Review Article

Clinical Usefulness of Response Profiles to Rapidly Incremental Cardiopulmonary Exercise Testing

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Received 29 July 2012; Revised 17 December 2012; Accepted 15 January 2013

Academic Editor: Bruce D. Johnson

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The advent of microprocessed "metabolic carts" and rapidly incremental protocols greatly expanded the clinical applications of cardiopulmonary exercise testing (CPET). The response normalcy to CPET is more commonly appreciated at discrete time points, for example, at the estimated lactate threshold and at peak exercise. Analysis of the response profiles of cardiopulmonary responses at submaximal exercise and recovery, however, might show abnormal physiologic functioning which would not be otherwise unraveled. Although this approach has long been advocated as a key element of the investigational strategy, it remains largely neglected in practice. The purpose of this paper, therefore, is to highlight the usefulness of selected submaximal metabolic, ventilatory, and cardiovascular variables in different clinical scenarios and patient populations. Special care is taken to physiologically justify their use to answer pertinent clinical questions and to the technical aspects that should be observed to improve responses’ reproducibility and reliability. The most recent evidence in favor of (and against) these variables for diagnosis, impairment evaluation, and prognosis in systemic diseases is also critically discussed.

1. Introduction

Cardiopulmonary exercise testing (CPET) provides a means of unraveling abnormal physiologic functioning which may not be apparent at rest [1, 2]. The advent of microprocessed CPET systems [3] increased our technical capabilities in recording several variables throughout a single exercise bout—even of a relatively “short” duration of 10 minutes [4, 5]. The response normalcy to rapidly incremental CPET is more commonly judged by comparing the observed values at discrete time points (e.g., at the estimated lactate threshold (LT) and at peak exercise) with those previously obtained in apparently healthy subjects [6, 7]. It should be noted, however, that relying only in such discrete analysis leads to substantial loss of physiologic information given by the observation of the responses profiles during submaximal exercise and recovery [8–11].

In this context, authoritative textbooks [2, 12] and guidelines [13, 14] advocated that the trending of certain variables is a crucial component of the interpretative strategy as they might show substantial abnormalities even when the discrete values are still within the expected range [15–17]. Moreover, the response dynamics are highly reproducible [8–11], encompassing a range of exercise intensities which are likely to be faced by the patients in daily life [18–26]. Although the scientific foundations supporting their use have long been established, [8–17] they are still not routinely assessed and clinically valued in practice.

The purpose of this brief review, therefore, is to emphasize the practical usefulness of analyzing the response profiles of selected variables during rapidly-incremental CPET. Special care is taken to physiologically justify their use to answer relevant clinical questions and to the technical details that
2. Metabolic Responses

2.1. Estimated Lactate Threshold

2.1.1. Physiological Background. The rate at which arterial lactate anions \([\text{Lac}^-]\) and the associated proton (\(\text{H}^+\)) accumulate as exercise progresses is directly related to the ratio between lactic acid (LA) release as a final byproduct of muscle anaerobic glycolysis and LA clearance by metabolism and buffering [29–31]. Although there seems to exist a period of time—not a discrete time point—in which LA production exceeds its rate of clearance, the term LA “threshold” (LT) [32, 33] is widely used. LA production increases as tissue \(\text{O}_2\) delivery diminishes [34] though some LA can be produced without any evidence of tissue hypoxia [35]. This justifies the notion that LA release during exercise is a reasonably sensitive (albeit non-specific) [36] marker of tissue anaerobiosis.

LA dissociates fast in \(\text{Lac}^-\) and \(\text{H}^+\) in the physiological pH; that is, it is a strong acid. Plasma bicarbonate \((\text{HCO}_3^-)\) is the main buffer of lactic acidosis leading to the formation of carbonic acid \((\text{H}_2\text{CO}_3)\) which in turn dissociates into carbon dioxide \((\text{CO}_2)\) and water; that is,

\[
\text{H}^+ + \text{Lac}^- + \text{HCO}_3^- \Leftrightarrow \text{H}_2\text{CO}_3 \Leftrightarrow \text{CO}_2 + \text{H}_2\text{O}. \tag{1}
\]

Although this reaction has the advantage to turn a fixed acid into a volatile gas, the "extra-CO\(_2\)" (approximately 22–26 mL of additional CO\(_2\) is produced from each mEq decrease of \([\text{HCO}_3^-]\)) [31] derived from buffering of \(\text{Lac}^-\) associated protons will not only accelerate \(\text{CO}_2\) output \((\dot{\text{V}}\text{CO}_2)\) relative to \(\text{O}_2\) uptake \((\dot{\text{V}}\text{O}_2)\) but also stimulate ventilation \((\dot{V}_E)\). These phenomena underlie the techniques for a noninvasive estimation of the LT.

2.1.2. Technical Considerations. As LA is buffered by \(\text{HCO}_3^-\), \(\dot{\text{V}}\text{CO}_2\) increases (1) out of proportion of \(\dot{\text{V}}\text{O}_2\), and a plot between these variables will show a discernible breakpoint; that is, the \(\dot{\text{V}}\text{CO}_2/\dot{\text{V}}\text{O}_2\) relationship evidences an increased slope at the point of \([\text{Lac}^-]\), increase. This is more commonly referred as the gas exchange threshold and determined by the V-slope method (Figure 1(a)) [37]. Increase in \(\dot{\text{V}}\text{CO}_2\), will drive \(\dot{V}_E\) in its direct proportion leading the latter to increase faster than \(\dot{\text{V}}\text{O}_2\). The consequent increase in \(\dot{V}_E/\dot{\text{V}}\text{O}_2\), and the end-tidal partial pressure for \(\text{O}_2\), \(P_{\text{ET}}\text{O}_2\) with a stable \(\dot{\text{V}}\text{O}_2/\dot{\text{V}}\text{CO}_2\) (and \(P_{\text{ET}}\text{CO}_2\)) establishes the so-called ventilatory threshold (Figure 1(b)) [38]. It should be noted that despite reflecting the same phenomenon (LA buffering), the gas exchange threshold slightly precedes the ventilatory threshold (VT) (Figure 1). After the LT, \(\dot{V}_E/\dot{\text{V}}\text{CO}_2\), and \(P_{\text{ET}}\text{CO}_2\) remain stable for a variable period of time during the “isocapnic buffering”. However, as more \(\text{H}^+\) is released with further increases in work rate, \(\dot{V}_E\) eventually increases out of proportion to \(\dot{\text{V}}\text{CO}_2\) at the respiratory compensation point (RCP) thereby leading to alveolar hyperventilation and progressive reductions in \(P_{\text{ET}}\text{CO}_2\) towards the end of the test (Figure 1(b)).

Irrespective of the denomination, the following technical aspects for the LT estimation should be noted:
(1) automatic estimations (by the CPET software) should be viewed with caution and routinely double-checked with manually determined values;

(2) if an unitary tangent is used to estimate the LT in the V-slope plot, the range of \( V_O_2 \) and \( V_CO_2 \) values should be the same as any discrepancy would invalidate its underlying mathematical (and physiological) principles [37] (Figure 1(b));

(3) use of discrete R (\( V_CO_2/V_O_2 \)) values (i.e., > 1 from tabular data) as indicative of the LT might lead to erroneous estimations;

(4) \( V_O_2 \) at any particular WR during a ramp-incremental test is lower than the steady-state \( V_O_2 \) value at that same WR due to a variable \( V_O_2 \) kinetics delay. As a result, the WR corresponding to \( V_O_2 \) LT precedes the WR in which the LT was identified by approximately 30–45 s (or even more in patients) [4]. Accordingly, if one is interested in exercising a subject at the \( V_O_2 \) LT, the selected WR should lead the WR-LT by this timeframe;

(5) a given change in \( V_E \) has a greater effect on CO\(_2\) release than \( O_2 \) uptake by the lungs; consequently, preexercise hyperventilation may deplete the amount of CO\(_2\) stored in the body without major effects on CO\(_2\) stores [39]. As the body capacitance for CO\(_2\) increases during the early phase of the ramp, replenition of the CO\(_2\) stores slows \( V_CO_2 \) relative to \( V_O_2 \); that is, \( V_CO_2/V_O_2 \) slope in this region becomes shallow (“\( S_1 \)” in Figure 1(a)). As the body CO\(_2\) reservoirs are filled in with exercise progression, the rate of CO\(_2\) storage will decrease thereby accelerating \( V_CO_2 \) relative to \( V_O_2 \) [40]. This might mistakenly suggest the onset of lactic acidosis, that is, a “pseudo-LT” [41]. Precautions should therefore be taken to avoid hyperventilation prior to the noninvasive estimation of LT by the V-slope method;

(6) LT should always be expressed relative to predicted \( V_O_2 \) peak not to the attained \( V_O_2 \) peak, especially in patient populations where the latter procedure might create a false concept of preserved (or even increased) \( V_O_2 \) LT, and

(7) \( V_O_2 \) peak declines with senescence at a steeper rate than \( V_O_2 \) LT; that is, \( V_O_2 \) LT (% of \( V_O_2 \) peak) increases as a function of age in both genders [41–43].

2.2.3. Clinical Usefulness. The physiologic changes associated with \([Lac]_a\) and H+ accumulation (e.g., metabolic acidosis, impaired muscle contraction, hyperventilation, and altered \( V_O_2 \) kinetics) are important to document clinically as they are associated with reduced cardiopulmonary performance. An early LT is a marker of impaired aerobic metabolism [44–49] due to insufficient \( O_2 \) delivery, increased recruitment of fast-twitch type II fibers which are metabolically less efficient than the slow-twitch type I fibers (i.e., have a greater \( O_2/ATP \) ratio), and/or mitochondrial enzymatic dysfunction. The isolated analysis of the LT does not allow the differentiation of cardiovascular limitation from sedentarity though a severely decreased LT (e.g., <40% predicted \( V_O_2 \) peak) [6] is more frequently found in patients. A low LT has been found useful to predict an increased risk of post-operatory complications in the elderly [50, 51], worse prognosis in chronic heart failure (CHF) [52], and disease severity in pulmonary arterial hypertension (PAH) [53]. On the other hand, improvements in LT after pharmacological and nonpharmacological inter-ventions have been associated with increased functional performance in a range of clinical populations [54–69]. Although there is lack of evidence that training at (or above) the \( V_O_2 \) LT is essential to improve exercise capacity in patients with CHF, coronary artery disease (CAD), and chronic obstructive pulmonary disease (COPD), training at higher intensities elicits larger physiological adaptations in less severe patients who are able to tolerate such regimens [54, 70, 71]. Training at the \( V_O_2 \) LT also seems to reduce the risk of complications during early phases of cardiac rehabilitation [72, 73]. In patients with COPD, however, LT cannot always be identified (even using the V-slope method), and when identified it varies widely as expressed in \( V_O_2 \)% peak [74]. In fact, important subjective improvements after rehabilitation can be found despite the lack of measurable physiological effects [75] which casts doubt on its usefulness to target exercise training intensity in these patients.

2.2. Δ Oxygen Uptake (\( V_O_2 \))/Δ Work Rate (WR)

2.2.1. Physiological Background. From a relatively constant value of 500 mL/min at unloaded pedaling, \( V_O_2 \) increases linearly as exercise progresses during a rapidly-incremental exercise test [4]. The slope of the \( ΔV_O_2/ΔWR \) relationship, therefore, is an index of the overall gain of the \( V_O_2 \) response, and normal values would indicate adequate metabolic cost for the production of a given power output [4, 8].

2.2.2. Technical Considerations. For an accurate calculation of the \( ΔV_O_2/ΔWR \) slope, any delay in \( V_O_2 \) increase at the start of the ramp or any eventual plateau near the end of exercise should be discarded (Figures 2(a) and 4). Considering that the LT can potentially distort the response’s linearity [157–160], it is advisable to check if there is an inflection point in the \( ΔV_O_2/ΔWR \) at the LT. If this is discernible, the slope should be calculated over the sub-LT range.

2.2.3. Interpretative Issues. \( ΔV_O_2/ΔWR \) is not significantly influenced by the training status, ageing, or gender (Figure 3(a)) [2, 10, 12–14]. A shallow \( ΔV_O_2/ΔWR \) over the entire range of values and/or a shift from a linearly increasing profile to a shallower rate of change has been shown to be indicative of circulatory dysfunction [77–80] (Figure 4) and severe impairment in mitochondrial function [81]. The latter pattern of response has been found to enhance ECG sensitivity to detect myocardial ischemia [82–86], and some studies suggested that it might be useful to unravel early abnormalities in the coronary microcirculation [87, 88].
Figure 2: Procedures to establish 3 dynamic submaximal relationships by simple linear regression during incremental CPET in young (24-yr-old, left panels) and old (70-yr-old, right panels) subjects. (a) Δ oxygen uptake (\(\Delta V_{O_2}\))/Δ work rate (WR); (b) Δ heart rate/Δ\(V_{O_2}\); (c) Δ minute ventilation (\(\Delta V_{E}\))/Δ carbon dioxide output (\(V_{CO_2}\)). The arrows show the range of values considered for analysis. RCP is the respiratory compensation point. (Modified with permission from [10].)
2.3. \( \dot{V}_O_2 \) Efficiency

2.3.1. Physiological Background. \( \dot{V}_E \) increases curvilinearly relative to \( \dot{V}_O_2 \) in response to a ramp-incremental exercise test. At least in theoretical grounds, several variables known to interfere with both \( \dot{V}_E \) and \( \dot{V}_O_2 \) would bear an influence in this relationship; that is, it is deemed to be modulated by cardiovascular, pulmonary, and muscular factors [161–168]. Most authors have expressed the \( \dot{V}_E-\dot{V}_O_2 \) relationship with \( \dot{V}_O_2 \) as the dependent variable [89,165,169]. In this construct, higher \( \dot{V}_O_2 \) values (or steeper rates of change) for a given \( \dot{V}_E \) would indicate a more “efficient” \( O_2 \) uptake by the lungs. It should be emphasized, however, that exercise \( \dot{V}_E \) is more closely related to \( \dot{V}_CO_2 \) than \( \dot{V}_O_2 \) [170] which makes the concept of \( \dot{V}_O_2 \) efficiency prone to misinterpretation (see Section 2.3.3).

2.3.2. Technical Considerations. Baba and coworkers [165] proposed a logarithmic transformation of \( \dot{V}_E \) over the entire exercise period to “linearize” this relationship, the so-called \( \dot{V}_O_2 \) efficiency slope (OUES) (Figure 5(a)). More recently, Sun
Figure 4: Oxygen uptake (\(\dot{V}_{O_2}\))/work rate (WR) relationship during ramp-incremental CPET before and after pulmonary endarterectomy in a 21-year-old male with thromboembolic occlusion of the left pulmonary artery. Note that after the surgery, peak \(V_{O_2}\) increased not only due to a higher peak WR but also owing to a large improvement in \(\Delta V_{O_2}/\Delta WR\).

et al. [89, 169] expressed the OUE as a ratio (\(V_{O_2}/V_F\) in mL/L) over time which, as expected, gives a mirror image of the ventilatory equivalent for \(O_2\). The authors proposed the term OUE plateau (OUEP) to the 90 s-average of the highest consecutive \(V_{O_2}/V_F\) measurements; that is, the values just before the LT (Figure 5(b)). Although they reported that OUEP was more reproducible than OUES, this was not yet independently confirmed. It has been claimed that both relationships are independent of interobserver variability and effort [90, 164, 171–173]. However, Williamson et al. [173] recently found that there was a significant increase in OUES as exercise moved from low to moderate intensity with a peak value at an RER value of 1.0. Oscillatory breathing (see Section 3.3) has been found to interfere little with OUE estimations [89]. It should be recognized that both OUES and OUEP require separate computation though some commercially available CPET systems allow logarithmic transformations for OUES calculation.

2.4. Postexercise \(\dot{V}_{O_2}\)

2.4.1. Physiological Background. After ramp-incremental exercise, \(\dot{V}_{O_2}\) does not decline immediately towards the resting level. The traditional view is that there would be a “debt payment” of energy deficit contracted at the start of effort (\(O_2\) deficit). Indeed, the time course of \(\dot{V}_{O_2}\) recovery after a moderate, constant test has been found to track the rate of phosphocreatine resynthesis [181]. At early recovery, replenishment of local \(O_2\) sources in muscles (oxymyoglobin and dissolved \(O_2\)) and reloading of haemoglobin are also needed [182]. At later stages, lactate metabolism (oxidation or gluconeogenesis) and increased catecholamines and temperature also interfere with the dynamics of \(\dot{V}_{O_2}\) decrease [183, 184].

2.4.2. Technical Considerations. \(\dot{V}_{O_2}\) during recovery has been evaluated by (a) the ratio between total \(\dot{V}_{O_2}\) during exercise and recovery [185], (b) the time constant of \(\dot{V}_{O_2}\) decay (i.e., time to reach 63% of the lowest value as obtained by fitting a decreasing monoexponential function) [182, 186, 187], (c) \(t^{1/2}\) (time required for \(\dot{V}_{O_2}\) to decrease to half of its peak value) [185, 188–190], and (d) \(\dot{V}_{O_2}\) t-slope (the response slope during the first minute of recovery by linear regression) [188, 189]. A further increase in \(\dot{V}_{O_2}\) during recovery [191] (i.e., a \(\dot{V}_{O_2}\) “overshoot”) has been found indicative of severe hemodynamic dysfunction as it reflects prolonged \(\dot{V}_{O_2}\) kinetics [192, 193]. Importantly, the level of effort seems not critical for a valid analysis of post-exercise \(\dot{V}_{O_2}\) dynamics [190].

2.4.3. Interpretative Issues. Delayed \(\dot{V}_{O_2}\) recovery has been related to functional impairment in CHF [188, 189, 192, 194], myocardial ischemia [195], COPD [196], and functional impairment in several conditions, including cystic fibrosis [197], diabetes [198], deconditioning [199], and obstructive relationship has been spread to other populations (cystic fibrosis, and surgical candidates) [174, 175]. A number of studies have found that OUES is strongly correlated with \(\dot{V}_{O_2}\) peak [90, 164, 165, 167, 171, 172, 176, 177] and may hold prognostic value in CHF [18, 89–94]. However, the prognostic advantage of OUES over \(\Delta V_F/\Delta V_{CO_2}\) slope remains unclear [178, 179]. In the pediatric group, mixed results were reported and at least one study found that OUES determined at different WRs differed significantly within patients with cystic fibrosis and correlated only moderately with \(V_{O_2}\) peak and VT [180]. Interestingly, OUES showed to be more sensitive to the effects of training than \(\Delta V_F/\Delta V_{CO_2}\) slope in patients with CHF [96], a finding correlated with enhanced cerebral and muscle hemodynamics in another study [95]. On a single investigation from the group which proposed OUEP, this relationship either on isolation or in combination with oscillatory breathing was prognostically superior to traditional key CPET parameters in CHF [89]. Predicting equations for OUES and OUEP have been recently published [169].
Figure 5: Relationship between oxygen uptake ($\dot{V}_O_2$) and minute ventilation ($\dot{V}_E$) during incremental exercise in a healthy subject (\textbullet\textbullet\textbullet\textbullet) and patients with mild (xxxx) and severe (\textbullet\textbullet\textbullet\textbullet\textbullet) CHF. (a) The slope of $\dot{V}_O_2$ upon $\log_{10}\dot{V}_E$ is the oxygen uptake efficiency slope (OUES) which gives the rate of increase in $\dot{V}_O_2$ for a 10-fold rise in $\dot{V}_E$. (b) The highest $\dot{V}_O_2/\dot{V}_E$ ratio is the $\dot{V}_O_2$ efficiency slope (OUEP) which is the average of values just prior to the estimated lactate threshold. Unl is unloaded pedaling.

Figure 6: Incremental cycle ergometer exercise tests in the same patient of Figure 4 with chronic thromboembolic pulmonary hypertension. After pulmonary endarterectomy (closed symbols), haemodynamic improvement (panel (a)) led to a higher oxygen uptake ($\dot{V}_O_2$) at peak exercise and a faster (lower half-time ($t_{1/2}$)) post-exercise decrease in $\dot{V}_O_2$ (panel (b)). Cardiac output was noninvasively estimated by impedance cardiography and the tests were time-aligned by total exercise duration. Unl is unloaded pedaling.

3. Ventilatory Responses

3.1. Excess Exercise Ventilation

3.1.1. Physiological Background. Adequate increases in alveolar ventilation ($\dot{V}_A$) are paramount to wash out metabolically
Figure 7: (a) Minute ventilation (\(\dot{V}_E\))/carbon dioxide output (\(\dot{V}_{CO_2}\)) relationship from the beginning of exercise to the respiratory compensation point (solid line) or up to peak exercise (dashed line) in a patient with CHF. Note that \(\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}\) (rest-PEAK) is steeper than \(\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}\) (rest-RCP) because it adds a component of hyperventilation to lactic acidosis and/or other stimuli after the respiratory compensation point. (b) \(\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}\) as a function of disease severity in pulmonary arterial hypertension (PAH). Higher values, however, are usually found in chronic thromboembolic pulmonary hypertension (CTEPH) due to pronounced increases in tidal volume ratio.
produced CO₂. Exercise $\dot{V}_E$ for a given $\dot{V}_{CO₂}$ is inversely related to the prevailing level at which $P_\text{ET}CO₂$ is regulated (the CO₂ "set-point") and the dead space ($V_D$/tidal volume ($V_T$) ratio; that is,

$$\frac{\dot{V}_E}{\dot{V}_{CO₂}} = \frac{1}{P_\text{ET}CO₂ (1-(\frac{V_D}{V_T}))}.$$  \hspace{1cm} (2)

Consequently, the largest $\dot{V}_E/\dot{V}_{CO₂}$ values will be found in those who chronically hyperventilate (low CO₂ "set-point") and have the large $V_D$ coupled with a low $V_T$ [202–206]. In the clinical literature, an increased slope of the $\dot{V}_E/\dot{V}_{CO₂}$ relationship has been termed ventilatory "inefficiency" though it could be argued that there is no "inefficiency" when increased $\dot{V}_E$ results from alveolar hyperventilation. "Excess exercise ventilation" seems therefore a more appropriate description of a greater-than-expected ventilatory response to metabolic demand [205].

3.1.3. Interpretative Issues. $\Delta\dot{V}_E/\Delta\dot{V}_{CO₂(rest-RCP)}$ in healthy young males is approximately 30 [25, 26]; however, it increases with age probably as a result of larger $V_D/V_T$ in older subjects [10, 11]. Females have lower $V_T$ for a given $\dot{V}_E$ than males independent of senescence which might explain their higher $\Delta\dot{V}_E/\Delta\dot{V}_{CO₂(rest-RCP)}$ across all age ranges (Figure 3(c)) [10, 11]. There is plenty of evidence that $\Delta\dot{V}_E/\Delta\dot{V}_{CO₂(rest-RCP)}$ is clinically useful as a prognostic marker in CHF [52, 108, 109, 163, 209–212] and, more recently, in PAH [97, 98, 213] with more discriminatory information than $\dot{V}_{O₂}$ peak. The prognostic value in CHF persisted in patients on β-blockers [99, 100]. Interestingly, $\Delta\dot{V}_E/\Delta\dot{V}_{CO₂(200-RCP)}$ has been found better than $\Delta\dot{V}_E/\Delta\dot{V}_{CO₂(200-RCP)}$ to predict 1-year cardiac mortality and hospitalization in these patients [207]. As expected, composite scores adding $\Delta\dot{V}_E/\Delta\dot{V}_{CO₂}$ to other cardiopulmonary variables improved even further their prognostic value [211]. A single study found that coexistence of COPD tends to “normalize” $\Delta\dot{V}_E/\Delta\dot{V}_{CO₂}$ in CHF patients which casts doubt on its prognostic usefulness in this specific subpopulation [214].

In patients with PAH, $\Delta\dot{V}_E/\Delta\dot{V}_{CO₂}$ and $\dot{V}_E/\dot{V}_{CO₂}$ (at rest, VT, and peak) are higher compared to CHF [215]. $\dot{V}_E/\dot{V}_{CO₂}$ by $\dot{V}_E/\dot{V}_{CO₂} > 37$ plus $P_\text{ET}CO₂VT < 30$ mmHg increased the probability of pulmonary vascular disease [III]. In those with idiopathic PAH, higher $\Delta\dot{V}_E/\Delta\dot{V}_{CO₂}$ and $\dot{V}_E/\dot{V}_{CO₂}$ (VT and nadir) were related to clinical [53] and hemodynamic impairment [104]. Importantly, these indexes improved with specific treatment [104, 105] and after pulmonary endarterectomy [106]. Although to date there is a lack of evidence that indices

![Figure 8: Exercise-induced right-to-left shunt as suggested by sudden decrease in oxyhemoglobin saturation by pulse oximetry (SpO₂) and abrupt increases in the ventilatory equivalents for CO₂ and O₂ ($\dot{V}_E/\dot{V}_{CO₂}$ and $\dot{V}_E/\dot{V}_{O₂}$) associated with a sustained decrease in the end-tidal partial pressure for CO₂ ($P_\text{ET}CO₂$) with a concomitant increase in $P_\text{ET}O₂$ in a patient with pulmonary arterial hypertension. Shunting of systemic venous blood in the arterial circulation stimulated the peripheral chemoreceptors thereby leading to this pattern of ventilatory and gas exchange responses. Unl is unloaded pedaling.](image-url)
of excess exercise ventilation in PAH hold the same prognostic importance as in CHF, Deboeck et al. recently described that \( \dot{V}_E/\dot{V}_{CO_{2}} \) (and the 6-min walking distance) were independent predictors of death [98]. Oudiz et al., however, found that \( \dot{V}_E/\dot{V}_{CO_{2}} \) was valuable to prognosis assessment only when exercise-induced right-to-left shunt (Figure 8) was absent [119]. Although \( \dot{V}_E/\dot{V}_{CO_{2}} \) is particularly disturbed in chronic thromboembolic pulmonary hypertension (CTEPH) (Figure 7(b)), thrombotic vessels occlusion increases \( V_D/V_T \) and excess exercise ventilation to levels which may not be proportionately related to hemodynamic impairment [216].

In patients with other chronic respiratory diseases, \( \Delta \dot{V}_E/\Delta \dot{V}_{CO_{2}} \) > 34 increased the risk of post-operative complications after lung resection surgery with better prediction power than \( \dot{V}_{O_2} \) peak and predicted post-operative \( \dot{V}_{O_2} \) peak [110]. It could also be empirically expected that a low \( \dot{V}_E/\dot{V}_{CO_{2}} \) would be rarely associated with increased \( V_D/V_T \) whereas the opposite would be likely at very high \( \dot{V}_E/\dot{V}_{CO_{2}} \). In fact, Roman and coworkers recently described that when \( \dot{V}_E/\dot{V}_{CO_{2}} \) was ≤ 28 and within 29–32, 96% and 83% of subjects had normal \( V_D/V_T \). On the other hand, \( V_D/V_T \) was abnormal in 87% of the cases when \( \dot{V}_E/\dot{V}_{CO_{2}} \) > 39. Unfortunately, intermediate values were not useful to discriminate the underlying mechanisms. Interestingly, 95% of the patients with an obstructive ventilatory defect (FEV1/FVC < 0.7) and \( \dot{V}_E/\dot{V}_{CO_{2}} \geq 39 \) had increased \( V_D/V_T \) [217].

3.2. End-Tidal Partial Pressure for CO2

3.2.1. Physiological Background. Expired CO2 concentration increases as air from the serial (“anatomic”) \( V_D \) is progressively enriched with \( CO_2 \) from the gas exchanging areas. Consequently, the largest partial pressures for CO2 are found at the end of tidal expiration (\( P_{ET-CO_2} \)). However, \( P_{ET-CO_2} \) is influenced not only by the metabolic rate (i.e., the rate of increase in mixed venous \( P_{CO_2} \)) but also by the deepness of the previous inspiration (i.e., VT) and the duration of the exhalation. \( P_{ET-CO_2} \) reflects poorly \( P_{A-CO_2} \), (ideal alveolar) as there are significant regional variations in alveolar \( P_{CO_2} \) (\( P_{A-CO_2} \)) and \( V_A/\dot{V}_{CO_{2}} \)-to-perfusion ratios—even in normal subjects [2, 16]. It should also be recognized that \( P_{ET-CO_2} \) becomes systematically greater than \( P_{A-CO_2} \) during incremental exercise as the first is the peak of the intrabreath oscillation of \( P_{A-CO_2} \) and \( P_{ET-CO_2} \) measured in peripheral arterial blood is an average of the oscillation over several breaths [2, 16].
Based on (2), it might be expected that if \( P_{ETCO_2} \) changed parallel to \( P_{ACO_2} \), a hyperbolic relationship between

\[ \frac{\Delta HR}{\Delta V_{O_2}} \]

and a triathlete (\( \Delta V_{O_2} = 65\) beats/L), a normal sedentary subject (\( \Delta V_{O_2} = 65\) beats/L), and a triathlete (\( \Delta V_{O_2} = 26\) beats/L).

**3.2.2. Technical Considerations.** \( P_{ETCO_2} \) increases from rest to LT (which is proportional to decrease in \( V_{E}/V_{CO_2} \)) in this time range, followed by a stable phase during the isocapnic buffering period, and then a fall after the RCP (Figures I(b) and 9(a)). As mentioned, \( P_{ETCO_2} \) underestimation by \( P_{ETCO_2} \) is roughly proportional to \( V_{D}/V_{T} \), consequently, computing \( V_{D}/V_{T} \) using \( P_{ETCO_2} \) instead of \( P_{ETCO_2} \) overestimates \( V_{D}/V_{T} \) in normal subjects and underestimates it in patients [218].

**3.2.3. Interpretative Issues.** \( P_{ETCO_2} \) differs from \( P_{ETCO_2} \) as a result of ventilation-to-perfusion inhomogeneities, right-to-left shunt, and changes in breathing pattern [2, 16]. However, arterial blood gases are not routinely measured during clinical CPET. Consequently, interpretation of a reduced \( P_{ETCO_2} \) is complex in the absence of \( P_{ETCO_2} \) measurements as it might be related to abnormal gas exchange, alveolar hyperventilation, or a tachypneic and shallow pattern of breathing. Regardless of the exact mechanism, abnormally low values at the LT have been found useful for the diagnosis of pulmonary vascular diseases in patients with unexplained dyspnea [III]. There is now established evidence that \( P_{ETCO_2} \) at rest [112–114], LT [115], and peak exercise [116] are valuable for prognosis estimation and disease severity assessment in CHF [219, 220]. Low \( P_{ETCO_2} \) values have also been found in PAH (see also later) [97, III, 117, 118]. Decreased \( P_{ETCO_2} \) at rest and during exercise seems to track the blunted cardiac output response to exercise in cardiovascular disease [219, 221]. Accordingly, exercise training after acute myocardial infarction increases both \( P_{ETCO_2} \) and cardiac output [120]. In addition to reduced cardiac output, an augmented ventilatory drive may also account for a reduction in \( P_{ETCO_2} \) whereas altered breathing pattern seems to have a minor role in CHF [204].

\( P_{ETCO_2} \) is typically lower in PAH than CHF [III, 219]. In fact, Yasunobu and co-workers suggested that observation of an unusually low \( P_{ETCO_2} \) at the LT (<30 mmHg or, in particular, <20 mmHg) in a patient with exertional dyspnea of unknown cause without evidence of acute hyperventilation (ie, normal R) should prompt the hypothesis of pulmonary vasculopathy [III]. \( P_{ETCO_2} \) response profile is also informative as failure to increase below the LT or progressive decreases from the start of exercise are associated with worsening clinical and hemodynamic impairment (Figures 9(b) to 9(e)) [111] and are rarely found in CHF [112–116]. Based on (2), it might be expected that if \( P_{ETCO_2} \) changed parallel to \( P_{ETCO_2} \), a hyperbolic relationship between
3.3. Exertional Oscillatory Ventilation (EOV)

3.3.1. Physiological Background. An abnormal pattern of ventilation consisting of cyclic hyperpnea and hypopnea without interposed apneas can be detected by CPET in some patients with advanced CHF. The EOV might occur throughout the test, but the oscillations frequently dampen as exercise progresses [121, 222–224]. The pathophysiological mechanisms are multifactorial including low cardiac output leading to a prolonged time of pulmonary venous blood to reach the central or peripheral chemoreceptors, low lung volume, pulmonary congestion, augmented chemoreceptor sensitivity, and the narrow difference between the eupneic $P_{ET}CO_2$ and the apneic (or hypoventilatory) threshold [27, 122, 123, 225–235].

![Fig 12: Change in Δ heart rate (HR)/Δ oxygen uptake (̇$VO_2$) (arrow) slope (arrow) during incremental CPET in a patient with severe cardiovascular limitation to exercise (panel (a)). Note that this led to a plateau in O₂ pulse (̇$VO_2$/HR ratio) as the y-intercept becomes zero; that is, the relationship passes through its origin (panel (b)). Unl is unloaded pedaling.](image)

$V_E/VCO_2$ and $P_{ET}CO_2$ at the LT would result. As this was observed by Yasunobu et al. [111] and confirmed by others [104, 216], it seems that alveolar hyperventilation is an important contributing mechanism to the excess exercise ventilation in PAH. Moreover, sharp decreases in $P_{ET}CO_2$ may indicate exercise-induced intracardiac shunt, a finding with ominous consequences (Figures (8) and 9(f)) [119]. Additionally, an abnormal increase in $P_{ET}CO_2$ during early recovery has been described in PAH (Figure 9(c)), even in mildly-impaired patients [111].

3.3.2. Technical Considerations. Different criteria for EOV might help explaining why its prevalence has been found to vary from 12% to 50% in CHF [123, 124, 236–238]. A widely used definition is as follows (Figure 10): (1) three or more regular oscillations (i.e., clearly discernible from inherent data noise); (2) standard deviation of three consecutive cycle lengths (time between 2 consecutive nadirs) within 20% of the average; (3) minimal average amplitude of $V_E$ oscillation of 5 L/min (peak value minus the average of two in-between consecutive nadirs) [27]. Alternative definitions require: (i) criteria for persistence of the EOV pattern (three or more consecutive cyclic oscillations) for at least 60% of exercise at an amplitude $\geq 15\%$ of the average resting value [122, 239–241] or (ii) 3 or more consecutive cyclic fluctuations with amplitude exceeding 30% of mean $V_E$ and oscillatory cycle within 40 to 140 s in 3 or more gas exchange/ventilatory variables [124].

3.3.3. Clinical Usefulness. There is now well-established evidence that EOV holds important negative prognostic implications in patients with CHF [27, 124, 222, 236, 239], being related to worsening clinical status [121, 122, 124], severe hemodynamic dysfunction [123], and reduced functional capacity [125, 126]. Unfortunately, EOV may preclude an adequate identification of the LT by either the $V$-slope or the ventilatory equivalent methods [242]. EOV is highly reproducible regardless of the CHF aetiology [121]. Interestingly, several interventions including inotropics [237], exercise and inspiratory muscle training [243–245], and transplantation [237] lessened of even abolished EOV. Future larger trials should establish whether EOV might add independent information to commonly used outcomes for interventional studies in CHF.

4. Cardiovascular Responses

4.1. $\Delta$ Heart Rate (HR)/$\Delta$ Oxygen Uptake (̇$VO_2$)

4.1.1. Physiological Background. Increases in HR with progressive exercise are initially mediated by parasympathetic tonus withdrawal and, subsequently, by increased sympathetic activity [246]. There is an effectively linear increase in
HR as a function of $\dot{V}_O_2$ during ramp-incremental exercise [3, 24, 25] though departs from linearity might occur at higher exercise intensities (Figure 2(b)) [247]. According to the Fick principle, reduced stroke volume (SV) and/or diminished C(a–v)$O_2$ would lead to a steeper $\Delta$HR/$\Delta\dot{V}_O_2$ slope. Consequently, cardiac dysfunction, decreased arterial $O_2$ content (anemia and hypoxemia), and impaired muscle aerobic capacity (e.g., deconditioning, mitochondrial dysfunction) can potentially increase $\Delta$HR/$\Delta\dot{V}_O_2$. On the other hand, training has a flattening effect on $\Delta$HR/$\Delta\dot{V}_O_2$ (Figure 11).

4.1.2. Technical Considerations. Although $\dot{V}_O_2$ is the appropriate dependent variable, this relationship has been traditionally described with HR on the $y$-axis [3, 24, 25]. Linearity of the HR response throughout the test duration should be firstly established. In event of late departures from linearity,
4.2. Heart Rate Recovery (HRR)

4.2.1. Physiological Background. At the start of exercise, HR increases as a result of early parasympathetic withdrawal and subsequent sympathetic activation [246]. After effort cessation, vagal reactivation (with opposition of the sympathetic drive) is primarily responsible for the return to baseline conditions [251], especially during the first 30 seconds of recovery [252]. Consequently, autonomic imbalance (increased sympathoexcitatory stimuli and/or impaired parasympathetic activity) might slow post-exercise HR decay.

4.2.2. Technical Considerations. HRR is the difference between peak HR and HR at selected time points after exercise (e.g., 30 sec and every minute thereafter). HRR analysis may be performed independent of the mode of exercise (treadmill [134, 135, 140, 152, 253], cycle ergometer [28, 254–256], or field tests [257]), and a cool-down period at the end of maximal effort seems not to interfere with its prognostic value [28, 134, 150].

4.2.3. Interpretative Issues. HRR has been found a simple and inexpensive prognostic marker in healthy populations [134], CHF [135], CAD [151, 258], PAH [28] (Figure 14), diabetes mellitus [136], and COPD [137]. Abnormal HRR has also been demonstrated in other systemic disorders such as metabolic syndrome [138], obstructive sleep apnea [139], sarcoidosis [140], rheumatological diseases [141, 142], polycystic ovary syndrome [143], polycystic kidney disease [144], and HIV infection [145]. Of note, it has been useful for risk stratification in CHF patients with mildly reduced peak VO2 [259]. HRR seems to be responsive to exercise training in some disorders [146–149], probably due to effects of exercise on autonomic regulation [260, 261]. Interestingly, these modifications were related to increased survival after rehabilitation in patients with previous myocardial infarction [262, 263].

5. Conclusions

Interpretation of incremental CPET is best performed by a judicious analysis of all available physiological information provided by the procedure (and by previous testing) taking into consideration the underlying clinical question(s).
Table I: Clinical usefulness and suggested cutoffs of selected dynamic responses to rapidly incremental CPET.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical usefulness</th>
<th>Cutoffs/patterns of abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated lactate threshold (LT)</td>
<td>(i) Prognosis in CHF [52] (ii) Marker of disease severity in PAH [53] (iii) Risk predictor of postoperative complications in the elderly [50, 51] (iv) Guide exercise training intensity [72, 73] (v) Responsive to rehabilitation in less impaired patients with chronic cardiopulmonary diseases [54, 70]</td>
<td>(i) ( \dot{V}<em>L ) LT &lt; 40% predicted ( \dot{V}</em>{O_2} ) peak [2] (ii) Influenced by age, gender, and fitness [4, 7, 42, 76]</td>
</tr>
<tr>
<td>( \Delta \dot{V}_{O_2} / \Delta \text{work rate} ) (mL/min/W)</td>
<td>(i) Indicative of impaired ( O_2 ) delivery and/or utilization [77–81] (ii) Adjunct for the diagnosis of myocardial ischemia [82–88]</td>
<td>(i) (&lt; ) lower limit of normality (&lt;8.5 mL/min/W) [4, 8] (ii) Decrease in slope (or plateau) as exercise progresses [77–81]</td>
</tr>
<tr>
<td>( \dot{V}_{O_2} ) efficiency slope (OUES)</td>
<td>(i) Functional impairment and prognosis in CHF [18, 89–94] (ii) Response to interventions in CHF [95] (iii) More sensitive to training than the ( \Delta \dot{V}<em>E / \Delta \dot{V}</em>{CO_2} ) slope in CHF [96]</td>
<td>Mortality in CHF &lt;1.05 L/min/log (L/min) or &lt;65% predicted [89]</td>
</tr>
<tr>
<td>( \dot{V}_{O_2} ) efficiency plateau (OUEP)</td>
<td>Functional impairment and prognosis in CHF [89]</td>
<td>Mortality in CHF &lt;25 mL/L or &lt;65% predicted [89]</td>
</tr>
<tr>
<td>Excess exercise ventilation</td>
<td>(i) Prognosis in PAH [97, 98] and CHF, even under ( \beta )-blocker therapy (CHF) [99, 100] (ii) Responsive to therapy in CHF [101–103], PAH [104, 105], and CTEPH [106] (iii) Responsive to exercise training [107]</td>
<td>&lt;age—and gender-specific lower limits of normality [10, 11] Mortality in CHF ( \Delta \dot{V}<em>E / \Delta \dot{V}</em>{CO_2,\text{rest-RCP}} ) ( \geq ) 34 [108] ( \Delta \dot{V}<em>E / \Delta \dot{V}</em>{CO_2,\text{rest-PEAK}} ) ( \geq ) 45 [109] Mortality in PAH ( \dot{V}<em>E / \dot{V}</em>{CO_2,\text{nadir}} ) ( \geq ) 52 [97] ( \dot{V}<em>E / \dot{V}</em>{CO_2,\text{LT}} \geq 54 ) [98] ( \Delta \dot{V}<em>E / \Delta \dot{V}</em>{CO_2,\text{rest-RCP}} ) ( \geq ) 62 [98] ( \Delta \dot{V}<em>E / \Delta \dot{V}</em>{CO_2,\text{rest-PEAK}} ) ( \geq ) 48 [97] Postoperative complications of lung resection ( \Delta \dot{V}<em>E / \Delta \dot{V}</em>{CO_2,\text{rest-RCP}} ) ( \geq ) 34 [110]</td>
</tr>
<tr>
<td>End-tidal partial pressure for ( CO_2 ) ( (P_{ET,CO_2}) )</td>
<td>(i) Adjunct for the diagnosis of PVD [111] (ii) Prognosis in CHF [112–116] (iii) Marker of disease severity in PAH [97, 111, 117, 118] (iv) Diagnosis of a patent foramen ovale in PAH [119] (v) Responsive to drug therapy in PAH [105] and CHF [101] (vi) Responsive to exercise training [120]</td>
<td>Diagnosis of PVD [111] &quot;likely&quot; ( \approx ) ≤ 30 mmHg at the LT &quot;very likely&quot; ( \approx ) ≤ 20 mmHg at the LT progressive reductions as exercise increases sudden increase with exercise cessation Mortality in CHF ( \leq 33 ) mmHg at rest [112, 114] ( \leq 36 ) mmHg at the LT [115] ( &lt; 31 ) mmHg at peak [116]</td>
</tr>
<tr>
<td>Exertional oscillatory ventilation</td>
<td>(i) Indicative of worsening clinical status, severe hemodynamic dysfunction, and reduced functional capacity in CHF [121–126] (ii) Responsive to interventions in CHF [101]</td>
<td>Three or more regular ( V_e ) oscillations (standard deviation of three consecutive cycle lengths within 20% of their average), with minimal average amplitude of ventilatory oscillation of 5 L/min [27]</td>
</tr>
<tr>
<td>( \Delta \text{Heart rate} / \Delta \dot{V}_{O_2} ) (beat/L)</td>
<td>(i) Indicative of abnormal cardiovascular response to exercise [127–130] (ii) Adjunct for the diagnosis of myocardial ischemia [88, 131–133]</td>
<td>&lt;age—and gender-specific lower limits of normality [9, 10] Changes in linearity with increases in steepness [88, 132, 133]</td>
</tr>
</tbody>
</table>
Table 1: Continued.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical usefulness</th>
<th>Cutoffs/patterns of abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate recovery (HRR) (beats/min)</td>
<td>(i) Prognosis in asymptomatic subjects referred for exercise testing [134], CHF [135], PAH [28], Type 2 diabetes [136], and COPD [137]</td>
<td>Mortality in patients referred for exercise testing</td>
</tr>
<tr>
<td></td>
<td>(ii) Disease severity in metabolic syndrome [138], obstructive sleep apnea [139], sarcoidosis [140], rheumatological diseases [141, 142], polycystic ovary syndrome [143], polycystic kidney disease [144], and HIV infection [145]</td>
<td>Treadmill, cooldown: ( HRR_{1\text{min}} \leq 12 ) [134, 150, 151]</td>
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<tr>
<td></td>
<td>(iii) Responsive to aerobic training in CHF, COPD, obstructive sleep apnea, and systemic lupus erythematosus [146–149]</td>
<td>Treadmill, no cooldown: ( HRR_{1\text{min}} \leq 18 ) [135] ( HRR_{2\text{min}} \leq 22 ) [152]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treadmill, no cooldown: ( HRR_{1\text{min}} \leq 42 ) [153]</td>
</tr>
</tbody>
</table>

Mortality in CHF
Treadmill, cooldown: \( HRR_{1\text{min}} < 6.5 \) [154]
Treadmill, no cooldown: \( HRR_{1\text{min}} \leq 12 \) [155]
Bike, cooldown: \( HRR_{1\text{min}} < 17 \) [156]
Mortality in PAH
Bike, cooldown: \( HRR_{1\text{min}} \leq 18 \) [28]
Mortality in COPD
Bike, cooldown: \( HRR_{1\text{min}} \leq 14 \) [137]
Mortality in Type 2 diabetes
Treadmill, cooldown: \( HRR_{1\text{min}} < 12 \) \( HRR_{2\text{min}} < 28 \) [136]

\( \dot{V}_{O_2} \): oxygen uptake; \( \dot{V}_{CO_2} \): carbon dioxide output; \( V_E \): minute ventilation; COPD: chronic obstructive pulmonary disease; CHF: chronic heart failure; PAH: pulmonary arterial hypertension; PVD: pulmonary vascular disease; RCP: respiratory compensation point.

Although a considerable lack of information on the individual diagnostic and prognostic value of the dynamic submaximal relationships still persists, the bulk of evidence is reassuring in relation to their practical usefulness. Large-scale, multicentric studies, however, are urgently needed to validate the suggested cutoffs of abnormality (Table 1) in different clinical scenarios and disease populations.

**Abbreviations**

- **CAD**: Coronary artery disease
- **CHF**: Chronic heart failure
- **COPD**: Chronic obstructive pulmonary disease
- **CPET**: Cardiopulmonary exercise testing
- **CTEPH**: Chronic thromboembolic pulmonary hypertension
- **EOV**: Exertional oscillatory ventilation
- **FEV₁**: Forced expiratory volume in one second
- **FVC**: Forced vital capacity
- **GET**: Gas exchange threshold
- **HR**: Heart rate
- **HRR**: Heart rate recovery
- **LA**: Lactic acid
- **LT**: Lactate threshold
- **OUES**: Oxygen uptake efficiency slope
- **OUEP**: Oxygen uptake efficiency plateau
- **PAH**: Pulmonary arterial hypertension
- **P_a**: Arterial partial pressure
- **P_A**: Alveolar pressure
- **P_{ET}**: End-tidal partial pressure
- **PVD**: Pulmonary vascular disease
- **R**: Respiratory exchange ratio
- **RCP**: Respiratory compensation point
- **SpO₂**: Pulse oxygen saturation
- **Unl**: Unloaded pedaling
- **\( \dot{V}_{CO_2} \)**: Carbon dioxide output
- **\( V_D/V_T \)**: Dead space to tidal volume ratio
- **\( V_A \)**: Alveolar ventilation
- **\( V_E \)**: Minute ventilation
References


