Effects of xenon on the performance of various respiratory flowmeters. *Anesthesiology* 1999; 90: 555–563.
 65. Porszasz J, Riley M. Incorrect calculation of breath-by-breath gas exchange following rejected breaths. *J Appl Physiol* 1995; 78: 1618–1619.
 66. Beaver WL. Water vapor corrections in oxygen consumption calculations. *J Appl Physiol* 1973; 35: 928–931.
 67. Mogue LR, Rantala B. Capnometers. *J Clin Monit* 1988; 4: 115–121.
 68. Fletcher GF, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for health professionals from the American Heart Association. *Circulation* 1990; 82: 2286–2322.
 69. Ribisl PM, Liu J, Mousa I, *et al.* Comparison of computer ST criteria for diagnosis of severe coronary artery disease. *Am J Cardiol* 1993; 71: 546–551.
 70. Ramsey M 3rd. Blood pressure monitoring: automated oscillometric devices. *J Clin Monit* 1991; 7: 56–67.
 71. ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription. 5th Edn. Baltimore, Lippincott Williams & Wilkins, 2005.
 72. Clark JS, Votteri B, Ariagno RL, *et al.* Noninvasive assessment of blood gases. *Am Rev Respir Dis* 1992; 145: 220–232.
 73. The use of pulse oximetry during conscious sedation. Council on Scientific Affairs, American Medical Association. *JAMA* 1993; 270: 1463–1468.
 74. Tobin MJ. Respiratory monitoring. *JAMA* 1990; 264: 244–251.
 75. Ries AL, Farrow JT, Clausen JL. Accuracy of two ear oximeters at rest and during exercise in pulmonary patients. *Am Rev Respir Dis* 1985; 132: 685–689.
 76. Carlin BW, Clausen JL, Ries AL. The use of cutaneous oximetry in the prescription of long-term oxygen therapy. *Chest* 1988; 94: 239–241.
 77. Carlin BW, Clausen JL, Ries AL. The effects of exercise testing on the prescription of oxygen therapy. *Chest* 1994; 106: 361–365.
 78. Orenstein DM, Curtis SE, Nixon PA, Hartigan ER. Accuracy of three pulse oximeters during exercise and hypoxemia in patients with cystic fibrosis. *Chest* 1993; 104: 1187–1190.
 79. Hansen JE, Casaburi R. Validity of ear oximetry in clinical exercise testing. *Chest* 1987; 91: 333–337.
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80. Gehring H, Hornberger C, Matz H, Konecny E, Schmucker P. The effects of motion artifact and low perfusion on the performance of a new generation of pulse oximeters in volunteers undergoing hypoxemia. *Respir Care* 2002; 47: 48–60.
81. Ries AL, Prewitt LM, Johnson JJ. Skin color and ear oximetry. *Chest* 1989; 96: 287–290.
82. Zeballos RJ, Weisman IM. Reliability of noninvasive oximetry in black subjects during exercise and hypoxia. *Am Rev Respir Dis* 1991; 144: 1240–1244.
83. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; 129: S49–S55.
84. Robinson TE, Sue DY, Huszczuk A, Weiler-Ravell D, Hansen JE. Intra-arterial and cuff blood pressure responses during incremental cycle ergometry. *Med Sci Sports Exerc* 1988; 20: 142–149.
85. Contes J, Woolmer R. A comparison between 27 laboratories of the results of analysis of an expired gas sample. *J Physiol* 1962; 163: 36P–37P.
86. Jones NL, Kane JW. Quality control of exercise test measurements. *Med Sci Sports* 1979; 11: 368–372.
87. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. *Eur Respir J* 1997; 10: 2662–2689.
88. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
89. Clark JH, Greenleaf JE. Electronic bicycle ergometer: a simple calibration procedure. *J Appl Physiol* 1971; 30: 440–442.
90. Russell JC, Dale JD. Dynamic torque meter calibration of bicycle ergometers. *J Appl Physiol* 1986; 61: 1217–1220.
91. Van Praagh E, Bedu M, Roddier P, Coudert J. A simple calibration method for mechanically braked cycle ergometers. *Int J Sports Med* 1992; 13: 27–30.
92. Myers J. Instrumentation: equipment, calculations and validation. In: Myers J, ed. *Essentials of Cardiopulmonary Exercise Testing*. Champaign, Human Kinetics, 1996; pp. 59–81.
93. Huszczuk A, Whipp BJ, Wasserman K. A respiratory gas exchange simulator for routine calibration in metabolic studies. *Eur Respir J* 1990; 3: 465–468.
94. Reville SM, Morgan MD. Biological quality control for exercise testing. *Thorax* 2000; 55: 63–66.
95. Porszasz J, Woodhouse LJ, Casaburi R, Nguyen A, Tsurugaya H, Whipp BJ. Use of physiological calibration to validate gas exchange measurements during exercise. *Med Sci Sports Exerc* 2004; 36: S27.

Laboratory tests

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Ergometry is performed to assess exercise capacity in order to: 1) determine whether or not there is evidence of exercise intolerance; 2) identify which factors may contribute to the exercise limitation; and 3) investigate the safety or risks of exercise. Furthermore, unexplained dyspnoea during exercise is a frequent reason for exercise testing. Exercise testing is particularly important in the context of cardiopulmonary rehabilitation. Dyspnoea, impaired exercise tolerance and reduced quality of life are common complaints in patients with chronic respiratory disease. However, several lines of evidence point to the fact that the symptoms associated with chronic obstructive pulmonary disease (COPD), for example, show only weak correlation with resting lung function impairment [1]. Prediction of exercise performance based solely on resting pulmonary function is inaccurate (fig. 1) [2–4]. Factors, such as peripheral and respiratory muscle weakness and deconditioning, are now recognised as important contributors to reduced exercise tolerance in chronic respiratory disease [5–7], as well as in chronic heart failure. Respiratory muscle weakness contributes to hypercapnia [8], dyspnoea [5, 9, 10] and nocturnal oxygen desaturation [11]. Signs of inspiratory muscle fatigue during exercise have been observed by several investigators [12–14], although they are debated by others [15]. Moreover, inspiratory muscle strength has been shown to correlate significantly with walking distance [6, 16]. A higher mortality rate has been observed in patients with severe muscle weakness due to steroid-induced myopathy [17]. These are important observations since peripheral and respiratory muscle training might be able to improve physical performance, symptoms, quality of life and, possibly, even survival in such patients.

In addition, exercise testing can be performed for specific diagnostic purposes (*e.g.* exercise-induced asthma). Specific questions related to exercise capacity may be asked (*e.g.* in employment contexts). In addition, prediction of risk may be the reason for performing an exercise test (*e.g.* operability for lung resection and survival). Exercise intolerance has been shown to be one of the most important predictors of mortality in a broad range of diseases, including COPD, primary pulmonary hypertension, interstitial lung disease, primary pulmonary hypertension, chronic heart failure and cystic fibrosis [18–26]. A further specific indication is for quantification of the gains following interventions, such as medication, surgical procedures and rehabilitation.

Depending upon the specific question, clinicians may rely on more complex exercise tests requiring accurate measurement of pulmonary gas exchange and cardiocirculatory and muscular system responses, or they may prefer simpler but still useful tests for addressing clinical questions. In the former case, maximal (*i.e.* symptom-limited) incremental or high-intensity constant work-rate endurance exercise tests may be required, whereas, in the latter, field walking tests may suffice.

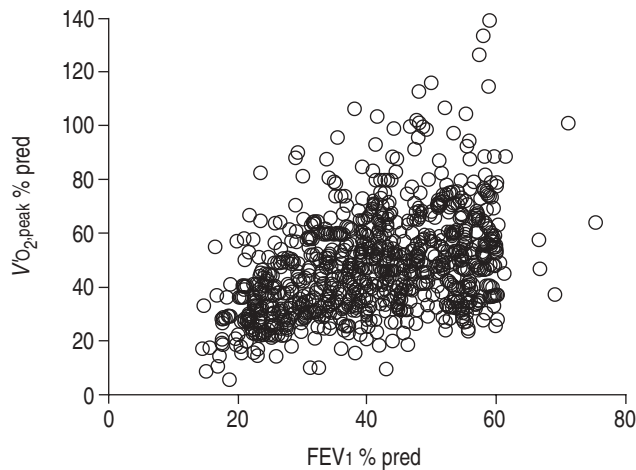


Fig. 1. – Relationship between pulmonary function (forced expiratory volume in one second (FEV₁)) and exercise capacity (peak oxygen uptake ($\dot{V}O_{2,\text{peak}}$)) in patients with chronic obstructive pulmonary disease. % pred: % predicted.

Available tests and how to choose the appropriate one

The gold standard in exercise testing is the laboratory-based maximal incremental test. Since it spans the entire range of tolerable work-rates, the incremental exercise test is the test of choice for: 1) assessment of impaired exercise capacity; 2) investigation into the factors limiting exercise performance; 3) assessment of risk of participation in exercise programmes; and 4) prescription of exercise training. For all of these indications, incremental exercise testing is necessary, as it provides clinicians with key data that cannot be obtained from resting measures of pulmonary function, cardiac function, arterial blood gas levels and acid/base status, or other less-comprehensive exercise tests. Furthermore, estimation of peak exercise responses based upon extrapolation of submaximal exercise data (mainly cardiac frequency (f_c)) are inappropriate in COPD patients, since these patients often do not reach their maximal predicted f_c . Therefore, standardised maximal exercise tests have been developed [27–29]. The introduction of computerised breath-by-breath equipment has made this test available to most clinical settings [30].

The most commonly selected ergometers for incremental exercise testing are the treadmill and cycle ergometer. The relative merits of each modality are detailed elsewhere [31]. It is worth noting, in this context, that treadmill walking may be particularly sensitive in the assessment of responses to bronchodilators, as it is less fatiguing for the lower-limb muscles [32]. Treadmill walking is also generally advised for paediatric exercise testing [33]. Symptom-limited constant work-rate tests (most usually on a cycle ergometer) and field walking tests are of considerable clinical value in the follow-up of interventions such as respiratory rehabilitation. As discussed in greater detail in Chapter 7 [34], field exercise tests, such as the 6- and 12-min walking tests [2], shuttle run or shuttle walk test [35], and stepping tests, are easy to perform and are attractive as they are more relevant to the activities of daily living [36, 37]. However, the lack of reference values for some of these tests and the absence of physiological measures should be viewed as important limitations. In healthy subjects, a fairly good correlation has been observed between peak oxygen uptake ($\dot{V}O_2$; $\dot{V}O_{2,\text{peak}}$) and walking test performance, however, this correlation is not sufficiently good to predict $\dot{V}O_{2,\text{peak}}$ in

individual subjects [38–40]. Nonetheless, incremental exercise testing and field testing have complementary value in assessment for pulmonary rehabilitation [41].

Maximal incremental exercise testing

Standardisation and technical procedures for reproducible exercise testing have been described [30, 42]. Since the mid 1990s, more extensive use of specially trained nonphysicians (physiologists, physiotherapists and technicians) in the conduct of exercise tests, with a physician immediately available for consultation or emergency situations, has become routine in hospitals and medical centres [43].

Test design

A maximal incremental exercise test consists of: 1) a resting baseline phase of ≥ 2 –3 min; 2) a period of unloaded pedalling (typically of ~ 3 min, normally sufficient for stabilisation of responses); 3) the incremental phase of the exercise test; and 4) a recovery period of unloaded pedalling or a very low work-rate in order to avoid any sudden drop in blood pressure due to pooling of venous blood. The choice of the appropriate work-rate increment size is of considerable importance in the tailoring of the test to the individual patient. Ideally, peak work-rate should be reached within 8–12 min [44]. The work-rate incrementation rate has important consequences when the incremental exercise results are used for exercise prescription in a pulmonary rehabilitation programme. That is, although the incrementation rate does not affect $\dot{V}O_{2,\text{peak}}$ or peak f_C , it does result in significant differences in peak work-rate; protocols with larger increments result in a higher peak work-rate (fig. 2) [45–47]. Consequently, this may impact upon the exercise prescription, as this is frequently based on peak work-rate. When patients are tested consecutively, the work-rate incrementation rate should be maintained constant between tests. Importantly, if a follow-up test of the patient is anticipated, it is important to standardise the positioning of the patient on the ergometer.

Measurements

For clinical purposes, primary and derived measurements typically include work-rate, 12-lead electrocardiography and f_C , pulmonary gas exchange ($\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$)), minute ventilation ($\dot{V}E$), end-tidal gas tensions, blood pressure, transcutaneous oxygen saturation and symptom scores (*e.g.* dyspnoea and exertion) [30, 46]. Assessment of blood lactate levels may be helpful in interpreting the level of deconditioning of patients. This may be particularly interesting in the context of exercise training prescription [48]. Symptom scores for dyspnoea and exertion have been shown to be valuable tools during exercise testing, at both peak exercise and specific time points during the test. Visual analogue and Borg scales are the most common methods used, and may be available in paper format or electronically. It should be noted that, although visual analogue and Borg scores cannot be interchanged, both show good agreement ($R^2=0.72$), and hence are valid assessment tools [49].

More recent technology permits the clinical use of inspiratory capacity during exercise, along with tidal flow–volume loop assessment [30]. The onset of dynamic hyperinflation parallels the onset of dyspnoea during exercise [50, 51]. Inclusion of arterial blood gas monitoring provides a further valuable adjunct.

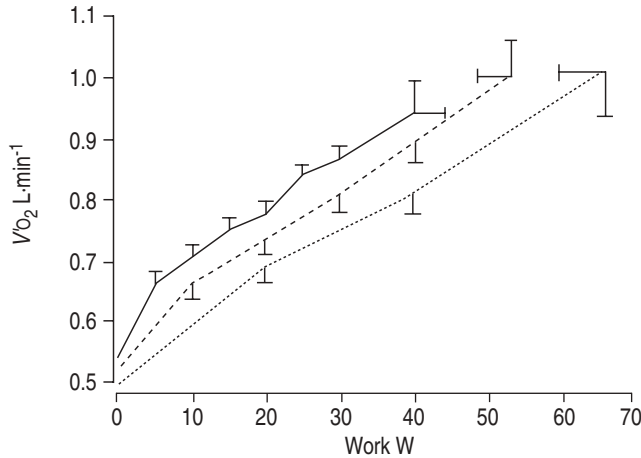


Fig. 2. – Exercise protocols for incremental exercise testing. —: 5 W·min⁻¹; - - - - -: 10 W·min⁻¹;: 20 W·min⁻¹. Data are presented as mean $\pm$ SD. It is of note that maximal oxygen uptake ($\dot{V}O_2$) does not differ between protocols, but maximal power output differs significantly. Reproduced from [45] with permission.

Interpretation

Responses at peak exercise (*e.g.* $\dot{V}O_{2,\text{peak}}$) and response profiles over the selected regions of the test (*e.g.* for lactate threshold discrimination) are integrated in order to answer questions regarding issues such as exercise capacity, safety of exercise, limitation of exercise and exercise prescription (for further details [52]). Comparison with appropriate reference values permits judgements to be made about the normalcy or otherwise of particular responses and functional indices (for further details [53]). For example, the European Respiratory Society (ERS) report on exercise impairment in patients with respiratory disease [54] reported on two equations for reference values for maximal $\dot{V}O_2$, with the cycle-ergometry equation of JONES *et al.* [55] having been particularly useful in clinical practice (table 1). In addition, exercise testing laboratories should be encouraged to test cohorts of healthy control subjects within the age span of interest in order to evaluate which normal values best suit their laboratory setting.

From a physiological perspective, exercise can be regarded as being maximal when one or more components related to oxygen transport or muscle force generation reach their operational limits. Ventilation, pulmonary gas exchange, and cardiocirculatory and muscle function (including peripheral gas exchange and bioenergetics) are considered to be the components of the oxygen transport chain. However, in the clinical context intolerable symptoms typically intercede prior to a true maximum being obtained. For example, KILLIAN *et al.* [56] found that Borg scores of 7–8 for either dyspnoea or exertion were perceived as intolerable symptoms.

Constant-load exercise testing

In the follow-up of patients after interventions, such as pulmonary rehabilitation or drug therapy, high-intensity constant-load or work-rate tests performed to the limit of tolerance on a cycle ergometer or treadmill have been shown to provide greater sensitivity than classical incremental tests [57, 58]. For example, the endurance time at the same work-rate is, on average, 80% greater following pulmonary rehabilitation

Table 1. – Reference values for maximal oxygen uptake $L \cdot min^{-1}$

	Reference equation
Whole population	$0.046H-0.021A-0.62S-4.31$ (SD 0.458)
Males	
Normal weight	$W(50.7-0.372A)$
Overweight	$(50.7-0.372A)+6(W-Wnl)$
Underweight	$0.5(Wnl+W)(50.7-0.372A)$
Females	
Normal weight	$(W+43)(22.78-0.17H)$
Overweight	$(W+43)(22.78-0.17A)+6(W-Wnl)$
Underweight	$0.5(Wnl+W+86)(22.78-0.17A)$

H: height cm; A: age yrs; S: sex (0 male; 1 female); W: weight kg; Wnl: predicted normal weight (0.65H–42.8).

compared to before training [59]. Test–retest reliability for these tests is also good [60]. Typically, such constant-load tests are performed at work-rates of $\sim 75\%$ of the peak work-rate attained in the preceding incremental test [60]. It is recommended, therefore, that at least one maximal incremental exercise test precedes the follow-up constant-load tests.

As described previously, [52, 61], a range of response parameters and indices can be extracted from constant-load test results, which can provide information on any associated exercise limitation. These range from simple considerations of exercise time and end-exercise $\dot{V}E$, f_c and symptom scores to the more formal kinetic analysis of systems responses (*e.g.* $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$; for further details [52, 61]). In addition, the measurement of ventilatory components, such as respiratory frequency, tidal volume and inspiratory capacity, yields unique insight into the mechanisms of action on respiratory mechanics of interventions such as bronchodilators, oxygen and pulmonary rehabilitation.

An index of note in this context is the critical power (CP; for further details [52, 61]). CP represents the highest sustainable work-rate, all higher work-rates lead to fatigue in a relatively short time and with a typically hyperbolic characteristic in not only healthy subjects but also patients with COPD [54, 62]. No large population studies have yet been performed to establish normal values for CP, but it has been shown to occur at $\sim 50\%$ of the $\dot{V}O_2$ range between the lactate threshold and $\dot{V}O_{2,peak}$ in normal subjects [63] and at $\sim 80\%$ in COPD patients [62]. It is problematic when CP is expressed as a percentage of the peak work-rate obtained from an incremental test, as this is influenced by the work-rate incrementation rate (see above). Thus, although not formally studied, it would be expected that CP, as a percentage of peak work-rate, would be lower with larger work-rate incrementation rates. This makes comparisons amongst studies particularly difficult.

Muscle testing

Assessment of skeletal muscle function contributes significantly to the evaluation of impairment, prognosis and effects of interventions in patients with COPD and congestive heart failure [64], sarcoidosis [65] and cystic fibrosis [66]. Skeletal muscle function is an independent marker of disease severity [67], since it contributes to the above-mentioned clinically relevant issues. Muscle function assessment enables diagnosis of muscle weakness, and thus the indication for rehabilitation. Indeed, isometric muscle testing has been shown to be helpful in selecting candidates for exercise training in health [68] and COPD [69]. COPD patients with muscle weakness seem to be

better responders to rehabilitation than patients with better preserved muscle strength [69]. Isometric muscle strength and endurance have also been found to be sensitive in the detection of changes in peripheral muscle function after rehabilitation [57, 70–73].

Skeletal muscle strength is, in general, reduced in COPD. However, the strength of arm muscle is less affected than that of the leg and respiratory muscles [74, 75], whereas the proximal arm muscles have been shown to be more affected than the distal arm and hand muscles [74]. This concurs with the enhanced mechanical efficiency in the upper limb, compared with the lower limb, in COPD [76]. Information on peripheral muscle function is helpful for optimising training prescription in a rehabilitation programme, permitting muscle training to be targeted specifically to more impaired muscle groups.

Assessment of respiratory and peripheral skeletal muscle function is discussed from the point of view of both the strength and endurance capacity of the muscles.

Peripheral muscle strength testing

Muscle strength, or, more precisely, the maximum muscle force or tension generated by a muscle or (more commonly) a group of muscles, can be measured in several ways and using a range of equipment.

Manual testing using the 0–5 UK Medical Research Council scale is often used in clinical practice, but is very insensitive in the assessment of differences in muscle strength above grade 3 (active movement against gravity over the full range of motion). Therefore, several systems have been developed to measure muscle strength more accurately.

One-repetition maximum weightlifting. For isotonic muscle force, one-repetition maximum (1-RM) weightlifting is a dynamic method for measuring the maximum amount of weight lifted on a single repetition during a standard weightlifting exercise. In order to achieve the maximum lift capacity, weight increments of 1–5 kg are typically used, with intervals of 1–5 min between attempts. In elderly people, 1-RM can be calculated from submaximal efforts [77]. For untrained persons, the calculated 1-RM (kg) is $1.554 \times (7-10\text{-RM}) - 5.181$, where 7–10-RM represents a set of 7–10 repetitions. The 7–10-RM weight (kg) represents ~70% of the 1-RM. For trained persons, the calculated 1-RM is $1.172 \times 7-10\text{-RM} + 7.704$, with the 7–10-RM representing ~80% of the 1-RM.

In COPD patients, these 1-RM tests have been shown to be safe [78] and sensitive for measuring changes after training [70]. However, to the best of the present authors' knowledge, no normative data exist for the 1-RM tests, and the recorded values are largely dependent upon the equipment used. Measurement of the 1-RM is often used for guiding muscle training programmes [79, 80].

Dynamometry. Dynamometry, using mechanical or electrical equipment, is used to measure isometric muscle force. With mechanical devices, a steel spring is most usually compressed, moving a pointer on a scale, as in the handgrip dynamometer (fig. 3) [81]. Handgrip dynamometry has been shown to be reliable, and reference values are available (table 2) [81, 82]. This approach has been used in several studies in COPD patients [6, 83–85].

For other upper and lower extremity muscle groups, hand-held electrical devices have been developed. These consist of an electronic force transducer connected to a computer (fig. 4). Two methods of isometric testing have been described, the make test and the break test. In the make test, the maximal force the subject can exert is equal to the force of the assessor. In the break test, the force of the assessor exceeds the force of the patient

slightly. Both tests are reproducible, but higher values have been obtained during break tests [86]. Hand-held dynamometry is a viable alternative to more costly modes of isometric strength measurement, provided the assessor's strength is greater than that of the specific muscle group being measured [86, 87]. Reference values are available, including for healthy elderly subjects (table 3) [88–90]. Hand-held devices for muscle testing have been used in COPD patients [74, 91]. In order to overcome bias by the investigator's strength, a hand-held device can be anchored in a specifically designed and fixed device. This then permits an isometric test to be performed with accuracy that is as good as that of computerised devices (see below).

Computer-assisted dynamometry. Computer-assisted dynamometers (fig. 5) for measuring isokinetic or isometric muscle strength have the advantage of measuring maximal muscle strength over a wide range of joint positions and velocities. This also takes into account the force–velocity characteristics of the muscle contraction. However, the equipment is very expensive and not available to many practitioners. Reference values are available for isometric [17] and isokinetic muscle testing [92]. In healthy subjects, isometric and isokinetic measurements correlate well [93, 94]. As peak muscle torque declines with increasing angular velocity, the peak torque is greatest for a given joint position in isometric tests. Although direct comparison between these measures has not been performed in COPD patients, two studies suggest that such a relationship also exists in COPD. Both isokinetic [5, 95] and isometric muscle strength [6, 96] were found to be significantly lower in COPD patients than in healthy subjects.

The limitation to the use of maximal voluntary contractions is the potential for the observation of submaximal contractions due to submaximal cortical drive [97, 98]. The use of superimposed electric or magnetic twitch contractions anticipates this potential variation in voluntary activation [97]. The technique of electrically superimposed twitch



Fig. 3. – Device for handgrip strength measurement.

Table 2. – Handgrip strength reference values[#]

Age range yrs	Side	Force kgf	
		Male	Female
22–24	R	55 ± 10	32 ± 7
	L	48 ± 10	28 ± 6
25–29	R	55 ± 10	34 ± 6
	L	50 ± 7	29 ± 5
30–34	R	56 ± 10	36 ± 9
	L	50 ± 10	31 ± 8
35–39	R	55 ± 11	34 ± 5
	L	51 ± 10	30 ± 5
40–44	R	53 ± 10	32 ± 6
	L	51 ± 9	28 ± 6
45–49	R	50 ± 10	28 ± 7
	L	46 ± 10	25 ± 6
50–54	R	52 ± 8	30 ± 5
	L	46 ± 8	26 ± 5
55–59	R	46 ± 12	26 ± 6
	L	38 ± 10	21 ± 5
60–64	R	41 ± 9	25 ± 5
	L	37 ± 9	21 ± 5
65–69	R	41 ± 10	23 ± 5
	L	35 ± 9	19 ± 4
70–74	R	35 ± 10	23 ± 5
	L	30 ± 8	19 ± 5
≥ 75	R	30 ± 10	20 ± 5
	L	25 ± 8	17 ± 4

Data are presented as mean ± SD. R: right; L: left. #: on scale of 1–100. 1 kgf = 9.80665 N. Data reproduced from [81] with permission.

contractions was developed, in 1954, by MERTON [99]. Twitch stimulation, however, is not suggested for routine clinical evaluation of muscle force. When standardised and maximal encouragement is given, isometric muscle strength assessment results in reliable and maximal data [98]. In order to address specific research questions, however, magnetic or electrical nerve stimulation may be useful. Magnetic stimulation is now a validated research procedure. It is less painful than electrical stimulation, and the twitch stimulations are relatively reproducible [100].

Peripheral muscle endurance testing

The evaluation of lower-limb muscle performance in patients with COPD has mainly focused on muscle strength. In addition to reduced muscle fibre [101] and muscle cross-sectional area [102], changes in the fibre type composition, resulting in a decrement of fatigue-resistant slow fibres [101–103] and a reduction in oxidative enzymes [104–106], are the main morphological and histochemical alterations found in lower-limb skeletal muscles. Based on these morphological and histochemical alterations in muscle biopsy specimens, it may be hypothesised that lower-limb muscle endurance is decreased more than muscle strength in patients with COPD. Indeed, the histochemical changes were shown to be related to skeletal muscle endurance in COPD [107]. NEWELL *et al.* [108] observed only a slight reduction in endurance capacity (torque reduction over 18 contractions) of elbow flexors in COPD patients compared with healthy subjects. The same was concluded for sustained contractions of the triceps and deltoid muscles, which



Fig. 4. – Hand-held device for assessment of isometric muscle strength.

Table 3. – Reference values for isometric muscle strength assessed via hand-held dynamometry

Movement	Reference equation
Knee extension	$y=358.455-87.581S+2.914W-3.136A$
Knee flexion	$y=142.244-52.112S+1.85W-0.892A$
Shoulder abduction	$y=198.341-68.686S+1.324W-1.462A$
Elbow flexion	$y=229.421-84.836S+1.618W-1.503A$
Elbow extension	$y=112.597-49.858S+1.364W-0.834A$



Fig. 5. – Computerised device for assessment of isometric and isokinetic muscle strength.

did not differ between healthy subjects and patients with mild COPD [95]. Along the same lines, the endurance (time to maintain 80% of peak torque) of the quadriceps muscle in hypoxaemic COPD patients was normal [109]. In contrast, several authors reported significant reductions in skeletal muscle endurance [107, 110–113]. For example, SERRES *et al.* [111] found a mean reduction of 50% in quadriceps muscle endurance (number of contractions made at submaximal (20–40% of peak) torque) in patients with moderate-to-severe COPD [111]. In most of these studies, the reduction in skeletal muscle endurance was more pronounced than the reduction in simple skeletal muscle peak force.

Unfortunately, there is no uniformity among the protocols used for assessing isolated muscle endurance. In one protocol, the time of a sustained maximal isometric muscle contraction until 60% of the initial maximal strength remains is measured [114]. During this test, blood supply is profoundly reduced and muscle contraction is very much dependent upon anaerobic metabolism. In a second, the decline in maximal force after a fixed number (18) of repetitive contractions, with a fixed contraction (10 s) and relaxation time (5 s), is assessed [115]. A third protocol consists of repeated contractions of 20% of the maximal voluntary contraction at a rate of 12 contractions·min⁻¹ until exhaustion [111, 116]. The latter two protocols are probably more related to oxidative capacity, since these dynamic muscle contractions, at a low percentage of peak torque, do not induce closure of capillaries in the muscle and thus do not deprive the muscle of its oxygen supply.

After a specific muscle endurance training programme, significant improvements in the number of repetitions of loaded and unloaded isotonic contraction of upper and lower extremities over a 30-s period have been observed [117]. Although no data have been reported regarding the reproducibility of this measurement, control subjects had not changed their performance at their second visit after 12 weeks [117]. This may suggest that the test is reproducible.

Respiratory muscle strength testing

In clinical practice, respiratory muscle strength is measured as maximal inspiratory and expiratory mouth pressure ($P_{I,max}$ and $P_{E,max}$, respectively). These pressure measurements are made *via* a small cylinder attached to the mouth by means of a circular mouthpiece (fig. 6). A small leak (diameter 2 mm, length 15 mm) prevents artificially high pressures due to contraction of cheek muscles [118]. An important part of the standardisation is the lung volume at which the pressures are measured [119]. In order to prevent contribution of chest wall and lung recoil pressure to the pressure generation of the inspiratory muscles, it is preferable to perform measurements at functional residual capacity. However, this lung volume is difficult to standardise. In clinical practice, $P_{I,max}$ is measured from residual volume, whereas $P_{E,max}$ is taken from total lung capacity. At least five repetitions should be performed. A recent American Thoracic Society/ERS statement describes respiratory muscle testing in more detail [120].

Several groups have developed normal values (table 4) [118, 123, 124]. However, regardless of which set of normal values is used, the SD is large. Since the technique is very much dependent upon the standardisation procedures and equipment, it is recommended that a series of healthy subjects are assessed in order to choose the most appropriate reference values. Even then, it is still not easy to define weakness [127]. Inspiratory weakness is accepted when $P_{I,max}$ is $<50\%$ of the predicted value [128]. Indeed, in studies investigating the effects of inspiratory muscle training, significant



Fig. 6. – Device for assessment of respiratory muscle strength.

improvement in exercise performance or nocturnal desaturation time has been observed in patients with a mean $P_{I,max}$ of $<60\%$ pred [11, 122, 130]. Finally, respiratory muscle strength has been reported to be a significant determinant of survival in patients with COPD [17].

Other techniques have also been developed to assess global respiratory muscle function, such as sniff manoeuvres [131]. The latter have been shown to be especially reliable when testing children with neuromuscular disease. More invasive techniques, such as electric or magnetic diaphragm stimulation, certainly provide more accurate information on diaphragm function [132, 133], and are useful in the diagnosis of diaphragmatic paresis. However, for clinical applications, assessment of $P_{I,max}$ and $P_{E,max}$ should be sufficient.

Respiratory muscle endurance testing

Several tests of endurance capacity have been described. The most frequently used are those in which the patient breathes against a submaximal inspiratory load ($60\text{--}75\%$ $P_{I,max}$) for as long as possible [130, 134]. This test has been shown to be sensitive to changes after inspiratory muscle training. Incremental threshold loading, *i.e.* breathing against an incremental load that is increased every 2 min (~ 5 cmH₂O), has also been shown to be reproducible [135]. The highest load that can be sustained for 2 min is the sustainable pressure, expressed as a percentage of the maximal load [135, 136]. Normal subjects have been reported to sustain 70% of the $P_{I,max}$ for 2 min [136]. JOHNSON *et al.* [135] found that this percentage varied considerably between subjects and tended to decrease with age. The sustainable pressure has been shown to be more reduced than $P_{I,max}$ and $P_{E,max}$ in COPD [137]. A third method is the performance of repetitive maximal inspiratory or expiratory manoeuvres against an occluded airway, with a well-defined contraction duration (10 s) and relaxation time (5 s) [114, 115, 138]. The relative decline in maximal pressure after 18 contractions is a measure of endurance capacity.

Tests of peripheral and respiratory muscle function are helpful in detecting muscle weakness. All of these tests have their limitations, such as motivation dependency, reproducibility, availability of reference values and costs. However, muscle weakness has been shown to be quite strongly associated with symptoms, exercise performance, utilisation of healthcare resources and mortality. Therefore, these measurements have

Table 4. – Reference values for maximal inspiratory and expiratory mouth pressure ($P_{I,max}$ and $P_{E,max}$, respectively) in adults

First author [Ref.]	Year	Sex	$P_{I,max}$	$P_{E,max}$
BLACK [118]	1969	M	124 ± 22	233 ± 42
		F	87 ± 16	152 ± 27
RINQVIST [121]	1966	M	130 ± 32	237 ± 46
		F	98 ± 25	165 ± 30
LEECH [122]	1983	M	114 ± 36	154 ± 82
		F	71 ± 27	94 ± 33
ROCHESTER [123]	1983	M	127 ± 28	216 ± 41
		F	91 ± 25	138 ± 39
WILSON [124]	1984	M	106 ± 31	148 ± 17
		F	73 ± 22	93 ± 17
VINCKEN [125]	1987	M	105 ± 25	140 ± 38
		F	71 ± 23	89 ± 24
BRUSCHI [126]	1992	M	120 ± 37	140 ± 30
		F	84 ± 30	95 ± 20

Data are presented as mean $\pm$ SD. M: male; F: female.

become more important in clinical practice, especially when low muscle function is associated with clinical symptoms of weakness (fatigue and dyspnoea). The addition of tests of muscle endurance needs further research in order to define its contribution to the diagnosis of muscle dysfunction.

Conclusion

Exercise testing has gained popularity in a variety of clinical conditions, and, specifically, in pulmonary rehabilitation. Maximal incremental exercise testing has its main emphasis on the diagnosis of exercise intolerance and the mechanisms underlying this impairment. Field tests have their application mostly in the longitudinal assessment of exercise performance, such as the evaluation of interventions. More detailed insight into skeletal muscle function is obtained by specific assessment of muscle force and endurance. These tests may, therefore, complement routine exercise testing.

Summary

Exercise and muscle testing have gained popularity in a variety of clinical conditions and, specifically, in pulmonary rehabilitation. Maximal incremental exercise testing has its main emphasis on the diagnosis of exercise intolerance and the mechanisms underlying this impairment. Field tests have their application mostly in longitudinal assessment of exercise performance, such as the evaluation of interventions. More detailed insight into skeletal (respiratory and peripheral) muscle function is obtained by specific assessment of muscle force and endurance. Therefore, these tests may complement routine exercise testing and help in indicating and tracking the effects of specific interventions addressing muscle weakness.

Keywords: Endurance exercise, incremental exercise, muscle endurance, muscle strength, peripheral, respiratory.

References

1. Wasserman K, Sue DY, Casaburi R, Moricca RB. Selection criteria for exercise training in pulmonary rehabilitation. *Eur Respir J* 1989; 2: Suppl. 7, 604s–610s.
2. McGavin CR, Gupta SP, McHardy GJR. Twelve-minute walking test for assessing disability in chronic bronchitis. *BMJ* 1976; 1: 822–823.
3. Morgan AD, Peck DF, Buchanan DR, McHardy GJR. Effect of attitudes and beliefs on exercise tolerance in chronic bronchitis. *BMJ* 1983; 286: 171–173.
4. Swinburn CR, Wakefield JM, Jones PW. Performance, ventilation, and oxygen consumption in three different types of exercise test in patients with chronic obstructive lung disease. *Thorax* 1985; 40: 581–586.
5. Hamilton N, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 1995; 152: 2021–2031.
6. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996; 153: 976–980.

7. Saey D, Debigare R, Leblanc P, *et al.* Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 168: 425–430.
8. Begin P, Grassino A. Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 143: 905–912.
9. Killian KJ, Jones NL. Respiratory muscles and dyspnea. *Clin Chest Med* 1988; 9: 237–248.
10. McParland C, Krishnan B, Wang Y, Gallagher CG. Inspiratory muscle weakness and dyspnea in chronic heart failure. *Am Rev Respir Dis* 1992; 146: 467–472.
11. Heijdra YF, Dekhuijzen PNR, van Herwaarden CLA, Folgering HTM. Nocturnal saturation improves by target-flow inspiratory muscle training in patients with COPD. *Am J Respir Crit Care Med* 1996; 153: 260–265.
12. Grassino A, Gross D, Macklem PT, Roussos C, Zigelbaum G. Inspiratory muscle fatigue as a factor limiting exercise. *Bull Eur Physiopathol Respir* 1979; 15: 105–111.
13. Pardy RL, Rivington RN, Despas PJ, Macklem PT. The effects of inspiratory muscle training on exercise performance in chronic airflow limitation. *Am Rev Respir Dis* 1981; 123: 426–433.
14. Fitting JW. Respiratory muscle fatigue limiting physical exercise? *Eur Respir J* 1991; 4: 103–108.
15. Polkey MI, Kyroussis D, Keilty SE, *et al.* Exhaustive treadmill exercise does not reduce twitch transdiaphragmatic pressure in patients with COPD. *Am J Respir Crit Care Med* 1995; 152: 959–964.
16. Wijkstra PJ, Ten Vergert EM, Van der Mark TW, *et al.* Relation of lung function, maximal inspiratory pressure, dyspnoea, and quality of life with exercise capacity in patients with chronic obstructive pulmonary disease. *Thorax* 1994; 49: 468–472.
17. Decramer M, de Bock V, Dom R. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 153: 1958–1964.
18. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003; 167: 544–549.
19. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004; 23: 28–33.
20. Corra U, Mezzani A, Bosimini E, Giannuzzi P. Cardiopulmonary exercise testing and prognosis in chronic heart failure: a prognosticating algorithm for the individual patient. *Chest* 2004; 126: 942–950.
21. Gibbons RJ, Balady GJ, Beasley JW, *et al.* ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 1997; 30: 260–311.
22. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following out-patient pulmonary rehabilitation. *Eur Respir J* 1996; 9: 431–435.
23. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med* 1992; 327: 1785–1788.
24. King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001; 164: 1171–1181.
25. Miki K, Maekura R, Hiraga T, *et al.* Impairments and prognostic factors for survival in patients with idiopathic pulmonary fibrosis. *Respir Med* 2003; 97: 482–490.
26. Wensel R, Opitz CF, Anker SD, *et al.* Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation* 2002; 106: 319–324.
27. Hermansen L, Saltin B. Oxygen uptake during maximal treadmill and bicycle exercise. *J Appl Physiol* 1969; 25: 31–37.
28. McArdle WD, Katch FI, Pechar GS. Comparison of continuous and discontinuous treadmill and bicycle tests for max $\dot{V}O_2$. *Med Sci Sports Exerc* 1973; 5: 156–160.
29. Astrand P-O, Saltin B. Maximal oxygen uptake and heart rate in various types of muscular activity. *J Appl Physiol* 1961; 16: 977–981.

-
30. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
 31. O'Donnell DE, Ofir D, Laveneziana P. Patterns of cardiopulmonary response to exercise in lung diseases. In: Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 40: 69–92.
 32. Pepin V, Saey D, Whittom F, Leblanc P, Maltais F. Walking versus cycling: sensitivity to bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 1517–1522.
 33. Carlsen K. Exercise testing in children. In: Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 40: 186–194.
 34. Singh S. Field tests. In: Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 40: 148–164.
 35. Singh SJ, Morgan MDL, Scott S, Walters, Hardman AE. The development of the shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992; 47: 1019–1024.
 36. Belza B, Steele BG, Hunziker J, Lakshminaryan S, Holt L, Buchner DM. Correlates of physical activity in chronic obstructive pulmonary disease. *Nurs Res* 2001; 50: 195–202.
 37. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 972–977.
 38. Astrand I. Aerobic work capacity in men and women. *Acta Physiol Scand* 1960; 49: Suppl. 169, 7–92.
 39. Froelicher VF, Brammel H, Davis G, Noguera I, Stewart A, Lancaster MC. A comparison of the reproducibility and physiologic response to three maximal treadmill exercise protocols. *Chest* 1974; 65: 512–517.
 40. Froelicher VF, Thompson AJ, Noguera I, Davis G, Stewart AJ, Triebwasser JH. Prediction of maximal oxygen consumption. Comparison of the Bruce and Balke protocols. *Chest* 1975; 68: 331–336.
 41. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 2001; 119: 256–270.
 42. Wasserman K, Stringer WW, Casaburi R, Koike A, Cooper CB. Determination of the anaerobic threshold by gas exchange: biochemical considerations, methodology and physiological effects. *Z Kardiol* 1994; 83: Suppl. 3, 1–12.
 43. Franklin BA, Gordon S, Timmis GC, O'Neill WW. Is direct physician supervision of exercise stress testing routinely necessary? *Chest* 1997; 111: 262–265.
 44. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessments. *J Appl Physiol* 1983; 55: 1558–1564.
 45. Debigare R, Maltais F, Mallet M, Casaburi R, Leblanc P. Influence of work rate incremental rate on the exercise responses in patients with COPD. *Med Sci Sports Exerc* 2000; 32: 1365–1368.
 46. Wasserman K, Hansen JE, Sue DY, Stringer W, Whipp BJ. Principles of Exercise Testing and Interpretation. 4th Edn. Philadelphia, Lea & Febiger, 2004.
 47. Whipp BJ. The bioenergetic and gas exchange basis of exercise testing. *Clin Chest Med* 1994; 15: 173–192.
 48. Nici L, Donner C, Wouters E, *et al.* American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006; 173: 1390–1413.
 49. Wilson RC, Jones PW. Differentiation between the intensity of breathlessness and the distress it evokes in normal subjects during exercise. *Clin Sci (Lond)* 1991; 80: 65–70.
 50. O'Donnell DE, Bertley JC, Chau LK, Webb KA. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med* 1997; 155: 109–115.
 51. O'Donnell D, Hamilton AL, Webb KA. Sensory–mechanical relationships during high intensity, constant work rate exercise in COPD. *J Appl Physiol* 2006; 101: 1025–1035.
 52. Ward SA. Discriminating features of responses in cardiopulmonary exercise testing. In: Ward SA, Palange P, eds. Clinical Exercise Testing. *Eur Respir Mon* 2007; 40: 36–68.
-

53. Puente-Maestu L, Roca J. Reference values in adults. *In: Ward SA, Palange P, eds. Clinical Exercise Testing. Eur Respir Mon* 2007; 40: 165–185.
54. Cotes JE. Rating respiratory disability: a report on behalf of a working group of the European Society for Clinical Respiratory Physiology. *Eur Respir J* 1990; 3: 1074–1077.
55. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985; 131: 700–708.
56. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJM. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992; 146: 935–940.
57. O'Donnell DE, McGuire MA, Samis L, Webb KA. General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. *Am J Respir Crit Care Med* 1998; 157: 1489–1497.
58. O'Donnell DE, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158: 1557–1565.
59. Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 19–38.
60. van 't Hul AJ, Gosselink R, Kwakkel G. Constant-load cycle endurance performance: test–retest reliability and validity in patients with COPD. *J Cardiopulm Rehabil* 2003; 23: 143–150.
61. Whipp BJ, Wagner PD, Agusti A. Factors determining the response to exercise in healthy subjects. *In: Ward SA, Palange P, eds. Clinical Exercise Testing. Eur Respir Mon* 2007; 40: 1–35.
62. Puente-Maestu L, SantaCruz A, Vargas T, Martinez-Abad Y, Whipp BJ. Effects of training on the tolerance to high-intensity exercise in patients with severe COPD. *Respiration* 2003; 70: 367–370.
63. Morton RH. The critical power and related whole-body bioenergetic models. *Eur J Appl Physiol* 2006; 96: 339–354.
64. Gosker HR, Wouters EF, van der Vusse GJ, Schols AM. Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: underlying mechanisms and therapy perspectives. *Am J Clin Nutr* 2000; 71: 1033–1047.
65. Spruit MA, Thomeer MJ, Gosselink R, *et al.* Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. *Thorax* 2005; 60: 32–38.
66. Pinet C, Scillia P, Cassart M, *et al.* Preferential reduction of quadriceps over respiratory muscle strength and bulk after lung transplantation for cystic fibrosis. *Thorax* 2004; 59: 783–789.
67. Marquis K, Debigare R, Lacasse Y, *et al.* Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 809–813.
68. Wilson GJ, Murphy AJ. Strength diagnosis: the use of test data to determine specific strength training. *J Sports Sci* 1996; 14: 167–173.
69. Troosters T, Gosselink R, Decramer M. Exercise training: how to distinguish responders from non-responders. *J Cardiopulm Rehabil* 2001; 21: 10–17.
70. Simpson K, Killian KJ, McCartney N, Stubbing DG, Jones NL. Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. *Thorax* 1992; 47: 70–75.
71. Troosters T, Gosselink R, Rollier H, Decramer M. Increases in peripheral muscle strength contribute to improved quality of life in COPD patients. *Am J Respir Crit Care Med* 1996; 153: A425.
72. Troosters T, Gosselink R, Rollier H, Decramer M. Change in lower limb muscle strength contributes to altered six minute walking distance in COPD. *Eur Respir J* 1996; Suppl. 23, 9: 144s.
73. Troosters T, Gosselink R, Decramer M. Short and long-term effects of outpatient pulmonary rehabilitation in COPD patients, a randomized controlled trial. *Am J Med* 2000; 109: 207–212.
74. Gosselink R, Troosters T, Decramer M. Distribution of respiratory and peripheral muscle weakness in patients with stable COPD. *J Cardiopulm Rehabil* 2000; 20: 353–358.

75. Bernard S, Leblanc P, Whittom F, *et al.* Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158: 629–634.
76. Franssen FM, Wouters EF, Baarends EM, Akkermans MA, Schols AM. Arm mechanical efficiency and arm exercise capacity are relatively preserved in chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2002; 34: 1570–1576.
77. Braith RW, Graves JE, Leggett SH, Pollock ML. Effect of training on the relationship between maximal and submaximal strength. *Med Sci Sports Exerc* 1993; 25: 132–138.
78. Kaelin ME, Swank AM, Adams KJ, Barnard KL, Berning JM, Green A. Cardiopulmonary responses, muscle soreness, and injury during the one repetition maximum assessment in pulmonary rehabilitation patients. *J Cardiopulm Rehabil* 1999; 19: 366–372.
79. Frontera WR, Meredith CN, O'Reilly KP, Knuttgen HG, Evans WJ. Strength conditioning in older men: skeletal muscle hypertrophy and improved function. *J Appl Physiol* 1988; 64: 1038–1044.
80. Frontera WR, Meredith CN, O'Reilly KP, Evans WJ. Strength training and determinants of $\dot{V}O_{2\max}$ in older men. *J Appl Physiol* 1990; 68: 329–333.
81. Mathiowetz V, Dove M, Kashman N, Rogers S. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil* 1985; 66: 69–72.
82. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. *J Hand Surg [Am]* 1984; 9A: 22–26.
83. Wilson DO, Rogers RM, Sanders MH, Pennock BE, Reilly JJ. Nutritional intervention in malnourished patients with emphysema. *Am Rev Respir Dis* 1986; 134: 672–677.
84. Kutsuzawa T, Shioya S, Kurita D, Haida M, Ohta Y, Yamabayashi H. Muscle energy metabolism and nutritional status in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152: 647–652.
85. Kutsuzawa T, Shioya S, Kurita D, Haida M, Ohta Y, Yamabayashi H. P-NMR study of skeletal muscle metabolism in patients with chronic respiratory impairment. *Am Rev Respir Dis* 1992; 146: 1019–1024.
86. Stratford PW, Balsor BE. A comparison of make and break tests using a hand-held dynamometer and the Kin-Com. *J Orthop Sports Phys Ther* 1994; 19: 28–32.
87. Troosters T, Gosselink R, Decramer M. How accurate are measures of peripheral muscle with hand held myometry? *Am J Respir Crit Care Med* 2000; 161: A752.
88. Andrews AW, Thomas MW, Bohannon RW. Normative values for isometric muscle force measurements obtained with hand-held dynamometers. *Phys Ther* 1996; 76: 248–259.
89. van der Ploeg RJO, Fidler V, Oosterhuis JHGH. Hand-held myometry: reference values. *J Neurol Neurosurg Psychiatr* 1991; 54: 244–247.
90. Phillips BA, Lo SK, Mastaglia FL. Muscle force measured using “break” testing with a hand-held myometer in normal subjects aged 20 to 69 years. *Arch Phys Med Rehabil* 2000; 81: 653–661.
91. Troosters T, Gosselink R, Decramer M. Reliability of handheld myometry to measure peripheral muscle strength in COPD. *Eur Respir J* 1999; 14: 481.
92. Neder JA, Nery LE, Shinzato GT, Andrade MS, Peres C, Silva AC. Reference values for concentric knee isokinetic strength and power in non-athletic men and women from 20 to 80 years old. *J Orthop Sports Phys Ther* 1999; 29: 116–126.
93. Borges O. Isometric and isokinetic knee extension and flexion torque in men and women aged 20–70. *Scand J Rehab Med* 1989; 21: 45–53.
94. Lord JP, Aitkens SG, McCrory MA, Bernauer EM. Isometric and isokinetic measurement of hamstring and quadriceps strength. *Arch Phys Med Rehabil* 1992; 73: 324–330.
95. Clark CJ, Cochrane LM, Mackay E, Paton B. Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training. *Eur Respir J* 2000; 15: 92–97.
96. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med* 1994; 150: 11–16.
97. Allen GM, Gandevia SC, McKenzie DK. Reliability of measurements of muscle strength and voluntary activation using twitch interpolation. *Muscle Nerve* 1995; 18: 593–600.

98. Polkey MI, Kyroussis D, Harris ML, Hughes PD, Green M, Moxham J. Are voluntary manoeuvres maximal in routine clinical testing? *Am J Respir Crit Care Med* 1996; 153: A785.
99. Merton PA. Voluntary strength and fatigue. *J Physiol* 1954; 123: 553–564.
100. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Quadriceps strength and fatigue assessed by magnetic stimulation of the femoral nerve in man. *Muscle Nerve* 1996; 19: 549–555.
101. Whittom F, Jobin J, Simard P-M, *et al.* Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 1998; 30: 1467–1474.
102. Jakobsson P, Jorfeldt L, Brundin A. Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure. *Eur Respir J* 1990; 3: 192–196.
103. Evans AB, Al-Himyary AJ, Hrovat MI, *et al.* Abnormal skeletal muscle oxidative capacity after lung transplantation by ³¹P-MRS. *Am J Respir Crit Care Med* 1997; 155: 615–621.
104. Payen J-P, Wuyam B, Levy P, *et al.* Muscular metabolism during oxygen supplementation in patients with chronic hypoxemia. *Am Rev Respir Dis* 1993; 147: 592–598.
105. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes P, Leblanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med* 1996; 153: 288–293.
106. Maltais F, Jobin J, Sullivan MJ, *et al.* Metabolic and hemodynamic responses of lower limb during exercise in patients with COPD. *J Appl Physiol* 1998; 84: 1573–1580.
107. Allaire J, Maltais F, Doyon JF, *et al.* Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. *Thorax* 2004; 59: 673–678.
108. Newell SZ, McKenzie DK, Gandevia SC. Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with chronic airflow limitation. *Thorax* 1989; 44: 903–912.
109. Zattara-Hartmann MC, Badier M, Guillot C, Tomei C, Jammes Y. Maximal force and endurance to fatigue of respiratory and skeletal muscles in chronic hypoxemic patients: the effects of oxygen breathing. *Muscle Nerve* 1995; 18: 495–502.
110. Van't Hul A, Harlaar J, Gosselink R, Hollander P, Postmus P, Kwakkel G. Quadriceps muscle endurance in patients with chronic obstructive pulmonary disease. *Muscle Nerve* 2004; 29: 267–274.
111. Serres I, Gautier V, Varray A, Prefaut C. Impaired skeletal muscle endurance related to physical inactivity and altered lung function in COPD patients. *Chest* 1998; 113: 900–905.
112. Coronell C, Orozco-Levi M, Mendez R, Ramirez-Sarmiento A, Galdiz JB, Gea J. Relevance of assessing quadriceps endurance in patients with COPD. *Eur Respir J* 2004; 24: 129–136.
113. Koechlin C, Couillard A, Simar D, *et al.* Does oxidative stress alter quadriceps endurance in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2004; 169: 1022–1027.
114. Gandevia SC, McKenzie DK, Neering IR. Endurance capacity of respiratory and limb muscles. *Respir Physiol* 1983; 53: 47–61.
115. McKenzie DK, Gandevia SC. Influence of muscle length on human inspiratory and limb muscle endurance. *Respir Physiol* 1987; 67: 171–182.
116. Monod H, Scherrer J. The work capacity of a synergic muscular group. *J Appl Physiol* 1965; 8: 329–338.
117. Clark CJ, Cochrane JE, Mackay E. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. *Eur Respir J* 1996; 9: 2590–2596.
118. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969; 99: 696–702.
119. Coast JR, Weise SD. Lung volume changes and maximal inspiratory pressure. *J Cardiopulm Rehabil* 1990; 10: 461–464.
120. American Thoracic Society, European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002; 166: 518–624.
121. Rinqvist T. The ventilatory capacity in healthy adults: an analysis of causal factors with special reference to the respiratory forces. *Scand J Clin Lab Invest* 1966; 18: 1–111.

-
122. Leech JA, Ghezzi H, Stevens D, Blecklake MR. Respiratory pressures and function in young adults. *Am Rev Respir Dis* 1983; 128: 17–23.
 123. Rochester D, Arora NS. Respiratory muscle failure. *Med Clin North Am* 1983; 67: 573–598.
 124. Wilson DO, Cooke NT, Edwards RHT, Spiro SG. Predicted normal values for maximal respiratory pressures in Caucasian adults and children. *Thorax* 1984; 39: 535–538.
 125. Vincken W, Ghezzi H, Cosio MG. Maximal static respiratory pressures in adults: normal values and their relationship to determinants of respiratory function. *Bull Eur Physiopathol Respir* 1987; 23: 435–439.
 126. Bruschi C, Cerveri I, Zoia MC. Reference values of maximal respiratory mouth pressures: a population-based study. *Am Rev Respir Dis* 1992; 146: 790–793.
 127. Polkey MI, Green M, Moxham J. Measurement of respiratory muscle strength. *Thorax* 1995; 50: 1131–1135.
 128. DeVito E, Grassino A. Respiratory muscle fatigue. Rationale for diagnostic tests. In: Roussos C, ed. *The Thorax*. 2nd Edn. New York, Marcel Dekker, Inc., 1995; pp. 1857–1879.
 129. Dekhuijzen PN, Folgering HT, Van Herwaarden CL. Target-flow inspiratory muscle training during pulmonary rehabilitation in patients with COPD. *Chest* 1991; 99: 128–133.
 130. Wanke T, Formanek D, Lahrmann H, *et al.* The effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD. *Eur Respir J* 1994; 7: 2205–2211.
 131. Koulouris N, Mulvey DA, Laroche CM, Sawicka EH, Green M, Moxham J. The measurement of inspiratory muscle strength by sniff esophageal, nasopharyngeal, and mouth pressures. *Am Rev Respir Dis* 1989; 139: 641–646.
 132. Yan S, Gauthier AP, Similowski T, Macklem PT, Bellemare F. Evaluation of human contractility using mouth pressure twitches. *Am Rev Respir Dis* 1992; 145: 1064–1069.
 133. Similowski T, Fleury B, Launois S, Cathala HP, Bouche P, Derenne JP. Cervical magnetic stimulation: a new painless method for bilateral phrenic nerve stimulation in conscious humans. *J Appl Physiol* 1989; 67: 1311–1318.
 134. Rochester DF. Tests of respiratory muscle function. *Clin Chest Med* 1988; 9: 249–261.
 135. Johnson PH, Cowley AJ, Kinnear W. Incremental threshold loading: a standard protocol and establishment of a reference range in naive normal subjects. *Eur Respir J* 1997; 10: 2868–2871.
 136. Martyn JB, Moreno RH, Pare PD, Pardy RL. Measurement of inspiratory muscle performance with incremental threshold loading. *Am Rev Respir Dis* 1987; 135: 919–923.
 137. van 't Hul AJ, Chadwick-Straver RVM, Wagenaar RC, Sol G, de Vries PMJM. Inspiratory muscle endurance is reduced more than maximal respiratory pressures in COPD patients. *Eur Respir J* 1997; 10: Suppl. 25, 168s.
 138. McKenzie DK, Gandevia SC. Strength and endurance of inspiratory, expiratory and limb muscles in asthma. *Am Rev Respir Dis* 1986; 134: 999–1004.
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Walking for the assessment of patients with chronic obstructive pulmonary disease

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Reduced functional capacity and the associated disability are arguably the most significant consequences for patients with chronic respiratory and cardiac disease. There is general agreement that the level of disability is reflected in measures of exercise tolerance. Laboratory-based tests are the gold standard by which cardiorespiratory fitness should be assessed. However, for practical reasons, this is not always possible. Equipment is expensive and it requires technical support to conduct the test and interpret the results. As an alternative to laboratory testing, simpler field-based exercise tests were, therefore, developed. These are largely based upon walking (although occasionally studies have included step or cycle ergometer modalities), as this is a common and acceptable form of activity to most people with chronic respiratory and cardiac disease. Stair- or step-climbing is a less frequently employed mode of testing in respiratory patients, but has been more widely used in cardiac populations.

Field exercise tests are performed for a number of reasons, not dissimilar to those reported for laboratory-based exercise tests. It had been assumed that simple spirometry provides information regarding an individual's overall functional status. However, prediction of functional capacity from resting spirometry is inaccurate and can be misleading. Figure 1 demonstrates the lack of relationship between forced expiratory volume in one second (FEV₁) and performance in a standard field-based walking test.

Reasons for completing an exercise test include: 1) identification of an individual's functional capacity; 2) broad identification of the cause of exercise limitation (dyspnoea, leg fatigue, *etc.*); and 3) measurement of the response to an intervention (*e.g.* pharmacological or exercise therapy). Field tests are employed less frequently for the accurate diagnosis of the reason for a reported reduction in functional capacity or to identify exercise-induced asthma. These tests are commonly used in order to provide an outcome measure for pulmonary rehabilitation. They should, therefore, ideally have the potential to permit exercise prescription using established principles of exercise training as the field test is often the only exercise test employed. More recently, simple exercise tests have been employed to predict morbidity and mortality. It should be acknowledged, however, that performance of a field-based exercise test does not necessarily indicate that an individual is safe to proceed with an intervention, as the level of monitoring is considerably less than with laboratory-based tests. Some testing facilities may be able to enhance the amount of physiological data retrieved from a simple field exercise test by using oxygen saturation monitors, telemetric monitoring and portable gas analysis equipment. In this situation, the amount of data retrieved from a field-based exercise test is comparable to a comprehensive laboratory-based test, but such sophisticated equipment is largely confined to research centres.

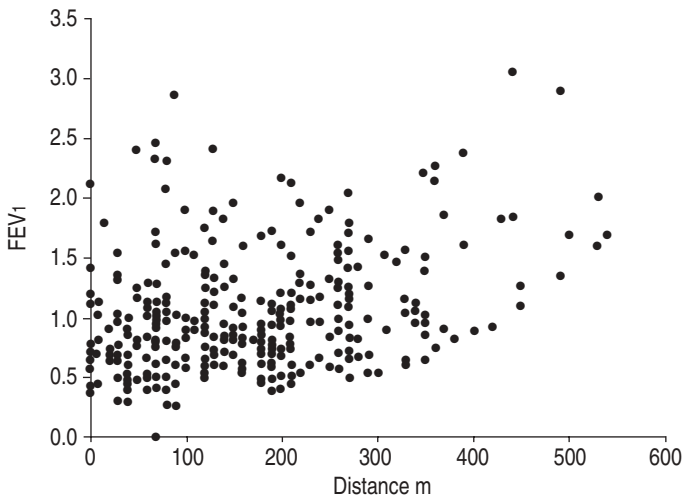


Fig. 1. – Relationship between simple spirometric data (forced expiratory volume in one second (FEV₁)) and walking distance (incremental shuttle walking test. $r=0.29$, $n=448$).

Development of field walking tests for the assessment of disability in patients with chronic cardiac and respiratory disease

Walking exercise tests in chronic obstructive pulmonary disease (COPD) were first described by MCGAVIN *et al.* [1], and represent a downgrade of a 12-min running test developed to assess the fitness of young healthy adults in the military [2]. Clearly, the vast majority of individuals with COPD are unable to run, and so the 12-min walking test (12MWT) was proposed. From this test, several developments have arisen that are more commonly employed today: 1) the 6MWT [3], 2MWT and 4MWT; 2) endurance walking test [4]; 3) 20-m shuttle running test [5]; 4) 10-m incremental shuttle walking test (SWT; ISWT) [6]; 5) 10-m modified SWT [7]; and 6) endurance SWT (ESWT) [8].

These tests are broadly divided into two categories: 1) self-paced tests, in which the patient self-selects the speed of walking to meet the aims of the test; and 2) externally paced tests, in which the speed of walking is imposed by pre-recorded signals.

Self-paced walking tests

Self-paced walking tests are commonly used in many parts of North America and Europe. Various studies have reported them as an outcome measure since the 1980s. The original 12MWT has been modified to a 6- and 2-min test [3]. The 6MWT is the most frequently cited revision in the literature. It is suggested that patients with chronic respiratory disease tolerate this test better than the 12MWT, largely because of the length of time required for completion. The 2MWT lacks the responsiveness observed in the 6MWT, especially in more able patients, in whom there is little realistic hope of enhanced performance within as short a period as 2 min post-intervention.

For all self-paced tests, patients are instructed to walk along a hospital corridor at a self-selected pace, aiming to cover as much ground as possible in the time allowed, during which the individual is permitted to stop and rest. Performance of the test is straightforward (table 1), and conduct of the 6MWT has recently been defined in a

statement from the American Thoracic Society (ATS). This statement identifies the fact that the test should be terminated “if the patient complains of chest pain, intolerable dyspnoea, leg cramps, staggering, diaphoresis or pale or ashen appearance” [9]. The test is widely used in patients with chronic respiratory and cardiac disease. Difficulties in standardisation have been documented [10], with significant variation in practice identified across pulmonary rehabilitation centres in the USA. These include variations in verbal encouragement and the number of practice walks. With this significant variation, it is practically impossible to make valid comparison between centres. In order to permit a realistic comparison of results in the future, it is essential that standards be adhered to.

Despite these drawbacks, self-paced walking tests remain attractive because they are simple for both the operator and the patient to complete. The reproducibility of the test is well defined in both the respiratory and cardiac populations [11]. Some authors suggest that at least two practice walks are required in order to secure reproducible results [12]. If the test is carefully standardised, it may be feasible to repeat the test just twice in order to establish a stable baseline. However, although there have been attempts to standardise conduct of the test, little attention has been paid to the precise layout of the course [13]. The layout of the course appears to have an important influence on results. Patients appear to cover more ground in their allocated time if they walk around a continuous track rather than to-and-fro along a hospital corridor. The difference is ~30 m. The overall length of the course has little influence on the results. The addition of verbal encouragement may significantly enhance the results of the test in a similar manner (mean increase 30.5 m) [14]. It is, therefore, vital that a standard protocol is defined, including advice about instructions to the patient and test conduct.

Baseline values for the 6MWT are ~400 m for a population of patients with moderate-to-severe COPD [15]. To date, the largest reported trial employing the 6MWT is the National Emphysema Treatment Trial (NETT) [16], conducted in the USA in order to evaluate the effectiveness of lung volume reduction surgery. The participants completed a baseline 6MWT prior to randomisation, but after completion of a course of

Table 1. – Conduct of field walking tests

	Requirements
Essential facilities	Space (30 m for 6MWT; 10 m for SWT) Appropriate flooring Quiet area Two cones to mark out the course Standard instructions (written or on CD) Chair Patient with sensible footwear and comfortable clothing
Equipment	Stopwatch Borg score or visual analogue score for breathlessness and perceived exertion CD player for the SWT Relevant medication Oxygen
Minimum data collection	Resting cardiac frequency Resting arterial oxygen saturation Resting breathlessness score Distance completed Peak cardiac frequency End-exercise arterial oxygen saturation End-exercise breathlessness score End-exercise perceived exertion score

rehabilitation. In >1,000 patients, the mean distance reported was ~400 m; however, this distance was measured after rehabilitation. Reference values have been published for the 6MWT; the two largest reports suggest that the anticipated range for a 60–65-yr-old male is ~600–700 m, and, for an equivalently aged female, 500–600 m. Differences in baseline regression equations from these two studies can be accounted for partly by the difference in study participants, but perhaps, most importantly, in the technique used to conduct the tests. TROOSTERS *et al.* [17] secured a larger mean distance (males 673 m, $n=54$; females 589 m, $n=54$) in an older population (mean age 65 yrs) by actively encouraging maximal performance. The larger population studies of ENRIGHT and SHERRILL [18] resulted in a lower mean distance despite involving a younger population (mean age 60 yrs; males 576 m, $n=173$; females 494 m, $n=173$). This study also described independent predictors of performance of the 6MWT to be age, sex, height and weight, although this anthropometric data does not necessarily describe the cause of performance variation. For patients, predictors of performance have been described using stepwise multiple regression analysis. The significant variables contributing to distance completed were quadriceps strength and maximum inspiratory pressure [19].

Additional clinical uses of the 6MWT

The 6MWT has been widely used in other clinical situations, including cystic fibrosis [20], chronic heart failure (CHF) [21], prior to lung transplantation [22] and primary pulmonary hypertension [23, 24]. It has also been employed in patients with interstitial lung disease ($n=40$) [25]. The mean (range) distance walked in this latter population was 487 (271–689) m, which is comparable to the COPD population. The test has also been employed in the assessment of patients with peripheral vascular disease [26].

Validation of the self-paced tests in chronic respiratory disease

The original work describing the 12MWT identified a moderate relationship with peak oxygen uptake ($\dot{V}O_{2,\text{peak}}$; $r=0.52$) [27]. The precise character of self-paced tests has been difficult to determine. Many would assert that the test is maximal in nature, whereas others assume that patients inevitably adopt a comfortable speed of walking and, therefore, the test becomes a measure of endurance capacity.

Although there have been a few studies exploring the relationship between self-paced tests and performance in the laboratory, self-paced tests appear to provoke a different pattern of response from that seen with a conventional incremental exercise test. Although $\dot{V}O_{2,\text{peak}}$ is comparable, other inconsistencies have been observed. For example, BAARENDS *et al.* [28] reported a higher carbon dioxide output ($\dot{V}CO_2$), blood lactate concentration and respiratory exchange ratio at the end of a conventional incremental cycle ergometer test compared with the 6MWT ($n=17$). $\dot{V}O_{2,\text{peak}}$ was attained early in the 12MWT (*i.e.* after only 4 min) compared to an incremental test, with walking speed being chosen within the first 2 min and then remaining stable. Similarly TROOSTERS *et al.* [29] showed that $\dot{V}O_{2,\text{peak}}$ was achieved in the third minute of a 6MWT (with encouragement), and sustained for the remainder of the test. However, again, there were differences in minute ventilation ($\dot{V}E$), $\dot{V}CO_2$ and blood lactate concentration compared with an incremental cycle ergometer test. These demonstrations that $\dot{V}O_{2,\text{peak}}$ in self-paced walking tests did not differ from conventional incremental cycle ergometry indicate that these tests can provoke a high sustainable outcome that is

comparable to laboratory-based tests. These results are interesting, given that the ATS statement on conduct of the 6MWT proposes that no warm-up is required [9]. Validation of self-paced walking test performance, as with more conventional indices of functional capacity, such as $\dot{V}O_{2,\text{peak}}$, against spirometry is variable, as is the relationship with dyspnoea. In addition, the relationships with measures of quality of life and functional status scales have been reported but lack consistency.

One of the reported advantages of corridor walking is that it replicates a normal activity. A small study recently demonstrated that, during moderate weather conditions, 6MWT performance outside was not significantly different from that for an indoor test [30]. The relationship between 6MWT and domestic activity has been explored with the use of activity monitors ($r=0.74$, $n=47$) [31]. More recently, PITTA *et al.* [32] explored the value of sophisticated physical activity monitors in patients with COPD, observing time spent walking and performing other domestic activities. The authors found there was a significant relationship between distance completed in the 6MWT and the overall amount of time spent walking in any 1 day.

Self-paced tests and CHF

For CHF patients, there is a similar relationship between performance in the 6MWT and $\dot{V}O_{2,\text{peak}}$ measured during a conventional incremental test ($r=0.64$, $n=45$ [33]; $r=0.77$, $n=180$ [34]). For the latter study, the relationship was improved by substituting the calculated work performed with the distance completed. Performance in the 6MWT test is also related to the New York Heart Association categories [35, 36]. However, there does not appear to be a strong relationship between performance in the 6MWT and quality-of-life questionnaire outcome or domestic activity measured with pedometers [37].

Response to intervention

The 6MWT has been widely used in many large cardiorespiratory disease trials in order to explore the benefits of rehabilitation, pharmacological intervention, oxygen supplementation and surgery. REDELMEIER *et al.* [38] proposed that a meaningful difference in performance for patients with COPD was 54 m, thus indicating the level at which the patient would evidence an improvement in functional capacity. For such patients, however, the magnitude of change varies enormously despite similar intervention. It would be expected that the degree of improvement would be much greater after a bout of physical training than after bronchodilator therapy. TROOSTERS *et al.* [39] reported a mean increase of 52 m in a study of the short- and longer-term benefits of pulmonary rehabilitation delivered over a 6-month period. Results from similar rehabilitation studies confirm this magnitude of change [40, 41]. Rehabilitation in patients with peripheral vascular disease also secured improvements in the performance distance [26].

Pharmacological interventions have employed the 6MWT as an outcome measure with some success in COPD patients [42]. The test has also been used as an outcome measure in rehabilitation of CHF patients [43], in whom only a modest improvement in walking distance after 3 months of exercise training has been reported (22 m, relative to a baseline of 434 m). This does not necessarily indicate that the 6MWT is an inappropriate outcome measure for patients with CHF; rather, it may simply be a failure of the intervention. Equally there was no meaningful change in the 6MWT in a pharmacological trial [36].

Additional self-paced walking tests

An endurance corridor walking test has been described previously [4]. In this test, patients were instructed to walk as if late for a bus for as long as possible along a hospital corridor, with both time and distance being recorded. Although not widely used, the authors suggest that this test provoked a higher mean speed than the 6MWT in some patients.

Treadmill self-paced exercise tests, which potentially permit the operator to define the work-rate more accurately, have also been described. Realistically, however, this is compromised by patient technique, which includes factors such as pacing, efficiency of treadmill walking and whether or not the individual holds on to the handrails. A study comparing distance completed in a self-paced treadmill test identified that, at comparable time-points, distances completed during corridor walking were significantly higher than in self-paced treadmill walking, the most likely explanation for this being lack of familiarity [44, 45]. However, although it may be advantageous to employ a treadmill protocol in order to monitor the precise speed of walking, the patients' physiological responses in such tests cannot be used interchangeably with those from more conventional self-paced walking tests.

Step tests

Although step tests are not frequently employed, they are of some merit. They replicate an important activity for some people. The patient remains in a restricted area and measures of cardiac frequency (f_c), blood pressure and symptoms can be made more easily than in field walking tests. One early study examined the mean power output of climbing a staircase as a function of FEV₁ [46]. A more recent study compared the 12MWT, a cycle ergometer test and a step test. The step test required the individual to mount and dismount a 25-cm platform at a speed dictated by signals. The stepping provoked the greatest metabolic and ventilatory response, with no steady state being attained [47]. Step testing can also employ a number of different protocols. Similar to walking tests, they can be self-paced or paced. Paced tests can be either performed at a constant work-rate or incrementally.

Externally paced exercise tests

Externally paced tests were developed as an alternative to self-paced tests in an attempt to improve standardisation and reproducibility [6]. These tests control the speed of walking by signals generated from a compact disc (CD). The ISWT for patients was derived from a 20-m shuttle running test described in the 1980s for the assessment of cardiorespiratory fitness of athletes [5]. The instructions and protocol are standardised and are pre-recorded on the CD for playing to the patient. The test requires that the patient walk around an elliptical course at speeds dictated by the CD. The speed is indicated by a series of bleeps, indicating when the patient should be turning around the marker and returning along the course. At the end of every minute, there is an additional signal that indicates that the individual should increase the speed of walking. The test is terminated if the patient: 1) feels they are too breathless to continue with the test; 2) fails to reach the cone in the time allowed, *i.e.* defined as being >0.5 m away from the cone when the signal indicating the patient should have completed that 10-m length occurs; and/or 3) exceeds 85% of their predicted maximal f_c . Upon completion of

the test, the patient should be seated immediately for recording of end-exercise physiological and subjective responses, *e.g.* $\dot{V}C$, arterial oxygen saturation, perceived breathlessness and exertion. The ISWT is reproducible after one practice walk. The original authors reported a 30-m difference between test 1 and test 2 for the ISWT [6].

Reported baseline responses in the ISWT range 140–457 m [48, 49]. Relationships with spirometric data and health-related quality of life have not been widely reported, but, as anticipated, are largely inconsistent. There is a correlation between ISWT performance and grades 3–5 of the UK Medical Research Council (MRC) dyspnoea scale, BESTALL *et al.* [50] reported significant differences in performance of the ISWT for each MRC grade. A recently published scale of activities of daily living, the London Chest Activity of Daily Living Scale, identified performance in the SWT decreasing with declined reported function ($r=0.58$) [51]. The ISWT has also been usefully employed in elderly patients with COPD [52]. The mean distance completed in this group was 177 m. These authors also reported a significant relationship with the Nottingham Extended Activities of Daily Living scale and shuttle performance ($r=0.51$). Predictors of performance in the ISWT are not dissimilar to those in the 6MWT; in 85 stable COPD patients, there was a significant correlation ($p<0.005$) with quadriceps strength ($r=0.47$). Linear regression identified that age, FEV₁ and quadriceps strength were the only important variables [53].

Validation of externally paced walking tests

Performance in an incremental treadmill test relates strongly to performance in the ISWT, measured as oxygen uptake ($\dot{V}O_2$; $r=0.88$; $r=0.88$ [54]; $r=0.81$ [55]). Detailed ventilatory and metabolic responses to the ISWT were compared, by PALANGE *et al.* [56], to those from a conventional incremental cycle-ergometry cardiopulmonary exercise test in patients with moderate-to-severe stable COPD, using a portable telemetric monitoring system. There were no significant differences in test duration, $\dot{V}O_{2,peak}$, $\dot{V}E_{peak}$, peak respiratory frequency or peak $\dot{V}C$; $\dot{V}C$ reserve and breathing reserve were also similar. However, like the results of BAARENDS *et al.* [28] and TROOSTERS *et al.* [29], this study found that the ISWT evoked a lower $\dot{V}CO_{2,peak}$ and blood lactate concentration than the incremental test, suggesting a reduced contribution from nonaerobic metabolism to energy production, influenced largely by the different muscle groups employed for the two activities. By contrast, the rate of increase in the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) and oxygen pulse ($\dot{V}C/\dot{V}O_2$) were higher in the ISWT, as was perceived breathlessness. Thus, as the ventilatory demands of walking are greater than those of cycling, a cycling test may not represent the metabolic requirements of walking and daily activity well. The ISWT appears to provoke a maximal response that may be more appropriate for the evaluation of functional capacity. Performance in the ISWT has also been compared with $\dot{V}O_{2,peak}$ in CHF [57] and in patients with severe CHF awaiting heart transplantation [58].

Endurance shuttle walking test

The ESWT is derived from the ISWT, but is designed to assess endurance capacity. The test has exactly the same format as the ISWT, requiring the individual to walk around cones placed 10 m apart. Unlike the ISWT, the ESWT has a warm-up period at a slower speed, and then continues at a constant pace for up to 20 min, with the speed of walking being selected from a series of 16 speeds [8]. The speed of walking is calculated

from the distance completed on an initial ISWT. A speed approximating to a percentage of peak performance is identified; this is commonly 60–85% (fig. 2). The contributing variables to performance on the ESWT were FEV₁ and ISWT distance [53].

Additional clinical uses of the shuttle walking test

The ISWT has been employed to assess functional capacity in other clinical groups. A modified ISWT has been described for patients with cystic fibrosis [7]. This test has additional levels for stressing younger fitter patients to a symptom-limited performance. The authors established a strong link between incremental exercise test and ISWT performance ($r=0.95$), with the ISWT demonstrating good reliability and sensitivity [59]. The mean distance completed in this study was 754 m, compared to a mean of 376 m in patients with COPD [6]. The ISWT has been reported as being valid and reproducible in patients with idiopathic pulmonary fibrosis [60], with the mean distance of 367 m being similar to that found in the COPD population. The authors, again, demonstrated a high correlation with incremental exercise testing ($r=0.74$). Functional capacity in advanced cancer patients has also been defined using the ISWT (mean distance 245 m) [61]. Recently, the ISWT has been used to assess patients with intermittent claudication, demonstrating good reliability, but provoking a lower level of cardiovascular stress compared to a treadmill test [62]. The ISWT is safe and acceptable for patients with CHF, KEELL *et al.* [57] first compared ISWT performance (as $\dot{V}O_2$) with that obtained using conventional incremental exercise testing in this population ($r=0.84$). The ISWT test has also been employed in the evaluation of cardiac patient with pacemakers [63] and in patients awaiting heart transplantation [58].

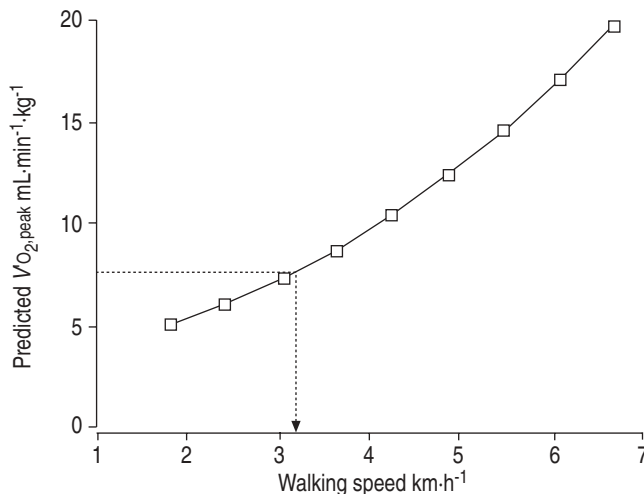


Fig. 2. — The speed of walking is calculated from the distance completed on an initial incremental shuttle walking test (ISWT). The predicted peak oxygen uptake ($\dot{V}O_{2,peak}$) is $4.19+0.025ISWT$. Endurance capacity is measured at the walking speed requiring, for example, 85% of this $\dot{V}O_{2,peak}$. For example (.....), if the ISWT distance is 200 m, the predicted $\dot{V}O_{2,peak}$ is $9.2 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ and the endurance test should be performed at $7.8 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$, corresponding to a speed of $3.3 \text{ km}\cdot\text{h}^{-1}$, i.e. endurance test level 6.

Responsiveness to interventions

The ISWT has been cited in significant rehabilitation studies [48, 64, 65]. There is considerable evidence that the test is sensitive to change, although the minimum clinically important difference has not yet been published. A large rehabilitation study reported mean changes of 75.9 m (61.0–90.8 m) [64]. Recently, the ISWT was employed in a study of community rehabilitation immediately following exacerbation [66]. The test, not surprisingly, is able to detect important changes after exercise training in patients with intermittent claudication [67]. Use of the ISWT has been reported in a few pharmaceutical trials [68, 69]; however, the magnitude of change falls well below those observed in rehabilitation. The ESWT is more sensitive to change after a course of rehabilitation than the ISWT. REVILL *et al.* [8] secured a mean increase in time of 160%, compared to the ISWT change of 32%. The ESWT is also sensitive to supplemental oxygen administration [70]. A recent study suggested that the ESWT may be more responsive to bronchodilation than a standard laboratory based cycle test [71]. The ISWT and ESWT complement each other and can be considered the field equivalent of conventional incremental and constant work-rate exercise tests.

Adjuncts to field exercise testing

Performance in a field exercise test is largely reported as the distance completed or the time for which the individual could continue with the test. However, this information can be greatly enhanced as it is now possible to collect precise physiological data during these tests. Commonly, measures of f_c (using short-range telemetric devices), oxygen saturation (using small pulse oximeters) and perceived symptoms are used. Either a visual analogue scale or the Borg breathlessness (symptom) scale [72] can be used to record breathlessness during an exercise test. These scales can be used to report additional symptoms, *e.g.* leg fatigue. An additional Borg perceived exertion score can record how hard the patients found the test overall.

Comparison of self-paced and externally paced shuttle walking tests

Although the self- and externally paced SWTs are fundamentally different, attempts have been made to compare the two protocols. The original study describing the SWT included a comparison with the 6MWT [6]. The authors found that the distance completed in both tests was similar for the majority of patients, but that the pattern of response was different. More recently, EISER *et al.* [73] compared the reliability, reproducibility and sensitivity to change of the 6MWT, 2MWT and ISWT in 57 moderate-to-severe COPD patients. The mean baseline distance for the 6MWT was significantly greater than that for the ISWT (424 *versus* 270 m, respectively). All three tests demonstrated satisfactory reproducibility and reliability, and established reproducibility over successive days and a 2-week period. After nebulised bronchodilator administration, a significant change was detected for all three tests, although the 6MWT distance was below the previously defined threshold. The authors suggested that the 2MWT may be less sensitive to change than either the 6MWT or the ISWT.

ORONATI *et al.* [54] identified significant differences in the physiological response to the 6MWT and the ISWT using a portable telemetric device. The distance (and duration) completed on the two field tests was not significantly different (369 *versus* 391 m for the 6MWT and SWT, respectively). There was a progressive increase in the

values of physiological variables in all subjects in the ISWT, in contrast to the 6MWT responses, which attained peak values by the third minute. Interestingly the maximum speed of walking was achieved in the first minute. The distance completed in the ISWT was strongly related to $\dot{V}O_{2,\text{peak}}$ ($r=0.86$), $\dot{V}CO_{2,\text{peak}}$ ($r=0.87$) and $\dot{V}E_{\text{peak}}$ ($r=0.74$), unlike in the 6MWT. The ISWT also provoked a significantly higher $\dot{V}O_{2,\text{peak}}$, $\dot{V}CO_{2,\text{peak}}$, $\dot{V}E_{\text{peak}}$ and peak f_c than the 6MWT ($p<0.01$), and the total energy expenditure was also higher for the paced test. The ISWT distance and $\dot{V}O_{2,\text{peak}}$ showed significant correlation with $\dot{V}O_{2,\text{peak}}$ attained with conventional incremental exercise (distance, $r=0.72$; $\dot{V}O_2$, $r=0.92$). No significant correlations were noted between other physiological responses to the conventional incremental exercise test and those to the 6MWT. More recently, TURNER *et al.* [15] compared the physiological responses to incremental cycle ergometry, the 6MWT and the ISWT. They found a linear increase in f_c for the cycle-ergometry test and ISWT, but a disproportionate increase early in the 6MWT. The linear dyspnoea response (Borg score) during the 6MWT was unexpected, in contrast to the progressive increases seen with cycle ergometry and the ISWT. These authors, therefore, suggested that patients titrate their effort against breathlessness in order to achieve a peak tolerable intensity. A comparison of the ESWT and the 6MWT after a course of rehabilitation suggested that the ESWT may have a more sensitive outcome measure after this intervention [74].

A comparative study of the 6MWT and ISWT has also been conducted in CHF patients. Again, $\dot{V}O_{2,\text{peak}}$ correlated with distance walked in the ISWT, but less so in the 6MWT [75]. Additionally, all patients completing ≥ 450 m exhibited a $\dot{V}O_{2,\text{peak}}$ of $>14 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg body weight}^{-1}$, which is an important threshold for referral for cardiac transplantation [76]. In a subsequent study [21], the distance completed in the ISWT was a predictor of outcome, whereas that in the 6MWT was not. Overall, there was a meaningful difference between tertiles and event-free survival for the ISWT (0.0004) but not the 6MWT (0.09). This study suggested that performance in the ISWT of <450 m identified a group at high risk of a major cardiac event in the short term.

Use of field exercise tests in selection for surgery

The risk of peri-operative complications is usually stratified by $\dot{V}O_{2,\text{peak}}$. A value of $15 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg body weight}^{-1}$ is a commonly employed threshold indicating a significant risk of complications following thoracic surgery. Data from field exercise tests are limited. For patients with COPD, a distance of 250 m on the ISWT would correspond approximately to this threshold value. Equivalent data do not exist for the 6MWT. KADIKAR *et al.* [22] retrospectively observed the sensitivity and specificity of the 6MWT in predicting death in 145 patients who had undergone lung transplantation. A distance of <400 m appeared to be a reasonable marker for listing patients for transplantation. For lung volume reduction surgery, the threshold for a successful outcome has been reported to be ~ 150 m for the ISWT [77], or ~ 200 m for the 6MWT [78]. The NETT proposed that, in patients with predominantly upper lobe pathology and lower exercise capacity who underwent surgery, mortality was lower than for conventional rehabilitation. Conversely, for those with nonupper-lobe emphysema and higher exercise capacity, mortality was higher in the surgical group [16].

Prognosis

The prognostic value of functional impairment has been established in laboratory-based studies [79]. Perhaps the earliest investigation of field test performance as a

predictor of mortality was that of GERARDI *et al.* [80], following rehabilitation in COPD patients. These authors concluded that the post-rehabilitation 12MWT distance was the most important predictor of survival up to 3 yrs post-intervention, and this appeared to be independent of the cause of death. The 6MWT has been studied independently and as a component of a composite scale. A recent study [81] reporting on the decline in 6MWT distance over 2 yrs found that the magnitude of change in the group that survived was significantly less than that in the nonsurvivors ($p < 0.001$); interestingly, the decline in FEV₁ over this time was comparable between the two cohorts. The body mass index, airflow obstruction, dyspnoea and exercise capacity (BODE) index (assessed with the 6MWT) is a composite measure designed to categorise and predict outcome in patients with COPD [80]. In a cohort of 207 COPD patients, the BODE index was better than FEV₁ at predicting death from any cause [82]. However, the value of the index as an outcome measure remains to be established.

The prognostic value of the 6MWT has been reported by other clinical groups. In CHF, the utility of the 6MWT has been examined in mild-to-moderate patients ($n=214$) [83] and more severe patients ($n=45$) [33]. Both studies associated a distance of <300 m with medium-to-long-term overall and event-free survival. In more severe CHF patients, baseline 6MWT distance was a strong independent predictor of mortality and hospitalisation at 1 yr [84]. The prognostic value of the 6MWT has been extended to investigate arterial oxygen desaturation in patients with interstitial disease, exercise-induced desaturation being associated with higher mortality [85]. Performance in the 6MWT in patients with primary pulmonary hypertension relates well to $\dot{V}O_{2,\text{peak}}$ determined using conventional incremental exercise testing. Again, there appears to be some prognostic value for the test, and the distance walked on the 6MWT is the strongest independent predictor of mortality, with the threshold distance associated with increased mortality at follow-up being ~ 300 m [23]. The prognostic value of the test has explored desaturation in patients with interstitial lung disease, exercise induced desaturation was associated with higher mortality [86].

To date, no studies have reported the prognostic value of the ISWT in patients with COPD. However, studies have compared the prognostic value of the ISWT and 6MWT in other groups of patients. One study found a difference between tertiles of the ISWT and event-free survival, not observed for the 6MWT. This study suggested that performance in the ISWT of <450 m identified a group at high risk of a major cardiac event in the short term [21].

Safety

The indications for performing a test have been outlined above. However, for safety reasons, there are a number of contraindications. These have been defined in the ATS statement [9]. A more exhaustive list of contraindications to clinical exercise testing has been produced by the American College of Sports Medicine [87]. A supervising physician is not routinely required for field-exercise testing. However, the resuscitation team should know the location of any testing. The area should be equipped with a resuscitation trolley and ready access to oxygen, glyceryl trinitrate and bronchodilators. The operator should terminate the test if the patient reports central chest pain, excessive joint pain or excessive breathlessness, or becomes unstable or looks unwell. It is advisable to monitor arterial oxygen saturation during and immediately after the test, although this is not indicated in the ATS statement for the 6MWT [9].

Oxygen and field exercise tests

A field-based test is often the assessment upon which the prescription of ambulatory oxygen is based. National guidelines usually recommend a threshold for identifying benefit. Recent guidelines from the UK suggest that ambulatory oxygen should be considered if a patient shows desaturation on exercise and an improvement in exercise performance and/or dyspnoea with oxygen, and is motivated to use it [88]. The anticipated improvement in walking distance or dyspnoea has been suggested as 10%. It is recognised that there is a differential response depending upon the mode of testing and protocol used. For example, walking has been reported to induce a greater degree of arterial oxygen desaturation than cycling [89, 90], as does a constant work-rate test compared to an incremental test [91]. It should be remembered that improvement in a field-based walking test does not necessarily confer advantages when using supplemental oxygen in the domestic environment. Field tests have been used to identify the acute benefit of supplemental oxygen, although it should be noted that some studies require the individual to carry the cylinder whilst others provide trolleys. GARROD *et al.* [92] identified a 27 m improvement in the ISWT with supplemental oxygen. There may be greater improvements with the ESWT, a mean improvement of 62 m having been reported [70]. Further research is required in order to identify the acute response to oxygen in field-based tests, and how these test results relate to benefit in the community.

Conclusion

Walking tests have the advantage of being simple to perform compared to laboratory-based tests. If appropriately standardised, the tests yield a great deal of information that can be usefully employed in the evaluation of level of functional capacity and assessment of the outcome of therapies in patients with COPD. It is important, however, that standardised procedures are followed in order to optimise the utility of such tests.

Summary

It is important to quantify an individual's exercise capacity. Although laboratory-based tests (with the full complement of equipment) are acknowledged to be the gold standard, it is not always feasible or even desirable to complete such tests in an increasingly elderly and frail population. As a viable alternative, field tests have been developed.

Initially, this was a simple self-paced corridor-walking test. The later development of externally paced tests has imposed a defined protocol upon the participant. It is increasingly possible to collect complex physiological data beyond the laboratory, and studies have demonstrated that the externally paced tests, particularly the incremental shuttle walking test, best reflect the physiological response observed in comparable laboratory tests. Walking tests are simple to perform compared with laboratory-based tests, and require little expensive equipment in order to collect the most basic of data. Field tests have been described in a number of patient populations with chronic cardiac and respiratory diseases. Studies have identified threshold values that are associated with successful clinical outcomes, or an increased mortality risk. Field test results are used as an outcome measure, particularly in rehabilitation studies, with the 6-min walking test and the incremental shuttle walking test being most frequently reported. Attempts have been made to describe what constitutes an important

difference to the patient. In order to identify the maximal change achieved after an intervention, for example rehabilitation or pharmaceutical agents, a high-intensity endurance test yields the greatest improvements. In the field, this is provided by the endurance shuttle walking test.

If standardised, the field test yields information that can be usefully employed to evaluate the level of functional capacity and assess the outcome of therapies. For all patients, it is important that standardised procedures are followed in order to optimise their utility.

Keywords: Disability, field exercise tests.

References

1. McGavin CR, Artvinli M, Naoe H, McHardy GJ. Dyspnoea, disability, and distance walked: comparison of estimates of exercise performance in respiratory disease. *Br Med J* 1978; 2: 241–243.
2. Cooper KH. A means of assessing maximal oxygen intake. Correlation between field and treadmill testing. *JAMA* 1968; 203: 201–204.
3. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed)* 1982; 284: 1607–1608.
4. Davidson AC, Leach R, George RJ, Geddes DM. Supplemental oxygen and exercise ability in chronic obstructive airways disease. *Thorax* 1988; 43: 965–971.
5. Leger LA, Lambert J. A maximal multistage 20-m shuttle run test to predict $\text{VO}_2 \text{ max}$. *Eur J Appl Physiol Occup Physiol* 1982; 49: 1–12.
6. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992; 47: 1019–1024.
7. Bradley J, Howard J, Wallace E, Elborn S. Validity of a modified shuttle test in adult cystic fibrosis. *Thorax* 1999; 54: 437–439.
8. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax* 1999; 54: 213–222.
9. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
10. Elpern EH, Stevens D, Kesten S. Variability in performance of timed walk tests in pulmonary rehabilitation programs. *Chest* 2000; 118: 98–105.
11. Guyatt GH, Sullivan MJ, Thompson PJ, *et al*. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985; 132: 919–923.
12. Knox AJ, Morrison JF, Muers MF. Reproducibility of walking test results in chronic obstructive airways disease. *Thorax* 1988; 43: 388–392.
13. Sciurba F, Criner GJ, Lee SM, *et al*. Six-minute walk distance in chronic obstructive pulmonary disease: reproducibility and effect of walking course layout and length. *Am J Respir Crit Care Med* 2003; 167: 1522–1527.
14. Guyatt GH, Pugsley SO, Sullivan MJ, *et al*. Effect of encouragement on walking test performance. *Thorax* 1984; 39: 818–822.
15. Turner SE, Eastwood PR, Cecins NM, Hillman DR, Jenkins SC. Physiologic responses to incremental and self-paced exercise in COPD: a comparison of three tests. *Chest* 2004; 126: 766–773.
16. Fishman A, Martinez F, Naunheim K, *et al*. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.
17. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; 14: 270–274.

-
18. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998; 158: 1384–1387.
 19. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996; 153: 976–980.
 20. Gulmans VA, van Veldhoven NH, de Meer K, Helders PJ. The six-minute walking test in children with cystic fibrosis: reliability and validity. *Pediatr Pulmonol* 1996; 22: 85–89.
 21. Morales FJ, Montemayor T, Martinez A. Shuttle versus six-minute walk test in the prediction of outcome in chronic heart failure. *Int J Cardiol* 2000; 76: 101–105.
 22. Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. *J Heart Lung Transplant* 1997; 16: 313–319.
 23. Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161: 487–492.
 24. Paciocco G, Martinez FJ, Bossone E, Pielsticker E, Gillespie B, Rubenfire M. Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. *Eur Respir J* 2001; 17: 647–652.
 25. Chetta A, Aiello M, Foresi A, *et al.* Relationship between outcome measures of six-minute walk test and baseline lung function in patients with interstitial lung disease. *Sarcoidosis Vasc Diffuse Lung Dis* 2001; 18: 170–175.
 26. Gardner AW, Katzel LI, Sorokin JD, *et al.* Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *J Am Geriatr Soc* 2001; 49: 755–762.
 27. McGavin CR, Gupta SP, McHardy GJ. Twelve-minute walking test for assessing disability in chronic bronchitis. *Br Med J* 1976; 1: 822–823.
 28. Baarends EM, Schols AM, Mostert R, Janssen PP, Wouters EF. Analysis of the metabolic and ventilatory response to self-paced 12-minute treadmill walking in patients with severe chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 1998; 18: 23–31.
 29. Troosters T, Vilaro J, Rabinovich R, *et al.* Physiological responses to the 6-min walk test in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2002; 20: 564–569.
 30. Brooks D, Solway S, Weinacht K, Wang D, Thomas S. Comparison between an indoor and an outdoor 6-minute walk test among individuals with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2003; 84: 873–876.
 31. Steele BG, Holt L, Belza B, Ferris S, Lakshminaryan S, Buchner DM. Quantitating physical activity in COPD using a triaxial accelerometer. *Chest* 2000; 117: 1359–1367.
 32. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 972–977.
 33. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 1996; 110: 325–332.
 34. Hendrican MC, McKelvie RS, Smith T, *et al.* Functional capacity in patients with congestive heart failure. *J Card Fail* 2000; 6: 214–219.
 35. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. *Br Med J (Clin Res Ed)* 1986; 292: 653–655.
 36. Demers C, McKelvie RS, Negassa A, Yusuf S. Reliability, validity, and responsiveness of the six-minute walk test in patients with heart failure. *Am Heart J* 2001; 142: 698–703.
 37. Houghton AR, Harrison M, Cowley AJ, Hampton JR. Assessing exercise capacity, quality of life and haemodynamics in heart failure: do the tests tell us the same thing? *Eur J Heart Fail* 2002; 4: 289–295.
 38. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997; 155: 1278–1282.
-

39. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Am J Med* 2000; 109: 207–212.
40. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance *versus* endurance training in patients with COPD and peripheral muscle weakness. *Eur Respir J* 2002; 19: 1072–1078.
41. Ries AL, Kaplan RM, Myers R, Prewitt LM. Maintenance after pulmonary rehabilitation in chronic lung disease: a randomized trial. *Am J Respir Crit Care Med* 2003; 167: 880–888.
42. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. *Lancet* 1998; 351: 773–780.
43. McKelvie RS, Teo KK, Roberts R, *et al*. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). *Am Heart J* 2002; 144: 23–30.
44. Swerts PM, Mostert R, Wouters EF. Comparison of corridor and treadmill walking in patients with severe chronic obstructive pulmonary disease. *Phys Ther* 1990; 70: 439–442.
45. Stevens D, Elpern E, Sharma K, Szidon P, Ankin M, Kesten S. Comparison of hallway and treadmill six-minute walk tests. *Am J Respir Crit Care Med* 1999; 160: 1540–1543.
46. Johnson AN, Cooper DF, Edwards RH. Exertion of stairclimbing in normal subjects and in patients with chronic obstructive bronchitis. *Thorax* 1977; 32: 711–716.
47. Swinburn CR, Wakefield JM, Jones PW. Performance, ventilation, and oxygen consumption in three different types of exercise test in patients with chronic obstructive lung disease. *Thorax* 1985; 40: 581–586.
48. Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. *Eur Respir J* 1998; 12: 363–369.
49. Ortega F, Toral J, Cejudo P, *et al*. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 669–674.
50. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; 54: 581–586.
51. Garrod R, Bestall JC, Paul EA, Wedzicha JA, Jones PW. Development and validation of a standardized measure of activity of daily living in patients with severe COPD: the London Chest Activity of Daily Living scale (LCADL). *Respir Med* 2000; 94: 589–596.
52. Dyer CA, Singh SJ, Stockley RA, Sinclair AJ, Hill SL. The incremental shuttle walking test in elderly people with chronic airflow limitation. *Thorax* 2002; 57: 34–38.
53. Steiner MC, Singh SJ, Morgan MD. The contribution of peripheral muscle function to shuttle walking performance in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2005; 25: 43–49.
54. Onorati P, Antonucci R, Valli G, *et al*. Non-invasive evaluation of gas exchange during a shuttle walking test *vs.* a 6-min walking test to assess exercise tolerance in COPD patients. *Eur J Appl Physiol* 2003; 89: 331–336.
55. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA. Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. *Eur Respir J* 1994; 7: 2016–2020.
56. Palange P, Forte S, Onorati P, Manfredi F, Serra P, Carlone S. Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. *J Appl Physiol* 2000; 88: 1715–1720.
57. Keell SD, Chambers JS, Francis DP, Edwards DF, Stables RH. Shuttle-walk test to assess chronic heart failure. *Lancet* 1998; 352: 705.
58. Lewis ME, Newall C, Townend JN, Hill SL, Bonser RS. Incremental shuttle walk test in the assessment of patients for heart transplantation. *Heart* 2001; 86: 183–187.
59. Bradley J, Howard J, Wallace E, Elborn S. Reliability, repeatability, and sensitivity of the modified shuttle test in adult cystic fibrosis. *Chest* 2000; 117: 1666–1671.

-
60. Moloney ED, Clayton N, Mukherjee DK, Gallagher CG, Egan JJ. The shuttle walk exercise test in idiopathic pulmonary fibrosis. *Respir Med* 2003; 97: 682–687.
 61. Booth S, Adams L. The shuttle walking test: a reproducible method for evaluating the impact of shortness of breath on functional capacity in patients with advanced cancer. *Thorax* 2001; 56: 146–150.
 62. Zwierska I, Nawaz S, Walker RD, Wood RF, Pockley AG, Saxton JM. Treadmill *versus* shuttle walk tests of walking ability in intermittent claudication. *Med Sci Sports Exerc* 2004; 36: 1835–1840.
 63. Payne GE, Skehan JD. Shuttle walking test: a new approach for evaluating patients with pacemakers. *Heart* 1996; 75: 414–418.
 64. Griffiths TL, Burr ML, Campbell IA, *et al.* Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000; 355: 362–368.
 65. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 1335–1341.
 66. Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ* 2004; 329: 1209–1213.
 67. Walker RD, Nawaz S, Wilkinson CH, Saxton JM, Pockley AG, Wood RF. Influence of upper- and lower-limb exercise training on cardiovascular function and walking distances in patients with intermittent claudication. *J Vasc Surg* 2000; 31: 662–669.
 68. Brightling CE, Monteiro W, Ward R, *et al.* Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000; 356: 1480–1485.
 69. Wadbo M, Lofdahl CG, Larsson K, *et al.* Effects of formoterol and ipratropium bromide in COPD: a 3-month placebo-controlled study. *Eur Respir J* 2002; 20: 1138–1146.
 70. Revill SM, Singh SJ, Morgan MD. Randomized controlled trial of ambulatory oxygen and an ambulatory ventilator on endurance exercise in COPD. *Respir Med* 2000; 94: 778–783.
 71. Pepin V, Saey D, Whittom F, LeBlanc P, Mattais F. Walking *versus* cycling: sensitivity to bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 1517–1522.
 72. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377–381.
 73. Eiser N, Willsher D, Dore CJ. Reliability, repeatability and sensitivity to change of externally and self-paced walking tests in COPD patients. *Respir Med* 2003; 97: 407–414.
 74. Eaton T, Young P, Nicol K, Kolbe J. The endurance shuttle walking test: a responsive measure in pulmonary rehabilitation for COPD patients. *Chron Respir Dis* 2006; 3: 3–9.
 75. Green DJ, Watts K, Rankin S, Wong P, O'Driscoll JG. A comparison of the shuttle and 6 minute walking tests with measured peak oxygen consumption in patients with heart failure. *J Sci Med Sport* 2001; 4: 292–300.
 76. Morales FJ, Martinez A, Mendez M, *et al.* A shuttle walk test for assessment of functional capacity in chronic heart failure. *Am Heart J* 1999; 138: 291–298.
 77. Geddes D, Davies M, Koyama H, *et al.* Effect of lung-volume-reduction surgery in patients with severe emphysema. *N Engl J Med* 2000; 343: 239–245.
 78. Szekely LA, Oelberg DA, Wright C, *et al.* Preoperative predictors of operative morbidity and mortality in COPD patients undergoing bilateral lung volume reduction surgery. *Chest* 1997; 111: 550–558.
 79. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003; 167: 544–549.
 80. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following out-patient pulmonary rehabilitation. *Eur Respir J* 1996; 9: 431–435.
 81. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004; 23: 28–33.
-

82. Celli BR, Cote CG, Marin JM, *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
83. Rostagno C, Olivo G, Comeglio M, *et al.* Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *Eur J Heart Fail* 2003; 5: 247–252.
84. Shah MR, Hasselblad V, Gheorghiade M, *et al.* Prognostic usefulness of the six-minute walk in patients with advanced congestive heart failure secondary to ischemic or nonischemic cardiomyopathy. *Am J Cardiol* 2001; 88: 987–993.
85. Lama VN, Flaherty KR, Toews GB, *et al.* Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 1084–1090.
86. Lama VN, Flaherty KR, Toews GB, *et al.* Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 1084–1090.
87. American College of Sports Medicine. ACSM's Guideline for Exercise Testing and Prescription. Philadelphia, Lippincott Williams and Wilkins, 2005.
88. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004; 59: Suppl. 1, 1–232.
89. Poulain M, Durand F, Palomba B, *et al.* 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. *Chest* 2003; 123: 1401–1407.
90. Spence DP, Hay JG, Carter J, Pearson MG, Calverley PM. Oxygen desaturation and breathlessness during corridor walking in chronic obstructive pulmonary disease: effect of oxitropium bromide. *Thorax* 1993; 48: 1145–1150.
91. Carlin BW, Clausen JL, Ries AL. The effects of exercise testing on the prescription of oxygen therapy. *Chest* 1994; 106: 361–365.
92. Garrod R, Paul EA, Wedzicha JA. Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. *Thorax* 2000; 55: 539–543.

Reference values in adults

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Background

Exercise testing provides an array of measurements characterising an individual's physiological response. The amount of information obtained depends on the type of test: some tests, such as field tests, yield one or, at most, a few variables, while the classical laboratory cardiopulmonary exercise test (CPET) yields a large amount of data. When exercise testing is used to find out whether a response is abnormal or not, it becomes necessary to compare the response with what it would be expected to be in "normal" circumstances, *i.e.* a "reference" or "predicted" value is needed. Reference values exist for many of the physiological variables monitored or derived during a CPET. They are estimations of the population mean commonly obtained from large samples of presumed healthy subjects. It should be recognised that inherent biological variability imposes a distribution of individual values around the mean, usually in a symmetrical fashion (or closely so) that is well described by a Gaussian or normal distribution. Thus, lower probabilities are associated with values which lie at greater distances from the distribution mean. This form of distribution is well characterised by the mean or central value and a measure of the spread of the distribution, *i.e.* the SD. The distributions of most of the commonly used CPET indices follow a Gaussian distribution, and hence ~95% of the values falling on both sides of the mean will lie within 2 SD of the mean (actually 1.96 SD).

To decide whether the measured response is abnormal or not, statistical inferential procedures are relied upon, which consist of the following steps: 1) stating the statistical (null) hypothesis; 2) specifying the significance level; 3) specifying a decision rule; and 4) drawing a conclusion. A decision can be made only as to whether the observed measurement is different from the reference value obtained in a healthy population, as statistical descriptions of diseased populations are rarely available. Therefore, the only hypotheses that can be tested statistically would be either whether the measurement in question yields a result that is not different from the healthy population mean, regardless of direction (*i.e.* a two-tailed hypothesis), or whether the measured value is lower or higher than the population mean (*i.e.* a one-tailed hypothesis). One-tailed hypotheses are logically sound if the concern is only about deviations in one direction, as is frequently the case [1]; *i.e.* usually the only point of interest is whether a subject is below or above the population reference value for the parameter of interest. However, two-tailed hypotheses are generally adopted because they are considered safer. The 95% confidence interval (CI) is broader (1.96 *versus* 1.65) which, therefore, reduces the risk of false-positive decisions.

There are two types of error that can be made when performing a statistical inference (table 1): a type I error, which is when the alternative hypothesis is incorrectly chosen; and a type II error, when the statistical (null) hypothesis fails to be rejected when it is

Table 1. – Outcomes of hypothesis testing

Hypothesis accepted	True state of nature	
	Null hypothesis	Alternative hypothesis
Null hypothesis	Correct decision	False-negative decision: type II error
Alternative hypothesis	False-positive decision: type I error	Correct decision

actually false. A type I error is the probability of a false-positive decision occurring; conventionally, it is considered that a two-tailed 5% chance of error (one in 20) is low enough. As stated previously, since the characteristics of specific patient populations are typically not known, the probability of a type II error is usually not known. This is one of the main reasons why it must be remembered that the term normal actually refers to “not abnormal” or to “within the reference 95% confidence range of the population mean”. Type I and II errors are inversely related, *i.e.* lowering one has the effect of increasing the other.

A few variables have a very narrow range of normal values in healthy subjects (*e.g.* resting arterial blood gas tensions, pH and lactate), reflecting, in large, their lack of dependence on physical characteristics, such as height and age. For the majority, however, the normal value range is quite broad. A significant part of this variability is due to differences in physical characteristics, such ethnicity, sex, height, weight and age. Therefore, regression equations may be developed from large populations of healthy subjects and used to predict narrower ranges of reference values for subjects with specific characteristics. Predictive equations for reference values are usually expressed as linear regression equations, incorporating physical characteristics that contribute statistically significantly to reductions in the variability of the predictive values.

Peak oxygen uptake

The criterion used to define a subject’s exercise capacity has classically been based on the peak oxygen uptake ($\dot{V}O_{2,\text{peak}}$) standardised by weight [2, 3], and this is still usual practice in sports medicine and stress testing. Normal values in healthy young adults lie in the range 35–40 mL·min⁻¹·kg⁻¹, being appreciably less in those with low activity levels [4] and substantially higher (*e.g.* >80 mL·min⁻¹·kg⁻¹) in young elite endurance athletes [5]. An alternative index of the oxygen uptake ($\dot{V}O_2$) standardised by weight, which is widely used by cardiologists, is the “Met”, *i.e.* the $\dot{V}O_2$ required for a given task divided by the resting $\dot{V}O_2$, with the latter being considered equivalent to a standard 3.5 mL·min⁻¹·kg⁻¹.

However, other factors, such as age and sex, are also widely documented to influence $\dot{V}O_{2,\text{peak}}$ [6–12]. Furthermore, as is the case with lung function [13, 14], aerobic capacity is better related to height than weight in populations which include the overweight and those who are not particularly fit [15–18], *i.e.* populations more akin to the subjects typically tested for clinical purposes. Thus, it is recommended that, for clinical exercise testing, measured values of $\dot{V}O_{2,\text{peak}}$ are standardised by referring to them as the percentage of the population predicted peak, derived from equations that take into account sources of variability such as age, sex and height (or both height and weight). As noted earlier, aerobic capacity varies with the level of activity; even brief periods of physical training can increase $\dot{V}O_{2,\text{peak}}$ by $\geq 25\%$ [4, 19–22]. However, as physical activity cannot be measured accurately, its effect is not incorporated into the reference values.

A common convention used to relate measured $\dot{V}O_{2, \text{peak}}$ values to reference values is: >80% not abnormal or within the 95% CI; 71–80% mildly reduced; 51–70% moderately reduced; and <50% severely reduced.

Adults

Several series of reference values for incremental exercise test indices, including $\dot{V}O_{2, \text{peak}}$, have been published for males and females of relatively normal body weight obtained from North American, Brazilian and Japanese populations [4, 15, 16, 23–31]. The important features of these studies are presented in tables 2 and 3. Each study has some limitations related to factors such as: 1) the precision of the values (sample size, heterogeneity of the population regarding racial background, level of physical activity or smoking incidence); 2) methodological defects that may have introduced information bias (insufficient information about quality control or analysis of retrospective samples); and 3) selection bias (lack of randomisation, retrospective samples). There are significant differences in the population characteristics, sample size, equipment, methodology and reported measurements. The values produced by HANSEN *et al.* [15] and JONES *et al.* [16] are the most widely used. For male populations, both studies gave reasonably similar $\dot{V}O_{2, \text{peak}}$ values for average subjects (height 170–180 cm, age 30–70 yrs); however, there are larger discrepancies beyond these limits. Another study carried out in Brazil, which included subjects of different ethnic groups, yielded lower reference values [17].

For female populations there is less agreement between the values reported by HANSEN *et al.* [15] and JONES *et al.* [16], with the former study yielding lower $\dot{V}O_{2, \text{peak}}$ values at extreme heights (*i.e.* 150 cm and 180 cm) and higher values at average heights (160–170 cm). However, the values for females obtained by HANSEN *et al.* [16] and NEDER *et al.* [17] are similar.

Table 2. – Published reference values for treadmill exercise

First author [Ref.]	Sample size M/F	Age range yrs	Sample characteristics	Protocol	Variables measured	Methodology	Period of breath-by-breath data averaging s
BRUCE [25]	138/157	29–73	General population; sedentary/active; prospective/retrospective	Bruce	$\dot{V}O_2$	Douglas bag, gas analyser	60/25
DRINKWATER [26]	109 [#]	10–68	General population; prospective	Balke; elevated 1%·min ⁻¹	$\dot{V}O_2$, $\dot{V}E$, <i>fc</i> , venous lactate	Automated system, gas analysers, gas meter	60
FROELICHER [28]	519/191 [†]	20–53; 25–40	Air force medical referrals; physically very fit group	Balke; elevated 1%·min ⁻¹	$\dot{V}O_2$, <i>fc</i>	Douglas bag	60
VOGEL [31]	1514/375	17–55	USA soldiers; prospective; physically active; random	Discontinuous; 3-min stages	$\dot{V}O_2$	Douglas bag, gas analysers	60

Data are presented as n. M: male; F: female; $\dot{V}O_2$: oxygen uptake; $\dot{V}E$: minute ventilation; *fc*: cardiac frequency. [#]: females only; [†]: both samples are males.

Table 3. – Published reference values for cycle ergometer exercise

First author [Ref.]	Sample size M/F	Age range yrs	Sample characteristics	Protocol	Primary variables measured	Methodology	Period of breath-by-breath data averaging s
BLACKIE [23]	47/81	55–80	Hospital based; senior centres; prospective	Incremental; 16 W·min ⁻¹	WR, V _O ₂	Turbine, mixing chamber	30
BLACKIE [24]	111/120	20–80	General population; prospective; sedentary?	Incremental; 16 W·min ⁻¹	V _O ₂ , V _{CO} ₂ , V _E	Turbine, mixing chamber	30
HANSEN [15]	77 [#]	34–74	Asbestos exposed; referrals: retro- spective; V _O ₂ adjusted to Bruce references and corrected for cycle	Incremental; 10–30 W·min ⁻¹	V _O ₂ , V _{CO} ₂ , V _E , f _c , t _{EL} , P _{ET} O ₂ , P _{ET} CO ₂ , ABGs, V _D /V _T , P(A-a)O ₂	Gas exchange by automated system, arterial line	20
FAIRBARN [27]	110/120	20–80	General population; prospective; uneven distribution of groups	Incremental; 16 W·min ⁻¹	V _O ₂ , f _c	Gas exchange by automated system,	30
JONES [16]	50/50	15–71	University workers/general popula- tion; prospective	Incremental; 16 W·min ⁻¹	V _O ₂ , V _{CO} ₂ , V _E , f _c , t _{EL}	Dry gas meter, mass spectrometer, mixing chamber	15
JONES [18]	732/339	20–70	Hospital referrals; retrospective	Incremental; 16 W·min ⁻¹	WR	Electronic cycle ergometer	60/30
STORER [30]	115/116	20–70	General population; prospective; sedentary	Incremental; 15 W·min ⁻¹	V _O ₂ , WR	Mixing chamber/ B by B, turbine	30

Data are presented as n. WR: work rate; V_O₂: maximal uptake; V_{CO}₂: carbon dioxide production; V_E: minute ventilation; f_c: cardiac frequency; t_{EL}: lactate threshold; P_{ET}O₂: end-tidal oxygen tension; P_{ET}CO₂: end-tidal carbon dioxide tension; ABGs: arterial blood gases; V_D/V_T: dead space volume/tidal volume; P(A-a)O₂: alveolar–arterial oxygen tension difference. [#]: males only.

The unavoidable conclusion from the previous discussion is that no single set of currently published reference values is applicable to all laboratories and patient populations, given the differences noted between them. The recommended approach is therefore as follows.

- 1) Make a preliminary selection of one predictive regression equation, which might not be the same for males and females. The equations from studies whose testing equipment, methodology and patient population most clearly resemble those used in the particular testing laboratory are recommended.

- 2) Compare against the values obtained in a small number ($n=10-20$) of healthy male and female subjects who are anthropometrically representative (ethnicity, age, height, weight) of the patient population normally studied. If more than three out of 10 of the presumed normal subjects have observed values that fall outside the 95% CI of the reference equation, the testing procedures should be reviewed. If the study of another 10 subjects again results in three or more falling outside the limits and no doubts exist about the accuracy of the equipment system, then alternative prediction equations should be tried. If no equation performs better, choose the one closest to the specific population, with the recognition that particular caution is warranted when deciding on whether a response is abnormal or not.

Children

COOPER *et al.* [32] reported $\dot{V}O_{2,\text{peak}}$ in 109 normal children (51 young females and 58 young males, aged 6–17 yrs), using a ramp test on a cycle ergometer. $\dot{V}O_{2,\text{peak}}$ was highly correlated with height and the values for the young males were significantly higher than for young females. With regard to $\dot{V}O_{2,\text{peak}}$ in young males, these results are comparable with those obtained over 20 yrs earlier by ASTRAND [6]. However, in the study by COOPER *et al.* [32], young females had significantly lower $\dot{V}O_{2,\text{peak}}$ values than those in the study by ASTRAND [6] (for further details see Chapter 9).

Exercise modality

Several studies [4, 6] have shown that $\dot{V}O_{2,\text{peak}}$ attained on the treadmill is 10–15% higher than $\dot{V}O_{2,\text{peak}}$ obtained on the cycle ergometer (table 3). The type of ergometer should, therefore, be taken into consideration when choosing reference values.

Lactate threshold

As described previously (Chapter 1), there is a $\dot{V}O_2$ above which exercise cannot be sustained for a long period of time and which is associated with a continuous accumulation of lactate in the blood [33–35]. This is commonly termed the lactate threshold (θL). The θL can be a useful parameter to complement the information provided by $\dot{V}O_{2,\text{peak}}$ and has the advantage of being independent to the subject motivation [36, 37]. It is most commonly estimated noninvasively using pulmonary gas exchange criteria (for further details see Chapter 2).

As with $\dot{V}O_{2,\text{peak}}$, θL can be normalised to weight (*e.g.* $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$). Normal values in healthy young adults are in the range $15-25 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ but can be in excess of $50 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ in elite endurance athletes. For clinical purposes, it is more useful to relate θL to the predicted $\dot{V}O_{2,\text{peak}}$. On average, θL occurs at $\sim 50\%$ of $\dot{V}O_{2,\text{peak}}$ in normal subjects, although the range extends from $\sim 40-80\%$ [15, 38]. θL is also modality specific and is particularly influenced by physical activity, decreasing less than $\dot{V}O_{2,\text{peak}}$

with age [15, 16, 39–42]. DAVIS *et al.* [40] have provided a prediction equation for nonsmoking, relatively unfit males ($n=103$) and females ($n=101$) in the 20–70-yr age range, based on weight and height, which gives values for $\dot{V}O_{2L}$ approximately similar to those proposed by HANSEN *et al.* [15], *i.e.* $>40\%$ of predicted $\dot{V}O_{2,peak}$. In the current author's experience, the mean values of JONES *et al.* [16] are fairly high for the sedentary populations usually tested.

$\dot{V}O_2$ –work-rate slope

In normal subjects, the slope of the linear portion of the relationship between $\dot{V}O_2$ and work rate ($\Delta\dot{V}O_2/\Delta WR$) for incremental cycle ergometer exercise is $\sim 10 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$, with 95% CI $8.5\text{--}12.5 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$ [43, 44]. $\Delta\dot{V}O_2/\Delta WR$ is relatively independent of age, sex and fitness. As discussed in Chapters 1 and 2, $\Delta\dot{V}O_2/\Delta WR$ is also unaffected by body mass, as long as pedalling frequency is maintained at a reasonable constant throughout the test. If not, there will be a variable contribution to the measured $\dot{V}O_2$ from the O_2 cost of moving the mass of the legs, which can be appreciable in the obese and in strength-trained athletes with large leg mass.

Peak cardiac frequency

The peak cardiac frequency (f_C) achieved by healthy subjects on a symptom-limited exercise test decreases with age, with no consistent differences having been found between males and females or across exercise modality. The two most commonly used predictive equations are 220–age yrs [45] and 210–0.65 age yrs [46], although others can be used (table 4). The SD of peak f_C is 10 min^{-1} , with the lower confidence limit, therefore, being $15\text{--}20 \text{ min}^{-1}$ or 10–13% below the mean value [9, 46].

An abnormal value for the post-exercise recovery of f_C , defined as a reduction of 12 beats during the first minute after symptom-limited incremental exercise, has been shown to be a powerful independent predictor of overall mortality [49].

f_C – $\dot{V}O_2$ slope

For incremental exercise, the relationship between f_C and $\dot{V}O_2$ is normally reasonably linear over most of its range. In clinical assessment, the f_C – $\dot{V}O_2$ response is often interpreted by visual comparison against a reference response line, obtained by connecting the target predicted $\dot{V}O_{2,peak}$ – f_C point to the measured resting $\dot{V}O_{2,f_C}$ point. SPIRO *et al.* [50] have proposed reference values for the f_C – $\dot{V}O_2$ slope ($\Delta f_C/\Delta\dot{V}O_2$) of $42\text{--}43\cdot\text{L}^{-1}$ for males and $63\text{--}71\cdot\text{L}^{-1}$ for females. $\Delta f_C/\Delta\dot{V}O_2$ varies with fitness, being higher in the less fit and lower in highly fit subjects, consequent to differences in $\dot{V}O_{2,peak}$ [51]. A $\Delta f_C/\Delta\dot{V}O_2$ value $>50\cdot\text{L}^{-1}$ in males has been suggested to be an indicator of a hyperdynamic cardiovascular response [52], although this assertion requires formal validation.

Oxygen pulse

The oxygen pulse is given by the ratio of $\dot{V}O_2$ to f_C , and is determined by stroke volume and the arterio-mixed venous O_2 content difference (for further details see

Chapter 1). As the f_c – $V'O_2$ relationship has a negative intercept on the $V'O_2$ axis (for further details see Chapters 1 and 2), the O_2 pulse will increase with a hyperbolic profile as WR increases (for further details see Chapters 1 and 2) [53]. The steeper f_c – $V'O_2$ relationship in unfit subjects means that their O_2 pulse profile will be relatively shallow [54]. Therefore, the O_2 pulse at peak exercise is dependent on fitness, as well as body mass, sex, age and haemoglobin concentration, for example, being low in anaemic conditions. Larger than predicted peak oxygen pulse values are seen in patients with heart transplants [55], β -blockers and chronotropic incompetence [56] and fixed cardiac pacemakers [57]. Predicted peak values for adults are presented in table 4.

Stroke volume

In sedentary adults, stroke volume (SV) at peak exercise is usually in the range of 100–120 mL [58, 59], with appreciably higher values occurring in endurance-trained individuals (*e.g.* of the order of 200 mL) [51]. Some commercial CPET systems provide estimations of SV that have been shown to be reasonably similar to the directly measured SV during exercise in a small series of normal subjects [60] and in patients with cardiac disease [61]. These approaches have yet to be evaluated more formally for larger population groups.

Table 4. – Reference values for maximal incremental test on cycle ergometer

Variable	First author [Ref.]	Equations	SEE	R ²
Peak work rate W [#]	JONES [16]	3.34 (Ht)–1.43 (age)–47 (sex)–312	35	0.74
Peak $V'O_2$ L·min ^{-1†}	JONES [16]	0.046 (Ht)–0.021 (age)–0.62 (sex)–4.31	0.46	0.76
Peak $V'O_2$ L·min ^{-1†}	HANSEN [15], WASSERMAN [4] ⁺	M: PW × (50.75–0.372 (age)) F: (PW+43) × (22.78–0.17 (age))		
Peak $V'O_2$ L·min ^{-1†}	FAIRBARN [27]	M: 0.023 (Ht)–0.031 (age)+0.0177 (W)–0.332 F: 0.0158 (Ht)–0.027 (age)+0.00899 (W)+0.207		
Peak f_c beats·min ⁻¹	ASTRAND [45]	220–(age)		
Peak f_c beats·min ⁻¹	FAIRBARN [27]	M: 209–0.86 (age) F: 207–0.78 (age)		
Peak f_c beats·min ⁻¹	JONES [16]	202–0.72 (age)	10.3	0.52
Peak f_c beats·min ⁻¹	LANGE-ANDERSON [46]	210 × 0.65 (age)		
Peak O_2 pulse mL·beat ⁻¹	JONES [16]	0.28 (Ht)–3.3 (sex)–26.7	2.8	0.75
$V'E$ L·min ⁻¹	JONES [16]	26.3 (VC)–34	23.1	0.69
$\dot{V}L$ L·min ^{-1†}	JONES [16]	0.024 (Ht)–0.0074 (age)–2.43	0.316	0.74
$\dot{V}L$ L·min ^{-1†}	HANSEN [15]	>40% pred peak $V'O_2$		
$\dot{V}L$ L·min ^{-1†}	DAVIS [40]	M: 0.0093 (Ht)–0.0136 (age)+0.4121 F: 0.0064 (Ht)–0.0053 (age)+0.1091	0.228 0.131	0.49 0.36
$V'E/V'CO_2$ at $\dot{V}L$	SUN [47]	28.25+0.105 × age+0.97 × sex–0.037 5 × Ht	2.39	0.36
Lowest $V'E/V'CO_2$	SUN [47]	27.94+0.108 × age+1 × sex–0.0376 × Ht	2.43	0.36
$V'E/V'CO_2$	SUN [47]	34.28+0.082 × age–0.0723 × Ht	3.03	0.36
Peak breathlessness CR-10	JONES [48]	0.565 × Ht ^{0.7} × age ^{-0.34}		
Peak leg effort CR-10	JONES [48]	(0.41–0.036 (sex)) × Ht × age ^{-0.35}		

SEE: standard error of estimate; $V'O_2$: oxygen uptake; f_c : cardiac frequency; $V'E$: minute ventilation; $\dot{V}L$: lactate threshold; $V'CO_2$: carbon dioxide production; CR-10: category ratio-10; Ht: height; M: male; F: female; W: weight; % pred: % predicted; PW: predicted weight; VC: vital capacity. PW males: 0.79 × Ht–60.7. PW females: 0.65 × Ht–42.8. When actual W is more than predicted, the PW should be used in the equations. WASSERMAN *et al.* [4] introduced new correction factors for overweight and underweight subjects, which have not yet been published in peer-reviewed journals. [#]: kpm·min⁻¹ in the original, 1 kpm·min⁻¹=0.1634 W; [†]: units for $V'O_2$ are mmol·min⁻¹, 1 L·min⁻¹=44.6 mmol·min⁻¹; ⁺: the values for females appear in [4], but not in a peer-reviewed paper, where it is said that they are derived from [15] and [25].

Arterial blood pressure

During incremental exercise, systolic blood pressure (SBP) increases $\sim 7\text{--}10$ mmHg for every $0.2\text{ L}\cdot\text{min}^{-1}$ increment of $\dot{V}'\text{O}_2$, achieving an increase above resting of $\sim 50\text{--}70$ mmHg at peak exercise. In contrast, diastolic blood pressure (DBP) tends to decrease slightly with exercise, by $\sim 4\text{--}8$ mmHg [62, 63]. Criteria for exercise hypertension have been defined in many different ways but an exaggerated SBP response to exercise has been most consistently used and is likely to be the most reliable and reproducible criterion [64]. The Framingham Heart Study considered males with a SBP ≥ 210 mmHg and females with a SBP ≥ 190 mmHg at peak exercise as having a hypertensive response [65]. Isolated exercise hypertension is a risk factor for major cardiovascular event and new resting hypertension [66–68].

Blood pressure normally falls rapidly following the cessation of symptom-limited exercise. Elevated SBP and DBP at 3-min post-exercise have been associated with an increased risk of resting hypertension [69].

Breathing reserve

Breathing reserve (BR) may be defined as peak minute ventilation ($\dot{V}'_{E,\text{peak}}$) expressed as a percentage of the maximum voluntary ventilation (MVV) or as the difference between MVV and $\dot{V}'_{E,\text{peak}}$ [4, 15, 70]. MVV can either be measured directly or estimated from the forced expiratory volume in one second (FEV₁) using one of several published formulae [4], *e.g.* FEV₁ $35\text{ L}\cdot\text{min}^{-1}$ [71], FEV₁ $40\text{ L}\cdot\text{min}^{-1}$ [72] or FEV₁ $20+20\text{ L}\cdot\text{min}^{-1}$ [73]. It should be noted that the estimated MVV may not be appropriate in patients with respiratory muscle weakness [74]. It is important to emphasise that as $\dot{V}'_{E,\text{peak}}$ is not fixed in a given individual but rather is protocol-dependent, the BR value will depend on the actual exercise protocol used (for further details see Chapter 2).

In adults of average fitness, BR is normally in the range of 50–75%, although there is appreciable variability. A lower limit of 15% (*i.e.* $\dot{V}'_E/\text{MVV} \times 100 > 85\%$) appears to be a reasonable criterion for ventilatory limitation based on the 95% confidence limits of normative data sets [4, 15, 16, 24, 26], particularly if it is associated with a high physiological dead space fraction of the breath (dead space volume (V_D)/ tidal volume (V_T)) at peak exercise coupled with an increased carbon dioxide arterial tension (P_{a,CO_2}) or a normal (rather than falling) P_{a,CO_2} in the presence of a metabolic acidosis [75]. BR is also low, or becomes so low that it almost disappears, in highly fit endurance athletes and the healthy fit elderly [16, 76]. This reflects the high $\dot{V}'_{E,\text{peak}}$ in such subjects because of their high $\dot{V}'\text{O}_{2,\text{peak}}$, while MVV is largely independent of fitness (for further details see Chapter 1).

Inspiratory capacity and exercise flow–volume loops

As described in Chapter 3, indices more closely related to expiratory flow limitation and dynamic hyperinflation (*i.e.* derived from spontaneous flow–volume loops relative to the maximal resting flow–volume loop (MFVL)) [77, 78] may provide better criteria for ventilatory limitation during exercise than BR. Displaying spontaneous flow–volume loops within the MFVL allows a visual assessment of whether expiratory flow during exercise closely approaches, impacts on or even slightly exceeds, the maximum flow defined by the MFVL (*i.e.* “encroachment”). This analysis is critically dependent on the accuracy of the placement of the exercise tidal flow–volume loops within the MFVL.

In normal young adults of average fitness, encroachment is rare. However, in highly fit endurance athletes, flow limitation is evident [79–81], consistent with a limited BR. In older healthy subjects, expiratory encroachment may be seen at lower WR [82].

Dynamic hyperinflation, evident as an increase in the end-expiratory lung volume (EELV), is also an important mechanism causing mechanical limitation to ventilation during exercise because it either increases elastic load to breathing, constrains the normal $\dot{V}_T$ increase or both [83]. In healthy young adults, EELV normally falls (and consequently inspiratory capacity (IC) rises) with increasing WR, by as much as 0.5–1.0 L below functional residual capacity [84]. In contrast, EELV is seen to increase in subjects who manifest significant expiratory flow limitation during exercise (*e.g.* in chronic obstructive pulmonary disease (COPD) [83] or the healthy fit elderly [82]. As described in Chapter 3, serial IC measurements can be used to monitor EELV changes during exercise. However, guidelines for standardisation of IC measurement during exercise have not yet been issued and normative data do not exist.

$\dot{V}'E$ –carbon dioxide production slope

As described in Chapter 2, $\dot{V}'E$ during incremental exercise increases linearly with carbon dioxide production ($\dot{V}'CO_2$) over a wide range of WRs. In healthy young adults, when $\dot{V}'E$ and $\dot{V}'CO_2$ are reported in $L \cdot min^{-1}$ BTPS (body temperature, ambient pressure, saturated with water vapour) and STPD (standard temperature, pressure and dry), respectively, the $\dot{V}'E$ – $\dot{V}'CO_2$ relationship has a slope ($\Delta \dot{V}'E / \Delta \dot{V}'CO_2$) of ~ 23 in young males and 25 in young females and a SD of ~ 3 , with a small positive intercept on the $\dot{V}'E$ axis (~ 3 – $5 L \cdot min^{-1}$) [17, 47, 85–87]. $\Delta \dot{V}'E / \Delta \dot{V}'CO_2$ increases with age up to mean levels of ~ 28 (3 SD) in both sexes [47] after 50 yrs. The slope can also be appreciably higher when $\dot{V}_D / \dot{V}_T$ is high and/or when the “set point” for P_{a,CO_2} is low, as is the case in many pulmonary and cardiac diseases. Indeed, there has been recent interest in using $\Delta \dot{V}'E / \Delta \dot{V}'CO_2$, in addition to $\dot{V}'O_{2,peak}$, for assessing the prognosis of subjects with heart failure [88, 89] (for further details see Chapter 10). A $\Delta \dot{V}'E / \Delta \dot{V}'CO_2$ value > 34 has been shown to be a better predictive index for early death from congestive heart failure than $\dot{V}'O_{2,peak}$ [90].

Ventilatory equivalent for CO_2

The ventilatory equivalent for CO_2 ($\dot{V}'E / \dot{V}'CO_2$) during exercise, for example at its nadir or at θ_L , has also been shown to have prognostic value during exercise (for further details see Chapter 10). As described in Chapter 2, during incremental exercise $\dot{V}'E / \dot{V}'CO_2$ declines hyperbolically with respect to $\dot{V}'CO_2$ to attain its minimum at or above the θ_L , prior to increasing as respiratory compensation for the metabolic acidosis develops. In healthy young adults, the minimum $\dot{V}'E / \dot{V}'CO_2$ is in the region of 23–25 (~ 2.5 SD), increasing with age up to levels of ~ 29 because of higher $\dot{V}_D / \dot{V}_T$ values (~ 2.5 SD) [15, 47]. Therefore, the upper confidence limit is ~ 34 but slightly lower in young adults. In one study a $\dot{V}'E / \dot{V}'CO_2$ at a θ_L of 34 had a sensitivity of 79% and a specificity of 88% to differentiate patients with or without increased pulmonary vascular resistance [91].

Physiological $\dot{V}_D / \dot{V}_T$ ratio

At rest, $\dot{V}_D / \dot{V}_T$ in healthy young adults is ~ 0.33 with an upper 95% CI limit of 0.45 [91, 92] decreasing to attain values at peak exercise of ~ 0.19 with an upper 95% CI limit of 0.29

[15, 92, 93]. Higher V_D/V_T values are characteristic of many forms of lung disease. Indeed, V_D/V_T is deemed to be a sensitive, albeit unspecific index of disease. However, both false-positive results due to changes in breathing pattern as well as false-negative results have been reported [94, 95], particularly if the breathing pattern is rapid and shallow [96].

Calculation of the V_D/V_T must be carefully performed, taking into account the apparatus dead space and using simultaneously measured values of mixed expired and arterial carbon dioxide tension with blood samples being drawn over an integral number of breaths, to avoid bias from intra-breath fluctuations which can become prominent in exercise. Due to the poor reliability of predictive equations for $P_a\text{CO}_2$, even in normal individuals, noninvasive measurements of V_D/V_T are not reliable in individual subjects.

V_T , breathing frequency and breath timing

Tidal volume

As described in Chapters 1 and 2, in healthy individuals V_T is primarily responsible for increases in ventilation at low levels of exercise [97], with breathing frequency (f_R) becoming progressively more important as peak WRs are approached [97, 98]. In COPD patients and also in highly fit subjects with very high ventilatory demands, V_T may actually decrease as f_R increases [99, 100]. Normal resting V_T varies with body height. At peak exercise, V_T normally plateaus ($V_{T,\max}$) at 50–60% of vital capacity (VC); however, there is considerable variation with an upper limit of the 95% CI $\sim 80\%$ [5, 15, 24, 50, 101]. Early work suggested that the $V_{T,\max}/VC$ ratio could distinguish restrictive lung diseases from COPD [102] and pulmonary disorders from cardiac disorders [103]. However, more recent work has not demonstrated significant differences in $V_{T,\max}/VC$ between patients with COPD ($44 \pm 15\%$), interstitial lung diseases ($54 \pm 11\%$), bronchial asthma ($56 \pm 12\%$) and heart disease ($54 \pm 12\%$), leading to the conclusion that differences in $V_{T,\max}$ between patients are more likely to be due to differences in ventilatory mechanics affecting the VC and not to the use of the available ventilatory reserve [104].

Values of $V_T > 80\%$ of resting IC have been considered typical of patients with restrictive disease, particularly if high V_T/IC levels are reached early during a progressive test [4, 54]. While in interstitial lung diseases the lung restriction results in a larger proportion of the IC being used at rest and early during exercise, $V_{T,\max}/IC$ is not affected and may even be lower than in healthy subjects [15, 105].

Current knowledge suggests that the use of peak V_T and the $V_{T,\max}/VC$ and $V_{T,\max}/IC$ ratios have limited differential diagnostic utility due to their wide variability and their lack of specificity [106].

Breathing frequency

Typical resting values are $8\text{--}12 \text{ min}^{-1}$, although these can be affected by the laboratory environment and the mouthpiece. At peak exercise, f_R in normal healthy adults is typically $\sim 30\text{--}40 \text{ min}^{-1}$, and seldom exceeds 55 min^{-1} [15, 24, 50, 97, 98, 101] with the exception of very fit endurance athletes who may increase f_R six- to seven-fold over resting values [99].

Inspiratory duty cycle

This is defined as the ratio of inspiratory duration to total breath duration (t_I/t_{tot}). It is normally 0.4–0.5 at rest. In healthy young adults, the increase in f_R with exercise

reflects a decrease in both time taken for inspiration (t_I) and expiratory time (t_E). However, as the t_E response is more marked, t_I/t_{tot} increases, typically from 0.4 at rest to 0.50–0.55 at peak exercise [107, 108]. t_I/t_{tot} tends to remain low in subjects with COPD (<0.45 and maybe even reaching 0.35), reflecting a longer t_E [83, 100, 109]. To date, this measurement is not commonplace in clinical exercise testing and its diagnostic value is not proven.

Arterial oxygen saturation

The normal resting arterial oxygen saturation (P_{a,O_2}) and oxygen saturation (S_{a,O_2}) depend on age, body posture and (of course) the altitude of the laboratory. During incremental exercise, P_{a,O_2} and S_{a,O_2} normally remain relatively stable. For example, S_{a,O_2} normally changes $<\sim 2\%$, although arterial desaturation is often seen at or near peak exercise in highly fit endurance athletes [110]. A fall in S_{a,O_2} of $\geq 4\%$ or an absolute $S_{a,O_2} \leq 88\%$ are usually considered clinically significant, *i.e.* may limit exercise tolerance [111]. It is important to recognise that S_{a,O_2} measured by pulse oximetry may differ from the directly measured value by $\sim 2\text{--}6\%$ during exercise, particularly when carboxyhaemoglobin (CO-Hb) levels are elevated [112–117]. Thus, it is highly recommended to calibrate the pulse oximeter at rest against a direct measurement of S_{a,O_2} , CO-Hb and methaemoglobin [111]. The inaccuracy of pulse oximeters is increased in people with high levels of skin pigmentation [118].

The severity of desaturation during exercise has a modest correlation with the carbon monoxide transfer factor (TL_{CO}) [119, 120]. According to one study the only case in which resting measurements have a sufficiently high predictive value to be clinically useful for (absence of) exercise desaturation is when high TL_{CO} is accompanied by a high resting S_{a,O_2} (*i.e.* $\geq 95\%$) [121]. In any other circumstances, desaturation cannot be anticipated from TL_{CO} , as was confirmed by a large retrospective study in which overall sensitivity and specificity were both a mediocre 75%, with a cut-off point of 62% for TL_{CO} as percentage of predicted determined by receiver operating characteristic analysis percentage of predicted [122]. While desaturation may occur with any type of high-intensity leg exercise, walking either on a treadmill [123] or on the flat elicits a greater degree of hypoxaemia than cycling [124]. Assessing the intensity at which arterial hypoxaemia is produced may be of interest for counselling on demanding activities or for deciding the prescription of ambulatory oxygen therapy.

Desaturation during exercise is a common feature of advanced COPD, being more frequent in emphysematous-type patients [124, 125]. It also occurs in most patients with moderate or severe pulmonary fibrosis [126–128] and it is also common in subjects with pulmonary vascular diseases [129]. On the contrary, it is rare in patients with heart diseases other than right-to-left shunt [130] and, importantly, is not seen in patients with anaemia, carboxyhaemoglobinaemia, deconditioning, obesity, heart failure or mitochondrial myopathy [131].

Alveolar–arterial oxygen difference

Studies in adult males have indicated that untrained subjects normally widen their alveolar–arterial oxygen tension difference (P_{A-a,O_2}) two- to three-fold from rest to maximal exercise (≤ 4.7 kPa); they also hyperventilate, which raises P_{a,O_2} sufficiently during strenuous exercise to prevent P_{a,O_2} from falling below resting levels [15, 92, 93]. In a study of 77 asbestos-exposed males (some of them smokers), P_{A-a,O_2} at peak

exercise was >4.74 kPa in only three subjects [15]. Higher values can be seen in elite endurance athletes, often in combination with arterial desaturation [110, 132–134]. The cause is believed to be due to an excessive widening of the alveolar–arterial oxygen difference, an insufficient hyperventilatory response [132] and, to a lesser extent, intrapulmonary arteriovenous shunts [135].

To date, there are few published arterial blood-gas data sets that allow direct comparison of pulmonary gas exchange between sexes. A recent review has discussed in detail sex and pulmonary gas exchange during exercise [136]. In the review by HOPKINS *et al.* [136], data compiled from previously published studies of 57 females ($\dot{V}O_{2,\text{peak}}$ 32–70 mL·kg⁻¹·min⁻¹) and 135 males ($\dot{V}O_{2,\text{peak}}$ 30–83 mL·kg⁻¹·min⁻¹) showed that PA_{a,O_2} during heavy to peak exercise is greater in females than males for the same metabolic rate. Furthermore, 12% of the females with a $\dot{V}O_{2,\text{peak}}$ of <50 mL·kg⁻¹·min⁻¹ had evidence of gas exchange impairment. In males of the same fitness level, $<2\%$ had evidence of gas exchange impairment. It should be kept in mind that when lung size and fitness levels are controlled for, many of the gas exchange differences between sexes seem to be lost.

Exercise-induced arterial hypoxaemia also occurs in the highly fit elderly individuals with $\dot{V}O_{2,\text{peak}}$ values in the 40–60 mL·kg⁻¹·min⁻¹ range (1.5–2.5 times greater than the age-predicted normal $\dot{V}O_{2,\text{peak}}$ value) but the prevalence of hypoxaemia is less than in younger highly fit males able to reach much higher absolute $\dot{V}O_2$ values [137]. Therefore, apparently, in most fit, healthy subjects the age-related decline in $\dot{V}O_{2,\text{peak}}$ and in pulmonary oxygen transport capacity are similar.

Most often PA_{a,O_2} reflects the presence of a parenchymal or vascular lung disease [124–128] and, less frequently, an intra-cardiac left-to-right shunt, although it too may increase in patients with heart failure [130].

Symptoms

Apart from chest pain or dizziness, which usually prompt cessation of an exercise test, the majority of normal subjects report that breathlessness or leg discomfort are the major causes of quitting [138]. Several psychophysical rating scales have been used to quantify the intensity of symptom perceptions.

The Borg scale is a ratio scale that incorporates verbal descriptors assigned to specific scale values. With the 6–20 scale [139], a symptom-limited maximal effort rating of perceived exertion (RPE) is normally expected to be in the region of 16–18 [140–142].

The Visual Analogue Scale (VAS) [143] is less restrictive, having a scale defined by only two descriptors (0 and 100) positioned at the top and bottom as anchors [109, 144].

The Category Ratio (CR)-10 Scale [145] incorporates verbal descriptors of severity corresponding to specific numbers. There are some features of the CR-10 that make it theoretically preferable over the VAS, as it is open-ended, allowing the patient to select a rating of >10 , and the presence of descriptors makes it more suitable for comparison between individuals. It may also be easier to administer. Its reproducibility for the measurement of breathlessness during exercise in patients with COPD is good [146].

Continuous rating measurements during exercise allow both the threshold and the profile of the symptom intensity response to be characterised, in addition to responses at peak exercise [138]. In normal subjects, RPE and dyspnoea at a given submaximal WR are systematically greater in females than males, in smaller than in larger subjects, and in older rather than in younger people, although the values at peak exercise tend to be similar [147].

For reliable symptom measurement, it is crucial that the subjects receive clear instructions before the test. Some prediction equations have been produced both for

breathlessness and leg effort [48], but in general, patients stop exercise at ratings of five to eight on the CR-10 Scale (or of 50–80 on the VAS) [47, 148]. Healthy individuals and patients with COPD usually report similar maximum ratings on the VAS and CR-10 Scale during incremental exercise, albeit the latter at lower metabolic rates and ventilation levels [48, 147, 148].

6-min walk distance

In certain diseases, other functional dimensions, such as activities of daily living, may be of interest. Daily living activities may be better reflected by the 6-min walk distance [149] (for further details see Chapter 7). The American Thoracic Society has issued guidelines for standardisation of the 6-min walk test [150], which have raised some criticism regarding the shape of the track to be utilised and the encouragement given to the patients [151]. There is also some controversy regarding whether a practice test is needed or not [150, 152, 153]. Published reference values are shown in table 5 [154–157] and reference values in table 6.

Conclusion

Reference values are key for the clinical interpretation of exercise testing. Abundant data exist in the literature regarding several of the physiological responses and parameters used in clinical exercise tests in healthy people, which allow the expected ranges of response to be defined. However, it is important to check whether published values fit with the study population. For some indices, there is a lack of large population-based studies that have systematically addressed the simultaneous measurement of the more relevant physiological

Table 5. – Published reference values for 6-min walking distance

First author [Ref.]	Sample size	Age yrs	Sample characteristics	Characteristics of the test
ENRIGHT [154]	117 M/177 F	40–80	General population/ prospective	Standardised encouragement/33-m corridor/no practice test/linear track
ENRIGHT [155]	315 F/437 M	>67	Hospital-attending population/ prospective/retrospective	Standardised encouragement/33-m corridor/no practice test/linear track
GIBBONS [156]	519M/1911 M	20–80	General population/ prospective	Standardised encouragement/20-m corridor/three practice tests (four tests in total)/linear track
TROOSTERS [157]	29 M/22 F	50–80	Healthy elderly volunteers/ prospective	Standardised encouragement/50-m corridor/one practice test/linear track

M: males; F: females.

Table 6. – Reference values for 6-min walk distance

First authors [Ref.]	Equations	SEE	R ²
ENRIGHT [154]	M: 7.57 (Ht)-5.02 (age yrs)-1.76 (W)-309 m F: 2.11 (Ht)-5.78 (age yrs)-2.29 (W)+667 m	78 m	0.4
ENRIGHT [155]	22 (Ht)-5.3 (age yrs)-0.93 (W)+17 (sex)+493 m	50 m	0.2
GIBBONS [156]	2.99 (age yrs)-74.7 (sex)+868.8 m		0.41
TROOSTERS [157]	5.14 (Ht)-5.32 (age yrs)-0.8 (W)+51.3 (sex)+218 m	56 m	0.66

SEE: standard error of estimate; M: males; Ht: height (cm); W: predicted weight (kg); F: females.

responses in nonpathological populations. More information is also needed about the physiological responses for sub-maximal exercise and about the standardisation of useful measurements, such as the inspiratory capacity.

Summary

Exercise testing provides an array of measurements that characterise an individual's physiological response. To decide whether a measured response is abnormal or not, observations have to be compared with mean reference values obtained from the study of large samples of, supposedly, healthy subjects.

There is certain biological inter-individual variability in the response to exercise between individuals. As this usually follows a normal distribution, the criterion to decide whether a response is abnormal is approximately twice the SD or the SE of the estimates (regression equations) below or above the mean.

Many exercise responses are predicted by regression equations, which attempt to reduce the variability by accounting for the anthropometric characteristics of the subjects. When selecting reference values an important consideration that must be kept in mind is whether the individuals being tested match the population from which the reference values were obtained. This can be done by evaluating a group of representative healthy subjects as described in the present chapter.

This chapter intends to comprehensively evaluate the most relevant information regarding reference values of the physiological response to exercise in nonpathological populations. Several tables describe reference equations with brief methodological notes and information about the variability of the estimates (SE) and the strength of the relationship (R^2), when provided by the authors.

Keywords: Decision making, exercise test, laboratory techniques and procedures, lactate threshold, oxygen uptake, reference values.

References

1. Standardized lung function testing. Report working Party. *Bull Eur Physiopathol Respir* 1983; 19: Suppl. 5, 1–95.
2. Evaluation of impairment/disability secondary to respiratory disorders. American Thoracic Society. *Am Rev Respir Dis* 1986; 133: 1205–1209.
3. Weber KT, Janicki JS, McElroy PA. Determination of aerobic capacity and the severity of chronic cardiac and circulatory failure. *Circulation* 1987; 76: VI40–VI45.
4. Wasserman K, Hansen JE, Sue DY, Stringer W, Whipp BJ, eds. Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications. 4th Edn. Philadelphia, Lippincott Williams & Wilkins, 2005.
5. Åstrand PO, Rodahl K, eds. Textbook of Work Physiology. 3rd Edn. New York, McGraw-Hill, 1986.
6. Astrand I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand* 1960; 49: Suppl. 169, 1–92.
7. Hermansen L, Saltin B. Oxygen uptake during maximal treadmill and bicycle exercise. *J Appl Physiol* 1969; 26: 31–37.
8. Dehn MM, Bruce RA. Longitudinal variations in maximal oxygen intake with age and activity. *J Appl Physiol* 1972; 33: 805–807.

-
9. Astrand I, Astrand PO, Hallback I, Kilbom A. Reduction in maximal oxygen uptake with age. *J Appl Physiol* 1973; 35: 649–654.
 10. Ogawa T, Spina RJ, Martin WH 3rd, *et al.* Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation* 1992; 86: 494–503.
 11. Proctor DN, Joyner MJ. Skeletal muscle mass and the reduction of V'O₂ max in trained older subjects. *J Appl Physiol* 1997; 82: 1411–1415.
 12. Toth MJ, Gardner AW, Ades PA, Poehlman ET. Contribution of body composition and physical activity to age-related decline in peak V'O₂ in men and women. *J Appl Physiol* 1994; 77: 647–652.
 13. Dockery DW, Ware JH, Ferris BG Jr, *et al.* Distribution of forced expiratory volume in one second and forced vital capacity in healthy, white, adult never-smokers in six U.S. cities. *Am Rev Respir Dis* 1985; 131: 511–520.
 14. Roca J, Sanchis J, Agusti-Vidal A, *et al.* Spirometric reference values from a Mediterranean population. *Bull Eur Physiopathol Respir* 1986; 22: 217–224.
 15. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; 129: S49–S55.
 16. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985; 131: 700–708.
 17. Neder JA, Nery LE, Peres C, Whipp BJ. Reference values for dynamic responses to incremental cycle ergometry in males and females aged 20 to 80. *Am J Respir Crit Care Med* 2001 15, 164: 1481–1486.
 18. Jones NL, Summers E, Killian KJ. Influence of age and stature on exercise capacity during incremental cycle ergometry in men and women. *Am Rev Respir Dis* 1989; 140: 1373–1380.
 19. Bhambhani Y, Singh M. The effects of three training intensities on VO₂ max and VE/VO₂ ratio. *Can J Appl Sport Sci* 1985; 10: 44–51.
 20. Hardman AE, Williams C, Wootton SA. The influence of short-term endurance training on maximum oxygen uptake, submaximum endurance and the ability to perform brief, maximal exercise. *J Sports Sci* 1986; 4: 109–116.
 21. Yoshida T, Udo M, Ohmori T, Matsumoto Y, Uramoto T, Yamamoto K. Day-to-day changes in oxygen uptake kinetics at the onset of exercise during strenuous endurance training. *Eur J Appl Physiol Occup Physiol* 1992; 64: 78–83.
 22. Hickson RC, Hagberg JM, Ehsani AA, Holloszy JO. Time course of the adaptive responses of aerobic power and heart rate to training. *Med Sci Sports Exerc* 1981; 13: 17–20.
 23. Blackie SP, Fairbairn MS, McElvaney GN, Morrison NJ, Wilcox PG, Pardy RL. Prediction of maximal oxygen uptake and power during cycle ergometry in subjects older than 55 years of age. *Am Rev Respir Dis* 1989; 139: 1424–1429.
 24. Blackie SP, Fairbairn MS, McElvaney NG, Wilcox PG, Morrison NJ, Pardy RL. Normal values and ranges for ventilation and breathing pattern at maximal exercise. *Chest* 1991; 100: 136–142.
 25. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973; 85: 546–562.
 26. Drinkwater BL, Horvath SM, Wells CL. Aerobic power of females, ages 10 to 68. *J Gerontol* 1975; 30: 385–394.
 27. Fairbairn MS, Blackie SP, McElvaney NG, Wiggs BR, Pare PD, Pardy RL. Prediction of heart rate and oxygen uptake during incremental and maximal exercise in healthy adults. *Chest* 1994; 105: 1365–1369.
 28. Froelicher VF Jr, Allen M, Lancaster MC. Maximal treadmill testing of normal USAF air crew men. *Aerosp Med* 1974; 45: 310–315.
 29. Itoh H, Koike A, Taniguchi K, Marumo F. Severity and pathophysiology of heart failure on the basis of anaerobic threshold (AT) and related parameters. *Jpn Circ J* 1989; 53: 146–154.
 30. Storer TW, Davis JA, Caiozzo VJ. Accurate prediction of VO₂max in cycle ergometry. *Med Sci Sports Exerc* 1990; 22: 704–712.
 31. Vogel JA, Patton JF, Mello RP, Daniels WL. An analysis of aerobic capacity in a large United States population. *J Appl Physiol* 1986; 60: 494–500.
-

32. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. Aerobic parameters of exercise as a function of body size during growth in children. *J Appl Physiol* 1984; 56: 628–634.
33. Wasserman K, McIlroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. *Am J Cardiol* 1964; 14: 844–852.
34. Wasserman K, Whipp BJ, Koyal SN, Cleary MG. Effect of carotid body resection on ventilatory and acid-base control during exercise. *J Appl Physiol* 1975; 39: 354–358.
35. Davis JA. Anaerobic threshold: review of the concept and directions for future research. *Med Sci Sports Exerc* 1985; 17: 6–21.
36. Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine parameters of aerobic function during exercise. *J Appl Physiol* 1981; 50: 217–221.
37. Medoff BD, Oelberg DA, Kanarek DJ, Systrom DM. Breathing reserve at the lactate threshold to differentiate a pulmonary mechanical from cardiovascular limit to exercise. *Chest* 1998; 113: 913–918.
38. Whipp BJ, Rossiter HB, Ward SA. Exertional oxygen uptake kinetics: a stamen of stamina? *Biochem Soc Trans* 2002; 30: 237–247.
39. Older PO, Smith RER, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest* 1993; 104: 701–704.
40. Davis JA, Storer TW, Caiozzo VJ. Prediction of normal values for lactate threshold estimated by gas exchange in men and women. *Eur J Appl Physiol Occup Physiol* 1997; 76: 157–164.
41. Reinhard U, Muller PH, Schmulling RM. Determination of anaerobic threshold by the ventilation equivalent in normal individuals. *Respiration* 1979; 38: 36–42.
42. Schneider DA, Phillips SE, Stoffolano S. The simplified V-slope method of detecting the gas exchange threshold. *Med Sci Sports Exerc* 1993; 25: 1180–1184.
43. Hansen JE, Sue DY, Oren A, Wasserman K. Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. *Am J Cardiol* 1987; 59: 669–674.
44. Hansen JE, Casaburi R, Cooper DM, Wasserman K. Oxygen uptake as related to work rate increment during cycle ergometer exercise. *Eur J Appl Physiol Occup Physiol* 1988; 57: 140–145.
45. Astrand I, Astrand PO, Hallback I, Kilbom A. Reduction in maximal oxygen uptake with age. *J Appl Physiol* 1973; 35: 649–654.
46. Lange-Andersen K, Shepard RJ, Denolin H, Varnauskas E, Masironi R. Fundamentals of Exercise Testing. Geneva, World Health Organization, 1971.
47. Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med* 2002; 166: 1443–1448.
48. Jones NL. Clinical Exercise Testing. 4th Edn. Philadelphia, W.B. Saunders, 1997; pp. 124–149.
49. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999; 341: 1351–1357.
50. Spiro SG, Juniper E, Bowman P, Edwards RH. An increasing work rate test for assessing the physiological strain of submaximal exercise. *Clin Sci Mol Med* 1974; 46: 191–206.
51. Rowell LB. Human Cardiovascular Control. New York, Oxford University Press, 1993.
52. Eschenbacher WL, Mannina A. An algorithm for the interpretation of cardiopulmonary exercise tests. *Chest* 1990; 97: 263–267.
53. Whipp BJ. The bioenergetic and gas-exchange basis of exercise testing. *Clin Chest Med* 1994; 15: 173–192.
54. Wasserman K, Whipp BJ. Exercise physiology in health and disease. *Am Rev Respir Dis* 1975; 112: 219–249.
55. Gullestad L, Haywood G, Ross H, *et al.* Exercise capacity of heart transplant recipients: the importance of chronotropic incompetence. *J Heart Lung Transplant* 1996; 15: 1075–1083.
56. Gauri AJ, Raxwal VK, Roux L, Fearon WF, Froelicher VF. Effects of chronotropic incompetence and beta-blocker use on the exercise treadmill test in men. *Am Heart J* 2001; 142: 136–141.
57. Meine M, Achtelik M, Hexamer M, Kloppe A, Werner J, Trappe HJ. Assessment of the chronotropic response at the anaerobic threshold: an objective measure of chronotropic function. *Pacing Clin Electrophysiol* 2000; 23: 1457–1467.

58. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982; 65: 1213–1223.
59. Weber KT, Janicki JS. Cardiopulmonary exercise testing for evaluation of chronic cardiac failure. *Am J Cardiol* 1985; 55: 22A–31A.
60. Stringer WW, Hansen JE, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. *J Appl Physiol* 1997; 82: 908–912.
61. Agostoni PG, Wasserman K, Perego GB, *et al.* Non-invasive measurement of stroke volume during exercise in heart failure patients. *Clin Sci* 2000; 98: 545–551.
62. Astrand PO, Ekblom B, Messin R, Salitin B, Stemberg J. Intra-arterial blood pressure during exercise with different muscle groups. *J Appl Physiol* 1965; 20: 253–256.
63. Robinson TE, Sue DY, Huszczuk A, Weiler-Ravell D, Hansen JE. Intra-arterial and cuff blood pressure responses during incremental cycle ergometry. *Med Sci Sports Exerc* 1988; 20: 142–149.
64. Franz IW, ed. *Ergometry in Hypertensive Patients. Implications for Diagnosis and Treatment.* Berlin, Springer, 1985.
65. Lauer MS, Levy D, Anderson KM, Plehn JF. The Framingham Heart Study: is there a relationship between exercise systolic blood pressure response and left ventricular mass? *Ann Intern Med* 1992; 116: 203–210.
66. Filipovsky J, Ducimetiere P, Safar ME. Prognostic significance of exercise blood pressure and heart rate in middle-aged men. *Hypertension* 1992; 20: 333–339.
67. Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Exercise blood pressure predicts cardiovascular mortality in middle-aged men. *Hypertension* 1994; 24: 56–62.
68. Allison TG, Cordeiro MAS, Miller TD, Daida H, Squires RW, Gau Gt. Prognostic significance of exercise-induced systemic hypertension in healthy subjects. *Am J Cardiol* 1999; 83: 371–375.
69. Gibbons RJ, Balady GJ, Bricker JT, *et al.* ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002; 106: 1883–1892.
70. American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
71. Clark TJ, Freedman S, Campbell EJ, Winn RR. The ventilatory capacity of patients with chronic airways obstruction. *Clin Sci* 1969; 36: 307–316.
72. Campbell SC. A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation. *J Occup Med* 1982; 24: 531–533.
73. Spiro SG. Exercise testing in clinical medicine. *Br J Dis Chest* 1977; 71: 145–172.
74. Gosselink R, Kovacs L, Ketelaer P, Carton H, Decramer M. Respiratory muscle weakness and respiratory muscle training in severely disabled multiple sclerosis patients. *Arch Phys Med Rehabil* 2000; 81: 747–751.
75. Diaz O, Villafranca C, Ghezzi H, *et al.* Breathing pattern and gas exchange at peak exercise in COPD patients with and without tidal flow limitation at rest. *Eur Respir J* 2001; 17: 1120–1127.
76. Johnson BD, Reddan WG, Seow KC, Dempsey JA. Mechanical constraints on exercise hyperpnea in a fit aging population. *Am Rev Respir Dis* 1991; 143: 968–977.
77. McClaran SR, Wetter TJ, Pegelow DF, Dempsey JA. Role of expiratory flow limitation in determining lung volumes and ventilation during exercise. *Appl Physiol* 1999; 86: 1357–1366.
78. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 770–777.
79. Beck KC, Staats BA, Hyatt RE. Dynamics of breathing during exercise. *In:* Whipp BJ, Wasserman K, eds. *Pulmonary Physiology and Pathophysiology of Exercise.* Dekker, New York, 1991; pp. 67–97.
80. Dempsey JA, Adams L, Ainsworth DM, *et al.* Airway, lung and respiratory muscle function. *In:* Rowell LB, Shepherd JT, eds. *Handbook of Physiology. Section 12. Exercise: Regulation and Integration of Multiple Systems.* New York, Oxford University Press, 1996; pp. 448–514.

81. Whipp BJ, Pardy R. Breathing during exercise. *In*: Macklem P, Mead J, eds. *Handbook of Physiology. Section 3: The Respiratory System. Vol III: Pulmonary Mechanics*. Washington DC, American Physiological Society, 1986; pp. 605–629.
82. Johnson BD, Badr MS, Dempsey JA. Impact of the aging pulmonary system on the response to exercise. *Clin Chest Med* 1994; 15: 229–246.
83. Younes M. Determinants of thoracic excursion during exercise. *In*: Whipp BJ, Wasserman K, eds. *Exercise Pulmonary Physiology and Physiopathology*. New York, Marcel Dekker, 1991; pp. 1–65.
84. Henke KG, Sharratt M, Pegelow D, Dempsey JA. Regulation of end-expiratory lung volume during exercise. *J Appl Physiol* 1988; 64: 135–146.
85. Davis JA, Whipp BJ, Wasserman K. The relation of ventilation to metabolic rate during moderate exercise in man. *Eur J Appl Physiol* 1980; 44: 97–108.
86. Habedank D, Reindl I, Vietzke G, *et al*. Ventilatory efficiency and exercise tolerance in 101 healthy volunteers. *Eur J Appl Physiol* 1998; 77: 421–426.
87. Davis JA, Sorrentino KM, Ninness EM, Pham PH, Dorado S, Costello KB. Test-retest reliability for two indices of ventilatory efficiency measured during cardiopulmonary exercise testing in healthy men and women. *Clin Physiol Funct Imaging* 2006; 26: 191–196.
88. Chua T, Ponikowski P, Harrington D, *et al*. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997; 29: 1585–1590.
89. Kleber FX, Vietzke G, Wernecke KD, *et al*. Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation* 2000; 101: 2803–2809.
90. Gitt AK, Wasserman K, Kilkowski C, *et al*. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation* 2002; 106: 3079–3084.
91. Markowitz DH, Systrom DM. Diagnosis of pulmonary vascular limit to exercise by cardiopulmonary exercise testing. *J Heart Lung Transplant* 2004; 23: 88–95.
92. Jones NL, McHardy GJ, Naimark A, Campbell EJ. Physiological dead space and alveolar-arterial gas pressure differences during exercise. *Clin Sci* 1966; 31: 19–29.
93. Wasserman K, Van Kessel AL, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol* 1967; 22: 71–85.
94. Martinez FJ, Stanopoulos I, Acero R, Becker FS, Pickering R, Beamis JF. Graded comprehensive cardiopulmonary exercise testing in the evaluation of breathlessness unexplained by routine evaluation. *Chest* 1994; 105: 168–174.
95. Mohsenifar Z, Tashkin DP, Levy SE, Bjerke RD, Clements PJ, Furst D. Lack of sensitivity of measurements of VD/VT at rest and during exercise in detection of hemodynamically significant pulmonary vascular abnormalities in collagen vascular disease. *Am Rev Respir Dis* 1981; 123: 508–512.
96. Mohsenifar Z, Brown HV, Koerner SK. Effect of breathing pattern on dead space ventilation VD/VT during exercise. *Respiration* 1985; 47: 232–236.
97. Gallagher CG, Brown E, Younes M. Breathing pattern during maximal exercise and during submaximal exercise with hypercapnia. *J Appl Physiol* 1987; 63: 238–244.
98. Johnson BD, Saupé KW, Dempsey JA. Mechanical constraints on exercise hyperpnea in endurance athletes. *J Appl Physiol* 1992; 73: 874–886.
99. Jensen JI, Lyager S, Pedersen OF. The relationship between maximal ventilation, breathing pattern and mechanical limitation of ventilation. *J Physiol* 1980; 309: 521–532.
100. Puente-Maestu L, García de Pedro J, Martínez-Abad Y, Ruiz de Ona JM, Llorente D, Cubillo JM. Breathlessness, ventilatory pattern, and changes in dynamic hyperinflation related to the intensity of constant work rate exercise in COPD. *Chest* 2005; 128: 651–656.
101. Younes M, Kivinen G. Respiratory mechanics and breathing pattern during and following maximal exercise. *J Appl Physiol* 1984; 57: 1773–1782.
102. Burdon JG, Killian KJ, Jones NL. Pattern of breathing during exercise in patients with interstitial lung disease. *Thorax* 1983; 38: 778–784.
103. Weber KT, Janicki JS, Likoff MJ. Exercise testing in the evaluation of cardiopulmonary disease. A cardiologist's point of view. *Clin Chest Med* 1984; 5: 173–180.

-
104. Gowda K, Zintel T, McParland C, Orchard R, Gallagher CG. Diagnostic value of maximal exercise tidal volume. *Chest* 1990; 98: 1351–1354.
 105. O'Donnell DE, Chau LK, Webb KA. Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. *J Appl Physiol* 1998; 84: 2000–2009.
 106. Gallagher CG, Younes M. Breathing pattern during and after maximal exercise in patients with chronic obstructive lung disease, interstitial lung disease, and cardiac disease, and in normal subjects. *Am Rev Respir Dis* 1986; 133: 581–586.
 107. McParland C, Krishnan B, Lobo J, Gallagher CG. Effect of physical training on breathing pattern during progressive exercise. *Respir Physiol* 1992; 90: 311–323.
 108. Syabbalo NC, Zintel T, Watts R, Gallagher CG. Carotid chemoreceptors and respiratory adaptations to dead space loading during incremental exercise. *J Appl Physiol* 1993; 75: 1378–1384.
 109. Nield M, Arora A, Dracup K, Hoo GW, Cooper CB. Comparison of breathing patterns during exercise in patients with obstructive and restrictive ventilatory abnormalities. *J Rehabil Res Dev* 2003; 40: 407–414.
 110. Dempsey JA, Hanson PG, Henderson KS. Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *J Physiol* 1984; 355: 161–175.
 111. AARC clinical practice guideline: exercise testing for evaluation of hypoxemia and/or desaturation. American Association for Respiratory Care. *Respir Care* 1992; 37: 907–912.
 112. Ries AL, Farrow JT, Clausen JL. Accuracy of two ear oximeters at rest and during exercise in pulmonary patients. *Am Rev Respir Dis* 1985; 132: 685–689.
 113. Gehring H, Hornberger C, Matz H, Konecny E, Schmucker P. The effects of motion artifact and low perfusion on the performance of a new generation of pulse oximeters in volunteers undergoing hypoxemia. *Respir Care* 2002; 47: 48–60.
 114. Powers SK, Dodd S, Freeman J, Ayers GD, Samson H, McKnight T. Accuracy of pulse oximetry to estimate HbO₂ fraction of total Hb during exercise. *J Appl Physiol* 1989; 67: 300–304.
 115. McGovern JP, Sasse SA, Stansbury DW, Causing LA, Light RW. Comparison of oxygen saturation by pulse oximetry and co-oximetry during exercise testing in patients with COPD. *Chest* 1996; 109: 1151–1155.
 116. Hannhart B, Haberer JP, Saunier C, Laxenaire MC. Accuracy and precision of fourteen pulse oximeters. *Eur Respir J* 1991; 4: 115–119.
 117. Carone M, Patessio A, Appendini L, *et al.* Comparison of invasive and noninvasive saturation monitoring in prescribing oxygen during exercise in COPD patients. *Eur Respir J* 1997; 10: 446–451.
 118. Zeballos RJ, Weisman IM. Reliability of noninvasive oximetry in black subjects during exercise and hypoxia. *Am Rev Respir Dis* 1991; 144: 1240–1244.
 119. Ries AL, Farrow JT, Clausen JL. Pulmonary function tests cannot predict exercise-induced hypoxemia in chronic obstructive pulmonary disease. *Chest* 1988; 93: 454–459.
 120. Sue DY, Oren A, Hansen JE, Wasserman K. Diffusing capacity for carbon monoxide as a predictor of gas exchange during exercise. *N Engl J Med* 1987; 316: 1301–1306.
 121. Knowler MT, Dunagan DP, Adair NE, Chin R Jr. Baseline oxygen saturation predicts exercise desaturation below prescription threshold in patients with chronic obstructive pulmonary disease. *Arch Intern Med* 2001; 161: 732–736.
 122. Hadeli KO, Siegel EM, Sherrill DL, Beck KC, Enright PL. Predictors of oxygen desaturation during submaximal exercise in 8,000 patients. *Chest* 2001; 120: 88–92.
 123. Christensen CC, Ryg MS, Edvardsen A, Skjongsberg OH. Effect of exercise mode on oxygen uptake and blood gases in COPD patients. *Respir Med* 2004; 98: 656–660.
 124. Poulain M, Durand F, Palomba B, *et al.* 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. *Chest* 2003; 123: 1401–1407.
 125. Mak VH, Bugler JR, Roberts CM, Spiro SG. Effect of arterial oxygen desaturation on six minute walk distance, perceived effort, and perceived breathlessness in patients with airflow limitation. *Thorax* 1993; 48: 33–38.
-

126. Chetta A, Aiello M, Foresi A, *et al.* Relationship between outcome measures of six-minute walk test and baseline lung function in patients with interstitial lung disease. *Sarcoidosis Vasc Diffuse Lung Dis* 2001; 18: 170–175.
127. Lee YC, Singh B, Pang SC, de Klerk NH, Hillman DR, Musk AW. Radiographic (ILO) readings predict arterial oxygen desaturation during exercise in subjects with asbestosis. *Occup Environ Med* 2003; 60: 201–206.
128. Lama VN, Flaherty KR, Toews GB, *et al.* Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 1084–1090.
129. Badesch DB, Abman SH, Ahearn GS, *et al.* American College of Chest Physicians. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: Suppl. 1, 35S–62S.
130. Wasserman K, Zhang YY, Gitt A, *et al.* Lung function and exercise gas exchange in chronic heart failure. *Circulation* 1997; 96: 2221–2227.
131. Wesiman IM, Zeballos RJ. An integrated approach to the interpretation of cardiopulmonary exercise testing. *Clinics Chest Med* 1994; 15: 421–445.
132. Dempsey JA, Wagner PD. Exercise-induced arterial hypoxemia. *J Appl Physiol* 1999; 87: 1997–2006.
133. Harms CA. Does gender affect pulmonary function and exercise capacity? *Respir Physiol Neurobiol* 2006; 151: 124–131.
134. Harms CA, Stager JM. Low chemoresponsiveness and inadequate hyperventilation contribute to exercise-induced hypoxemia. *J Appl Physiol* 1995; 79: 575–580.
135. Eldridge MW, Dempsey JA, Haverkamp HC, Lovering AT, Hokanson JS. Exercise-induced intrapulmonary arteriovenous shunting in healthy humans. *J Appl Physiol* 2004; 97: 797–805.
136. Hopkins SR, Harms CA. Gender and pulmonary gas exchange during exercise. *Exerc Sport Sci Rev* 2004; 32: 50–56.
137. Johnson BD, Badr MS, Dempsey JA. Impact of the aging pulmonary system on the response to exercise. *Clin Chest Med* 1994; 15: 229–246.
138. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992; 146: 935–940.
139. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377–381.
140. Borg G, Hassmen P, Lagerstrom M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. *Eur J Appl Physiol Occup Physiol* 1987; 56: 679–685.
141. Noble BJ, Borg GA, Jacobs I, Ceci R, Kaiser P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med Sci Sports Exerc* 1983; 15: 523–528.
142. Cooper CB, Storer TW, eds. *Exercise Testing and Interpretation: A Practical Approach*. Cambridge, University Press, 2001.
143. Gift AG. Visual analogue scales: measurement of subjective phenomena. *Nurs Res* 1989; 38: 286–288.
144. de Torres JP, Pinto-Plata V, Ingenito E, *et al.* Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. *Chest* 2002; 121: 1092–1098.
145. Borg G, Ljunggren G, Ceci R. The increase of perceived exertion, aches and pain in the legs, heart rate and blood lactate during exercise on a bicycle ergometer. *Eur J Appl Physiol Occup Physiol* 1985; 54: 343–349.
146. Mador MJ, Rodis A, Magalang UJ. Reproducibility of Borg Scale measurements of breathlessness during exercise in patients with COPD. *Chest* 1995; 107: 1590–1597.
147. Killian KJ, Summers E, Jones NL, Campbell EJM. Breathlessness and leg effort during incremental cycle ergometry. *Am Rev Respir Dis* 1992; 145: 1339–1345.
148. Hamilton AL, Killian KJ, Summers E, Jones NL. Symptom intensity and subjective limitation to exercise in patients with cardiorespiratory disorders. *Chest* 1996; 110: 1255–1263.
149. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 2001; 119: 256–270.

-
150. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
 151. Enright PL. The six minute walk test. *Respir Care* 2003; 48: 783–785.
 152. Kervio G, Carre F, Ville NS. Reliability and intensity of the six-minute walk test in healthy elderly subjects. *Med Sci Sports Exerc* 2003; 35: 169–174.
 153. Knox AJ, Morrison JF, Muers MF. Reproducibility of walking test results in chronic obstructive airways disease. *Thorax* 1988; 43: 388–392.
 154. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998; 158: 1384–1387.
 155. Enright PL, McBurnie MA, Bittner V, *et al.* Cardiovascular Health Study. The 6-min walk test: a quick measure of functional status in elderly adults. *Chest* 2003; 123: 387–398.
 156. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. *J Cardiopulm Rehabil* 2001; 21: 87–93.
 157. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; 14: 270–274.

CHAPTER 9

Exercise testing in children with respiratory diseases

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Background

Physical activity plays an important part in the natural and daily life of children and adolescents. During childhood, the ability to participate in physical activity determines the child's success in play and recognition among peers and, therefore, may influence the normal development, growth and psychological development during childhood [1–3]. Equally important during adolescence, the ability to participate in sports represents a way of personal fulfilment.

Level of physical activity has been shown to have an impact upon the long-term prognosis of several serious diseases during adult life [4–6]. It is during childhood and adolescence that the individual's pattern of physical activity and future activity level is often founded, and this may have an impact upon quality of life in adulthood as well as mortality.

Asthma is the most common chronic disease in childhood and the most common cause of admission to hospital among children [7]. Asthma influences the ability to participate in physical activity and sports. An American national study in 1988 demonstrated that up to 30% of asthmatic children had a limitation to daily physical activity due to their asthma [8].

The ability to perform physical activity is closely related to respiratory function. Respiratory diseases may influence the ability to perform physical activity and the ability to succeed in sports in several ways. The interrelationship between physical activity, respiratory diseases and bronchial hyperresponsiveness is complex.

First, physical activity may provoke respiratory symptoms through exercise-induced bronchoconstriction (EIB) in individuals with established respiratory disorders, such as asthma. Secondly, high levels of repetitive physical activity may, together with other environmental stimuli such as respiratory infections, contribute to the incitement of respiratory illness as frequently seen in top endurance athletes. Thirdly, reduced lung function in itself may limit the achievable level of physical activity, due to the increased demands placed on the airways during physical activity. Whereas reduced lung function in itself limits exercise capacity in patients with chronic lung disorders and reduced baseline lung function, in patients with bronchial asthma, EIB is the limiting factor despite normal baseline lung function. Thus, management of EIB should greatly improve the potential for physical activity in the asthmatic patient.

EIB is the limiting factor for physical activity in many asthmatic children. EIB occurs in up to 70–80% of asthmatic patients without anti-inflammatory treatment [9]. Thus, it is important to control EIB and, according to the International Paediatric Consensus Group, treating and mastering EIB is one of the main objectives in asthma management [10, 11]. The level of EIB may be assessed by exercise testing. Exercise testing in children with bronchial asthma may serve different purposes: it can be used to assess diagnosis and differential diagnoses of EIB, and also in the follow-up and monitoring of EIB, seen as a measure of indirect bronchial responsiveness [12] and asthma control.

Due to the frequent occurrence of asthma in childhood and the importance of mastering EIB for the asthmatic child, exercise testing employed for assessment of EIB is the single most important use of exercise testing in children. However, exercise testing can be performed in several ways, and may have different uses. Different chronic respiratory diseases may affect physical performance in different ways. In other chronic respiratory disorders with reduced baseline lung function, lung function may limit exercise performance by limiting maximum oxygen uptake ($\dot{V}O_{2\max}$). Other chronic conditions may limit exercise performance through an effect upon limb muscle strength, as has been shown for 5–7-yr-old children with low birth weight [13].

Therefore, there is a clear need for exercise testing of children in health and disease. Exercise testing in children may be performed in different ways, with different purposes and the need will vary with respect to health or disease and to the type of illness. The testing protocols may vary according to age of the child, type of illness and the physical ability of the child. In the healthy child, physical performance increases with increasing age, *i.e.* the opposite of the healthy adult. Growth heavily influences performance and reference values for standardised exercise testing.

Diagnosis of exercise-induced asthma and EIB

Exercise-induced asthma (EIA) is a condition with EIA symptoms, whereas EIB can be understood as the demonstration of EIB by lung function measurements after an exercise test or spontaneous exercise.

EIA and EIB can be diagnosed in several ways. The optimal way is to employ a standardised exercise test and measure lung function before and after exercise. Standardisation is particularly important in the follow-up of EIA over time, when comparing different individuals and in epidemiological studies. Previously, EIB diagnosed by exercise testing was reported to be found in 70–80% of asthmatic patients [9]. However, presently this has changed dramatically with the widespread use of anti-inflammatory treatment of asthma with inhaled steroids. EIB is rapidly and markedly influenced by inhaled steroids [14–16], and this puts increased demands upon the standardisation of exercise test with respect to work-rate (WR) and environmental factors.

Tests with different types of exercise have been standardised for the diagnosis of EIA and EIB, exemplified by the investigations of ANDERSON *et al.* [17] in the early 1970s. Running provokes EIA (EIB) in children more easily than cycling, and free running has a greater effect than running on a treadmill [17]. Furthermore, running for 6–8 min provokes a greater decrease in post-exercise forced expiratory volume in one second (FEV₁) than running for shorter or longer time periods [18]. Whereas these early studies [17] led to the recommendation of a sub-maximal exercise WR with cardiac frequency (f_c) at the level of 170 beats·min⁻¹ [19], the latest American Thoracic Society (ATS) guidelines recommend that a WR of 80–90% of the calculated maximum is employed in the testing of EIB, with inhalation of air having a relative humidity (RH) <50% and an

ambient temperature of 20–25°C, while running on a treadmill for 6–8 min [20]. However, it was later demonstrated that there are significant differences in the magnitude of EIB between a WR of 85 and 95% [21]. Furthermore, EIB is heavily influenced by the humidity and temperature of the inhaled air [22, 23], and the use of inhaled cold air (–20°C) during exercise testing markedly increased the sensitivity in diagnosing EIB without decreasing specificity in asthmatic children [24]. An excellent reproducibility of testing for EIB has been demonstrated when controlled for environmental conditions [25]. Thus, strict environmental standardisation with a sufficiently high WR is important in the testing for EIB and in using EIB as a monitoring device for asthma. Both European Respiratory Society and ATS recommendations set a 10% reduction in FEV₁ as a criterion for EIB [20, 26].

For standardisation purposes, running on a motor-driven treadmill is particularly useful. One commonly used set-up employs a treadmill inclination of 5.5% (3°) during running, with rapid increments in speed until a steady *f*C of ~95% of the predicted maximum is reached within the first 2 min of running. This speed is then maintained for 4–6 min. WR during running is often assessed indirectly from *f*C. Maximum *f*C can be estimated by subtracting the age (yrs) of the patient from 220 [21]. *f*C can be measured electronically by devices such as the Polar Vantage™ (Polar Electro, Kempele, Finland). As outlined in the ATS recommendations [20], the running test should be performed at a room temperature of ~20°C and a RH of ~40%. Lung function is measured before, immediately after running and 3, 6, 10, 15 and 20 min after running. FEV₁ is the common lung function index employed. Presently, the demonstration of at least a 10% reduction in FEV₁ after running compared to before is used as the criterion of EIB [20]. Instead of expressing EIB as a percentage reduction in FEV₁ from the starting value, results can be expressed as percentage of predicted values, thereby taking into account baseline lung function. In an attempt to increase sensitivity, indices derived from the area under the curve of the FEV₁ decrement following exercise have been employed as outcomes, in particular in clinical trials of asthma drugs [27]. However, the maximum post-exercise reduction in FEV₁ remains the primary outcome variable of testing for EIB.

Differential diagnosis of EIB

There are several important differential diagnoses relating to EIA or EIB in children and adolescents, and particularly in adolescents who participate in sports. One frequent differential diagnosis is exercise-induced inspiratory stridor or exercise-induced vocal cord dysfunction [28]. The symptoms are inspiratory stridor occurring during maximum exercise, which ceases when exercise is terminated unless hyperventilation is maintained. During exercise testing, audible inspiratory sounds can be heard arising from the laryngeal area, which is not alleviated by bronchodilators or other asthma medication. The condition most often occurs in young well-trained athletic females aged 15–16 yrs. Symptoms only occur during maximum exercise. One possible differential diagnosis of this syndrome is paradoxical movement of the vocal cords with adduction during inspiration. This may also occur without exercise. The diagnoses are made by direct fiberoptic laryngoscopy during exercise.

Other chronic disorders, including heart diseases, may have an effect upon physical performance and, thus, represent a possible differential diagnosis related to EIA.

In addition, poor physical fitness, in contrast to enthusiastic parental expectations, is a frequent occurrence among children and adolescents participating in sports. Among adolescent athletes undertaking heavy training, overtraining may sometimes represent a possible differential diagnosis for EIA.

Finally, exercise-induced arterial hypoxaemia should be considered [29]. This occurs especially in highly trained, highly fit endurance athletes and is thought to be primarily due to diffusion limitations and regional ventilation–perfusion inequalities. It has been postulated that, in the healthy lung, incomplete diffusion may be due to a rapid red blood cell transit time through the pulmonary capillaries. And while this condition is rare even among athletic adolescents, it should be kept in mind.

Assessment of physical fitness in paediatric chronic lung diseases

EIB is a specific occurrence for bronchial asthma, although it has a low sensitivity [24]. This is the same for several other measures of indirect bronchial responsiveness. However, measures for direct bronchial responsiveness, such as responsiveness to metacholine, have a greater sensitivity but lower specificity. Also, in other chronic lung disorders, a moderate bronchial responsiveness to metacholine may be found, whereas this is not the case for EIB [24]. Therefore, testing specifically for EIB may be of differential diagnostic value, but otherwise has a minor role in the assessment of other chronic lung disorders. Cardiopulmonary exercise testing (CPET) is of value in children with chronic lung disorders, as it provides important information for assessing disease severity and the ability to perform physical exercise. However, it should be noted that the level of physical fitness in children with mild-to-moderate asthma has been found to be comparable to that of healthy children [30–32].

Several CPET protocols have been developed for use in children. Most usually, progressive stepwise procedures have been proposed for the determination of peak exercise responses, such as peak oxygen uptake ($\dot{V}O_{2,\text{peak}}$), peak ventilation ($\dot{V}E_{\text{peak}}$), respiratory exchange ratio, maximum $\dot{f}C$ and WR. Several authors have published CPET and related reference values, typically based on the responses to incremental exercise [33–36]. However, doubt has been expressed as to how to optimally assess exercise capacity in young children. In a recent study, COOPER [37] maintained that short bouts of high-intensity exercise are the optimal physiological way of studying children, rather than maximal incremental exercise testing.

Many different modalities are used for CPET in adults, including ergometry (cycle and treadmill), walking and free running, employing both incremental and steady-state protocols (for further information see Chapter 5). For children, while protocols developed for adults have often been employed, it has been maintained that protocols especially suited for children should be developed [38]. The most widely used of these, with particular relevance to respiratory disorders in children, will now be discussed.

In 1952, ÅSTRAND [38] published his first results on physical fitness in children, including $\dot{V}O_{2,\text{peak}}$ or $\dot{V}O_{2,\text{max}}$. ÅSTRAND *et al.* [39] were instrumental in developing specific CPET-based guidelines for testing in children. Most often, for practical reasons, the exercise modality has been cycle ergometry or treadmill running. CPET has also been adapted to the specific requirements of sports, which is well exemplified in young swimmers [40] and rowers [41]. It should be noted that, regardless of the specific purpose, special consideration must be given in children when assessing physical performance with regard to factors such as age, sex and growth. It has been maintained that in children it is preferable to employ running rather than cycling in testing, partly because of cycle mechanics but also because the involved muscle groups differ between running and cycling [42].

While the classical method of assessing CPET-based responses relies on expired gas analysis by the Douglas bag technique, it is now more common to employ automated mixing-chamber or breath-by-breath systems (refer to Chapter 5). $\dot{f}C$ during running can

readily be measured by electronic devices such as the Polar Vantage™ or ECG. In children with cardiovascular diseases, the latter method should be used.

Exercise protocols used in children vary widely with regard to increment format, *e.g.* size and duration. For example, the classical Balke treadmill protocol, developed for assessment of fitness in military personnel [43], employs a constant speed of $5.3 \text{ km}\cdot\text{h}^{-1}$ with an increasing inclination of 1° per min; its disadvantage is that it may take up to 20 min to complete. The Bruce treadmill protocol, developed for testing cardiopulmonary fitness in adults with cardiac disease, employs a combination of increments of speed and inclination, with the initial speed being low but the incline steep [44, 45]. FREDRIKSEN *et al.* [46] modified the Bruce protocol for testing children with cardiac disease, using a higher initial speed and a lower inclination to provide smaller WR increments. There were no significant differences between the modified and the original Bruce protocols with respect to $\dot{V}\text{O}_{2,\text{peak}}$ and peak f_c , although blood [lactate] values and the respiratory exchange ratio were higher with the original Bruce protocol.

However, for children with respiratory disorders such as asthma, these slow progressions of speed and inclination prolong the test duration and consequently may result in poorer outcomes because of subject boredom. Therefore, COOPER [37] suggested that a more rapid protocol might be preferable. This issue was studied by STENSRUD *et al.* [47] who demonstrated that $\dot{V}\text{O}_{2,\text{max}}$ and $\dot{V}\text{E}_{\text{peak}}$ in a group of healthy children and adolescents were not significantly different regardless of whether they were tested using an incremental exercise protocol with a 20-min warm up, as described by HERMANSEN *et al.* [48], or using a shorter test designed for EIB (see above), in which a submaximal WR was attained after 2 min running and then maintained for 8 min. This finding is important, as a test used for demonstrating EIB may be used at the same time to assess physical fitness.

It should be noted that, in contrast to adults, the $\dot{V}\text{O}_{2,\text{max}}$ criterion of the oxygen uptake ($\dot{V}\text{O}_2$) response levelling off, despite further WR increments, is not evident in children. Therefore, the outcome of maximum exercise testing should be reported as $\dot{V}\text{O}_{2,\text{peak}}$ [49].

COOPER and co-workers [50, 51] determined reference values for physical fitness in children of varying ages and according to sex, based upon cycle ergometry. Interestingly, these values do not differ significantly from those published in 1968 by ASTRAND [52] using a quite different protocol. ROSENTHAL and BUSH [35] have defined reference values for $\dot{V}\text{O}_2$ and $\dot{V}\text{E}_{\text{peak}}$ in healthy children using cycle ergometry. Predictive equations for $\dot{V}\text{O}_{2,\text{max}}$ have been developed by KRAHENBUHL *et al.* [53], based on a meta-analysis of 66 studies comprising a total of 5,793 young males and 3,508 young females of different ages. All children were healthy, and none participated in regular physical training [53]. This yielded the following equations for predicted $\dot{V}\text{O}_{2,\text{max}}$ (y ; $\text{L}\cdot\text{min}^{-1}$) as a function of age (x ; yrs):

$$\text{Young males: } y = 0.859 - 0.013x + 0.010x^2 \quad (1)$$

$$\text{Young females: } y = 3.539 - 0.915x + 0.104x^2 - 0.003x^3 \quad (2)$$

Taking account of body weight by expressing $\dot{V}\text{O}_{2,\text{max}}$ as $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ yields [54]:

$$\text{Young males: } y = 52.35 + 0.071x \quad (3)$$

$$\text{Young females: } y = 58.90 - 1.15x \quad (4)$$

Assessment of tidal breathing during exercise

The simultaneous assessment of tidal breathing expiratory flow–volume loops during CPET can provide important additional information pertaining to operating lung volumes and flows during exercise, when related to the maximal forced expiratory flow–volume loop [54, 55]. For further information, please refer to Chapters 2 and 3.

Safety measures during paediatric exercise testing

Paediatric exercise testing in children with respiratory disorders should be looked upon as a bronchial provocation test, and similar precautions should be taken. Equipment for inhaling β_2 -agonists should be present, as well as adrenaline ($0.1 \text{ mg}\cdot\text{mL}^{-1}$) for injection and equipment for tracheal intubation and assisted ventilation, if needed. A doctor trained in respiratory medicine or critical care medicine should be present for the assessment of the patient before the exercise test, and to take therapeutic measurements during testing if needed.

Conclusion

Exercise testing is now an important element in the diagnosis of paediatric lung disease. For example, the diagnosis of EIA and bronchoconstriction by means of exercise provocation tests remains the most important application of exercise testing. The results of such tests can be considered as indirect measures of bronchial responsiveness. This type of exercise testing can be used both as a diagnostic and a monitoring tool. The same type of exercise test may be used for differential diagnoses in EIA, such as exercise-induced vocal cord dysfunction. In addition, objective assessment of physical fitness by measuring $\dot{V}\text{O}_{2,\text{max}}$ and $\dot{V}\text{E}_{\text{peak}}$ is becoming increasingly important, especially in the assessment of chronic lung disease of varying aetiology. This form of exercise testing is particularly important when it is combined with measurements of flow–volume loops during tidal breathing.

Summary

Paediatric exercise testing is becoming increasingly important for diagnosis in paediatric respiratory medicine. Testing for exercise-induced asthma (EIA) is still the most important and most frequently used exercise test for children. Standardisation of this test is very important, including standardisation of exercise load at a level of 90–95% of maximum exercise load and standardising environmental conditions, such as temperature, humidity and altitude. Treadmill running is most frequently used, but free range running and cycling are other options.

Exercise testing is important for the differential diagnosis of EIA. The most frequent differential diagnosis is exercise induced vocal cord dysfunction, which demonstrates inspiratory stridor at maximum performance during exercise testing.

Testing for physical fitness has become increasingly popular in paediatric respiratory medicine. Traditionally, a gradual stepwise protocol for exercise intensity has been used, but it has been shown that more short-term intensive protocols may give similar maximum oxygen uptakes and peak ventilation. The protocol may be varied according to the child's condition. Cardiac illnesses usually require gradual stepwise protocols, whereas children with respiratory disorders manage a quicker protocol. Of importance for respiratory diagnosis and assessment of possible physical training is measuring tidal breathing during exercise, which is obtainable through modern equipment.

Keywords: Asthma, exercise-induced bronchoconstriction, exercise-induced vocal chord dysfunction, exercise testing, maximum oxygen uptake, peak ventilation.

References

1. Strunk RC, Mrazek DA, Fukuhara JT, Masterson J, Ludwick SK, LaBrecque JF. Cardiovascular fitness in children with asthma correlates with psychologic functioning of the child. *Pediatrics* 1989; 84: 460–464.
 2. Cooper DM. Evidence for and mechanisms of exercise modulation of growth—an overview. *Med Sci Sports Exerc* 1994; 26: 733–740.
 3. Scheett TP, Mills PJ, Ziegler MG, Stoppani J, Cooper DM. Effect of exercise on cytokines and growth mediators in prepubertal children. *Pediatr Res* 1999; 46: 429–434.
 4. Anderssen S, Holme I, Urdal P, Hjermann I. Diet and exercise intervention have favourable effects on blood pressure in mild hypertensives: the Oslo Diet and Exercise Study (ODES). *Blood Press* 1995; 4: 343–349.
 5. Smith GD, Shipley MJ, Batty GD, Morris JN, Marmot M. Physical activity and cause-specific mortality in the Whitehall study. *Public Health* 2000; 114: 308–315.
 6. Hill MJ. Diet, physical activity and cancer risk. *Public Health Nutr* 1999; 2: 397–401.
 7. Jonasson G, Lodrup Carlsen KC, Leegaard J, Carlsen KH, Mowinckel P, Halvorsen KS. Trends in hospital admissions for childhood asthma in Oslo, Norway, 1980–95. *Allergy* 2000; 55: 232–239.
 8. Taylor WR, Newacheck PW. Impact of childhood asthma upon health. *Pediatrics* 1992; 90: 657–662.
 9. Lee TH, Anderson SD. Heterogeneity of mechanisms in exercise-induced asthma. *Thorax* 1985; 40: 481–487.
 10. Asthma: a follow up statement from an international paediatric asthma consensus group. *Arch Dis Child* 1992; 67: 240–248.
 11. Warner JO, Naspitz CK. Third International Pediatric Consensus statement on the management of childhood asthma. International Pediatric Asthma Consensus Group. *Pediatr Pulmonol* 1998; 25: 1–17.
 12. Pauwels R, Joos G, Van der Straten M. Bronchial hyperresponsiveness is not bronchial hyperresponsiveness is not asthma. *Clin Allergy* 1988; 18: 317–321.
 13. Keller H, Bar-Or O, Kriemler S, Ayub BV, Saigal S. Anaerobic performance. *Med Sci Sports Exerc* 2000; 32: 278–283.
 14. Henriksen JM, Dahl R. Effects of inhaled budesonide alone and in combination with low-dose terbutaline in children with exercise-induced asthma. *Am Rev Respir Dis* 1983; 128: 993–997.
 15. Waalkens HJ, van Essen-Zandvliet EE, Gerritsen J, Duiverman EJ, Knol K. The effect of an inhaled corticosteroid (budesonide) on exercise-induced asthma in children. Dutch CNSLD Study Group. *Eur Respir J* 1993; 6: 652–656.
 16. Jonasson G, Carlsen KH, Hultquist C. Low-dose budesonide improves exercise-induced bronchospasm in schoolchildren. *Pediatr Allergy Immunol* 2000; 11: 120–125.
 17. Anderson SD, Silverman M, Tai E, Godfrey S. Specificity of exercise in exercise-induced asthma. *BMJ* 1971; 4: 814–815.
 18. Godfrey S, Silverman M, Anderson SD. The use of the treadmill for assessing exercise-induced asthma and the effect of varying the severity and duration of exercise. *Pediatrics* 1975; 56: Suppl. 2, 893–898.
 19. Silverman M, Anderson SD. Standardization of exercise tests in asthmatic children. *Arch Dis Child* 1972; 47: 882–889.
 20. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med* 2000; 161: 309–329.
 21. Carlsen KH, Engh G, Mork M. Exercise-induced bronchoconstriction depends on exercise load. *Respir Med* 2000; 94: 750–755.
 22. Amirav I, Dowdeswell RJ, Plit M. Respiratory heat loss in exercise-induced asthma. Measurement and clinical application. *S Afr Med J* 1986; 69: 227–232.
 23. Deal ECJ, McFadden ERJ, Ingram RHJ, Strauss RH, Jaeger JJ. Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol* 1979; 46: 467–475.
-

24. Carlsen KH, Engh G, Mørk M, Schrøder E. Cold air inhalation and exercise-induced bronchoconstriction in relationship to metacholine bronchial responsiveness. Different patterns in asthmatic children and children with other chronic lung diseases. *Respir Med* 1998; 92: 308–315.
25. Henriksen JM. Reproducibility of exercise-induced asthma in children. *Allergy* 1986; 41: 225–231.
26. Sterk PJ, Fabbri LM, Quanjer PH, *et al.* Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, 53–83.
27. Leff JA, Busse WW, Pearlman D, *et al.* Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998; 339: 147–152.
28. McFadden ER Jr, Zawadski DK. Vocal cord dysfunction masquerading as exercise-induced asthma. A physiologic cause for “choking” during athletic activities. *Am J Respir Crit Care Med* 1996; 153: 942–947.
29. Powers SK, Williams J. Exercise-induced hypoxaemia in highly trained athletes. *Sports Med* 1987; 4: 46–53.
30. Bevegard S, Eriksson BO, Graff-Lonnevig V, Kraepelien S, Saltin B. Respiratory function, cardiovascular dimensions and work capacity in boys with bronchial asthma. *Acta Paediatr Scand* 1976; 65: 289–296.
31. Hedlin G, Graff-Lonnevig V, Freyschuss U. Working capacity and pulmonary gas exchange in children with exercise- induced asthma. *Acta Paediatr Scand* 1986; 75: 947–954.
32. Santuz P, Baraldi E, Filippone M, Zacchello F. Exercise performance in children with asthma: is it different from that of healthy controls? *Eur Respir J* 1997; 10: 1254–1260.
33. Eriksson BO, Grimby G, Saltin B. Cardiac output and arterial blood gases during exercise in pubertal boys. *J Appl Physiol* 1971; 31: 348–352.
34. Astrand PO. Methods of ergometry in children. Definitions, testing procedures, accuracy and reproducibility. *Acta Paediatr Scand Suppl* 1971; 217: 9–12.
35. Rosenthal M, Bush A. Haemodynamics in children during rest and exercise: methods and normal values. *Eur Respir J* 1998; 11: 854–865.
36. Armon Y, Cooper DM, Flores R, Zanconato S, Barstow TJ. Oxygen uptake dynamics during high-intensity exercise in children and adults. *J Appl Physiol* 1991; 70: 841–848.
37. Cooper DM. Rethinking exercise testing in children: a challenge. *Am J Respir Crit Care Med* 1995; 152: 1154–1157.
38. Åstrand PO. The aerobic capacity. In: Åstrand PO, ed. *Experimental Studies of Physical Working Capacity in Relation to Sex and Age*. 1st Edn. Copenhagen, Munksgard, 1952; pp. 103–123.
39. Åstrand PO, Rodahl K, eds. *Textbook of Work Physiology*. New York, McGraw-Hill, 1986.
40. Carlsen KH, Oseid S, Odden H, Mellbye E. The response to heavy swimming exercise in children with and without bronchial asthma. In: Oseid S, Carlsen KH, eds. *Children and Exercise XIII*. Champaign, Human Kinetics Publishers Inc., 1989; pp. 351–360.
41. Gibson PB, Szimonisz SM, Rowland TW. Rowing ergometry for assessment of aerobic fitness in children. *Int J Sports Med* 2000; 21: 579–582.
42. Klein AA. Pediatric exercise testing. *Pediatr Ann* 1987; 16: 546–547, 550–551: 554–558.
43. Balke B, Ware RW. An experimental study of physical fitness of Air Force personnel. *US Armed Forces Med J* 1959; 10: 875–888.
44. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. *Ann Clin Res* 1971; 3: 323–332.
45. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973; 85: 546–562.
46. Fredriksen PM, Ingjer F, Nystad W, Thaulow E. Aerobic endurance testing of children and adolescents--a comparison of two treadmill-protocols. *Scand J Med Sci Sports* 1998; 8: 203–207.
47. Stensrud T, Nordahl B, Vilberg A, Carlsen KH. Maximal oxygen uptake testing – a comparison of two test protocols. *Am J Respir Crit Care Med* 2005; 2: A494.

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48. Hermansen L. Oxygen transport during exercise in human subjects. *Acta Physiol Scand Suppl* 1973; 399: 1–104.
 49. Rowland TW. Does peak VO₂ reflect VO₂max in children?: evidence from supramaximal testing. *Med Sci Sports Exerc* 1993; 25: 689–693.
 50. Cooper DM, Weiler-Ravell D. Gas exchange response to exercise in children. *Am Rev Respir Dis* 1984; 129: S47–S48.
 51. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. Growth-related changes in oxygen uptake and heart rate during progressive exercise in children. *Pediatr Res* 1984; 18: 845–851.
 52. Astrand PO. Physical performance as a function of age. *JAMA* 1968; 205: 729–733.
 53. Krahenbuhl GS, Skinner JS, Kohrt WM. Developmental aspects of maximal aerobic power in children. *Exerc Sport Sci Rev* 1985; 13: 503–538.
 54. Dempsey JA, Johnson BD, Saupe KW. Adaptations and limitations in the pulmonary system during exercise. *Chest* 1990; 97: Suppl. 3, 81S–87S.
 55. Johnson BD, Reddan WG, Pegelow DF, Seow KC, Dempsey JA. Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. *Am Rev Respir Dis* 1991; 143: 960–967.

Exercise testing in the prognostic evaluation of patients with lung and heart diseases

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Exercise tolerance is a well recognised predictor of mortality in healthy subjects [1–3], as well as in patients with pulmonary and cardiovascular disease [4]. In clinical practice, physiological measurements obtained during the most commonly used exercise protocols, such as cardiopulmonary exercise testing (CPET) and the 6-min walking test (6MWT), are proving more useful than resting physiological measurements in the prognostic evaluation of these patients. CPET and 6MWT also represent the tests of choice for the selection of candidates for therapeutic procedures, such as transplantation and thoracic surgery.

The aim of the present chapter is to focus on the main cardiac and respiratory diseases for which exercise tolerance evaluation is indicated, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), interstitial lung disease (ILD), primary pulmonary hypertension (PPH), chronic heart failure (CHF) and congenital heart disease (CHD). This chapter also focuses on the exercise variables/indices that best predict mortality, such as the oxygen uptake ($\dot{V}O_2$) measured at peak exercise ($\dot{V}O_{2,\text{peak}}$), minute ventilation ($\dot{V}E$) relative to carbon dioxide production ($\dot{V}CO_2$; $\dot{V}E-\dot{V}CO_2$ slope), lactate threshold (θ_L), arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) and distance achieved on the 6MWT (6MWD; table 1) [5].

Table 1. – Exercise indices shown to predict the prognosis of patients with chronic respiratory and cardiac diseases

	COPD	ILD	PPH	CF	CHF
$\dot{V}O_{2,\text{peak}}$	+	+	+	+	+
θ_L					+
$\dot{V}E-\dot{V}CO_2$ slope and $\dot{V}E/\dot{V}CO_2$ at θ_L		+			++
Arterial desaturation		++	+	+	
6MWD	+		+		+

COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; PPH: primary pulmonary hypertension; CF: cystic fibrosis; CHF: chronic heart failure; $\dot{V}O_{2,\text{peak}}$: oxygen uptake at peak exercise; θ_L : lactate threshold; $\dot{V}E$: minute ventilation; $\dot{V}CO_2$: carbon dioxide production; $\dot{V}E/\dot{V}CO_2$: ventilatory equivalent for carbon dioxide; 6MWD: 6-min walking distance. +: sensitive; ++: more sensitive. Reproduced from [5] with permission.

COPD

In COPD patients, several resting variables/indices have been proven to predict mortality. The best known is the forced expiratory volume in one second (FEV₁) [6]. More recently, other indices have been studied: body mass index (BMI) [7, 8]; inspiratory capacity/total lung capacity ratio [9]; arterial hypoxaemia during sleep [10]; pulmonary arterial pressure [11] mixed venous oxygen pressure [12]; and degree of breathlessness [13]. Since the mid 1990s, however, given the systemic nature of the disease, more and more attention has been paid to skeletal muscle dysfunction [14–16] and, therefore, to the prognostic value of correlates of exercise intolerance. Among CPET variables, $\dot{V}O_{2,\text{peak}}$ has been reported, in a large prospective series (n=150), to better predict mortality at 5 yrs than post-bronchodilator FEV₁ (fig. 1) [17].

In particular, OGA *et al.* [17] found that a $\dot{V}O_{2,\text{peak}} < 654 \text{ mL}\cdot\text{min}^{-1}$ was associated with 60% mortality after 5 yrs, whereas a $\dot{V}O_{2,\text{peak}} > 793 \text{ mL}\cdot\text{min}^{-1}$ was associated with only 5% mortality. In a retrospective study (n=120), HIRAGA *et al.* [18] confirmed this result, reporting a 5-yr mortality of 62% for a $\dot{V}O_{2,\text{peak}} < 10 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}$, but finding that exercise-induced hypoxaemia, expressed as the slope of the relationship between arterial oxygen tension (P_{a,O_2}) and $\dot{V}O_2$ (P_{a,O_2} slope), was a better predictor of prognosis, *i.e.* a P_{a,O_2} slope $< -10.64 \text{ kPa}\cdot\text{L}^{-1}\cdot\text{min}^{-1}$ was associated with a mortality of $> 80\%$ (table 2).

The autonomic cardiac dysfunction observed in COPD patients has also recently been investigated as a possible prognostic factor. LACASSE *et al.* [19] used heart rate recovery (HRR), defined as the difference between cardiac frequency ($\dot{f}_C$) at peak exercise and $\dot{f}_C$ 1 min later, as a marker of autonomic dysfunction in order to test the hypothesis that HRR could correlate to an increased risk of mortality in COPD patients. They reported that a HRR of $\leq 14 \text{ beats}\cdot\text{min}^{-1}$ was a strong predictor of mortality (hazard ratio (HR) 5.12; 95% confidence interval (CI) 1.54–17.00; $p=0.008$). In addition, patients with both abnormal HRR and an FEV₁ $< 50\%$ of the predicted value had a worse prognosis than those with normal HRR.

In addition, walking test distance has been found to be a strong predictor of mortality in COPD 3 yrs after intervention [20, 21]. This is also the case for longer periods;

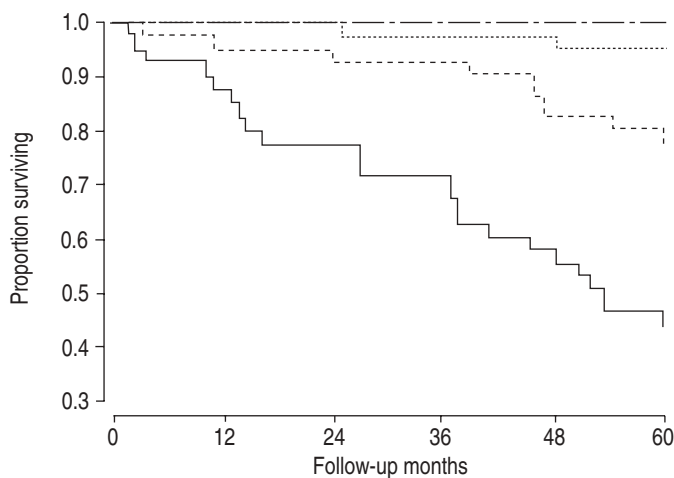


Fig. 1. – Kaplan–Meier survival curves (n=150) using peak oxygen uptake quartiles. — - - —: $> 995 \text{ mL}\cdot\text{min}^{-1}$ (n=37);: $793\text{--}995 \text{ mL}\cdot\text{min}^{-1}$ (n=38); - - - - -: $654\text{--}792 \text{ mL}\cdot\text{min}^{-1}$ (n=38); —: $< 654 \text{ mL}\cdot\text{min}^{-1}$ (n=37). Reproduced from [17] with permission.

a recent study that followed the decline in 6MWD over a 2-yr period found that survivors showed a slower decline than nonsurvivors [22]. The 6MWD has also been integrated into a grading system termed the Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity (BODE) index [23]. It is based on a four-point scoring system (0–3; best to worst) for FEV₁, 6MWD and dyspnoea (modified UK Medical Research Council dyspnoea scale) and two-point scoring (0 or 1; >21 or ≤21) for BMI. First studied in 207 COPD patients, the BODE index was subsequently validated in a cohort of 625 subjects. Patients with a higher BODE score were at greater risk of death, and the BODE score provided a better prognostic predictor of mortality than FEV₁ alone (fig. 2) [23].

Walking distance has also been studied as a possible pre-operative predictor of mortality in COPD patients presenting as candidates for lung volume reduction surgery (LVRS). A 6MWD <200 m before or after pulmonary rehabilitation predicts an unacceptable operative risk [24]. Similar results for LVRS were found using a cut-off for the shuttle walking test (SWT) distance (SWD) of 150 m [25].

IMFELD *et al.* [26] retrospectively investigated whether or not the BODE index also maintained its predictive value in COPD patients following LVRS. They found that post-operative BODE index was a powerful predictor of survival in patients with similar pre-operative characteristics (BODE index included). A reduction in BODE index to a lower score class after surgery was associated with lower mortality, and the predictive power of the score was better than that of FEV₁, dyspnoea or 6MWD [26].

The National Emphysema Treatment Trial introduced exercise tolerance, expressed as peak work rate, as an index for identifying those patients who would benefit from surgical treatment; the cut-off point was <25 W and <40 W for females and males, respectively [27]. Similarly, a 6MWD cut-off of <400 m has been suggested as appropriate for listing patients for lung transplantation [28].

Exercise tolerance has also been taken into account in the evaluation of pre-operative risk in COPD patients undergoing other kinds of surgical intervention, a $\dot{V}O_{2,\text{peak}}$ <15 mL·min⁻¹·kg⁻¹ or a 6MWD <250 m indicating a high risk of complication.

Cystic fibrosis

In patients with CF, resting pulmonary function has been used to provide prognostic indices of mortality. Among these indices, the most widely utilised for prognostic

Table 2. – Prognostic factors: Cox's regression analysis results

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
BMI <17 kg·m ⁻²	2.738 (1.334–5.623)	0.0061	1.632 (0.768–3.468)	0.2026
FEV ₁ <35% pred	6.753 (2.375–19.204)	0.0003	3.721 (1.222–11.332)	0.0207
$\dot{V}E_{\text{peak}}$ <20 L·min ⁻¹	3.594 (1.751–7.380)	0.0005	1.426 (0.631–3.223)	0.3933
$\dot{V}O_{2,\text{peak}}$ <10 mL·min ⁻¹ ·kg ⁻¹	3.368 (1.649–6.880)	0.0009	1.487 (0.676–3.268)	0.3238
$\dot{V}O_{2,\text{peak}}$ <14 mL·min ⁻¹ ·kg ⁻¹	4.041 (1.758–9.291)	0.0010		
P_{a,O_2} slope <-80 mmHg·L ⁻¹ ·min ⁻¹	6.646 (3.359–13.150)	<0.0001	3.095 (1.415–6.767)	0.0046
P_{a,O_2} slope <-50 mmHg·L ⁻¹ ·min ⁻¹	5.130 (2.385–11.037)	<0.0001		

HR: hazard ratio; CI: confidence interval; BMI: body mass index; FEV₁: forced expiratory volume in one second; % pred: % predicted; $\dot{V}E_{\text{peak}}$: minute ventilation at peak exercise; $\dot{V}O_{2,\text{peak}}$: oxygen uptake ($\dot{V}O_2$) at peak exercise; P_{a,O_2} : arterial oxygen tension; P_{a,O_2} slope: change (Δ) in $P_{a,O_2}/\Delta \dot{V}O_2$ relationship. 1 mmHg=0.133 kPa. Reproduced from [18] with permission.

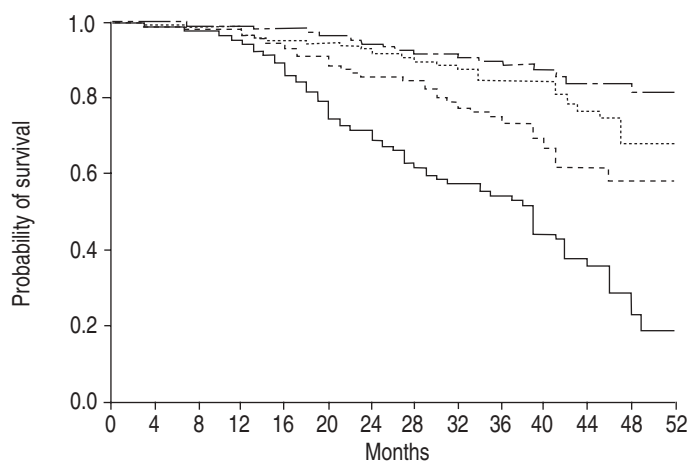


Fig. 2. – Kaplan–Meier survival curves for the four quartiles of the body mass index, airflow obstruction, dyspnoea and exercise capacity (BODE) index. — - — - : Quartile 1;: quartile 2; - - - : quartile 3; —: quartile 4. $p < 0.001$. Reproduced from [23] with permission.

evaluation and thus for referral for lung transplantation are FEV₁, arterial blood gas tensions, age and sex [29–31]. Nonetheless, since CF patients with similar functional results at rest show different clinical outcomes, other factors, such as recurrent respiratory tract infections (by *Pseudomonas* sp. and *Burkholderia cepacia*) and poor nutritional status, have been introduced into this evaluation [32–35]. In addition, exercise tolerance is a marker of severity and progression of the disease, and its inclusion can add further prognostic information. NIXON *et al.* [32] reported the results of a prospective study on 109 patients followed for 8 yrs, showing that a normal level of exercise tolerance, as demonstrated by a $\dot{V}O_{2,\text{peak}} \geq 82\%$ pred, was associated with a survival rate of 83%, whereas mortality increased as aerobic fitness deteriorated, *i.e.* survival was 49% for a $\dot{V}O_{2,\text{peak}}$ 59–81% pred and 72% for a $\dot{V}O_{2,\text{peak}} \leq 58\%$ pred. After adjustment for other risk factors, CF patients with higher levels of aerobic fitness were at much lower risk of death (*e.g.* three times lower) compared to those with lower fitness levels [32]. These results have been confirmed by other studies. For example, MOORCROFT *et al.* [36] and STANGHELLE *et al.* [37] found that $\dot{V}O_{2,\text{peak}}$ and work rate, $\dot{V}E$ and ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) at peak exercise were all significant predictors of mortality.

Besides CPET, other exercise tests have also been used in the prognostic evaluation of patients with CF. BALFOUR-LYNN *et al.* [38] compared a 3-min step test with a 6MWT in children with CF, and found both tests to be useful in the assessment of exercise tolerance, as did SELVADURAI *et al.* [39] and POUESSEL *et al.* [40] for a SWT. The most commonly used walk test indices in CF are the distance walked, Sp,O_2 and f_c [41]. For example, 6MWD has been shown to correlate with $\dot{V}O_{2,\text{peak}}$ in patients with CF, the correlation coefficient being increased with the addition of age, weight, forced vital capacity (FVC), FEV₁ and pulmonary diffusing capacity for carbon monoxide (DL_{CO}) to the prediction equation [42, 43]. In contrast, SHARPLES *et al.* [31] were unable to demonstrate any prognostic significance for the 12MWD. CHETTA *et al.* [44] found similar 6MWD and end-exercise f_c in a group of patients with CF compared to controls (consistent with CF patients having reasonably normal degrees of habitual physical activity), whereas the two groups differed in Sp,O_2 and dyspnoea. Therefore, they suggested that Sp,O_2 is better than exercise tolerance (*i.e.* 6MWD) for prognostic

evaluation in CF patients, as arterial desaturation better reflects the associated lung function impairment. Other authors reported that an elevated breathing reserve at the θ_L , defined as $\dot{V}_E$ at θ_L divided by maximum voluntary ventilation, is associated with an increased risk of death in CF patients awaiting lung transplantation [45]. This index is very useful, since it is obtainable even in patients who can not perform a maximal exercise test.

Interstitial lung disease

Besides its utility in the early detection of ventilatory and gas exchange abnormalities in patients affected by ILD who demonstrate normal resting function, CPET has proven useful in prognostic evaluation. For example, arterial desaturation $<88\%$ during a 6MWT is a strong predictor of mortality, and is easily measured. In addition, in patients with usual interstitial pneumonia, the presence of desaturation during exercise has been found to be associated with an increased hazard of death (HR 4.2; 95% CI 1.40–12.56; $p=0.01$) after adjusting for age, sex, smoking, baseline DL_{CO} , FVC and resting Sp_{O_2} [46]. KING *et al.* [47] developed a clinical–radiological–physiological scoring system for the prediction of survival in patients with usual interstitial pneumonia, and found that Pa_{O_2} at peak exercise was significantly predictive of survival, accounting for as much as 10.5% of the maximum score. In patients with idiopathic pulmonary fibrosis (IPF), $\dot{V}O_{2,peak}$, oxygen pulse, $\dot{V}_E/\dot{V}CO_2$ at peak exercise and Pa_{O_2} slope were all significant predictors of survival, with Pa_{O_2} slope being the most sensitive [48]. More recently, LEDERER *et al.* [49] found that 6MWD was predictive of survival in a cohort of 454 patients with IPF; a distance of <207 m was associated with a mortality at 6 months of $\sim 50\%$, and was a better predictor than FVC (% pred). Conversely, in a similar study on 197 patients with IPF, FLAHERTY *et al.* [50] found that the decreases in 6MWD and DL_{CO} were less significant in predicting an increase in mortality than the serial increase in arterial desaturation and decrease in FVC over time.

Primary pulmonary hypertension

Since the early studies in the 1980s, exercise was considered dangerous in patients with PPH. However, since the late 1990s exercise testing has been introduced into the clinical and prognostic evaluation of these patients, and has proved to be a useful tool for the evaluation of the severity of the disease and its response to therapeutic interventions. Both CPET and walking tests are used. Among CPET indices, $\dot{V}O_{2,peak}$ has been reported as a very significant predictor of survival in PPH. WENSEL *et al.* [51] reported that a $\dot{V}O_{2,peak} \leq 10.4 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}$ is associated with a 50% risk of death at 1 yr and 85% at 2 yrs, whereas the risk decreases to 10 and 30%, respectively, if $\dot{V}O_{2,peak}$ is $>10.4 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}$ (fig. 3). The predictive value of $\dot{V}O_{2,peak}$ can be further improved by adding the peak systolic blood pressure. Those patients with $\dot{V}O_{2,peak} \leq 10.4 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}$ and a peak systolic blood pressure of <120 mmHg have a worse prognosis (77% mortality at 1 yr) than those with only one of the two risk factors (21% mortality) [51].

In patients with PPH, the 6MWT is a simple test able to provide important information regarding disease severity and prognosis. For example, the 6MWD correlates well with $\dot{V}O_{2,peak}$. A 6MWD <332 m is associated with a survival of 20% at 20 months, whereas those patients who walk >332 m have a survival rate of 90% [52]. Another important prognostic index that is easily measurable during a 6MWT is arterial

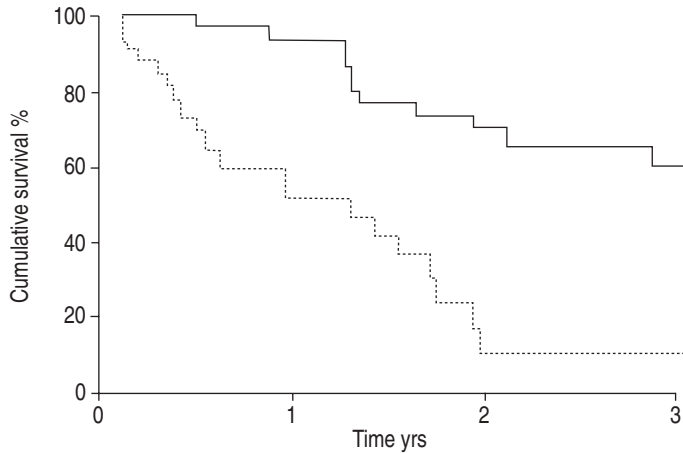


Fig. 3. – Kaplan–Meier cumulative survival curves in patients with primary pulmonary hypertension (n=70) using peak oxygen uptake. —: $> 10.4 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$;: $\leq 10.4 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. Reproduced from [51] with permission.

desaturation. PACIOCCO *et al.* [53] studied 34 PPH patients for a median follow-up time of 26 months. They found that the only significant variables related to survival were S_{p,O_2} during a 6MWT, the decrease in S_{p,O_2} during the test and pulmonary vascular resistance. In particular, they found a 26% increase in risk of death for each percentage decrease in S_{p,O_2} , even after adjustment for haemodynamic variables and pulmonary vascular resistance. In addition, although a 50-m increase in 6MWD was associated with an 18% reduction in risk of death, this was no longer predictive of mortality after adjustment for decrease in S_{p,O_2} [53].

Chronic heart failure

Exercise tolerance in patients affected by cardiac disease has been widely studied, because of its implications for clinical and prognostic evaluation [54]. Many CPET variables, such as $\dot{V}O_{2,\text{peak}}$, θ_L and indices of the $\dot{V}E$ – $\dot{V}CO_2$ relationship, have been used as measures of functional status in patients with CHF. Such variables have proved to be good predictors of survival in CHF patients, including those treated with β -blockers [55, 56]. Thus $\dot{V}O_{2,\text{peak}}$ shows a strong power in predicting mortality and listing patients for heart transplantation. MANCINI *et al.* [57] found a $\dot{V}O_{2,\text{peak}} > 14 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ to be associated with 94% survival at 1 yr and 84% at 2 yrs; in contrast, patients with a $\dot{V}O_{2,\text{peak}} \leq 14 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, who were rejected for transplantation for noncardiac reasons, showed survival rates at 1 and 2 yrs of only 47 and 32%, respectively. KLEBER *et al.* [58] reported a better prognosis at 30 months for patients with a $\dot{V}O_{2,\text{peak}} > 45\%$ pred than for those with a $\dot{V}O_{2,\text{peak}} < 45\%$ pred. SZLACHCIC *et al.* [59] reported that a $\dot{V}O_{2,\text{peak}} < 10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ is associated with 77% mortality at 1 yr, whereas, in patients with a $\dot{V}O_{2,\text{peak}} > 10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, the mortality rate at 1 yr is $\sim 20\%$ [60]. More recently, GITT *et al.* [61] reported that CHF patients with a $\dot{V}O_{2,\text{peak}} \leq 14 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (or $\leq 50\%$ pred) exhibited a three-fold increased risk of death at 6 months. This was reinforced by the poor prognosis (sensitivity 84%; specificity 48%) demonstrated by ARENA *et al.* [62] for CHF patients with a $\dot{V}O_{2,\text{peak}} < 14 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. There is now a general consensus that CHF patients with a $\dot{V}O_{2,\text{peak}} < 14 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ should be

considered for heart transplantation, as originally stated in the report of the 24th Bethesda Conference [63].

Some authors prefer to use θL , rather than $\dot{V}O_{2,peak}$, to assess a patient's functional status, because it is less effort-dependent, and because lactic acidemia occurs prematurely early in the course of an incremental exercise test; thus it should be more sensitive in the evaluation of cardiovascular adaptation to exercise. However, to date, only one study has examined the prognostic value of θL in CHF patients, demonstrating that a $\theta L < 11 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ is associated with a mortality risk ratio at 6 months of 2.7 [61].

The $\dot{V}E-\dot{V}CO_2$ slope and $\dot{V}E/\dot{V}CO_2$ are proving highly sensitive in the detection of lung impairment and exercise-induced pulmonary hypertension in patients with CHF, in the absence of any pre-existing pulmonary disease or any hyperventilation unrelated to acute exercise *per se* (e.g. metabolic and psychogenic). An enhanced ventilatory response to exercise in CHF may reflect, in part, decreased ventilatory efficiency (increased dead space/tidal volume), and is predictive of outcome in patients with preserved exercise capacity. Many studies have also utilised $\dot{V}E-\dot{V}CO_2$ slope in the prognostic evaluation of these patients [58, 61, 64–69]. A $\dot{V}E-\dot{V}CO_2$ slope $> 130\%$ pred is associated with a $> 40\%$ 1-yr mortality rate [58]. In a study of 470 CHF patients, an abnormal elevation in peak exercise $\dot{V}E/\dot{V}CO_2 \geq 44.7$ was found to be the strongest predictor of death during a 1.5-yr follow-up [69]. A $\dot{V}E-\dot{V}CO_2$ slope > 34 has been shown to be a better predictive index for early death (6 months) in CHF than $\dot{V}O_{2,peak}$ [61]. In another study of 123 CHF patients with a $\dot{V}O_{2,peak} \geq 18 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, 3-yr survival was significantly lower in those with a peak $\dot{V}E/\dot{V}CO_2 \geq 34$ (57 versus 93% for a $\dot{V}E/\dot{V}CO_2 \leq 34$) [65]. These findings have been confirmed in a more recent study by NANAS *et al.* [70], an overall mortality of 52% being found in CHF patients with $\dot{V}E-\dot{V}CO_2$ slope ≥ 34 , and of 18% in those with a $\dot{V}E-\dot{V}CO_2 \leq 34$. Furthermore, in a subgroup of CHF patients with a $\dot{V}O_{2,peak}$ of 10–18 $\text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, $\dot{V}E-\dot{V}CO_2$ slope was a significant predictor of mortality [70]. Some of the previously mentioned studies showed that a combination of CPET variables (*i.e.* $\dot{V}O_{2,peak}$, θL and $\dot{V}E-\dot{V}CO_2$ slope) better identifies patients at high risk of early death due to CHF than $\dot{V}O_{2,peak}$ alone [58, 61, 62]. GITT *et al.* [61] reported that a $\theta L < 11 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, combined with a $\dot{V}E-\dot{V}CO_2$ slope > 34 , better identified CHF patients at high risk of early death than $\dot{V}O_{2,peak}$ ($\leq 14 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ or $\leq 50\%$ pred) alone or in combination with either θL ($< 11 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) or $\dot{V}E-\dot{V}CO_2$ slope (> 34 ; table 3) [61].

Recently, in a study of 84 CHF patients, BILSEL *et al.* [71] examined the ability of HRR to predict mortality. During the follow-up period, an abnormal HRR, defined as a

Table 3. – Cox's regression analysis: calculation of risk of death at 6 months[#]

	Risk ratio (95% CI)	p-value
$\dot{V}O_{2,peak} \leq 14 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$	2.9 (1.5–5.4)	0.002
$\dot{V}O_{2,peak} \leq 10 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$	2.1 (1.1–4.3)	0.04
$\dot{V}O_{2,peak} \leq 50\%$ pred	2.0 (1.1–3.7)	0.03
$\theta L < 11 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$	2.7 (1.3–5.6)	0.007
$\dot{V}E-\dot{V}CO_2$ slope > 34	2.7 (1.5–5.1)	0.001
$\dot{V}O_{2,peak} \leq 14$; $\theta L < 11$	3.2 (1.5–6.7)	0.003
$\dot{V}O_{2,peak} \leq 14$; $\dot{V}E-\dot{V}CO_2$ slope > 34	4.5 (2.1–10)	< 0.001
$\theta L < 11$; $\dot{V}E-\dot{V}CO_2$ slope > 34	5.1 (2.0–12.7)	0.001

CI: confidence interval; $\dot{V}O_{2,peak}$: oxygen uptake at peak exercise; % pred: % predicted; θL : lactate threshold; $\dot{V}E$: minute ventilation; $\dot{V}CO_2$: carbon dioxide production; $\dot{V}E-\dot{V}CO_2$ slope: slope of relationship between $\dot{V}E$ and $\dot{V}CO_2$. [#]: allowing for sex, age, left ventricular ejection fraction and New York Heart Association Functional Class. Reproduced from [61] with permission.

difference ≤ 18 beats $\cdot$ min $^{-1}$ between f_C at peak exercise and f_C 1 min later, and a low $\dot{V}O_{2,\text{peak}}$ (*i.e.* ≤ 14 mL $\cdot$ min $^{-1}\cdot$ kg) were found to be the only significant predictors of mortality.

LEWIS *et al.* [72] compared SWT and treadmill CPET outcomes in the selection of patients for heart transplantation; an SWD of >450 m was found to equate with a $\dot{V}O_{2,\text{peak}}$ for treadmill walking >14 mL $\cdot$ min $^{-1}\cdot$ kg. Similarly MORALES *et al.* [73] found that SWD was a predictor of outcome at 1-yr of follow-up, although 6MWD was not; in particular, a poor performance in the SWT (*e.g.* distance of <450 m) identified a subgroup of CHF patients with a high risk of major cardiac events in the short term. Other studies found a 6MWD <300 m to be associated with reduced overall and event-free survival [74, 75]. In more severe CHF patients, baseline 6MWD was a strong independent predictor of mortality and hospitalisation at 1 yr [76].

In CHF, other exercise indices that have been studied include the presence of exercise-related periodic breathing, which seems to independently predict cardiac mortality [77], and the slowing of the time constant of the $\dot{V}O_2$ response to low-intensity constant-load exercise. In a study of 260 patients with mild-to-moderate CHF, the survival rate was 89% for patients with a $\dot{V}O_2$ time constant of <80 s and 71.7% for those with a $\dot{V}O_2$ time constant of ≥ 80 s ($p=0.0028$) [78–81].

Congenital heart disease

Major advances in surgical approach in patients with CHD have greatly improved life expectancy. Nonetheless, these patients continue to show a higher mortality than healthy subjects over both the medium and long term. Thus, risk stratification of adult patients with CHD could be of help in defining the timing of therapeutic intervention. As in other cardiac diseases, CPET has been introduced in the evaluation of CHD, with great interest in the functional and prognostic information that it can add. Recently, DIMOPOULOS *et al.* [82] found, in a cohort of 560 adult patients with CHD, that the $\dot{V}E$ – $\dot{V}CO_2$ slope was the most powerful univariate predictor of mortality in noncyanotic patients and the only independent predictor of mortality among exercise parameters with multivariate analysis; in cyanotic patients, however, no predictive parameter was found. This group also followed a cohort of 727 adult patients with CHD for a 28-month period, focusing on the autonomic dysfunction, suggested by an abnormal f_C response to exercise, and its possible prognostic implications. This study found that f_C reserve, peak HRR and $\dot{V}O_{2,\text{peak}}$ were all reduced and associated with increased mortality. In particular, f_C reserve predicted mortality independently of antiarrhythmic therapy, functional class and $\dot{V}O_{2,\text{peak}}$ [83].

Conclusions

The evaluation of exercise tolerance, by CPET or 6MWT, in patients with lung and heart diseases is of great prognostic value. This is particularly true for chronic diseases, such as COPD, CF, ILD, PPH and CHF. Importantly, some physiological indices obtained during exercise, such as $\dot{V}E$ – $\dot{V}CO_2$ slope during CPET, in CHF and PPH, and arterial oxygen desaturation during the 6MWT, in ILD, have proven particularly helpful in prognostic stratification. In addition, exercise testing is recommended for the pre-operative evaluation of candidates for major surgery and heart–lung transplantation. Finally, nowadays, exercise testing is mandatory for the correct prognostic evaluation of chronic pulmonary and cardiac diseases.

Summary

Exercise tolerance is recognised to be a good predictor of mortality in healthy subjects, ranging from young adults to the elderly. This also appears to be the case in a wide range of pulmonary and cardiovascular disease states. Data are available concerning the value of exercise indices in chronic obstructive lung disease, interstitial lung disease (ILD), pulmonary vascular disease (PVD), cystic fibrosis and chronic heart failure (CHF). In these patients, the evaluation of the level of exercise tolerance, by cardiopulmonary exercise test (CPET) or by walking tests, has proven to be very useful not only for functional evaluation but also for prognostic evaluation. Scientific evidence also exists demonstrating that physiological measurements obtained during CPET (*e.g.* increased minute ventilation/carbon dioxide productions in CHF and in PVD) as well as during walking tests (*e.g.* arterial oxygen desaturation in ILD) provide additional important prognostic information. Exercise testing is recommended for pre-operative risk evaluation of candidates for major surgery and heart–lung transplantation. As pulmonary and cardiac function testing obtained at rest provide little prognostic information, exercise testing is recommended for the correct evaluation of patients with chronic pulmonary and cardiac diseases.

Keywords: Cardiopulmonary exercise testing, heart diseases, lung diseases, prognosis.

References

1. Laukkanen JA, Lakka TA, Rauramaa R, *et al.* Cardiovascular fitness as a predictor of mortality in men. *Arch Intern Med* 2001; 161: 825–831.
2. Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. *Arch Intern Med* 2004; 164: 1092–1097.
3. Sherman SE, D'Agostino RB, Cobb JL, Kannel WB. Does exercise reduce mortality rates in the elderly? Experience from the Framingham Heart Study. *Am Heart J* 1994; 128: 965–972.
4. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346: 793–801.
5. Palange P, Ward SA, Carlsen KH, *et al.* Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; 29: 185–209.
6. Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 14–20.
7. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1791–1797.
8. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 1856–1861.
9. Casanova C, Cote C, de Torres JP, *et al.* Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 591–597.
10. Fletcher EC, Donner CF, Midgren B, *et al.* Survival in COPD patients with a daytime PaO₂ greater than 60 mmHg with and without nocturnal oxyhemoglobin desaturation. *Chest* 1992; 101: 649–655.

11. Oswald-Mammosser M, Weitzenblum E, Quoix E, *et al.* Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. *Chest* 1995; 107: 1193–1198.
12. Chodosowska E, Skwarski K, Zielinski J. Mixed venous blood oxygen tension is not a good predictor of survival in patients with chronic obstructive lung disease. *Eur J Respir Dis* 1987; 71: 233–238.
13. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002; 121: 1434–1440.
14. Casaburi R. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2001; 33: S662–S670.
15. Palange P, Wagner PD. The skeletal muscle in chronic respiratory diseases. *Eur Respir J* 2000; 15: 807–815.
16. Skeletal muscle dysfunction in obstructive pulmonary disease. A Statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med* 1999; 159: S1–S40.
17. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003; 167: 544–549.
18. Hiraga T, Maekura R, Okuda Y, *et al.* Prognostic predictors for survival in patients with COPD using cardiopulmonary exercise testing. *Clin Physiol Funct Imaging* 2003; 23: 324–331.
19. Lacasse M, Maltais F, Poirier P, *et al.* Post-exercise heart rate recovery and mortality in chronic obstructive pulmonary disease. *Respir Med* 2005; 99: 877–886.
20. Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following out-patient pulmonary rehabilitation. *Eur Respir J* 1996; 9: 431–435.
21. Bowen JB, Votto JJ, Thrall RS, *et al.* Functional status and survival following pulmonary rehabilitation. *Chest* 2000; 118: 697–703.
22. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004; 23: 28–33.
23. Celli BR, Cote CG, Marin JM, *et al.* The body mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
24. Szekely LA, Oelberg DA, Wright C, *et al.* Preoperative predictors of operative morbidity and mortality in COPD patients undergoing bilateral lung volume reduction surgery. *Chest* 1997; 111: 550–558.
25. Geddes D, Davies M, Koyama H, *et al.* Effect of lung-volume-reduction surgery in patients with severe emphysema. *N Engl J Med* 2000; 343: 239–245.
26. Imfeld S, Bloch KE, Weder W, Russi E. The BODE index after volume reduction surgery correlates with survival. *Chest* 2006; 129: 873–878.
27. National Emphysema Treatment Trial Research Group. Cost effectiveness of lung-volume-reduction-surgery for patients with severe emphysema. *N Engl J Med* 2003; 348: 2092–2102.
28. Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. *J Heart Lung Transplant* 1997; 16: 313–319.
29. Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992; 326: 1187–1191.
30. Augarten A, Akons H, Aviram M, *et al.* Prediction of mortality and timing of referral for lung transplantation in cystic fibrosis patients. *Pediatr Transplant* 2001; 5: 339–342.
31. Sharples L, Hathaway T, Dennis C, Caine N, Higenbottam T, Wallwork J. Prognosis of patients with cystic fibrosis awaiting heart and lung transplantation. *J Heart Lung Transplant* 1993; 12: 669–674.
32. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med* 1992; 327: 1785–1788.
33. Huang NN, Schidlow DV, Szatrowski TH, *et al.* Clinical features, survival rate, and prognostic factors in young adults with cystic fibrosis. *Am J Med* 1987; 82: 871–879.

-
34. Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988; 41: 583–591.
 35. Schwebel C, Pin I, Barnoud D, *et al.* Prevalence and consequences of nutritional depletion in lung transplant candidates. *Eur Respir J* 2000; 16: 1050–1055.
 36. Moorcroft AJ, Dodd ME, Webb AK. Exercise testing and prognosis in adult cystic fibrosis. *Thorax* 1997; 52: 291–293.
 37. Stanghelle JK, Skyberg D, Haanaes OC. Eight-year follow-up of pulmonary function and oxygen uptake during exercise in 16-year-old males with cystic fibrosis. *Acta Paediatr* 1992; 81: 527–531.
 38. Balfour-Lynn IM, Prasad SA, Laverty A, Whitehead BF, Dinwiddie R. A step in the right direction: assessing exercise tolerance in cystic fibrosis. *Pediatr Pulmonol* 1998; 25: 278–284.
 39. Selvadurai HC, Cooper PJ, Meyers N, *et al.* Validation of shuttle tests in children with cystic fibrosis. *Pediatr Pulmonol* 2003; 35: 133–138.
 40. Pouessel G, Santos C, Thumerelle C, *et al.* Reproducibility of the shuttle walk test in children with cystic fibrosis. *Rev Mal Respir* 2003; 20: 711–718.
 41. Aurora P, Wade A, Whitmore P, Whitehead B. A model for predicting life expectancy of children with cystic fibrosis. *Eur Respir J* 2000; 16: 1056–1060.
 42. Cahalin L, Pappagianopoulos P, Prevost S, Wain J, Ginns L. The relationship of the 6-min walk test to maximal oxygen consumption in transplant candidates with end-stage lung disease. *Chest* 1995; 108: 452–459.
 43. Gulmans VA, van Veldhoven NH, de Meer K, Helders PJ. The six-minute walking test in children with cystic fibrosis: reliability and validity. *Pediatr Pulmonol* 1996; 22: 85–89.
 44. Chetta A, Pisi G, Zanini A, *et al.* Six-minute walking test in cystic fibrosis adults with mild to moderate lung disease: comparison to healthy subjects. *Respir Med* 2001; 95: 986–991.
 45. Tantisira KG, Systrom DM, Ginns LC. An elevated breathing reserve index at lactate threshold is a predictor of mortality in patients with cystic fibrosis awaiting lung transplantation. *Am J Respir Crit Care Med* 2002; 165: 1629–1633.
 46. Lama VN, Flaherty KR, Toews GB, *et al.* Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 1084–1090.
 47. King TE Jr, Tooez JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001; 164: 1171–1181.
 48. Miki K, Maekura R, Hiraga T, *et al.* Impairments and prognostic factors for survival in patients with idiopathic pulmonary fibrosis. *Respir Med* 2003; 97: 482–490.
 49. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006; 174: 659–664.
 50. Flaherty KR, Andrei AC, Murray S, *et al.* Idiopathic pulmonary fibrosis. Prognostic value of changes in physiology and six-minute-walk test. *Am J Respir Crit Care Med* 2006; 174: 803–809.
 51. Wensel R, Opitz CF, Anker SD, *et al.* Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation* 2002; 106: 319–324.
 52. Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise-testing. *Am J Respir Crit Care Med* 2000; 161: 487–492.
 53. Paciocco G, Martinez FJ, Bossone E, Pielsticker E, Gillespie B, Rubenfire M. Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. *Eur Respir J* 2001; 17: 647–652.
 54. Gibbons RJ, Balady GJ, Beasley JW, *et al.* ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 1997; 30: 260–311.
-

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55. Peterson LR, Schechtman KB, Ewald GA, *et al.* The effect of β -adrenergic blockers on the prognostic value of peak exercise oxygen uptake in patients with heart failure. *J Heart Lung Transplant* 2003; 22: 70–77.
 56. O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving β -blockers. *Circulation* 2005; 111: 2313–2318.
 57. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991; 83: 778–786.
 58. Kleber FX, Vietzke G, Wernecke KD, *et al.* Impairment of ventilatory efficiency in heart failure. *Circulation* 2000; 101: 2803–2809.
 59. Szlachet J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. *Am J Cardiol* 1985; 55: 1037–1042.
 60. Opasich C, Pinna GD, Bobbio M, *et al.* Peak exercise oxygen consumption in chronic heart failure: toward efficient use in the individual patient. *J Am Coll Cardiol* 1998; 31: 766–775.
 61. Gitt AK, Wasserman K, Kilkowski C, *et al.* Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation* 2002; 106: 3079–3084.
 62. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO₂ and VE/VCO₂ slope in patients with heart failure: a prognostic comparison. *Am Heart J* 2004; 147: 354–360.
 63. Mudge GH, Goldstein S, Addonizio LJ, *et al.* 24th Bethesda conference: cardiac transplantation. Task Force 3: Recipient guidelines/prioritization. *J Am Coll Cardiol* 1993; 22: 21–31.
 64. Chua T, Ponikowski P, Harrington D, *et al.* Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997; 29: 1585–1590.
 65. Ponikowski P, Francis DP, Piepoli MF, *et al.* Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation* 2001; 103: 967–972.
 66. Arena R, Humphrey R. Comparison of ventilatory expired gas parameters used to predict hospitalization in patients with heart failure. *Am Heart J* 2002; 143: 427–432.
 67. Corra U, Mezzani A, Bosimini E, Scapellato F, Imparato A, Giannuzzi P. Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. *Am Heart J* 2002; 143: 418–426.
 68. Francis DP, Shamin W, Davies LC, *et al.* Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO₂ slope and peak VO₂. *Eur Heart J* 2000; 21: 154–161.
 69. Robbins M, Francis G, Pashkow FJ, *et al.* Ventilatory and heart rate responses to exercise: better predictors of heart failure mortality than peak oxygen consumption. *Circulation* 1999; 100: 2411–2417.
 70. Nanas SN, Nanas JN, Sakellariou D, *et al.* VE/VCO₂ slope is associated with abnormal resting haemodynamics and is a predictor of long-term survival in chronic heart failure. *Eur J Heart Fail* 2006; 8: 420–427.
 71. Bilsel T, Terzi S, Akbulut T, Sayar N, Hobikoglu G, Yesilcimen K. Abnormal heart rate recovery immediately after cardiopulmonary exercise testing in heart failure patients. *Int Heart J* 2006; 47: 431–440.
 72. Lewis ME, Newall C, Townend JN, Hill SL, Bonser RS. Incremental shuttle walk test in the assessment of patients for heart transplantation. *Heart* 2001; 86: 183–187.
 73. Morales FJ, Montemayor T, Martinez A. Shuttle *versus* six-minute walk test in the prediction of outcome in chronic heart failure. *Int J Cardiol* 2000; 76: 101–105.
 74. Rostagno C, Olivo G, Comeglio M, *et al.* Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *Eur J Heart Fail* 2003; 5: 247–252.
 75. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 1996; 110: 325–332.
-

-
76. Shah MR, Hasselblad V, Gheorghiade M, *et al.* Prognostic usefulness of the six-minute walk in patients with advanced congestive heart failure secondary to ischemic or nonischemic cardiomyopathy. *Am J Cardiol* 2001; 88: 987–993.
 77. Leite JL, Mansur AJ, de Freitas HFG, *et al.* Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J Am Coll Cardiol* 2003; 41: 2175–2181.
 78. Sietsema KE, Ben-Dov I, Zhang YY, Sullivan C, Wasserman K. Dynamics of oxygen uptake for submaximal exercise and recovery in patients with chronic heart failure. *Chest* 1994; 105: 1693–1670.
 79. Koike A, Yajima T, Adachi H, *et al.* Evaluation of exercise capacity using submaximal exercise at a constant work rate in patients with cardiovascular disease. *Circulation* 1995; 91: 1719–1724.
 80. Koike A, Koyama Y, Itoh H, Adachi H, Marumo F, Hiroe M. Prognostic significance of cardiopulmonary exercise testing for 10-year survival in patients with mild to moderate heart failure. *Jpn Circ J* 2000; 64: 915–920.
 81. Rickli H, Kiowski W, Brehm M, *et al.* Combining low-intensity and maximal exercise test results improves prognostic prediction in chronic heart failure. *J Am Coll Cardiol* 2003; 42: 116–122.
 82. Dimopoulos K, Okonko DO, Diller GP, *et al.* Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation* 2006; 113: 2796–2802.
 83. Diller GP, Dimopoulos K, Okonko DO, *et al.* Heart rate response during exercise predicts survival in adults with congenital heart disease. *J Am Coll Cardiol* 2006; 48: 1250–1256.

Role of exercise testing in defining the response to interventions in chronic obstructive pulmonary disease patients

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Background

Management of patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) has been shown to consist of different interventions which can be used during the different stages of the disease [1]. Consequently, different primary outcomes have been used in clinical research to assess the effectiveness of COPD management. For example, improvements in disease-specific health status [2–8], a reduction in the number of acute exacerbations of COPD [4, 9–13] and cost-effectiveness of the different interventions have been used repeatedly [14–23]. Exercise intolerance has also become an important outcome measure in patients with moderate-to-severe COPD, mostly because evidence has been presented that exercise testing is superior to functional measurements obtained at rest (*e.g.* pulmonary function [24–26]) in demonstrating the positive effect of pharmacological treatments, exercise training, nutritional modulation or a combination thereof [8, 27–33]. In addition, exercise intolerance has been shown to be related to mortality in patients with moderate-to-severe COPD, irrespective of the degree of airway obstruction [34–36].

The present chapter will provide an overview of the additional value of whole-body exercise testing in designing an exercise training programme, prescribing oxygen therapy, estimating daily physical activity level, prescribing walking aids, testing quadriceps muscle fatigue and as a metabolic stress paradigm to investigate altered regulation of intermediary metabolism in patients with moderate-to-severe COPD.

Exercise testing in the design of an exercise training programme

Exercise training has been shown to be the cornerstone of a pulmonary rehabilitation programme in patients with moderate-to-severe COPD [29, 37, 38]. To optimise the training stimulus during the pulmonary rehabilitation, it is important to tailor exercise training programmes to individual patients based on appropriate phenotyping and exercise capacity. Physiotherapists can choose between several interventions (*i.e.* endurance training, interval training and resistance training) or a combination thereof [8, 39]. Whole-body exercise testing can be indicative for different types of exercise training.

This is, at least in part, based on factors that limit performance on the symptom-limited incremental cycle ergometer test, which has to be considered as the gold standard for evaluating the causes of exercise intolerance in patients with COPD [40].

It is generally acknowledged that endurance types of exercise (*e.g.* treadmill walking and cycle ergometry) are indicated for patients with moderate COPD, who have a cardio-circulatory limitation during a symptom-limited incremental exercise test. Interval types of exercise, however, are indicated for patients with severe COPD who have a ventilatory limitation at the end of a symptom-limited incremental exercise test or in those patients with exercise-induced arterial oxygen desaturation [41, 42]. Indeed, patients with moderate-to-severe COPD (mean $\pm$ SD forced expiratory volume in one second (FEV₁): $52 \pm 15\%$ predicted; mean breathing reserve at the end of a symptom-limited incremental cycling test: $\sim 12 \text{ L} \cdot \text{min}^{-1}$) have been shown to be able to sustain a 60-min period of interval cycling training at 70% of the predetermined peak work rate (WR) (exercise to rest ratio of 1:1); however, they could not complete 30 min of endurance (*i.e.* continuous) cycle training at the same WR [43]. In addition, patients with severe-to-very severe COPD (mean $\pm$ SE FEV₁: $35 \pm 2\%$ pred) have been shown to have different patterns of dynamic hyperinflation during a symptom-limited incremental cycle ergometer test [44], which may even determine the amount of rest that is necessary during exercise training in order to achieve an optimal training stimulus. It may, however, be difficult to detect patterns of dynamic lung hyperinflation because optoelectronic plethysmography, which has been shown to be capable of accurately measuring breath-by-breath changes in the volume of the entire chest wall and its ribcage and abdominal chest wall compartments [45], is not generally available in the clinical setting.

The achieved peak WR can be used to determine the training intensity at which COPD patients start their exercise training to effect an overload training stimulus (60–70% for a total of 10–20 min). In addition, the distance walked in 6 min (6MWD) can be used to determine the initial treadmill walking speed of 70–80% of baseline mean walking speed (expressed in $\text{km} \cdot \text{h}^{-1}$; calculated by dividing the 6MWD by 100) [8, 28, 32]. Physiotherapists have to be aware of the fact that patients are allowed to rest during the 6-min walking test (6MWT) [46]. When patients rest during their 6MWT the physiotherapist has to consider a correction of the mean treadmill walking speed to prevent an underestimation of the training load during treadmill walking. A patient with severe COPD experienced severe dyspnoea during the 6MWT. The patient therefore stopped for 65 s during the test, in which they walked a total of 200 m. The mean walking speed would be $2 \text{ km} \cdot \text{h}^{-1}$ without correction for the rested time, but $2.4 \text{ km} \cdot \text{h}^{-1}$ with correction.

Exercise testing in prescription of oxygen therapy

Supplemental oxygen has been proposed in the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease of the World Health Organization as one of the principal nonpharmacological treatments for patients with very severe COPD [1]. Indeed, long-term administration of oxygen ($>15 \text{ h} \cdot \text{day}^{-1}$) has been shown to increase survival in COPD patients with chronic respiratory failure [47] but not in patients with mild-to-moderate hypoxaemia or in those with only arterial oxygen desaturation at night [48]. Nevertheless, the National Heart, Lung and Blood Institute has recently advocated the prescription of oxygen therapy to COPD patients who are normoxaemic or only moderately hypoxaemic at rest, but who do have substantial exercise-induced hypoxaemia, should also be considered [49]. Therefore, it is of great importance to monitor arterial oxygen saturation (Sa_2O_2) during whole-body

exercise testing in COPD patients who are normoxaemic at rest to determine the possible eligibility for domiciliary oxygen therapy. The lack of a relationship between transcutaneous S_{a,O_2} before and during/after exercise testing (*i.e.* a symptom-limited incremental cycle ergometry test or a self-paced 6MWT) also emphasises the need for regular exercise testing in the clinical routine of patients with moderate-to-very severe COPD. In fact, ~50% of COPD patients with a normal resting S_{a,O_2} have been shown to have a significant fall in transcutaneous S_{a,O_2} during a self-paced 6MWT [50].

Exercise tests can also be used in the clinical setting to determine the effectiveness of an activity-dependent prescription of supplemental oxygen. Walking tests may be more suitable to determine exercise-induced oxygen desaturation than cycling tests. For example, arterial partial pressure of oxygen has been shown to fall to a lower level during treadmill-walking exercise than cycle ergometry in COPD patients who were known to have exercise-induced oxygen desaturation [51]. A similar pattern in exercise-induced arterial hypoxaemia has been found in patients with COPD following an incremental shuttle test [52] and a self-paced 6MWT [50]. Consequently, cycle ergometer testing may seriously underestimate the exercise-induced oxygen desaturation, which can occur during walking tests in patients with moderate-to-severe COPD and, in turn, may compromise the prescription of domiciliary oxygen therapy in these patients. In fact, only 41% of the COPD patients with exercise-induced oxygen desaturation during a self-paced 6MWT had exercise-induced oxygen desaturation during a symptom-limited incremental cycling ergometer test [50]. Therefore, the self-paced 6MWT is a field test that appears to be suitable and reproducible to detect exercise-induced oxygen desaturation in patients with COPD [50].

The acute response of supplemental oxygen on exercise capacity has been reported in patients with moderate-to-severe COPD. Indeed, oxygen supplements have been shown to improve exercise capacity and to decrease dyspnoeic sensation in COPD patients, whether hypoxaemic or nonhypoxaemic at rest [53–55]. A dose-dependent improvement in cycling endurance time has been found in nonhypoxaemic COPD patients up to an inspired $[O_2]$ of 50% (fig. 1) [56]. This improved exercise performance was partly related to a lower ventilatory requirement through direct peripheral chemoreceptor inhibition [57] and, in turn, a slower breathing pattern [57] and decreased dynamic lung hyperinflation [56].

Whole-body exercise tests have also been used to evaluate the effects of breathing a low-density gas mixture (*i.e.* heliox, 79% helium and 21% oxygen) and/or an increased inspired oxygen concentration during high-intensity constant WR cycle ergometry to the limit of tolerance. PALANGE *et al.* [58] found significant improvements in high-intensity exercise endurance capacity during heliox breathing, compared with air breathing, in patients with severe-to-very severe COPD, together with an increased maximal ventilatory capacity, reduced dyspnoeic sensation and reduced lung dynamic hyperinflation. In addition, breathing a mixture of 72% helium and 28% oxygen increased endurance shuttle walking distance and reduced Borg score for dyspnoea more than a mixture of 79% helium and 21% oxygen, 72% nitrogen and 28% oxygen, or 79% nitrogen and 21% oxygen in patients with moderate-to-severe COPD, with the largest changes being found in the latter group of patients [59]. This positive effect on exercise capacity is probably due to a combination of changes: a reduced expiratory flow resistance, improved lung emptying and a reduced dyspnoeic sensation [60].

Exercise testing in the estimation of daily physical activity levels

Patients with moderate-to-severe COPD have been shown to be physically inactive during daily life. In fact, the total time spent in weight-bearing positions has been shown

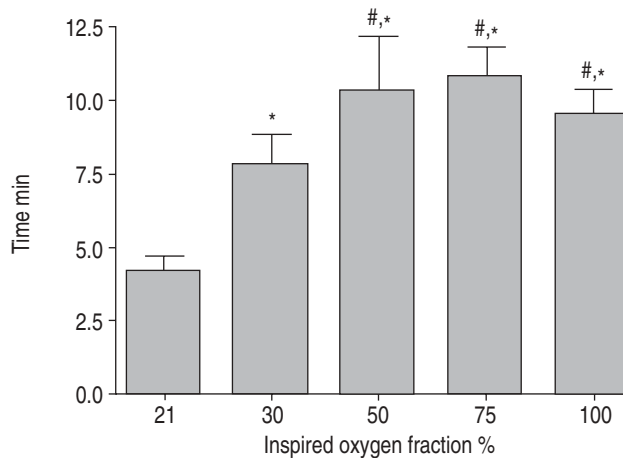


Fig. 1. – Exercise times for a constant work rate cycling test at 75% of the predetermined peak work rate for patients with chronic obstructive pulmonary disease breathing room air (inspired $[O_2]=21\%$) or air with an increased $[O_2]$. *: $p<0.05$ versus 21% inspired $[O_2]$; #: $p<0.05$ versus 30% inspired $[O_2]$. Data obtained from [56] with permission.

to be significantly lower compared with age-matched healthy control subjects [61–65]. In addition, weight-bearing activities were performed at a lower pace than in healthy controls [65]. Physical inactivity may increase the risk of hospital readmission following an acute exacerbation of COPD [10] and may even compromise survival [66]. It is therefore important to have knowledge of the daily physical activity levels of patients with COPD in order to undertake specific treatment. To date, a number of motion sensors and activity monitors are commercially available for measurement of daily physical activity in the patient's home environment [67]. Unfortunately, these devices are not always validated and/or available in clinical practice [67]. However, the 6MWD has shown to be significantly related to the motion counts assessed with a Tritrac R3D® Research Ergometer (Reining International, Madison, WI, USA) in patients with moderate-to-severe COPD ($r=0.74$) [61]. In addition, daily walking time and standing time assessed with a DynaPort® Activity Monitor (McRoberts BV, the Hague, the Netherlands) have been shown to be significantly related to 6MWD ($r=0.75$ and $r=0.62$, respectively) and to peak WR ($r=0.64$ and $r=0.57$, respectively), determined with symptom-limited incremental cycle ergometry [65]. In fact, weaker or no significant correlations were found between daily physical activity levels and the degree of severity of airways obstruction, peak oxygen uptake ($\dot{V}O_{2,peak}$) and body mass index (BMI) [63, 65]. Therefore, it is reasonable to conclude that 6MWD can be used as a surrogate marker of daily physical inactivity in patients with moderate-to-severe COPD, especially in those who walk ≤ 400 m [65]. In contrast, daily walking time did not significantly correlate with 6MWD in healthy elderly subjects but was correlated with $\dot{V}O_{2,peak}$ ($r=0.47$), peak WR ($r=0.45$) and BMI ($r=-0.47$) [65].

Exercise testing in the prescription of walking aids

The ability to stand and walk without assistance can be compromised in the healthy elderly living independently in the community, as well as in the elderly with chronic organ failure [26, 68, 69]. This, in turn, may increase the fear of activity-related falling, which has been shown to be an independent risk factor for decreased mobility and a loss

of quality of life [70]. Walking aids (*i.e.* canes and walkers) can therefore be considered to provide independent living and safe mobility. However, walking aids can also interfere with the ability to maintain balance in certain situations and the associated metabolic demands can even be excessive [71].

The 6MWT has been used to determine the effects of walking aids on walking distance, exercise-induced hypoxaemia, exercise-induced dyspnoea and rest time during the test in patients with moderate-to-very severe COPD. For example, gutter frames have been shown to improve 6MWD (mean change: +24 m) and to prevent exercise-induced oxygen desaturation compared with an unaided 6MWT; whereas unwheeled Zimmer frames were found to limit functional capacity (mean change: -45 m) [72]. The usefulness of rollators has been assessed in several studies with differing results. ROOMI *et al.* [72] found no difference between 6MWT performance with or without rollator in patients with very severe COPD, who walked 210 m during an unaided 6MWT accompanied with a mean oxygen desaturation of 6% at the end of the test. SOLWAY *et al.* [73] corroborated these findings in patients with severe-to-very severe COPD (mean 6MWD unaided *versus* 6MWD with rollator: 311 *versus* 317 m). However, COPD patients with an unaided 6MWD of <300 m (mean 6MWD: 220 m) showed a benefit from rollator use (mean change: +26 m; $p=0.02$), although patients with an unaided 6MWD >300 m (mean 6MWD: 384 m) did not demonstrate a statistically significant improvement (mean change: +10 m; $p=0.3$) [73]. The former improvement in walking distance was accompanied by a significant decrease in the duration of rest during the test (mean change: -40 s) [73]. Moreover, patients reported a significantly lower Borg symptom score for dyspnoea while using the rollator, irrespective of their unaided 6MWD [73]. GUPTA *et al.* [74] also found a significant increase in 6MWD with rollator use (mean change: +29 m). PROBST *et al.* [75] did find significant improvements in 6MWD (mean change: +46 m) especially in patients with a low unaided 6MWD (<400 m). Thus, the use of a rollator has been shown to result in an improved functional exercise capacity in patients with very severe COPD, accompanied by significant reductions in oxygen desaturation and breathlessness during the 6MWT. The benefits of a rollator appear, at least in part, to be determined by the unaided 6MWD.

Exercise testing as a model to test quadriceps muscle fatigue

KILLIAN *et al.* [76] were the first to demonstrate that patients with moderate-to-severe COPD (mean FEV₁: 47% pred) suffer from unpleasant symptoms during and following a symptom-limited incremental cycling test. Only 26% of these patients reported an unpleasant sensation of dyspnoea as the main reason to stop exercise. Indeed, in 43% of the patients, an unpleasant feeling of leg fatigue was the main reason for stopping the test. The remaining 31% of the patients stopped due to a combination of both symptoms [76].

JEFFERY MADOR *et al.* [77] presented one of the first studies to objectify the presence of quadriceps muscle fatigue in patients with moderate-to-severe COPD (mean FEV₁: 42% pred) following a constant WR cycling test to the limit of tolerance at 60–70% of the predetermined peak WR, using superimposed twitches due to magnetic stimulations of the femoral nerve. On average, quadriceps muscle twitch force fell significantly after the cycle endurance test and remained significantly decreased for 1 h post-exercise. A significant decrease in quadriceps twitch force following a constant WR cycling test (a 15% reduction in quadriceps twitch force 10 min post-exercise was defined as contractile fatigue of the quadriceps muscle) was found in 58% of the patients [77]. Moreover, patients with moderate-to-severe COPD have been shown to have significantly greater

contractile fatigue following a constant WR cycling test at 60% of peak WR than healthy age-matched control subjects who cycled at the same absolute mean WR for the same duration [78]. However, a constant WR test at 65% of the predetermined peak WR has also been shown to result in reductions of quadriceps peak force in healthy, relatively sedentary, elderly subjects [79]. The occurrence of contractile muscle fatigue during a constant WR cycle ergometer exercise test at 80% of the predetermined peak WR may, at least in part, explain why optimal bronchodilation fails to improve exercise tolerance in ~50% of patients with moderate-to-severe COPD [80].

Whether and to what extent walking may also result in contractile fatigue of the quadriceps muscle has recently been studied by MAN *et al.* [81], who found that leg effort assessed by subjective scoring on a modified Borg scale is a frequent symptom during incremental and endurance cycle ergometry, but infrequent during incremental and endurance walking. This would imply that interventions specifically targeted at skeletal muscle function should preferably be evaluated by endurance cycle ergometry and not by walking tests.

Exercise-induced contractile fatigue of the quadriceps muscle can, at least in part, be restored following pulmonary rehabilitation. An 8-week (24 sessions) combination of cycle ergometry, treadmill walking, stretching, calisthenics and weekly education sessions resulted in an improvement in quadriceps fatigability in patients with moderate-to-severe COPD. This was assessed using an involuntary technique (*i.e.* unpotentiated and potentiated twitch forces using magnetic stimulation of the femoral nerve) [82]. As expected, addition of resistance training to the pulmonary rehabilitation programme did significantly improve skeletal muscle force, but did not augment the effects on quadriceps muscle fatigability [83]. These findings indicate that improved quadriceps muscle strength does not improve fatigue resistance of the quadriceps muscle during whole-body exercise in COPD patients with a normal-to-high BMI [83].

Exercise testing as a metabolic stress model to investigate altered control of intermediary metabolism

It is now well established that systemic inflammation and oxidative stress are present in COPD and that both can be exaggerated by whole-body exercise. In fact, systemic inflammation and oxidative stress are increasingly being recognised as playing an important role in skeletal muscle wasting and peripheral muscle dysfunction in COPD and, consequently, in exercise intolerance [84]. This underscores the importance of any intervention in diminishing or preventing bursts of systemic inflammation and oxidative stress after whole-body exercise in patients with COPD.

At present, only a few studies have examined the effects of whole-body exercise on the systemic inflammatory response in COPD. RABINOVICH *et al.* [85] studied the cytokine response to moderate-intensity constant WR exercise (11 min at 40% of the predetermined peak WR) in COPD patients. The authors observed an abnormal exercise-induced increase of circulating tumour necrosis factor- α levels, but this was not accompanied by changes of interleukin-6 levels [85]. Moreover, an increased inflammatory response has been observed after symptom-limited incremental exercise in moderate-to-very severe COPD [86]. An 8-week pulmonary rehabilitation programme did not modify the exercise-induced systemic inflammatory response [85].

Whole-body exercise tests have also been used to determine the exercise-induced systemic oxidative stress response in patients with moderate-to-severe COPD. VINA *et al.* [87] found a significant increase in blood oxidised glutathione levels following 6 min of cycling at 40 W (~180% of resting value) in patients with severe-to-very severe COPD.

In addition, a significant increase in blood oxidised glutathione has been found after symptom-limited incremental cycle-ergometry (~170% of resting value) in patients with severe COPD, while treatment with allopurinol (a specific inhibitor of the ubiquitous enzyme xanthine oxidase) prevented this exercise-induced elevation [88]. In addition, increased plasma malondialdehyde concentrations were found following symptom-limited cycling (~160% of resting value) and had increased a further 60 min after exercise (~194% of resting value). Again, patients who were treated with allopurinol did not show an exercise-induced increase in plasma lipid peroxidation [88]. Thus, symptom-limited cycling causes an increased systemic oxidative stress in patients with severe COPD, which can be prevented with allopurinol. Even though the latter study was not placebo-controlled, these findings indicate that xanthine oxidase may be involved in exercise-induced oxidative stress in patients with severe COPD [88]. In addition to the exercise-induced increase in systemic oxidative stress, one study has shown that COPD patients also have exercise-induced increases in pulmonary oxidative stress, as measured by increased hydrogen peroxide concentrations in exhaled breath condensate, following a symptom-limited incremental cycle-ergometer test [89]. These findings suggest that COPD patients are frequently exposed to oxidative damage as they perform their activities of daily living.

Supplemental oxygen and pulmonary rehabilitation may also decrease the exercise-induced oxidative stress. Indeed, short-term supplementary oxygen has been found to prevent a significant increase in thiobarbituric acid-reactive substances and protein carbonyls following a submaximal constant WR cycling test at 40 W in normoxaemic cachectic patients with severe COPD [90]. In addition, exercise-induced increases in blood oxidised glutathione levels following cycling at 40 W could partially be prevented by oxygen therapy in hypoxaemic patients with severe-to-very severe COPD [87].

MERCKEN *et al.* [91] were the first to demonstrate a decrease in whole-body exercise-induced oxidative stress following an 8-week in-patient pulmonary rehabilitation programme in patients with severe COPD having a normal body composition at baseline. The change was particularly evident following a constant WR cycling test at 60% of the predetermined peak work rate [91]. Thus, a submaximal cycling test appears to be more discriminatory in evaluating the effects of pulmonary rehabilitation on exercise-induced oxidative stress in patients with moderate-to-severe COPD. Whether and to what extent long-term oxygen supplementation during the pulmonary rehabilitation period of normoxaemic patients with moderate-to-severe COPD may amplify the effects of pulmonary rehabilitation on exercise-induced oxidative stress is currently unknown.

Basic knowledge of skeletal muscle intermediary metabolism during exercise may be important to establish whether there is a potential role for some specific substrates in modulating skeletal muscle wasting. Skeletal muscle energy metabolism is impaired in patients with COPD during exercise. For example, some studies have revealed prematurely early increases in blood lactate levels in exercise in COPD [92, 93]. STEINER *et al.* [94] demonstrated that this lower energy status in COPD is reflected in changes in intramuscular metabolites during exercise. Thus, the authors observed significant adenine nucleotide loss, activation of substrate level phosphorylation and inosine monophosphate accumulation in the muscles of COPD patients during a short constant WR exercise test at 80% of the predetermined peak WR. This suggests that significant metabolic stress occurs in the skeletal muscle of COPD patients during whole-body exercise at low-work rates similar to those required for activities of daily living [94]. Additionally, ENGELN *et al.* [95] studied the relationship between the early lactate response to incremental exercise and intrinsic alterations in exercise-related substrate levels in the skeletal muscle of COPD patients with and without emphysema. The authors showed that the early blood lactate response to incremental exercise was

related to resting muscle glutamate status. Stratification of patients into those with and without emphysema revealed that patients with emphysema had even more severe reductions in the lactate threshold and in exercise levels of glutamate [95]. Furthermore, ENGELEN *et al.* [96] also assessed the effect of a low-intensity constant WR cycling endurance test on whole-body protein turnover and breakdown in patients with severe COPD. Specifically, in those patients with emphysema, whole-body protein turnover was suppressed both during exercise and for ≥ 1 h post-exercise [96]. In addition, these investigators examined the amino acid profile in skeletal muscle and plasma after submaximal constant WR exercise in COPD patients [97]. The exercise was found to alter amino acid intermediary metabolism in patients with COPD, independent of the presence of fat-free mass wasting [97]. This implies that it might be important to stratify COPD patients according to their phenotype to obtain maximal treatment benefits.

Conclusions

Whole-body exercise tests have been shown to be a valuable adjunct in the assessment of systemic impairment in COPD, and also to assess changes in peak and functional exercise capacity following various interventions in patients with moderate-to-very severe COPD. Therefore, whole-body exercise tests are indispensable in the design of the exercise-training component of pulmonary rehabilitation programmes. Moreover, exercise tests can be of value to: 1) prescribe oxygen therapy and walking aids; 2) estimate daily physical activity levels; 3) assess quadriceps muscle fatigability; and 4) assess exercise-induced systemic oxidative stress and intermediary metabolism in patients with moderate-to-very severe COPD. In conclusion, whole-body exercise testing can be of additional value in patients with moderate-to-severe COPD to evaluate the effects of different interventions but also to explore and to prescribe new treatments for optimising the management of patients with moderate-to-severe COPD.

Summary

Various whole-body exercise tests (cycle ergometry and treadmill walking) have been used for many years to determine: 1) the level of physical fitness; 2) which factors may limit exercise tolerance; and 3) the safety of exhaustive physical exercise in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).

Whole-body exercise testing can also be of additional value in designing an exercise-training programme, to prescribe oxygen therapy, estimate daily physical activity levels, prescribe walking aids, assess quadriceps muscle fatigue, and as a stress model to investigate abnormal control of muscle metabolism and oxidative stress induction in patients with moderate-to-severe COPD.

Training load at the start of an exercise-training programme and tailored training components can be partially derived from the results of a symptom-limited incremental cycling test and a 6-min walking distance (6MWD) test. Moreover, 6MWD tests are used to prescribe oxygen therapy in normoxaemic COPD patients who suffer from exercise-induced oxygen desaturation. A 6MWD test can also be used to estimate the level of daily physical activity and to prescribe a walking aid, such as a rollator, to COPD patients with a low unaided 6MWD. In contrast to incremental and endurance shuttle walking tests, a high-intensity symptom-limited constant work-rate cycling test appears to be useful to discriminate between quadriceps muscle fatigue and dyspnoea as the dominant factor limiting exercise tolerance.

In conclusion, whole-body exercise testing can be of additional value in patients with moderate-to-severe COPD in evaluating the responses to different physiological and pharmacological interventions and in targeting novel treatment strategies.

Keywords: Cycling, muscle fatigue, oxygen therapy, physical activity, walking, walking aids.

References

1. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.
2. Donohue JF, van Noord JA, Bateman ED, *et al.* A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; 122: 47–55.
3. Euteneuer S, Windisch W, Suchi S, Kohler D, Jones PW, Schonhofer B. Health-related quality of life in patients with chronic respiratory failure after long-term mechanical ventilation. *Respir Med* 2006; 100: 477–486.
4. Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ* 2004; 329: 1209.
5. Monnickhof E, van der Valk P, van der Palen J, van Herwaarden C, Zielhuis G. Effects of a comprehensive self-management programme in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: 815–820.
6. Smeritschnig B, Jaksch P, Kocher A, *et al.* Quality of life after lung transplantation: a cross-sectional study. *J Heart Lung Transplant* 2005; 24: 474–480.
7. Spencer S, Jones PW. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax* 2003; 58: 589–593.
8. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance *versus* endurance training in patients with COPD and peripheral muscle weakness. *Eur Respir J* 2002; 19: 1072–1078.
9. Casas A, Troosters T, Garcia-Aymerich J, *et al.* Integrated care prevents hospitalisations for exacerbations in COPD patients. *Eur Respir J* 2006; 28: 123–130.
10. Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003; 58: 100–105.
11. Griffiths TL, Burr ML, Campbell IA, *et al.* Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000; 355: 362–368.
12. Decramer M, Rutten-van Molken M, Dekhuijzen PN, *et al.* Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005; 365: 1552–1560.
13. Tuggey JM, Plant PK, Elliott MW. Domiciliary non-invasive ventilation for recurrent acidotic exacerbations of COPD: an economic analysis. *Thorax* 2003; 58: 867–871.
14. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax* 2001; 56: 779–784.
15. Grossman RF. Cost-effective therapy for acute exacerbations of chronic bronchitis. *Semin Respir Infect* 2000; 15: 71–81.
16. Groen H, van der Bij W, Koeter GH, TenVergert EM. Cost-effectiveness of lung transplantation in relation to type of end-stage pulmonary disease. *Am J Transplant* 2004; 4: 1155–1162.

17. Gordoio A, Scuffham P, Gibbons D. The cost-effectiveness of outreach respiratory care for COPD patients. *Prof Nurse* 2002; 17: 504–507.
18. Gallefoss F, Bakke PS. Cost-benefit and cost-effectiveness analysis of self-management in patients with COPD—a 1-year follow-up randomized, controlled trial. *Respir Med* 2002; 96: 424–431.
19. Jasmer RM, Matthay MA. Cost-effectiveness of noninvasive ventilation for acute chronic obstructive pulmonary disease: cashing in too quickly. *Crit Care Med* 2000; 28: 2170–2171.
20. Oostenbrink JB, Rutten-van Molken MP, Al MJ, Van Noord JA, Vincken W. One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. *Eur Respir J* 2004; 23: 241–249.
21. Sin DD, Golmohammadi K, Jacobs P. Cost-effectiveness of inhaled corticosteroids for chronic obstructive pulmonary disease according to disease severity. *Am J Med* 2004; 116: 325–331.
22. Ramsey SD, Berry K, Etzioni R, Kaplan RM, Sullivan SD, Wood DE. Cost effectiveness of lung-volume-reduction surgery for patients with severe emphysema. *N Engl J Med* 2003; 348: 2092–2102.
23. Plant PK, Owen JL, Parrott S, Elliott MW. Cost effectiveness of ward based non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease: economic analysis of randomised controlled trial. *BMJ* 2003; 326: 956.
24. Hamilton AL, Killian KJ, Summers E, Jones NL. Symptom intensity and subjective limitation to exercise in patients with cardiorespiratory disorders. *Chest* 1996; 110: 1255–1263.
25. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996; 153: 976–980.
26. Gosker HR, Lencer NH, Franssen FM, van der Vusse GJ, Wouters EF, Schols AM. Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD. *Chest* 2003; 123: 1416–1424.
27. van't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Training with inspiratory pressure support in patients with severe COPD. *Eur Respir J* 2006; 27: 65–72.
28. Spruit MA, Gosselink R, Troosters T, Kasran A, Van Vliet M, Decramer M. Low-grade systemic inflammation and the response to exercise training in patients with advanced COPD. *Chest* 2005; 128: 3183–3190.
29. Spruit MA, Troosters T, Trappenburg JC, Decramer M, Gosselink R. Exercise training during rehabilitation of patients with COPD: a current perspective. *Patient Educ Couns* 2004; 52: 243–248.
30. Creutzberg EC, Wouters EF, Mostert R, Pluymers RJ, Schols AM. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. *Chest* 2003; 124: 1733–1742.
31. Broekhuizen R, Wouters EF, Creutzberg EC, Welting-Scheepers CA, Schols AM. Polyunsaturated fatty acids improve exercise capacity in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 376–382.
32. Franssen FM, Broekhuizen R, Janssen PP, Wouters EF, Schols AM. Effects of whole-body exercise training on body composition and functional capacity in normal-weight patients with COPD. *Chest* 2004; 125: 2021–2028.
33. Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005; 127: 809–817.
34. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003; 167: 544–549.
35. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004; 23: 28–33.
36. Celli BR, Cote CG, Marin JM, *et al*. The body-mass index, airflow obstruction, dyspnoea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
37. Franssen FM, Broekhuizen R, Janssen PP, Wouters EF, Schols AM. Limb muscle dysfunction in COPD: effects of muscle wasting and exercise training. *Med Sci Sports Exerc* 2005; 37: 2–9.

38. Wouters EF, Creutzberg EC, Schols AM. Systemic effects in COPD. *Chest* 2002; 121: Suppl. 5, 127S–130S.
39. Bernard S, Whittom F, Leblanc P, *et al.* Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 159: 896–901.
40. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
41. Coppoolse R, Schols AM, Baarends EM, *et al.* Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J* 1999; 14: 258–263.
42. Gosselink R, Troosters T, Decramer M. Exercise training in COPD patients: interval training versus endurance training. *Eur Respir J* 1998; 12: Suppl. 28, S2.
43. Sabapathy S, Kingsley RA, Schneider DA, Adams L, Morris NR. Continuous and intermittent exercise responses in individuals with chronic obstructive pulmonary disease. *Thorax* 2004; 59: 1026–1031.
44. Vogiatzis I, Georgiadou O, Golemati S, *et al.* Patterns of dynamic hyperinflation during exercise and recovery in patients with severe chronic obstructive pulmonary disease. *Thorax* 2005; 60: 723–729.
45. Vogiatzis I, Aliverti A, Golemati S, *et al.* Respiratory kinematics by optoelectronic plethysmography during exercise in men and women. *Eur J Appl Physiol* 2005; 93: 581–587.
46. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
47. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980; 93: 391–398.
48. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005; 4: CD001744.
49. Croxton TL, Bailey WC. Long-term oxygen treatment in COPD: recommendations for future research An NHLBI Workshop Report. *Am J Respir Crit Care Med* 2006; 174: 373–378.
50. Poulain M, Durand F, Palomba B, *et al.* 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. *Chest* 2003; 123: 1401–1407.
51. Cockcroft A, Beaumont A, Adams L, Guz A. Arterial oxygen desaturation during treadmill and bicycle exercise in patients with chronic obstructive airways disease. *Clin Sci (Lond)* 1985; 68: 327–332.
52. Palange P, Forte S, Onorati P, Manfredi F, Serra P, Carlone S. Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. *J Appl Physiol* 2000; 88: 1715–1720.
53. O'Donnell DE, Bain DJ, Webb KA. Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation. *Am J Respir Crit Care Med* 1997; 155: 530–535.
54. Woodcock AA, Gross ER, Geddes DM. Oxygen relieves breathlessness in “pink puffers”. *Lancet* 1981; 1: 907–909.
55. Dean NC, Brown JK, Himelman RB, Doherty JJ, Gold WM, Stulbarg MS. Oxygen may improve dyspnoea and endurance in patients with chronic obstructive pulmonary disease and only mild hypoxemia. *Am Rev Respir Dis* 1992; 146: 941–945.
56. Somfay A, Porszasz J, Lee SM, Casaburi R. Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients. *Eur Respir J* 2001; 18: 77–84.
57. Somfay A, Porszasz J, Lee SM, Casaburi R. Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients. *Chest* 2002; 121: 393–400.
58. Palange P, Valli G, Onorati P, *et al.* Effect of heliox on lung dynamic hyperinflation, dyspnoea, and exercise endurance capacity in COPD patients. *J Appl Physiol* 2004; 97: 1637–1642.
59. Laude EA, Duffy NC, Baveystock C, *et al.* The effect of helium and oxygen on exercise performance in COPD: a randomised crossover trial. *Am J Respir Crit Care Med* 2006; 173: 865–870.
60. Palange P, Crimi E, Pellegrino R, Brusasco V. Supplemental oxygen and heliox: ‘new’ tools for exercise training in chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2005; 11: 145–148.
61. Steele BG, Holt L, Belza B, Ferris S, Lakshminaryan S, Buchner DM. Quantitating physical activity in COPD using a triaxial accelerometer. *Chest* 2000; 117: 1359–1367.

-
62. Steele BG, Belza B, Cain K, Warms C, Coppersmith J, Howard J. Bodies in motion: monitoring daily activity and exercise with motion sensors in people with chronic pulmonary disease. *J Rehabil Res Dev* 2003; 40: Suppl. 2, 45–58.
 63. Sandland CJ, Singh SJ, Curcio A, Jones PM, Morgan MD. A profile of daily activity in chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2005; 25: 181–183.
 64. Schonhofer B, Ardes P, Geibel M, Kohler D, Jones PW. Evaluation of a movement detector to measure daily activity in patients with chronic lung disease. *Eur Respir J* 1997; 10: 2814–2819.
 65. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 972–977.
 66. Yohannes AM, Baldwin RC, Connolly M. Mortality predictors in disabling chronic obstructive pulmonary disease in old age. *Age Ageing* 2002; 31: 137–140.
 67. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Quantifying physical activity in daily life with questionnaires and motion sensors in COPD. *Eur Respir J* 2006; 27: 1040–1055.
 68. Hendrican MC, McKelvie RS, Smith T, *et al.* Functional capacity in patients with congestive heart failure. *J Card Fail* 2000; 6: 214–219.
 69. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; 14: 270–274.
 70. Cumming RG, Salkeld G, Thomas M, Szonyi G. Prospective study of the impact of fear of falling on activities of daily living, SF-36 scores, and nursing home admission. *J Gerontol A Biol Sci Med Sci* 2000; 55: M299–M305.
 71. Bateni H, Maki BE. Assistive devices for balance and mobility: benefits, demands, and adverse consequences. *Arch Phys Med Rehabil* 2005; 86: 134–145.
 72. Roomi J, Yohannes AM, Connolly MJ. The effect of walking aids on exercise capacity and oxygenation in elderly patients with chronic obstructive pulmonary disease. *Age Ageing* 1998; 27: 703–706.
 73. Solway S, Brooks D, Lau L, Goldstein R. The short-term effect of a rollator on functional exercise capacity among individuals with severe COPD. *Chest* 2002; 122: 56–65.
 74. Gupta R, Goldstein R, Brooks D. The acute effects of a rollator in individuals with COPD. *J Cardiopulm Rehabil* 2006; 26: 107–111.
 75. Probst VS, Troosters T, Coosemans I, *et al.* Mechanisms of improvement in exercise capacity using a rollator in patients with COPD. *Chest* 2004; 126: 1102–1107.
 76. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992; 146: 935–940.
 77. Jeffery Mador M, Kufel TJ, Pineda L. Quadriceps fatigue after cycle exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 447–453.
 78. Mador MJ, Bozkanat E, Kufel TJ. Quadriceps fatigue after cycle exercise in patients with COPD compared with healthy control subjects. *Chest* 2003; 123: 1104–1111.
 79. Jeffery Mador M, Kufel TJ, Pineda LA. Quadriceps and diaphragmatic function after exhaustive cycle exercise in the healthy elderly. *Am J Respir Crit Care Med* 2000; 162: 1760–1766.
 80. Saey D, Debigare R, LeBlanc P, *et al.* Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 168: 425–430.
 81. Man WD, Soliman MG, Gearing J, *et al.* Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 168: 562–567.
 82. Mador MJ, Kufel TJ, Pineda LA, *et al.* Effect of pulmonary rehabilitation on quadriceps fatiguability during exercise. *Am J Respir Crit Care Med* 2001; 163: 930–935.
 83. Mador MJ, Bozkanat E, Aggarwal A, Shaffer M, Kufel TJ. Endurance and strength training in patients with COPD. *Chest* 2004; 125: 2036–2045.
-

-
84. Couillard A, Prefaut C. From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. *Eur Respir J* 2005; 26: 703–719.
 85. Rabinovich RA, Figueras M, Ardite E, *et al*. Increased tumour necrosis factor- α plasma levels during moderate-intensity exercise in COPD patients. *Eur Respir J* 2003; 21: 789–794.
 86. van Helvoort HA, van de Pol MH, Heijdra YF, Dekhuijzen PN. Systemic inflammatory response to exhaustive exercise in patients with chronic obstructive pulmonary disease. *Respir Med* 2005; 99: 1555–1567.
 87. Vina J, Servera E, Asensi M, *et al*. Exercise causes blood glutathione oxidation in chronic obstructive pulmonary disease: prevention by O₂ therapy. *J Appl Physiol* 1996; 81: 2198–2202.
 88. Heunks LM, Vina J, van Herwaarden CL, Folgering HT, Gimeno A, Dekhuijzen PN. Xanthine oxidase is involved in exercise-induced oxidative stress in chronic obstructive pulmonary disease. *Am J Physiol* 1999; 277: R1697–R1704.
 89. Mercken EM, Hageman GJ, Schols AM, Akkermans MA, Bast A, Wouters EF. Rehabilitation decreases exercise-induced oxidative stress in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 994–1001.
 90. van Helvoort HA, Heijdra YF, Heunks LM, *et al*. Supplemental oxygen prevents exercise-induced oxidative stress in muscle-wasted patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 1122–1129.
 91. Mercken EM, Hageman GJ, Schols AM, Akkermans MA, Bast A, Wouters EF. Rehabilitation decreases exercise-induced oxidative stress in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 994–1001.
 92. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis* 1991; 143: 9–18.
 93. Sue DY, Wasserman K, Moricca RB, Casaburi R. Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. *Chest* 1988; 94: 931–938.
 94. Steiner MC, Evans R, Deacon SJ, *et al*. Adenine nucleotide loss in the skeletal muscles during exercise in chronic obstructive pulmonary disease. *Thorax* 2005; 60: 932–936.
 95. Engelen MP, Schols AM, Does JD, Gosker HR, Deutz NE, Wouters EF. Exercise-induced lactate increase in relation to muscle substrates in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 1697–1704.
 96. Engelen MP, Deutz NE, Mostert R, Wouters EF, Schols AM. Response of whole-body protein and urea turnover to exercise differs between patients with chronic obstructive pulmonary disease with and without emphysema. *Am J Clin Nutr* 2003; 77: 868–874.
 97. Engelen MP, Wouters EF, Deutz NE, Does JD, Schols AM. Effects of exercise on amino acid metabolism in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 859–864.
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Indications for exercise testing: a critical perspective

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Since the first European Respiratory Society (ERS) Task Force guidelines on "Clinical Exercise Testing" were published in 1997 [1], exercise testing has become increasingly used for the functional evaluation of patients with a wide range of chronic lung and heart diseases characterised by exercise intolerance, such as chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), primary pulmonary hypertension (PPH), cystic fibrosis (CF) and chronic heart failure (CHF). Physiological indices of system function measured or estimated during cardiopulmonary exercise testing (CPET), as well as the distance covered during walking tests, such as the 6-min walk test (6MWT) and the shuttle walk test (SWT), have been shown to provide valuable information regarding functional status, prognosis and outcome evaluation of therapeutic interventions. Importantly, such exercise-based interrogation has proved to be superior to resting spirometric and electrocardiographic measures.

The widespread popularity of exercise testing in clinical practice reflects, to a considerable degree, developments related to the following. 1) The availability of computerised systems that allow accurate noninvasive measurement and display of pulmonary gas exchange responses on a breath-by-breath basis in real time. 2) The standardisation of exercise protocols, such as the maximal incremental cycle-ergometer, treadmill test and walking tests (e.g. 6MWT and SWT). 3) Disease-specific interpretative strategies for the identification of system function and limiting foci pertinent to differential diagnosis, prognosis and therapeutic intervention. These advances have been variously captured in a range of key consensus statements [1–3].

Therefore, it was timely that the second ERS Task Force on clinical exercise testing recently presented a consensus statement entitled "Recommendations on the use of exercise testing in clinical practice" [4]. This was an evidence-based document targeted at the practising clinician to better inform decisions on whether, when and how to employ exercise testing. As set out in the introduction section, the purpose of the document was "to present recommendations on the clinical use of exercise testing in patients with cardiopulmonary disease, with particular emphasis on the evidence base for functional evaluation, prognosis and assessment of interventions" to "allow resolution of practical issues that often confront the clinician, such as: 1) When should an evaluation of exercise intolerance be sought?; 2) Which particular form of test should be asked for?; and 3) What cluster of variables should be selected when evaluating prognosis for a particular disease or the effect of a particular intervention?"

The aims of this chapter, therefore, are to: 1) briefly discuss the major indications for exercise testing in clinical practice; 2) critically address the major exercise outcomes; and 3) identify areas of uncertainty that may direct future research.

When should an evaluation of exercise intolerance be sought?

Exercise testing and CPET, in particular, rarely influences diagnosis in patients with pulmonary or cardiac disease, as in most instances the patient to be studied will have already presented with a primary diagnosis. What exercise testing can provide in such patients is: 1) an objective measure of exercise capacity; 2) information on the mechanism(s) limiting exercise tolerance; 3) indices related to the patient's prognosis; and 4) profiles of disease progression and the response to interventions. Importantly, exercise testing should be viewed as a key adjunct to a previous comprehensive medical evaluation comprising a medical history, physical examination and, depending on what disease is suspected, appropriate additional complementary tests (*e.g.* haematocrit, resting ECG, chest radiograph, arterial blood-gas and acid-base status, resting pulmonary function, echocardiography).

Exercise intolerance, which can be defined as an inability to successfully complete a specified physical task, is conventionally evaluated with CPET by measurement of oxygen uptake at peak exercise ($\dot{V}O_{2,\text{peak}}$). This measurement is highly reproducible both in healthy asymptomatic subjects and in situations where exercise is limited by symptoms, such as dyspnoea or leg fatigue [5–8]. However, where it is preferable that the index of exercise intolerance relate more closely to activities of daily living (*e.g.* as in COPD and CHF), walking tests such as the 6MWT [9, 10] are often used. The classical criterion for defining exercise intolerance and classifying degrees of impairment is $\dot{V}O_{2,\text{peak}}$ standardised by body mass [11]. As factors such as habitual physical activity, age, sex and height influence $\dot{V}O_{2,\text{peak}}$ and the distance walked on the 6MWT [12–14], it is recommended that the normalcy (or otherwise) of exercise capacity be judged relative to reference values for matched healthy populations, taking into account not only body mass but, also in certain conditions, fat-free mass. It is conventional practice that such “normalised” values of $\dot{V}O_{2,\text{peak}}$ that lie beyond 1.96 times the SD of the predicted mean are considered abnormal with 95% confidence, while values which fall <40% below the predicted mean indicate severe impairment [15]. One criticism that can be levelled at these criteria is that most of the reference values on which they depend were obtained in selected small groups of volunteers who, it could be reasonably argued, do not adequately represent the normal population.

CPET is also particularly useful in identifying the physiological mechanisms responsible for limiting exercise tolerance. There are several CPET response patterns that are not disease specific but nonetheless point to particular sites of system dysfunction, therefore, narrowing the differential diagnosis (table 1).

The absence of these defining response patterns can reasonably be taken as evidence against a significant association of particular system involvement in the exercise limitation. For patients with unexplained exercise intolerance and for whom initial test results (*e.g.* spirometry and echocardiography) are nondiagnostic, CPET may represent a useful tool in identifying whether the exercise intolerance is due to abnormalities in the oxygen transport pathway (consequent simply to deconditioning or to overt disease-specific dysfunction) or to psychological factors. Thus, while CPET response patterns may not be diagnostic of specific aetiology, taken together with previous medical evaluation they will help to direct further diagnostic testing [16–20].

Exercise testing has also been proven for: 1) distinguishing between normal and abnormal physiological responses to exercise; 2) differentiating between cardiovascular and pulmonary causes of exercise intolerance [2, 21–25]; and 3) identifying disorders of pulmonary gas exchange, certain muscle diseases and psychological disorders [16, 17, 19, 20]. Algorithms based on key measurements, such as $\dot{V}O_{2,\text{peak}}$ and anaerobic threshold, have been developed to assist in the identification of the causes of exercise intolerance [20].

Table 1. – Physiological mechanisms limiting exercise tolerance in disease states

Mechanism	Finding at CPET
Reduced oxygen delivery/utilisation	Low $\dot{V}O_{2,peak}$; low $\dot{V}L$
Ventilatory limitation	Low $\dot{V}O_{2,peak}$; reduced or absent breathing reserve ($\dot{V}E_{peak}/MVV$ or $MVV - \dot{V}E_{peak}$); increased $\dot{f}C$ reserve (predicted $\dot{f}C_{max} - \dot{f}C_{peak}$)
Abnormal ventilatory control	Increased or decreased $\dot{V}E - \dot{V}CO_2$ slope; increased $\dot{V}b/\dot{V}t$ at a given $\dot{V}CO_2$; increased or decreased P_{a,CO_2}
Pulmonary gas exchange abnormalities	Low $\dot{V}O_{2,peak}$; increased $P(A-a)O_2$ on exercise; arterial desaturation on exercise (i.e. $Sp_{O_2} < 88\%$)
Muscle metabolic dysfunction	Low $\dot{V}O_{2,peak}$; low $\dot{V}L$;
Deconditioning	Low $\dot{V}O_{2,peak}$; little or no $\dot{f}C$ reserve; leftward shift and steepening of $\dot{f}C - \dot{V}O_2$ relationship and a shallow O_2 -pulse profile
Excessive perception of symptoms	High dyspnoea and/or leg fatigue scores
Poor effort	Low $\dot{V}O_{2,peak}$; high $\dot{f}C$ reserve and breathing reserve

CPET: cardiopulmonary exercise testing; $\dot{V}O_{2,peak}$: oxygen uptake at peak exercise; $\dot{V}L$: lactate threshold; $\dot{V}E_{peak}$: peak minute ventilation; MVV: maximum voluntary ventilation; $\dot{f}C$: cardiac frequency; $\dot{f}C_{max}$: maximum cardiac frequency; $\dot{f}C_{peak}$: peak cardiac frequency; $\dot{V}E$: minute ventilation; $\dot{V}CO_2$: carbon dioxide production; $\dot{V}b$: dead space volume; $\dot{V}t$: tidal volume; P_{a,CO_2} : carbon dioxide arterial tension; $P(A-a)O_2$: alveolar–arterial oxygen tension difference; Sp_{O_2} : arterial oxygen saturation measured by pulse oximetry; $\dot{V}O_2$: oxygen uptake.

However, the major limitation of such algorithms is that they often fail when applied to early or mild disease. Furthermore, to date, none of the algorithms that have been proposed for differential diagnosis have been clinically validated.

Which particular form of test should be requested?

Test format

Laboratory-based exercise tests allow evaluation of therapeutic interventions primarily by detecting improvements of exercise capacity, as well as characterising any associated changes in the ventilatory, gas exchange, circulatory and metabolic response patterns, but they are limited by the setting and expensive equipment. However, walking tests can be readily used in a field setting and are inexpensive, but provide considerably less information regarding the specific physiological responses underlying an alteration in exercise capacity. Nonetheless, while a wide variety of tests are available, each being more or less suitable as a stressor of a particular component of a patient's pathophysiology, the appropriateness of the integrated physiological system response to exercise is best studied, certainly for any initial exercise evaluation, by means of a symptom-limited incremental test with a relatively rapid work-rate (WR) incrementation rate. That is, WR is progressively increased by a small fixed increment at a fixed interval, which is accomplished either in a discrete “staircase” fashion (when the ergometer is under manual control) or as a smooth continuous ramp (when operated *via* computer control) both for cycle ergometry [1, 2, 20, 26] and, more recently, for the treadmill [27].

Walking tests have been most extensively used in the functional and prognostic evaluation of patients with COPD, ILD, PPH and CHF (refer to Chapters 3, 4 and 10). In particular the 6MWT, shown to correspond to a high-intensity (but sub-maximal) constant-load test [28, 29], has been widely used in many large trials exploring the benefits of exercise-based rehabilitation, pharmacological intervention, oxygen supplementation and surgery in cardiorespiratory disease. For example, an inhaled fluticasone propionate intervention in COPD patients employed distance walked on the 6MWT as

an outcome measure with some success [30]. Distance walked on the 6MWT has also been used as an outcome measure in rehabilitation for CHF [31], where a modest change in walking distance after 3 months of exercise training was observed. A meaningful difference in performance of 54 m for patients with COPD has been proposed for the 6MWT [32], although a minimum clinically important difference has yet to be established. The interpretational power of the 6MWT can be extended by the addition of measurements of arterial oxygen saturation measured by pulse oximetry (S_pO_2) and cardiac frequency (f_C).

However, the SWT has not been extensively incorporated into pharmacological studies, although it has been cited in a number of significant rehabilitation studies [33, 34]. There is considerable evidence that the test outcome is sensitive to change, with the endurance shuttle walking test (ESWT) appearing to be more sensitive to change after a course of rehabilitation than the incremental test [35].

Exercise modality: cycle ergometry versus walking

In choosing an appropriate exercise test or a specific outcome marker, it is important to know the relationship of the modality-specific exercise response to the local or systemic impairment which is targeted for modulation by a given intervention. For example, MAN *et al.* [36] showed that in COPD patients leg effort assessed by subjective scoring on a Borg scale is a frequent symptom during incremental and endurance cycle-ergometry tests, but infrequent during incremental and endurance walking tests. This would seem to suggest that interventions specifically targeted at the skeletal muscles themselves should preferably be evaluated by means of cycle ergometry rather than by walking tests. Indeed, a recent study [37] on systemic corticosteroid treatment in COPD patients showed that, relative to exercise training alone, supplementation with anabolic steroids was associated with a greater improvement in peak exercise capacity during incremental cycle ergometry, but not in the distance walked on the 6MWT. Also, arterial desaturation during exercise is a common feature of advanced COPD [38, 39]. While this may occur with any type of intense leg exercise, walking either on a treadmill or freely along the ground elicits a greater degree of hypoxaemia than cycle ergometry [36, 39–41]. Thus, there is a need for studies designed to address the issue of which exercise modality (cycle ergometry, walking or both) should be used to assess the effects of particular therapeutic interventions.

Endurance tests

There is growing popularity for utilising indices that better reflect a patient's endurance capacity than classical measures such as $\dot{V}O_{2,peak}$. Of note in this regard is the time to symptom limitation (t_{lim}) measured on a high-intensity (typically 70–80% peak WR), constant WR-cycle ergometer test, coupled with measurement of symptoms (*e.g.* dyspnoea and leg fatigue) and pertinent CPET variables at “isotime” as well as t_{lim} (*e.g.* $\dot{V}O_2$, the slope of the linear region of the minute ventilation ($\dot{V}E$)–carbon dioxide output ($\dot{V}CO_2$) relationship, breathing frequency, f_C and inspiratory capacity to track the progression of dynamic hyperinflation). This test has been successfully utilised in COPD patients for a range of applications (table 2) [42–45].

Importantly, there is increasing evidence that t_{lim} measured using this protocol is superior to indices, such as $\dot{V}O_{2,peak}$, measured on the maximal incremental test and distance walked on the 6MWT in the evaluation of the effects of therapeutic interventions [46].

Table 2. – Effects of different therapeutic interventions on endurance performance for high-intensity constant-load exercise, lung hyperinflation and dyspnoea in chronic obstructive pulmonary disease

	Type of intervention [Ref.]			
	Tiotropium [43]	Oxygen [42]	Heliox [44]	Rehabilitation [45]
Work rate % max	75	75	80	75
FEV ₁ % pred	42	31	38	36
Δ Endurance time %	+21	+145	+115	+175
Δ IC at isotime %	+12	+24	+12	+13
Δ dyspnoea at isotime %	-14	-40	-25	

FEV₁: forced expiratory volume in one second; % pred: % predicted; IC: inspiratory capacity; Δ: changes at isotime expressed as a percentage of control condition. Reproduced from [4] with permission.

Naturally, the WR selected for a particular patient for the pre-intervention assessment should also be used for the post-intervention assessment. However, the current challenge of this test is that while the outcome measure for groups of patients has been shown to be sensitive to interventions, there is nonetheless considerable variation in the magnitude of change for individual patients. This reflects, to a considerable degree, the influence of the power–duration relationship. Not only should the WR chosen be above the asymptotic power of this hyperbolic relationship (*i.e.* critical power (CP)) [47–49], but it should also be recognised that the curvature of the power–duration relationship dictates that a given intervention-induced increase in CP will be expressed as a far greater increase in t_{lim} at WRs which are only slightly above CP, compared with WRs which are considerably higher (refer to online supplement [4]). However, there is currently no single test available that can rigorously define the power–duration relationship; at least four to five discrete supra-CP tests are required, and to be undertaken on different days, to allow sufficient time for recovery. Furthermore, additional studies are needed to demonstrate the utility of this kind of high-intensity endurance protocol in patient populations other than COPD. Finally, it is likely that endurance walking protocols, such as the ESWT, will become increasingly popular as a field-based alternative.

What cluster of variables should be selected when evaluating prognosis for a particular disease or the effect of a particular intervention?

Exercise tolerance is well recognised as a good predictor of mortality in healthy subjects, from young adults to the elderly [50–53]. This also appears to be the case for a wide range of pulmonary and cardiovascular disease states. CHF currently provides the best example of where a comprehensive cluster of CPET-based prognostic variables has been established. CPET variables, as well as distance walked on the 6MWT have proven useful in the prognostic evaluation of other diseases (*e.g.* COPD, ILD, PPH, CF and candidacy for transplantation and thoracic surgical procedures). Therefore, this is now a major indication for exercise testing in these patient groups. From the available literature, exercise tolerance ($\dot{V}O_{2,peak}$, distance walked on the 6MWT) and other CPET indices ($\dot{V}E-\dot{V}CO_2$ slope, lactate threshold, SpO_2) appear to be better predictors of prognosis than resting lung function and cardiac function in patients with respiratory and cardiac diseases (table 3; refer to Chapter 10).

Table 3. – Exercise indices that have been shown to predict the prognosis of patients with chronic respiratory and cardiac diseases

	COPD	ILD	PVD	CF	CHF
$\dot{V}O_{2,\text{peak}}$	+	+	+	+	+
θ_L					+
$\dot{V}E-\dot{V}CO_2$ slope and $\dot{V}E-\dot{V}CO_2$ at θ_L		+			++
Arterial desaturation		++	+	+	
6MWD	+		+		+

COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; PVD: pulmonary vascular disorders; CF: cystic fibrosis; CHF: chronic heart failure; $\dot{V}O_{2,\text{peak}}$: peak oxygen uptake; θ_L : lactate threshold; $\dot{V}E-\dot{V}CO_2$: ventilatory equivalent for carbon dioxide; 6MWD: 6-min walking test distance. +: sensitive; ++: more sensitive. Reproduced from [4] with permission.

Evidence based indications for exercise testing in clinical practice

By using an appropriate grading system commonly used for recommendations in evidence based guidelines [54], the ERS Task Force [4] has shown the level of recommendation for the most relevant indications to exercise testing in clinical practice (tables 4 and 5). However, as is evident from tables 4 and 5, in some instances the low power grades are not so much a reflection of well-powered statistical judgments as they are of weakness in the density of the relevant evidence base. Such areas should, therefore, be seen as important priority areas for future investigation.

Future directions

It is likely that the scope of exercise testing in clinical practice will extend beyond diseases such as COPD, ILD, PPH and CHF in the future to include diseases whose prevalence is increasing and which often express exercise intolerance, such as the metabolic syndrome [55]. It is also likely that exercise testing will assume greater

Table 4. – Indications for cardiopulmonary exercise testing in clinical practice

Indication	Recommendation grade
Detection of exercise-induced bronchoconstriction	A
Detection of exercise-induced arterial oxygen desaturation	B
Functional evaluation of subjects with unexplained exertional dyspnoea and/or exercise intolerance and normal resting lung and heart function	D
To recognise specific disease exercise response patterns that may help in the differential diagnosis of ventilatory <i>versus</i> circulatory causes of exercise limitation	C
Functional and prognostic evaluation of patients with COPD	B, C
Functional and prognostic evaluation of patients with ILD	B, B
Functional and prognostic evaluation of patients with CF	C, C
Functional and prognostic evaluation of patients with PPH	B, B
Functional and prognostic evaluation of patients with CHF	B, B
Evaluation of interventions	
Maximal incremental test	C
High-intensity constant work-rate "endurance" tests	B
Prescription of exercise training	B

With the use of this grading system, A is relatively rare and B is usually considered the best achievable. COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; CF: cystic fibrosis; PPH: primary pulmonary hypertension; CHF: chronic heart failure. Reproduced from [4] with permission.

Table 5 – Indications for 6-min and shuttle walking tests in clinical practice

Indication	Recommendation grade
Diagnosis of exercise-induced arterial desaturation	B
Functional evaluation of patients with COPD, ILD, PPH and CHF	B
Prognostic evaluation of patients with COPD, ILD, PPH and CHF	B
Functional evaluation of patients with CF	C
Prognostic evaluation of patients with COPD or CHF prior to surgery (LVRS, transplantation)	C
Evaluation of the benefits of therapeutic interventions (oxygen supplementation, rehabilitation, surgery)	B

With the use of this grading system, A is relatively rare and B is usually considered the best achievable. COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; PPH: primary pulmonary hypertension; CHF: chronic heart failure; CF: cystic fibrosis; LVRS: lung-volume reduction surgery. Reproduced from [4] with permission.

importance in improving the current understanding of the aetiology and management of particular disease processes, such as inflammation and cachexia.

A more widespread utilisation of walking tests in clinical practice is expected, not only because of their ease of implementation, but also because of the need to further investigate the physiological mechanisms responsible for the qualitatively different response profiles that have been demonstrated for walking and cycling in a range of diseases.

Although constant-WR endurance testing is a relatively recent addition to clinical research, its growing popularity among physicians and technicians working in pulmonary exercise laboratories suggests that the use of such protocols will extend beyond COPD and into many other patient populations. This is especially likely in the context of intervention assessment, with possibly greater emphasis being placed on walking-test protocols. Given the interpretational significance of the power–duration relationship in this context, it is likely that this will assume greater importance as a frame of reference in clinical populations in addition to COPD [56, 57], encouraging the development of robust single-test estimators. In turn this will allow better definition of the criteria for WR selection on such tests.

Finally, although little attention has been paid in the past to the analysis of the recovery phase of exercise in patients with lung and heart disease, recent data have been published on the possible utility of some recovery indices in patients with COPD and CHF [58–60]. This is an area which deserves more attention.

References

1. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. *Eur Respir J* 1997; 10: 2662–2689.
2. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; 167: 211–277.
3. Roca J, Whipp BJ, eds. Clinical Exercise Testing. *Eur Respir Mon* 1997; 6.
4. Palange P, Ward SA, Carlsen K-H, *et al.* Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 2007; 29: 185–209.
5. McLellan TM, Jacobs I. Reliability, reproducibility and validity of the individual anaerobic threshold. *Eur J Appl Physiol Occup Physiol* 1993; 67: 125–131.

6. Grant S, Aitchison T, Henderson E, *et al.* A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg scales, and Likert scales in normal subjects during submaximal exercise. *Chest* 1999; 116: 1208–1217.
7. Mercer TH. Reproducibility of blood lactate-anchored ratings of perceived exertion. *Eur J Appl Physiol* 2001; 85: 496–499.
8. Laursen PB, Shing CM, Jenkins DG. Reproducibility of the cycling time to exhaustion at VO_2 peak in highly trained cyclists. *Can J Appl Physiol* 2003; 28: 605–615.
9. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 2001; 119: 256–270.
10. Casas A, Vilaro J, Rabinovich R, *et al.* Encouraged 6-min walking test indicates maximum sustainable exercise in COPD patients. *Chest* 2005; 128: 55–61.
11. Weber KT, Janicki JS, McElroy A. Determination of aerobic capacity and the severity of chronic cardiac and circulatory failure. *Circulation* 1987; 76: VI40–VI45.
12. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; 14: 270–274.
13. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. *J Cardiopulm Rehabil* 2001; 21: 87–93.
14. Enright PL, McBurnie MA, Bittner V, *et al.* The 6-min walk test: a quick measure of functional status in elderly adults. *Chest* 2003; 123: 387–398.
15. Sue DY, Hansen JE. Normal values in adults during exercise testing. *Clin Chest Med* 1984; 5: 89–98.
16. Pratter MR, Curley FJ, Dubois J, Irwin RS. Cause and evaluation of chronic dyspnoea in a pulmonary disease clinic. *Arch Intern Med* 1989; 149: 2277–2282.
17. Martinez FJ, Stanopoulos I, Acero R, Becker FS, Pickering R, Beamis JF. Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnoea unexplained by routine evaluation. *Chest* 1994; 105: 168–174.
18. Weisman IM, Zeballos RJ. Clinical evaluation of unexplained dyspnoea. *Cardiologia* 1996; 41: 621–634.
19. Jones NL, ed, Clinical Exercise Testing. 4th Edn. Philadelphia, WB Saunders, 1997; pp. 67–69.
20. Wasserman K, Hansen JE, Sue DY, Stringer W, Whipp BJ, eds. Principles of Exercise Testing and Interpretation. 4th Edn. Philadelphia, Lea & Febiger, 2004.
21. Palange P, Carlone S, Forte S, Galassetti P, Serra P. Cardiopulmonary exercise testing in the evaluation of patients with ventilatory vs circulatory causes of reduced exercise tolerance. *Chest* 1994; 105: 1122–1126.
22. Messner-Pellenc P, Ximenes C, Brasileiro CF, Mercier J, Grolleau R, Prefaut CG. Cardiopulmonary exercise testing. Determinants of dyspnoea due to cardiac or pulmonary limitation. *Chest* 1994; 106: 354–360.
23. Working Group on Cardiac Rehabilitation and Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. Recommendations for exercise testing in chronic heart failure patients. *Eur Heart J* 2001; 22: 37–45.
24. Lainchbury JG, Richards AM. Exercise testing in the assessment of chronic congestive heart failure. *Heart* 2002; 88: 538–543.
25. Gibbons RJ, Balady GJ, Bricker JT, *et al.* ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002; 106: 1883–1892.
26. Whipp BJ, Davis JA, Torres F, Wasserman K. A test to determine the parameters of aerobic function during exercise. *J Appl Physiol* 1981; 50: 217–221.
27. Porszasz J, Casaburi R, Somfay A, Woodhouse LJ, Whipp BJ. A treadmill ramp protocol using simultaneous changes in speed and grade. *Med Sci Sports Exerc* 2003; 35: 1596–1603.
28. Onorati P, Antonucci R, Valli G, *et al.* Non-invasive evaluation of gas exchange during a shuttle walking test vs a 6-min walking test to assess exercise tolerance in COPD patients. *Eur J Appl Physiol* 2003; 89: 331–336.

-
29. Troosters T, Vilaro J, Rabinovich R, *et al.* Physiological responses to the 6-min walk test in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2002; 20: 564–569.
 30. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. *Lancet* 1998; 351: 773–780.
 31. McKelvie RS, Teo KK, Roberts R, *et al.* Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). *Am Heart J* 2002; 144: 23–30.
 32. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997; 155: 1278–1282.
 33. Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. *Eur Respir J* 1998; 12: 363–369.
 34. Griffiths TL, Burr ML, Campbell IA, *et al.* Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. *Lancet* 2000; 355: 362–368.
 35. Revill SM, Morgan MD, Singh SJ, Williams J, Hardman AE. The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax* 1999; 54: 213–222.
 36. Man WD, Soliman MG, Gearing J, *et al.* Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 168: 562–567.
 37. Creutzberg EC, Wouters EF, Mostert R, Pluymers RJ, Schols AM. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo controlled, randomized trial. *Chest* 2003; 124: 1733–1742.
 38. Mak VH, Bugler JR, Roberts CM, Spiro SG. Effect of arterial oxygen desaturation on six minute walk distance, perceived effort, and perceived breathlessness in patients with airflow limitation. *Thorax* 1993; 48: 33–38.
 39. Poulain M, Durand F, Palomba B, *et al.* 6-minute walk testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD. *Chest* 2003; 123: 1401–1407.
 40. Palange P, Forte S, Onorati P, Manfredi F, Serra P, Carlone S. Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. *J Appl Physiol* 2000; 88: 1715–1720.
 41. Turner SE, Eastwood PR, Cecins NM, Hillman DR, Jenkins SC. Physiologic responses to incremental and self-paced exercise in COPD: a comparison of three tests. *Chest* 2004; 126: 766–773.
 42. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. *Am J Respir Crit Care Med* 2003; 168: 1034–1042.
 43. O'Donnell DE, Fluge T, Gerken F, *et al.* Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004; 23: 832–840.
 44. Palange P, Valli G, Onorati P, *et al.* Effect of heliox on lung dynamic hyperinflation, dyspnoea, and exercise endurance capacity in COPD patients. *J Appl Physiol* 2004; 97: 1637–1642.
 45. Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. *Chest* 2005; 128: 2025–2034.
 46. Oga T, Nishimura K, Tsukino M, Hajiro T, Ikeda A, Izumi T. The effects of oxitropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease. A comparison of three different exercise tests. *Am J Respir Crit Care Med* 2000; 161: 1897–1901.
 47. Moritani T, Nagata A, deVries HA, Muro M. Critical power as a measure of physical work capacity and anaerobic threshold. *Ergonomics* 1981; 24: 339–350.
 48. Poole DC, Ward SA, Gardner GW, Whipp BJ. Metabolic and respiratory profile of the upper limit for prolonged exercise in man. *Ergonomics* 1988; 31: 1265–1279.
 49. Hill DW. The critical power concept: a review. *Sports Med* 1993; 16: 237–254.
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50. Sherman SE, D'Agostino RB, Cobb L, Kannel WB. Does exercise reduce mortality rates in the elderly? Experience from the Framingham Heart Study. *Am Heart J* 1994; 128: 965–972.
 51. Wei M, Kampert JB, Barlow CE, *et al.* Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. *JAMA* 1999; 282: 1547–1553.
 52. Laukkanen JA, Lakka TA, Rauramaa R, *et al.* Cardiovascular fitness as a predictor of mortality in men. *Arch Intern Med* 2001; 161: 825–831.
 53. Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. *Arch Intern Med* 2004; 164: 1092–1097.
 54. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001; 323: 334–336.
 55. Wijndaele K, Duvigneaud N, Matton L, *et al.* Muscular strength, aerobic fitness, and metabolic syndrome risk in Flemish adults. *Med Sci Sports Exerc* 2007; 39: 233–240.
 56. Neder JA, Jones PW, Nery LE, Whipp BJ. Determinants of the exercise endurance capacity in patients with chronic obstructive pulmonary disease. The power-duration relationship. *Am J Respir Crit Care Med* 2000; 162: 497–504.
 57. Puente-Maestu L, SantaCruz A, Vargas T, Martinez-Abad Y, Whipp BJ. Effects of training on the tolerance to high-intensity exercise in patients with severe COPD. *Respiration* 2003; 70: 367–370.
 58. Stevenson NJ, Calverley PM. Effect of oxygen on recovery from maximal exercise in patients with chronic obstructive pulmonary disease. *Thorax* 2004; 59: 688–672.
 59. Lacasse M, Maltais F, Poirier P, *et al.* Post-exercise heart rate recovery and mortality in chronic obstructive pulmonary disease. *Respir Med* 2005; 99: 877–886.
 60. Bilsel T, Terzi S, Akbulut T, Sayar N, Hobikoglu G, Yesilcimen K. Abnormal heart rate recovery immediately after cardiopulmonary exercise testing in heart failure patients. *Int Heart J* 2006; 47: 431–440.