Recommendations on the Use of Exercise Testing in Clinical Practice


ON-LINE SUPPLEMENT

NORMAL RESPONSE PROFILES IN CPET

This section addresses key CPET-derived response profiles characteristic of “normal” healthy subjects, and their functional basis, whose value in diagnosis, prognosis and/or the assessment of interventions is identified in the subsequent sections. For simplicity, we use cycle ergometry as our frame of reference.

1 INCREMENTAL EXERCISE TESTS

Cycle ergometers and motorized treadmills are widely used for CPET. The former is often preferred, however, because of: its lower cost, smaller space requirements, being less prone to movement artifacts and, perhaps most crucially, providing more accurate quantification of work rate (WR) [e.g. 1, 2, 3]. Electromagnetically-braked models are more flexible, as WR imposed by the cycle itself can be independent of pedaling frequency over quite a wide range. It is conventional practice to select the WR incrementation rate (ΔWR/Δt) so that the tolerable limit (t_{LIM})
is reached within ~10 (8-12) min [4]. This period provides sufficient data density to allow discrimination of pertinent response profiles and parameters (e.g. lactate threshold: see 1.3), while constraining the test duration so as to promote subject compliance. For a young adult of average “aerobic” fitness, a ΔWR/Δt of 15-20 Watts/min is often used; for a patient with cardiac or pulmonary disease, this may be 5 Watts/min or less, depending on the severity of the disease [e.g. 1, 2, 3].

In young children, however, use of the rapid-incremental test format is less widespread than in adults, and doubt has been expressed as to how to optimally measure exercise tolerance (i.e. as V’O₂ peak) [5]. Cooper has reported that short bouts of high-intensity exercise may represent a more natural way of studying children, rather than repeated stepwise exercise testing [5]. Also, special consideration needs to be given to factors such as age, gender, growth and physical performance. It has been maintained that, in children, it is preferable to employ running rather than cycling as the test modality, partly because of cycle mechanics, but also because (as in adults) the use of muscle groups will differ between running and cycling [6]. As a slow increase of speed and inclination for incremental treadmill tests may bore children, Cooper has therefore suggested that more-rapid protocols might be preferable [5].

1.1 V’O₂ peak

V’O₂ peak is simply the highest V’O₂ value achieved on the incremental, or other high-intensity, test designed to bring the subject to the limit of tolerance. With good subject effort, i.e. when the subject exercises to the limit of tolerance, V’O₂ peak is closely reflective of the subject’s "maximum" V’O₂ (V’O₂ max) – considered to be the “gold-standard” index of exercise tolerance (or intolerance). But whether or not the V’O₂ peak actually corresponds to the V’O₂ max depends on whether V’O₂ can be
demonstrated not to continue to increase with further increases in WR (i.e. the V’O₂ “plateau” criterion) [7]; if it cannot, the value should be reported as V’O₂ peak. The index is taken to reflect the attainment of a limitation at some point(s) in the O₂ conductance pathway from the lungs to the site of the mitochondrial O₂ consumption at the cytochrome-oxidase terminus of the electron transport chain; i.e. via the convective flows of O₂ into the lungs and through the vasculature, and the diffusive O₂ flows across the pulmonary and muscle capillary beds [e.g. 8, 9]. However, in some diseases, premature termination of a test can arise from perceptual influences, such as dyspnea, angina or claudicating pain.

Consideration of the normalcy (or otherwise) of V’O₂ peak should certainly take account of age, gender, height and body mass [10-14]. It is usual practice to normalize values for body mass (as ml/min/kg). A strong case can be made for normalizing to whole-body or leg fat-free mass [15-19] in conditions such as obesity or those associated with muscle wasting (e.g. COPD or the frail elderly) - or, failing that, scaling to the subject’s height rather than weight [3, 12, 14, 15]. The normal value in young healthy adults is commonly in the region of 35-40 ml/min/kg but can be considerably lower in chronically sedentary subjects [e.g. 3] and in excess of 80 ml/min/kg in young elite endurance athletes [e.g. 16]. Also, as the mass-specific V’O₂ max is higher in small than in large subjects, it has been suggested that it is more appropriate for V’O₂ max to be scaled to mass^{0.67} [16] or even to separate mass and height exponents [20]. Although these practices are currently not in widespread use, at least in adult populations, it is recommended that their use in CPET be evaluated.

With regard to patient populations, V’O₂ peak values of less than about 14 ml/min/kg suggest a very poor prognosis for patients with chronic heart failure (CHF) [21, 22]. However, it should be borne in mind that chronic inactivity, consequent to the
symptomology of the disease process(es), is likely also to be contributory. Furthermore, a “normal” V’O₂ peak can, in some instances, be compatible with disease-related abnormality, if the pre-existing value were to have been extremely high; e.g. as could occur in a highly-trained endurance athlete who develops incipient heart disease.

Reference values for V’O₂ peak in children that include considerations of age and gender have been developed for incremental cycle ergometry [23, 24]. Interestingly, these values do not differ significantly from those produced by Åstrand using a different exercise protocol [25]. Also, Krahenbuhl et al have produced predictive equations for age-dependent V’O₂ peak in healthy sedentary children [26], based on a meta-analysis of 66 studies on aerobic capacity that included 5793 boys and 3508 girls.

1.2 V’O₂-WR slope

Apart from a short initial lag-phase, imposed by the V’O₂ response “kinetics” (i.e. an index of the speed with which a new steady state is reached), V’O₂ typically increases linearly with time and therefore WR throughout the incremental test [27, 28]. Because of these kinetics, the V’O₂ response at any particular WR during the incremental test will be lower than the steady-state V’O₂ value at that same WR (Fig 1) [29]. Put another way, at a given V’O₂ (including the peak value) WR will be higher on the incremental test than for the steady-state requirement. This becomes functionally important when interpreting peak WR, as shown (Fig 1). Thus, it is not advisable to use peak WR as a reliable surrogate for V’O₂ peak, especially in an interventional context where one might expect V’O₂ kinetics to be speeded and V’O₂ peak increased.

**INSERT FIGURE 1**
In normal subjects, the slope of the linear phase of the $V'O_2$-WR relationship ($\Delta V'O_2/\Delta WR$) is the same as that determined from a series of discrete sub-$\theta_L$ constant-load (or constant-WR) steady-state tests, i.e. ~9-12 ml/min/Watt for cycle ergometry [13, 30-34] (Fig 2, panel 1). It may therefore be used to provide an approximate index of work efficiency if the substrate mixture being oxidized is assumed [27] (see 1.1). Accordingly, $\Delta V'O_2/\Delta WR$ is relatively independent of age, gender, fitness and body mass. The lack of influence of body mass on this slope in obese subjects and athletes with high lower-limb muscularity is only the case if pedaling frequency constrained to be relatively constant, therefore not influencing the $O_2$ cost of moving the legs per se. However, the position of the $V'O_2$-WR relationship will be displaced upwards in proportion to mass, as the $O_2$ cost of “unloaded” cycling ($V'O_2(0)$) is mass-dependent: $V'O_2(0)$ (ml/min) = 5.8 body mass (kg) + 151 [12, 30]. In some disease conditions, $\Delta V'O_2/\Delta WR$ may be abnormally low (e.g. ~8 ml/min/Watt or less), either over the entire tolerable range (e.g. peripheral vascular occlusive disease; hypertrophic cardiomyopathy) or as the tolerable limit is approached (e.g. ischemic heart disease) [e.g. 3, 31, 35]. In the latter case, caution is needed to ensure that estimates of $\Delta V'O_2/\Delta WR$ are confined to regions of the $V'O_2$-WR relationship which are appropriately linear, i.e. a single value over the entire range will blur important features of the response.

1.3 Lactate threshold ($\theta_L$)

The lactate threshold is the highest WR (or, more properly, $V'O_2$) at which arterial [lactate] ([L']a) is not systematically increased. It is thus an important functional demarcator of exercise intensity: sub-$\theta_L$ WRs can be designated “moderate”, as they can normally be comfortably sustained for prolonged periods. Supra-$\theta_L$ WRs, in contrast, may be termed “heavy” or “very heavy” as they lead to more-rapid fatigue, with [L']a
(and [H+]a) being increased in both cases but only increasing inexorably throughout the exercise in the latter (see 2). While controversy still surrounds the precise mechanisms underlying θL, the available evidence demonstrates that the [L]a increase during exercise is O2-dependent, e.g. being reduced with experimentally-induced hypoxic or anemic hypoxia at a particular level of V’O2, and increased with hyperoxia [reviewed in 1, 3, 29, 36].

As for V’O2 peak, θL is dependent on age, gender, body mass and fitness [e.g. 3]. It is also common practice to normalize θL values for body mass (e.g. ml/min/kg), and (as for V’O2 peak) a case can be made for normalizing to fat-free mass. Normal values for θL in young healthy adults lie in the region of 15-25 ml/min/kg, and may be 50 ml/min/kg or more in elite endurance athletes; values below 11 ml/min/kg suggest a poor prognosis in patient with CHF [21]. While, on average, θL occurs at ~ 50% of V’O2 peak in normal subjects, the range is very large, i.e. extending from ~ 40 to 80% [12, 37].

Rigorous non-invasive estimation of θL requires the demonstration of an augmented V’CO2 in excess of that produced by aerobic metabolism, reflecting additional non-metabolic CO2 released from bicarbonate (HCO3-) buffering of protons (H+) associated with L- accumulation - but which is not attributable to hyperventilation [38-42]. The V’CO2-V’O2 relationship below θL is often well characterized by a linear function (except in the very initial stages of the incremental phase, where there is a period of transient CO2 accumulation in the rapidly-exchanging body CO2 stores), with a slope (S1) normally below but close to 1 (Fig 2, panel 2), and the respiratory exchange ratio (RER) increasing modestly (Fig 2, panel 8). Above θL, the V’CO2-V’O2 relationship steepens (RER increasing at a greater rate (Fig 2, panel 8)), and is often essentially linear over about half the WR range between θL and V’O2 peak (with a slope
S2) to the point at which “respiratory compensation” for the metabolic acidemia (respiratory compensation point, RCP) becomes evident. At higher WRs, the slope increases further, reflecting the influence of compensatory hyperventilation on CO2 clearance. The point of [L]a increase has been demonstrated to coincide with the point at which the extrapolated S1 and S2 components intersect (i.e. the “V-slope” criterion) [39] (Fig 2, panel 2). For those instances when the V’CO2-V’O2 relationship cannot reliably be partitioned into two clearly linear segments, the point at which a unit tangent (i.e. ΔV’CO2/ΔV’O2 = 1) impacts on the curve may be used as an alternative [43].

**INSERT FIGURE 2**

The second criterion for θL discrimination derives from the recognition that V’E during moderate exercise responds to clear the CO2 load presented to the lungs rather than to the requirement for pulmonary O2 exchange [reviewed in 44, 45]. Arterial PCO2 (PaCO2) is therefore regulated close to control levels, with any consequent changes in arterial PO2 (PaO2) traversing the relatively flat upper reaches of the oxy-hemoglobin dissociation curve [reviewed in 46]. As is the case for V’CO2, V’E at θL therefore also starts to increase at a greater rate - while maintaining its proportionality to V’CO2, such that the V’E-V’CO2 relationship retains its sub-θL slope [3, 30, 47] (Fig 2, panel 3). As a result, alveolar (i.e. end-tidal) PCO2 (PEtCO2) and PaCO2 do not fall and the ventilatory equivalent for CO2 (V’E/V’CO2) does not increase over this region (Fig 2, panels 4 and 6). In contrast, as V’E is now of necessity increasing at a greater rate than V’O2, the ventilatory equivalent for O2 (V’E/V’O2) and end-tidal PO2 (PEtO2) both start to increase (Fig 2, panels 4 and 6). That is, as long as V’E is not constrained from increasing as a result of respiratory-mechanical dysfunction, there will be the onset of
hyperventilation relative to O$_2$ at $\theta_L$, but not to CO$_2$ - despite a falling arterial pH (pHa). It is only above the RCP that hyperventilation relative to CO$_2$ also develops, with $V'E/V'CO_2$ starting to increase and $P_{ET}CO_2$ to fall. The reasons for this apparently sluggish recruitment of respiratory compensation the rapid-incremental test remain to be elucidated [reviewed in 44, 45].

1.4 Oxygen pulse- $V'O_2$ relationship

HR normally increases reasonably linearly with respect to $V'O_2$ (Fig 2, panel 5) with a slope that is an inverse function of fitness, to attain values at peak exercise (HRmax) which are close to the predicted HRmax (HRmax$_{pred}$) [e.g. 9, 16]. Thus, the HR reserve (HRR, = HRmax$_{pred}$ - HRmax) is essentially zero. A demonstrable HRR in normal subjects is often taken as a marker of poor effort on the test - although the large standard deviation on the maximum HR (approx 10 min$^{-1}$) makes this a “soft” criterion value. Furthermore, in elderly hypertensive subjects, for example, this can also be reflective of the influence of beta-adrenergic blockade therapy.

A plot of $V'O_2$ as function of HR yields a linear $V'O_2$-HR relationship with a negative intercept on the $V'O_2$ axis (Fig 3, right). Consequently, the O$_2$-pulse rises hyperbolically as WR increases (Fig 2, panel 5; Fig 3, right) [29].

INSERT FIGURE 3

The O$_2$-pulse has important interpretational value, as it is defined as the product of the stroke volume and the arterio-venous O$_2$ content difference ($CaO_2 - C\nabla O_2$) - derived from the well-known “Fick Equation” i.e. as

$$V'O_2 = Q' \cdot (CaO_2 - C\nabla O_2) = HR \cdot SV \cdot (CaO_2 - C\nabla O_2)$$  \hspace{1cm} (1)
then,

\[ \text{V'O}_{2}/\text{HR} = \text{SV} \cdot (\text{CaO}_2 - \text{CvO}_2) = \text{O}_2\text{-pulse} \]  \hspace{1cm} (2)

However, it is important to not to be too readily tempted to interpret the O\textsubscript{2}-pulse profile as a function of either one of these variables in isolation. Only if it is possible to make a reasonable assumption regarding the change (or not) in one of the defining variables, may one interpret the non-invasive O\textsubscript{2}-pulse profile to reflect that of the alternative variable. This is difficult to determine directly and requires an invasive procedure.

If the O\textsubscript{2}-pulse fails to increase with increasing WR as peak exercise is approached, then the product of SV and the arterio-venous O\textsubscript{2} content difference has to be constant. This may be because each is constant, or because one is increasing while the other decreases. Apparent flatness in the O\textsubscript{2}-pulse profile should be considered with care, however. That is, normal subjects who are simply unfit have a shallower V'O\textsubscript{2}-HR relationship, and hence the curvature of the O\textsubscript{2}-pulse profile will also be shallow - appearing to be flat when, in fact, it may not be \cite{3, 30} (Fig 4). For the O\textsubscript{2}-pulse profile to be truly flat, there must be a change in the local V'O\textsubscript{2}-HR slope as a result of HR accelerating relative to V'O\textsubscript{2}, such that over this region the V'O\textsubscript{2}-HR slope extrapolates back to the origin of the plot (Fig 4, left). When this does occur, the continued increase in V'O\textsubscript{2} is HR-dependent \cite{3}.

**INSERT FIGURE 4**

1.5 \( V'_E - V'CO_2 \) slope and \( V'_E/V'CO_2 \)

There are two ineluctable considerations of the relationship between \( V'_E \) and \( V'CO_2 \) during muscular exercise: (a) that ventilation is a control variable with respect to
the regulation of PaCO$_2$ and pH$_a$, and (b) that the ventilatory response during exercise is demonstrably a highly linear function of V’CO$_2$ over a wide range of metabolic rate [reviewed in 44, 45, 48] (Fig 2, panel 3), with a slope (m, = ΔV’$_E$/ΔV’CO$_2$) in healthy young adults of ~25 (when V’$_E$ and V’CO$_2$ are reported in l/min) [34, 49, 50] and a small positive V’$_E$ intercept (c) of ~3-5 l/min [49] (Fig 3, left), i.e.:

\[ V'_E = m \cdot V'CO_2 + c \quad (3) \]

The slope estimation must, of course, be confined to that region of the V’$_E$-V’CO$_2$ relationship which is discernibly linear, i.e. not including the often curvilinear region above the RCP within which PaCO$_2$ is reduced to provide respiratory compensation for the metabolic acidosis. However, in disease states characterized by disturbances in PaCO$_2$ regulation and/or pulmonary gas exchange function, linearity below RCP should not be assumed a priori.

It is important to recognize, therefore, that the V’$_E$-V’CO$_2$ slope alone is not the decisive variable with respect to PaCO$_2$ and pH regulation, as apparent from the mass balance equation:

\[ V'_E = \frac{863 \cdot V'CO_2}{PaCO_2} \cdot \frac{1-V_D/V_T}{1} \quad (4) \]

where 863 is the constant which corrects for the different conditions of reporting the ventilatory volumes (BTPS, saturated, at a body temperature of 37°C) and the metabolic rate under “standard”, dry conditions (STPD) and also the transformation of the fractional concentration of CO$_2$ to its partial pressure; and V$_D$/V$_T$ is the physiologic dead space/tidal volume ratio. Hence,

\[ V'_E/V'CO_2 = \frac{863}{PaCO_2} \cdot \frac{1-V_D/V_T}{1} \quad (5) \]

or, alternatively

\[ PaCO_2 = \frac{863}{(V'_E/V'CO_2)} \cdot (1-V_D/V_T) \quad (6) \]
Consequently, as shown in equations 6 & 7, it is the ventilatory equivalent for CO₂ that is the crucial CO₂-linked variable with respect to PaCO₂ and pH regulation. Note that the \( V'_E/V'_CO₂ \) slope (m) differs from the actual value for \( V'_E/V'_CO₂ \) during exercise by the influence of the \( V'_E \) intercept (c), which is rarely considered in this context; i.e.

\[
V'_E/V'_CO₂ = m + c/ V'_CO₂
\]  

(7)

The ventilatory equivalent therefore declines hyperbolically as \( V'_CO₂ \) increases over this region (Fig 2, panel 4), projecting to an asymptote with the value (i.e. at high levels of \( V'_CO₂ \)) equal to the slope of the linear \( V'_E/V'_CO₂ \) relationship (i.e. m) [51] (Fig 3, left). \( V'_E/V'_CO₂ \) typically does not attain the asymptotic level as WR increases owing to a hyperventilatory influence of the lactic acidosis and/or developing hypoxemia (or even the apparent increase in \( V_D/V_T \) associated with a right-to-left shunt). Consequently, while there is relatively little difference between the minimum value of \( V'_E/V'_CO₂ \) (\( V'_E/V'_CO₂ \) min) during the test and the slope m in relatively fit subjects with a high \( \theta_L \) and RCP (the term c/\( V'_CO₂ \) becomes disappearingly small (eq. 7)), the difference can be more marked in sedentary subjects in whom \( \theta_L \) and RCP occur at a relatively low levels of \( V'_CO₂ \). This should be borne in mind when interpreting \( V'_E/V'_CO₂ \) at specific points on the incremental test. The \( V'_E/V'_CO₂ \) at \( \theta_L \) (\( V'_E/V'_CO₂@\theta_L \)) and \( V'_E/V'_CO₂\)min have both been proposed to provide non-invasive indices of ventilatory inefficiency [48, 52].

The decrease in \( V'_E/V'_CO₂ \) over the moderate WR range (Fig 2, panel 4; Fig 3, left) - over which PaCO₂ is normally regulated at or close to resting levels - therefore reflects the operation of an exquisite control system that provides the appropriate level of ventilation for the CO₂ exchange rate even as the functional efficiency of the lung improves, in this regard, as reflected by the declining \( V_D/V_T \) (Fig 5). Furthermore, as
the $V_D/V_T$ declines to, or close to, a constant value at high WRs \([48, 53-56]\), the subsequent increase in $V'_E/V'CO_2$ (\textbf{Fig 3, left}) reflects the provision of respiratory compensation for the metabolic acidosis, i.e. $P_{ET}CO_2$ and, more importantly, mean alveolar ($P_{A}CO_2$) (an estimator of $PaCO_2$ in normal subjects \([57-58]\)) fall (\textbf{Fig 5}).

\textbf{INSERT FIGURE 5}

In hyperventilatory conditions (e.g. metabolic acidaemia, arterial hypoxemia), both $\Delta V'_E/\Delta V'CO_2$ (i.e. the slope $m$) and $V'_E/V'CO_2$ are increased, reflecting the greater $V'_E$ requirement for $PaCO_2$ regulation; and less in hypoventilatory conditions (e.g. with blunted chemosensitivity). In a similar sense, both $\Delta V'_E/\Delta V'CO_2$ and $V'_E/V'CO_2$ are increased when $V_D/V_T$ is high (e.g. in the elderly and in COPD). Recognizing the exercise-related complexities of $PaCO_2$ and $V_D/V_T$ response in many cardiopulmonary diseases, interpretation of these CO$_2$ linked ventilatory relationships should be undertaken with caution. Certainly, unless constancy of $PaCO_2$ can be confidently assumed (or, better still, demonstrated), their interpretation \textit{solely} in terms of ventilatory efficiency is not warranted.

\textbf{1.6 Breathing reserve}

Breathing reserve (BR) provides an index of the proximity of the \textit{actual level} of exercise ventilation at the limit of tolerance ($V'_E$ max) to the \textit{maximal level achievable}, characterized as the subject’s maximum voluntary ventilation (MVV), usually at rest (MVV is either measured directly or estimated from the subject’s forced expiratory volume in one second (FEV$_1$), although it should be recognized that the conditions under which these two indices are not strictly comparable). BR can be defined either in
relative terms as $V'_E$ max as a percentage of MVV (i.e. $V'_E$ max · 100/MVV) or in absolute terms as the difference between the MVV and the $V'_E$ max (MVV - $V'_E$ max) [e.g. 1, 3] (again, it should be noted that MVV and $V'_E$ max are measured under quite different conditions: see Ref. 59 for discussion). As $V'_E$ max in normal subjects is higher with greater levels of fitness (i.e. $V''O_2$ peak) and MVV is, to a large extent, independent of fitness, BR will be correspondingly reduced.

However, a subject’s BR is not a single constant value but is dependent on the actual exercise protocol used. That is, the value that $V'_E$ attains values at the end of an incremental (or constant-load) test will depend not only on metabolic rate, $PaCO_2$ and $V_D/V_T$, but also the rate at which CO$_2$ is being evolved from body stores through buffering of metabolic acid - this is a function of the rate at which the $[HCO_3^-]$ decreases and not the amount by which it has decreased [41]. As rapid work rate incrementation rates yield commensurately-rapid rates of $[HCO_3^-]$ decrease, maximum $V'_E$ will therefore be higher than with tests employing slower work rate increases [41] - with a consequently-lower breathing reserve. A BR which is “minimal”, zero or negative is suggestive of a “ventilatory limitation” to exercise tolerance; a negative BR can occur as a result of exercise-induced bronchodilatation associated with increased catecholamine production in a subject with some ongoing bronchoconstriction (i.e. the resting MVV is now not appropriate as the frame of reference).

Some elite young endurance athletes and “athletic” elderly subjects can also demonstrate a low or absent of BR at end-exercise, in this case reflecting an inadequately-high MVV for the ventilatory demands of the extreme metabolic rates that can be achieved.
1.7 End-expiratory lung volume

The end-expiratory lung volume (EELV) plays an important role in the ventilatory response to exercise - especially its pattern of response. In normal subjects, EELV typically decreases with increasing WR by as much as 0.5-1.0 l below functional residual capacity (FRC) [e.g. 59-61]. This not only improves the mechanical advantage of the inspiratory muscles, but the consequently-increased inspiratory capacity (IC) provides a greater scope for the tidal volume (V_T) to operate on the relatively linear component of the thoracic volume-pressure (i.e. compliance) curve; this maintains a low elastic work of breathing [e.g. 59-61]. Normally, therefore, V_T makes the predominant contribution to the V'E response, except at very high WRs where further increases in V'E rely largely on breathing frequency (Fig 2, panel 7).

In contrast, in conditions such as COPD, the increased regional mechanical time constants of, especially, the lung (i.e. increased airflow resistance and compliance (low lung recoil)) predispose both to expiratory airflow limitation and an increase in EELV during exercise (i.e. impairing the spontaneous emptying rate often to an extent that FRC is not re-attained by the time for the next inhalation). The increase in EELV tends to ameliorate the flow limitation as it allows the expiration to proceed at a higher volume-specific limiting airflow. Thus, EELV increases throughout high-intensity exercise in spite of expiratory muscle activity [e.g. 59, 60, 62-65] - attempts to increase flow by further expiratory “effort” are typically counter-productive in patients with COPD. As this “dynamic hyperinflation” progresses, with an associated reduction in IC, not only are there increased demands on the inspiratory muscles but the scope for V_T increase is reduced, being constrained by end-inspiratory lung volume encroaching onto the flatter upper reaches of the compliance curve. In elderly subjects (i.e. ostensibly normal, but with the age-related reductions of lung recoil increasing the pulmonary-
mechanical time constant(s)), for example, EELV often declines over the moderate WR range but subsequently tends to increase back towards, or often beyond, resting levels [61, 66] as the pulmonary time constants become inadequate for the flow demands.

Direct measurement of EELV is not straightforward, especially during exercise. However, an indirect approach pioneered by O’Donnell and colleagues that is becoming widely used requires subjects to perform an IC maneuver at a selected point in the exercise test [64, 65], since TLC remains essentially unaltered during exercise [67, 68]. It is more usual that serial IC measurements are taken during symptom-limited constant-load tests, rather than in incremental tests; in the latter, the negative impact of the maximal maneuver on subsequent data profiles is likely to outweigh the advantages of tracking EELV.

Exercise inspiratory capacity [64, 69] and graphical analysis of tidal breathing exercise in comparison with maximal resting flow-volume loops [e.g. 59-61, 69, 70] may be better indices of ventilatory limitation than BR. Both IC and flow-volume loops can be recorded with reasonable accuracy during exercise [69, 71, 72]. (Fig 6)

**INSERT FIGURE 6**

### 1.8 Arterial O₂ saturation

Arterial O₂ saturation is normally well maintained throughout the tolerable WR range, in the region of ~97-98% for young adults but at progressively lower values with increasing age (largely as a consequence of the lung-recoil related changes in regional ventilation/perfusion (V’A-Q’) distribution) [e.g. 66]. However, it is not uncommon for: (a) highly-fit endurance athletes, (b) the “athletic” elderly, and (c) women to exhibit arterial desaturation and abnormal widening of the alveolar-arterial PO₂ difference
(P(A-a)O₂) as peak WRs are approached [e.g. 73-75]. This has been argued to reflect pulmonary capillary transit-time limitations (determined by the capillary “capacitance-to-conductance” ratios) resulting from the recruited pulmonary-capillary volume becoming inadequate for the high levels of pulmonary blood flow and, in addition, to increasing regional V’A/Q’ dispersion [e.g. 73-75].

There is some debate about whether indirect measurements of SpO₂ by pulse oximetry have a sufficiently high level of accuracy and reliability. The 95% confidence limits of pulse-oximetric values, relative to those directly measured, have been shown to be ~4-5% [reviewed in 1].

2 CONSTANT-LOAD EXERCISE TESTS

The incremental-type exercise test should be considered an essential prelude to any subsequent constant-load (or more properly, constant work rate) test that might be used to better characterize exercise intolerance, improve prognostic power, and provide more sensitive discrimination of interventions. This is because the investigator can then select the appropriate intensity domain within which the constant-load test is performed. The use of constant-load tests is becoming more prominent in clinical exercise testing, because of their relevance to characterizing: (a) the speed with which system responses attain (or attempt to attain) a new steady state (response “kinetics”) and (b) exercise endurance.

2.1 Response kinetics

The speed and manner in which V’O₂, V’CO₂, V’E respond to constant-load exercise is highly intensity-dependent; i.e. being complicated by the sequelae of the lactic acidosis for supra-θₐ WRs. Below θₐ, there is general agreement about the form of
these kinetics [e.g. 44, 45, 76]. There is an initial component (“phase 1”) of short duration (i.e. 15-20 s, reflecting the muscle-to-lung vascular transit delay) and of modest absolute amplitude; the response is usually quite abrupt from a resting baseline in the upright position but is more sluggish when the test is conducted from a baseline of prior unloaded (or light) exercise (Fig 7) - but, interestingly, it is also sluggish when initiated from rest in the supine position. This early phase 1 response is followed by a more prominent “phase 2” component which has an exponential time course (Fig 7). Its rate of development can therefore be described by a time constant (τ); this is quantified as the time taken to attain 63% of the steady-state response or, to a close approximation as 1.5 times the half-time of the response [77, 78].

\[ \tau V'O_2 \]

\[ \text{typically ~30-40 s in healthy young subjects. However, it can be as much as 2-3 fold longer in elderly subjects, in subjects with cardiopulmonary or muscular disease and others who are chronically sedentary [e.g. 3, 79]; in such subjects, this “slowing” can be largely reversed by endurance training [79, 80]. These considerations have an important impact on muscle energetics; i.e. whether the exercise can be sustained solely through aerobic ATP resynthesis, or whether there is a requirement to supplement this from anaerobic glycolytic sources (i.e. with its attendant lactic acidosis). This can be quantitated in terms of the “oxygen deficit” (O_2\text{def}), which may be defined as the O_2 equivalent of the energy utilized for the work which did not derive from aerobic mechanisms utilizing the increased pulmonary V'O_2. For moderate exercise, the decreases in muscle creatine phosphate (PCr) and mixed venous O_2 content (in addition to a small and usually-transitory increase in [lactate]) provide the energy resources making up the}
deficit, the value of which may be computed as the product of the overall $\tau V'O_2$ (i.e. utilizing the combined phase 1 and phase 2 responses) and the steady-state $V'O_2$ increment ($\Delta V'O_2$ ss) \[77, 81\]. While $\Delta V'O_2$ ss naturally will increase in proportion to the size of the applied WR step (i.e. $\Delta V'O_2/\Delta WR = \sim 9\text{-}11$ ml/min/Watt for cycle ergometry), it is essentially independent of factors such as fitness and age (see 1.2). This means that subjects with a long $\tau V'O_2$ will have an increased demand on muscle PCr and blood $O_2$ stores and also transient (at the least) lactate production to supplement the aerobic energy transfer; i.e. a larger $O_2$def necessarily predisposes towards anaerobiosis.

$\tau V'CO_2$ is appreciably longer than $\tau V'O_2$ (Fig 7), being $\sim 50\text{-}60$ s in healthy young adults [e.g. 44, 45], reflecting the influence of the high capacitance CO$_2$ stores (chiefly in the exercising muscle) during the exercise transient [27, 82]. During constant-load exercise, as for incremental-type and other kinds of WR forcings, the time course of the $V'_E$ response is in close proportion to that of $V'CO_2$, although with a small but discernible lag [e.g. 44, 45] (Fig 7) – undermining the view that the $V'CO_2$ dynamics are consequent to those of $V'_E$. Thus, $\tau V'_E$ is $\sim 60\text{-}70$ s in healthy young adults, and is responsive to experimental alterations in $\tau V'CO_2$: when $\tau V'CO_2$ is caused to be speeded, $\tau V'_E$ is also speeded. It is important to recognize that the close coupling of $\tau V'_E$ and $\tau V'CO_2$ means that there is a marked transient dissociation of $V'_E$ not only with $V'O_2$ but also with the actual metabolic CO$_2$ production rate in the muscle. As a result, PaO$_2$ falls transiently during phase 2 on-transients (and increase during off-transients) [78, 83, 84] (Fig 7). Furthermore, the small kinetic dissociation between $V'_E$ and $V'CO_2$ results in a small transient increase of PaCO$_2$ [78] (Fig 7), discerned to date only for sinusoidal exercise [85] and rapid-incremental exercise [86].

Above $\theta_L$, the kinetics of $V'O_2$, $V'CO_2$, $V'_E$ become complicated by additional time- and amplitude-related complexities, a detailed discussion of which is beyond the
scope of this article (the interested reader is referred to Refs. 45, 87 for further discussion). Of relevance, however, is the demonstration that the supra-$\theta_L$ WR range can be subdivided into two domains: (a) “heavy”, for which $V'O_2$ (and blood [lactate]) can attain a new steady-state although more slowly and at a greater $O_2$ cost (i.e. $\Delta V'O_2/\Delta WR$ is increased) than for sub-$\theta_L$ exercise; and (b) “very-heavy” where, for all WRs, $V'O_2$ is set on a trajectory to, or towards, $V'O_2$ peak and fatigue (attained more rapidly, the higher the WR) with blood [lactate] also increasing [87].

2.2 $T$-Lim criterion and “iso-time” measures

The fatigue process in the very-heavy domain in normal subjects is reflected in a hyperbolic relationship between WR (or power (P)) and the tolerable duration of the exercise (Fig 8) – this has been shown to be the case for cycle ergometry, treadmill running and swimming [reviewed in 88, 89]:

\[(WR - CP) \cdot t_{\text{Lim}} = W'\]  \hspace{1cm} (8)

where $t_{\text{Lim}}$ is the tolerable duration, CP is the critical power (i.e. the asymptote for this hyperbolic relationship), and $W'$ is the curvature constant for this relationship - with the mechanistically-provocative unit of work. If, however, WR is plotted as a function of $1/t_{\text{Lim}}$ rather than $t_{\text{Lim}}$, then the relationship is linear, with a slope equivalent to $W'$ and an intercept at CP [90] (Fig 8):

\[WR = W'/t_{\text{Lim}} + CP\]  \hspace{1cm} (9)

CP has been shown to be the upper constancy limit of $V'O_2$, blood [lactate] and [H$^+$], and hence is a crucial determinant of the endurability of a particular task. And in the context of CPET, it is of some interest that these characteristics have recently been demonstrated to be the case also in patients with COPD [91, 92].
CP has been demonstrated to occur, on average, at a blood lactate of some 4-5 mM (i.e. the highest sustainable blood lactate) in normal subjects \([90, 93]\). This value can vary markedly in different subjects, however, with values greater than 8 mM being sustainable in some. CP occurs at approximately half the \(V'\text{O}_2\) range between \(0_L\) and \(V'\text{O}_2\) peak in normal subjects [e.g. 88, 90] and at approximately 80\% in patients with COPD (i.e. peak WR and \(V'\text{O}_2\) in the latter case being limited by respiratory mechanics) [91, 92].

Furthermore, because of the hyperbolic shape of the \(P-t\) relationship, what may appear to be a relatively small percentage increase in \(V'\text{O}_2\) peak on an incremental test can translate to an appreciable increase in the tolerable duration of a particular constant-load test. That is, small increases in CP can result in large increases in tolerable duration for WRs slightly greater than the pre-training CP [94] (Fig 9). The magnitude of the apparent improvement in such cases will, naturally, depend on the position of the pre-training work rate on the subject’s power-duration relationship.

In the context of patient evaluation, it is important to recognize that the power-duration relationship cannot, at present, be defined by means of a single exercise test. A minimum of 3-4 tests is required (Figs 8 & 9), each of which should be conducted on a separate day. It is instructive, therefore, to consider what alternatives are currently available and what they can tell us about endurance in the context of the \(P-t\) relationship. Timed field tests (e.g. 6- and 12-minute walk tests (6-MWT, 12-MWT)) are growing in
popularity in large part because of their ease of administration and their potential prognostic value (see below).

A more sophisticated, laboratory-based test is the constant-load test at 80-90% of \( \text{V'\text{O}_2} \) peak performed to the limit of tolerance, usually with breath-by-breath monitoring. However, the dissociation between the \( \text{V'\text{O}_2} \) achieved at a particular work rate on an incremental-type test and that of the steady-state requirement (see 1.2 and Fig. 1) - a necessary consequence of the kinetics of the \( \text{V'\text{O}_2} \) response dynamics - means that it is preferable not to select a given percentage of the maximum work rate attained on an incremental test for the chosen constant-load test without correcting for this kinetic influence. As schematized in Fig. 1, while the maximum \( \text{V'\text{O}_2} \) attained on an incremental test is largely independent of the rate at which the work rate is incremented (except for tests of extremely long or short duration [4]), the maximum work rate achieved is higher the higher the incrementation rate. This may readily be corrected for by subtracting the product of the ramp slope (\( \Delta \text{WR}/\Delta t \)) and an estimated \( \text{V'\text{O}_2} \) response time constant (or mean response time (MRT)) from the maximum work rate achieved. For example, for a sedentary patient having undergone a 10 Watts/min incremental test and with an “expected” MRT of one minute, 10 Watts should be subtracted from the maximum work rate to give a more appropriate frame of reference for the constant-load endurance test.

However, such tests provide only a single point on the patient’s P-t relationship, the determinants of which (CP and \( W' \)) can differ markedly among subjects (see above). For example, the relationship between the average velocity on the standard (or encouraged) 6-MWT and the velocity-equivalent of six minutes on the P-t relationship is not, at present, known; i.e. the implications for interpretation of distinguishing what can possibly be done for six minutes from what is chosen to be done for six minutes. And on a
practical note, standardization with regard to walking-test design and conduct are needed (e.g. pacing strategies; the timing and degree of encouragement; whether only one test is completed on a given day).

It is becoming increasingly common to utilize a standardized time point (i.e. “iso-time”) for comparison of physiologic responses to an intervention on a symptom-limited constant-load laboratory test (usually at the limit of tolerance for the pre-intervention test) [95-97]. However, the functional significance of a certain magnitude of intervention-induced improvement will, as mentioned above, depend very much on where the point lies within the subject’s P-t relationship: a given increase in CP will be associated with a far greater increase in tolerable duration for a WR that lies relatively low, rather than high, on the P-t relationship (Fig 9).
REFERENCES


Fig 1: Schematic of the V’O$_2$ response to ramp incremental exercise (—) as a function of time at three different work-rate (WR) incrementation rates, and the corresponding WR profile ( - - - ). Note that V'O$_2$max is unaffected by WR incrementation rate. However, the influence of the V'O$_2$ time constant (—) results in WRmax progressively higher, the faster the incrementation rate. (See text for details). Modified from ref 29, with permission.
Fig 2: Responses to incremental exercise performed to the limit of tolerance by a healthy subject on a cycle ergometer. Panel 1: O₂ uptake (V'O₂) vs. work rate; panel 2: CO₂ output (V'CO₂) vs. V'O₂, showing the intersection of the lower S₁ and upper S₂ regression lines; panel 3: ventilation (V'E) vs. V'CO₂, with horizontal dashed line indicating maximum voluntary ventilation (MVV); panel 4: ventilatory equivalents for O₂ and CO₂ (V'E/V'O₂, V'E/V'CO₂) vs. V'O₂; panel 5: heart rate (HR) and O₂-pulse (V'O₂/HR) vs. V'O₂, with horizontal dashed line indicating predicted HRmax; panel 6: end-tidal PCO₂ and PO₂ (PetCO₂, PetO₂) vs. V'O₂; panel 7: tidal volume (Vₜ) vs. V'E, with horizontal dashed line indicating vital capacity (VC) and vertical dashed line indicating MVV; panel 8: respiratory exchange ratio (RER) vs. V'O₂. Solid vertical line is the estimated lactate threshold (θₑ). See text for further details.

Left panel Right panel

Fig 3: Schematic of responses to an incremental cycle-ergometer exercise test performed to the limit of tolerance. Left panel: ventilation (V'E) as a function of CO₂ output (V'CO₂) with V'E/V'CO₂ isopleths superimposed; and V'E/V'CO₂ vs. work rate.
(W’). Note that the asymptotic value of $V'_{E}/V'_{CO_2}$ approximates the slope (Sa) of the $V'_{E}$-$V'_{CO_2}$ relationship. Right panel: $O_2$ uptake ($V'O_2$) as a function of heart rate (HR) with $V'O_2$/HR isopleths superimposed; and $V'O_2$/HR vs. work rate (W’). Note that the asymptotic value of $V'O_2$/HR approximates the slope (Sd) of the $V'O_2$-HR relationship. See text for further details.

**Fig 4:** Schematic to show mechanism leading to flatness in the $O_2$-pulse profile. Right panel: $O_2$-pulse ($O_2P$) as a function of work rate (W’). Note flattening of $O_2$-pulse at higher work rates (relative to normal profile, which continues to increase, — — — ). Left panel: heart rate (HR) as a function of $O_2$ uptake ($V'O_2$), with discontinuity at higher work rates providing a steeper linear HR-$V'O_2$ segment that superimposes on HR/$V'O_2$ isopleth (i.e. constant $O_2$-pulse, - - - ). See text for further details.

**Fig 5:** Responses to incremental exercise (15 Watts/min). Left panel: Breath-by-breath end-tidal and flow-weighted mean alveolar $PCO_2$ ($P_{ET}CO_2$, $P_ACO_2$), with corresponding values from directly-sampled arterial blood ($PaCO_2$). Right panel: estimated series dead space ($\hat{V}_D$) as a function of tidal volume ($V_T$); dashed lines represent $V_D/V_T$ isopleths. $P_ACO_2$ and $V_D$ estimated from intra-breath analysis. Reproduced from ref 56, with permission.
Figure 6. Flow-volume loops showing the effects of exercise on tidal volume in a COPD patient and in age-matched healthy subject. The large solid loops represent the maximal limits of flow and volume, and the small inner solid loops represent resting tidal volumes. The larger dashed loops represent the increased tidal volumes and flows seen with exercise. The dotted line on the left panel represents the IC maneuver to TLC which is used to anchor tidal flow-volume loops within the respective maximal loops. Healthy subjects are able to increase both their tidal volumes and inspiratory and expiratory flows. In COPD, expiratory flow is already maximal during resting ventilation (for comparison, the predicted maximal flow-volume curve is also shown). In order to increase expiratory flow further, these patients must hyperinflate.

Fig 7: Schematic representation of time course of O\textsubscript{2} uptake (V'O\textsubscript{2}, \(\rightarrow\)), CO\textsubscript{2} output (V'CO\textsubscript{2}; \(\cdots\cdots\cdots\)) and ventilation (V'E; \(\longrightarrow\)) in response to a moderate work-rate step from rest (top panel) and unloaded pedaling (middle panel), with corresponding profiles of
arterial PCO$_2$ (PaCO$_2$; − − − ) and PO$_2$ (PaO$_2$; − · − ). Reproduced from ref 78, with permission.

**Fig 8:** Top panel: schematized relationship between power or work rate (WR) and its tolerable duration for exercise performed above critical power. Bottom panel: linearized form of the WR-t relationship, with the WR-intercept corresponding to critical power. See text for details.

**Fig 9:** The effects of endurance training on the power-duration relationship, which results in a given work rate being sustainable for a longer period (dashed horizontal arrow). Dashed line: pre-training; solid line: post-training. Note increase in lactate threshold with training. Reproduced from ref 94, with permission.