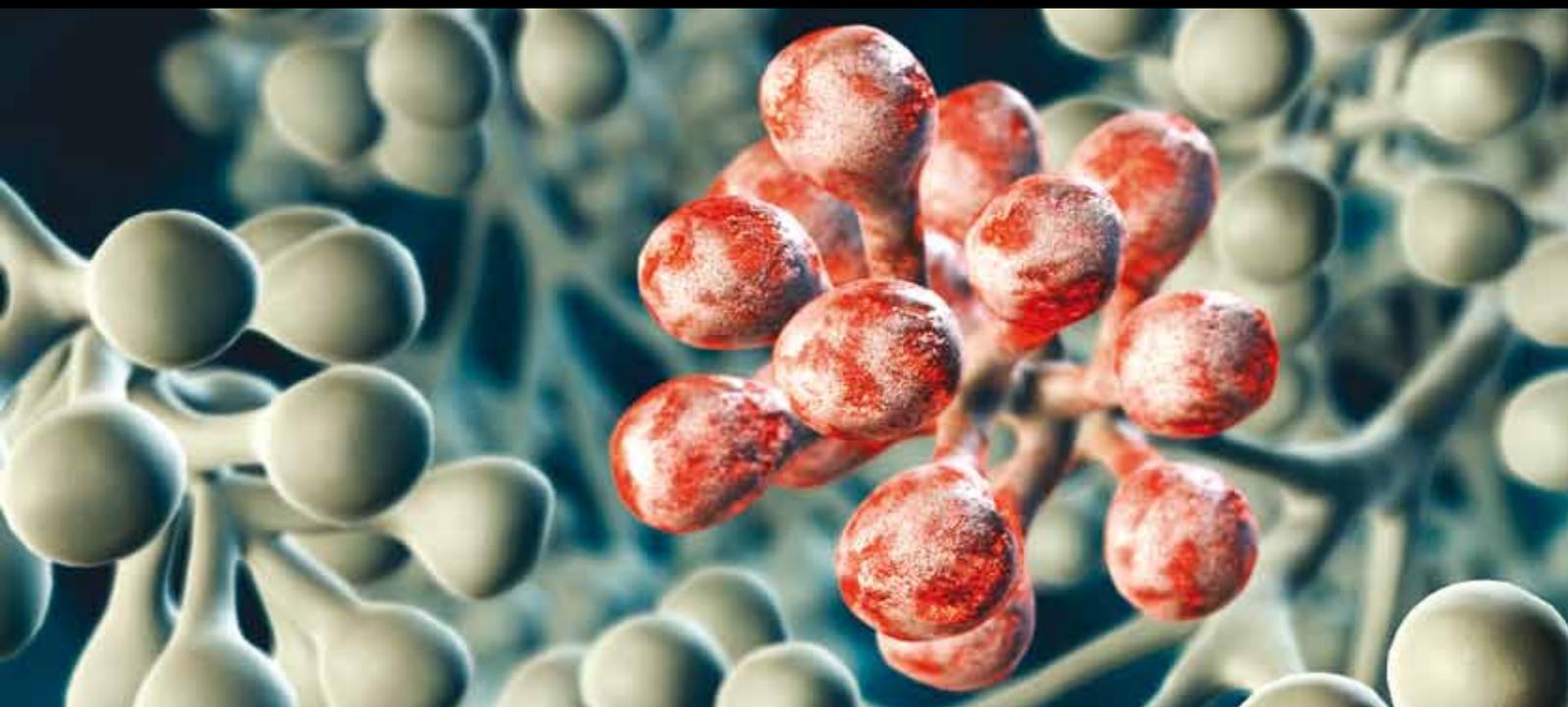


CARDIOPULMONARY EXERCISE TESTING

GUEST EDITORS: DARCY D. MARCINIUK, BRUCE D. JOHNSON,
J. ALBERTO NEDER, AND DENIS E. O'DONNELL





Cardiopulmonary Exercise Testing

Pulmonary Medicine

Cardiopulmonary Exercise Testing

Guest Editors: Darcy D. Marciniuk, Bruce D. Johnson,
J. Alberto Neder, and Denis E. O'Donnell



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Editorial

Cardiopulmonary Exercise Testing

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Cardiopulmonary exercise testing (CPET) allows the clinician to objectively evaluate symptoms and important functions. CPET also arms the investigator with a powerful tool to better understand the respiratory system role as an engaged participant of a fully integrated physiologic system in humans. The insights gained mean that CPET can aid in the assessment of activity limitation and dyspnea, in evaluating disability and disease severity, in judging risk and prognosis, and in considering the suitability for specific interventions such as transplantation. In the research laboratory, CPET can contribute to the complete evaluation of new therapeutic or management agents, provide physiologic understanding for various hypotheses and new-found research results, and aid in discovery to further our understanding of the complex behaviour and interaction of the human respiratory system. While these benefits are well known to those working closely in the field, the need for greater and more effective dissemination of these benefits is required. Hence, this special issue focuses on cardiopulmonary exercise testing.

We begin with M. K. Stickland et al. reviewing normal exercise physiology, as well as providing guidelines for the understanding of cardiopulmonary exercise test results. Techniques to ensure valid measurements of inspiratory capacity permitting a learned assessment of ventilatory constraint are outlined by J. A. Guenette and colleagues, while R. Ramos and others review the clinical usefulness of rapid incremental testing protocols. J. C. da Silva et al. examine the best criteria to determine ramp exercise testing speed in their original research study. Meanwhile, I. Vogiatzis and

colleagues undertake a detailed review of varied mechanisms contributing to activity limitation in chronic lung diseases. B. Borel et al. explore the responsiveness of different exercise testing protocols to therapeutic interventions in COPD. A. Apostolo et al. review the interaction and consequences for the lungs in the setting of chronic heart failure, while C. H. Kim and colleagues report original research assessing the validity of a new multivariate index for grading gas exchange severity in patients with pulmonary arterial hypertension and with heart failure. Finally, D. E. O'Donnell et al. review the respiratory consequences of obesity and its impact on exercise performance in both health and in COPD.

We hope you find these articles both interesting and useful. We are confident that they will become meaningful resources in this field.

Acknowledgments

We would like to genuinely thank the authors for sharing their expertise, their patience with the review process, and for their willingness to contribute to this special issue. Finally, we would also like to extend appreciation to the publishers for this opportunity to contribute to our understanding of cardiopulmonary exercise testing.

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Review Article

Clinical Usefulness of Response Profiles to Rapidly Incremental Cardiopulmonary Exercise Testing

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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

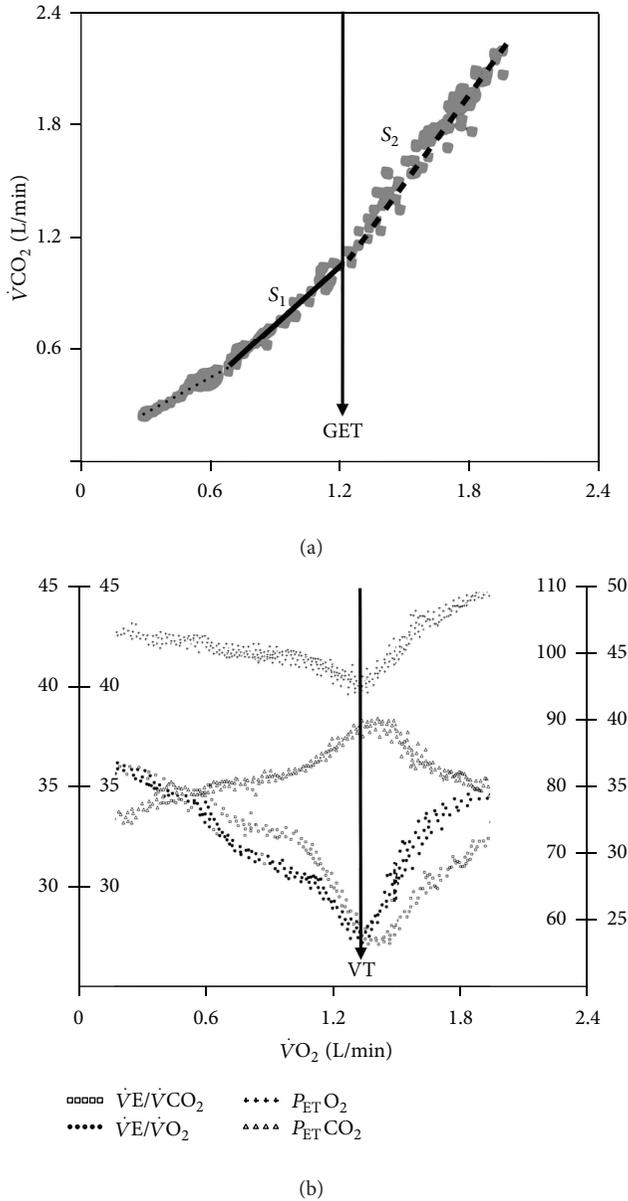


FIGURE 1: Noninvasive estimation of the lactate threshold by the V -slope method (gas exchange threshold (GET), panel (a)) and the ventilatory method (ventilatory threshold (VT), panel (b)) in a normal subject. Note that the GET slightly precedes the VT as the later depends on the ventilatory response to the “extra- CO_2 ” generated by buffering of H^+ associated with (lactate) increase. S_1 and S_2 refer to the two sequential slopes (before and after the GET) with S_2 being characteristically steeper than S_1 (i.e., slope inclination >1 .)

should be observed to improve responses’ reproducibility and reliability. The response profiles to be discussed, however, are applicable to ramp-incremental [4] cycle ergometry, and the practitioner should be aware that different patterns of response can be anticipated if other ergometers (e.g., treadmill) and protocols (e.g., step-like) are used.

2. Metabolic Responses

2.1. Estimated Lactate Threshold

2.1.1. Physiological Background. The rate at which arterial lactate anions $[Lac^-]_a$ and the associated proton (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 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 Lac^- and H^+ in the physiological pH; that is, it is a strong acid. Plasma bicarbonate (HCO_3^-) is the main buffer of lactic acidosis leading to the formation of carbonic acid (H_2CO_3) which in turn dissociates into carbon dioxide (CO_2) and water; that is,



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 $[HCO_3^-]$) [31] derived from buffering of Lac^- -associated protons will not only accelerate CO_2 output (\dot{V}_{CO_2}) relative to O_2 uptake (\dot{V}_{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 HCO_3^- , \dot{V}_{CO_2} increases (1) out of proportion of \dot{V}_{O_2} , and a plot between these variables will show a discernible breakpoint; that is, the \dot{V}_{CO_2} - \dot{V}_{O_2} relationship evidences an increased slope at the point of $[Lac^-]_a$ 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{V}_{CO_2} will drive \dot{V}_E in its direct proportion leading the latter to increase faster than \dot{V}_{O_2} . The consequent increase in \dot{V}_E/\dot{V}_{O_2} (and the end-tidal partial pressure for O_2 , $P_{ET}O_2$) with a stable \dot{V}_E/\dot{V}_{CO_2} (and $P_{ET}CO_2$) 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{V}_{CO_2} and $P_{ET}CO_2$ remain stable for a variable period of time during the “isocapnic buffering”. However, as more H^+ is released with further increases in work rate, \dot{V}_E eventually increases out of proportion to \dot{V}_{CO_2} at the respiratory compensation point (RCP) thereby leading to alveolar hyperventilation and progressive reductions in $P_{ET}CO_2$ 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 \dot{V}_{O_2} and \dot{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 ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) values (i.e., > 1 from tabular data) as indicative of the LT might lead to erroneous estimations;
- (4) \dot{V}_{O_2} at any particular WR during a ramp-incremental test is lower than the steady-state \dot{V}_{O_2} value at that same WR due to a variable \dot{V}_{O_2} kinetics delay. As a result, the WR corresponding to \dot{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 \dot{V}_{O_2} LT, the selected WR should lead the WR-LT by this timeframe;
- (5) a given change in \dot{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 O_2 stores [39]. As the body capacitance for CO_2 increases during the early phase of the ramp, repletion of the CO_2 stores slows \dot{V}_{CO_2} relative to \dot{V}_{O_2} ; that is, \dot{V}_{CO_2} - \dot{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 \dot{V}_{CO_2} relative to \dot{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* \dot{V}_{O_2} peak not to the *attained* \dot{V}_{O_2} peak, especially in patient populations where the latter procedure might create a false concept of preserved (or even increased) \dot{V}_{O_2} LT; and
- (7) \dot{V}_{O_2} peak declines with senescence at a steeper rate than \dot{V}_{O_2} LT; that is, \dot{V}_{O_2} LT (% \dot{V}_{O_2} peak) *increases* as a function of age in both genders [41–43].

2.1.3. Clinical Usefulness. The physiologic changes associated with $[Lac^-]_a$ and H^+ accumulation (e.g., metabolic acidosis, impaired muscle contraction, hyperventilation, and altered \dot{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 \dot{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-operative 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 interventions 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 \dot{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 \dot{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 \dot{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 (\dot{V}_{O_2})/ Δ Work Rate (WR)

2.2.1. Physiological Background. From a relatively constant value of 500 mL/min at unloaded pedaling, \dot{V}_{O_2} increases linearly as exercise progresses during a rapidly-incremental exercise test [4]. The slope of the $\Delta\dot{V}_{O_2}/\Delta WR$ relationship, therefore, is an index of the overall gain of the \dot{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 $\Delta\dot{V}_{O_2}/\Delta WR$ slope, any delay in \dot{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 $\Delta\dot{V}_{O_2}/\Delta WR$ at the LT. If this is discernible, the slope should be calculated over the sub-LT range.

2.2.3. Interpretative Issues. $\Delta\dot{V}_{O_2}/\Delta WR$ is not significantly influenced by the training status, ageing, or gender (Figure 3(a)) [2, 10, 12–14]. A shallow $\Delta\dot{V}_{O_2}/\Delta WR$ 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].

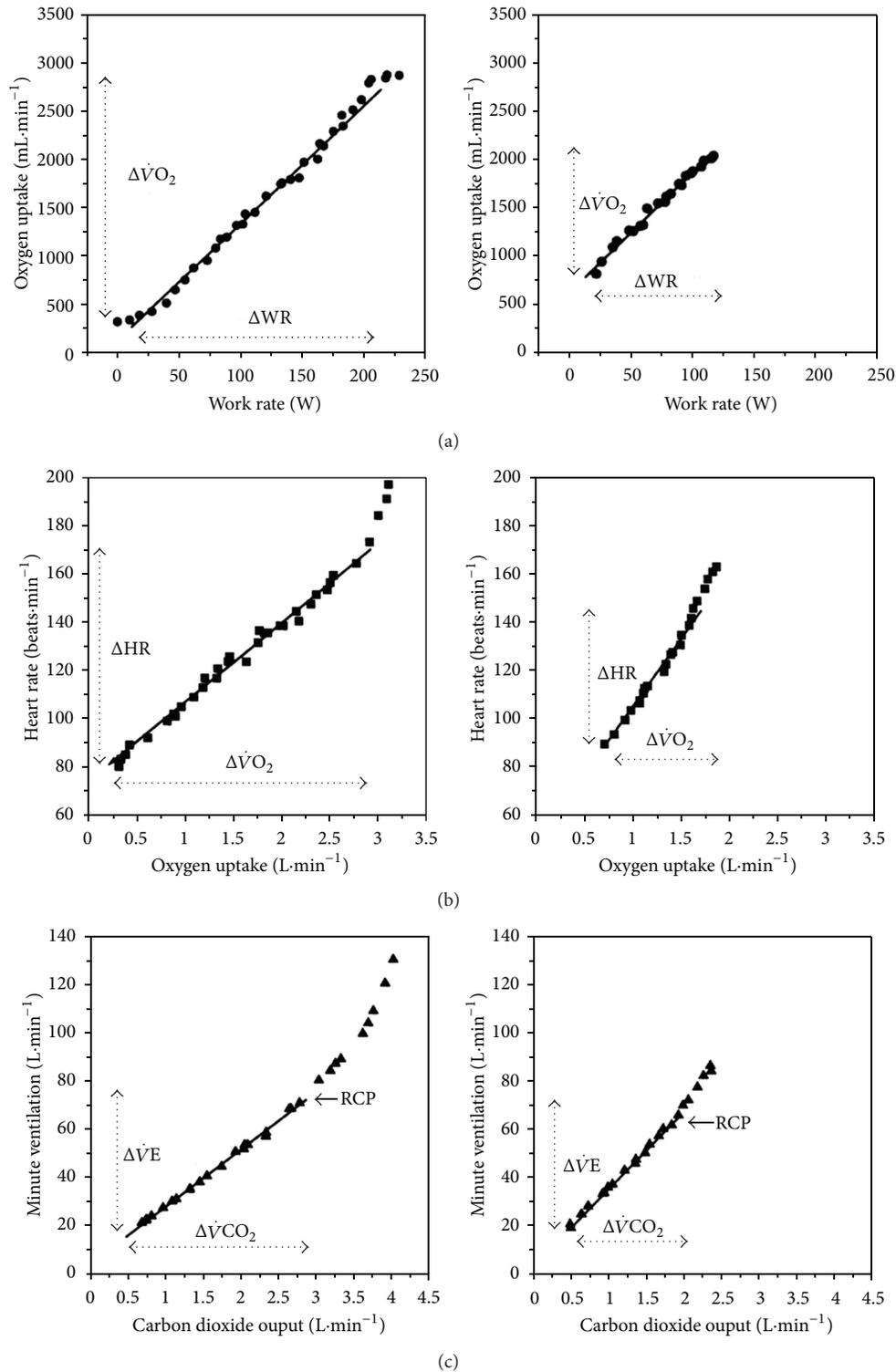


FIGURE 2: Procedures to establish 3 dynamic submaximal relationships by simple linear regression during incremental CPET in young (24-yr-old, left panels) and old (70-yr-old, right panels) subjects. (a) Δ oxygen uptake ($\dot{V}O_2$)/ Δ work rate (WR); (b) Δ heart rate/ $\Delta\dot{V}O_2$ (c) Δ minute ventilation ($\dot{V}E$)/ Δ carbon dioxide output ($\dot{V}CO_2$). The arrows show the range of values considered for analysis. RCP is the respiratory compensation point. (Modified with permission from [10].)

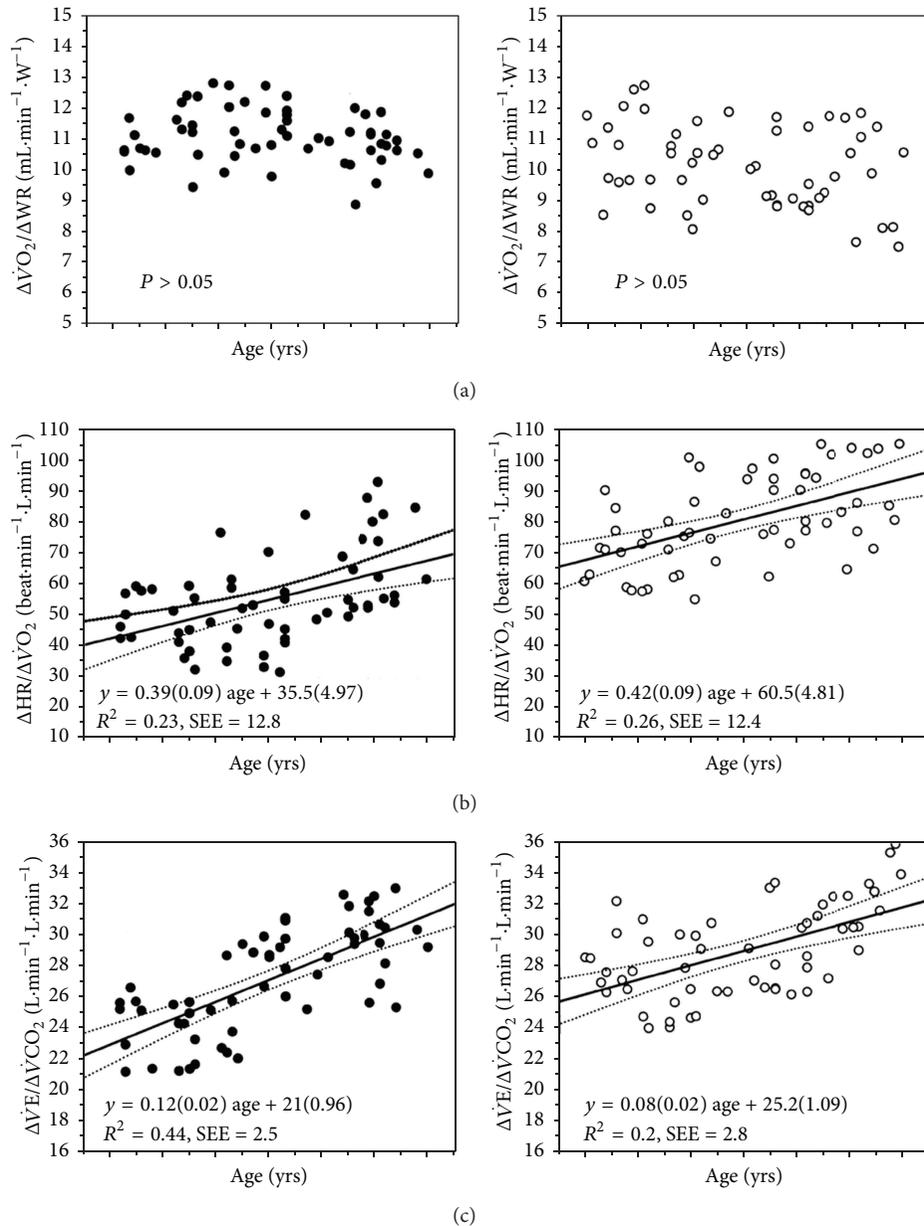


FIGURE 3: The submaximal relationships depicted in Figure 2 as a function of age in males (left panels) and females (right panels). Regression lines are shown with their respective 95% confidence intervals for those relationships in which the variables were influenced by age. Regression coefficients and intercepts of the linear prediction equations are depicted with their respective standard error of the estimate (SEE). (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

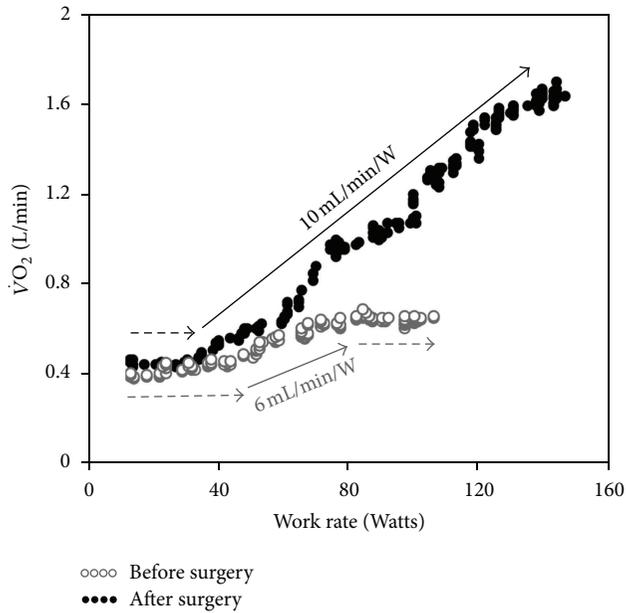


FIGURE 4: Oxygen uptake (\dot{V}_{O_2})/work rate (WR) relationship during ramp-incremental CPET before and after pulmonary endarterectomy in a 21-year-old male with thromboembolic occlusion of the left pulmonary artery. Note that after the surgery, peak \dot{V}_{O_2} increased not only due to a higher peak WR but also owing to a large improvement in $\Delta\dot{V}_{O_2}/\Delta WR$.

et al. [89, 169] expressed the OUE as a ratio (\dot{V}_{O_2}/\dot{V}_E 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 \dot{V}_{O_2}/\dot{V}_E 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.

2.3.3. Interpretative Issues. It is well established that exercise hyperpnea is under stronger influence of P_aCO_2 and pH_a (rather than P_aO_2) [170]. As detailed later (Section 3.1), changes in CO_2 set-point and ventilatory “efficiency” control the rate of CO_2 clearance. This brings substantial uncertainty on the exact physiological meaning of a disturbed relationship between \dot{V}_E and \dot{V}_{O_2} . Nevertheless, the literature pertaining to the clinical usefulness of OUES is rather vast in CHF [90, 164, 165, 167, 171, 172], and interest in this

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 $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ 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 \dot{V}_{O_2} peak and VT [180]. Interestingly, OUES showed to be more sensitive to the effects of training than $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ 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].

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

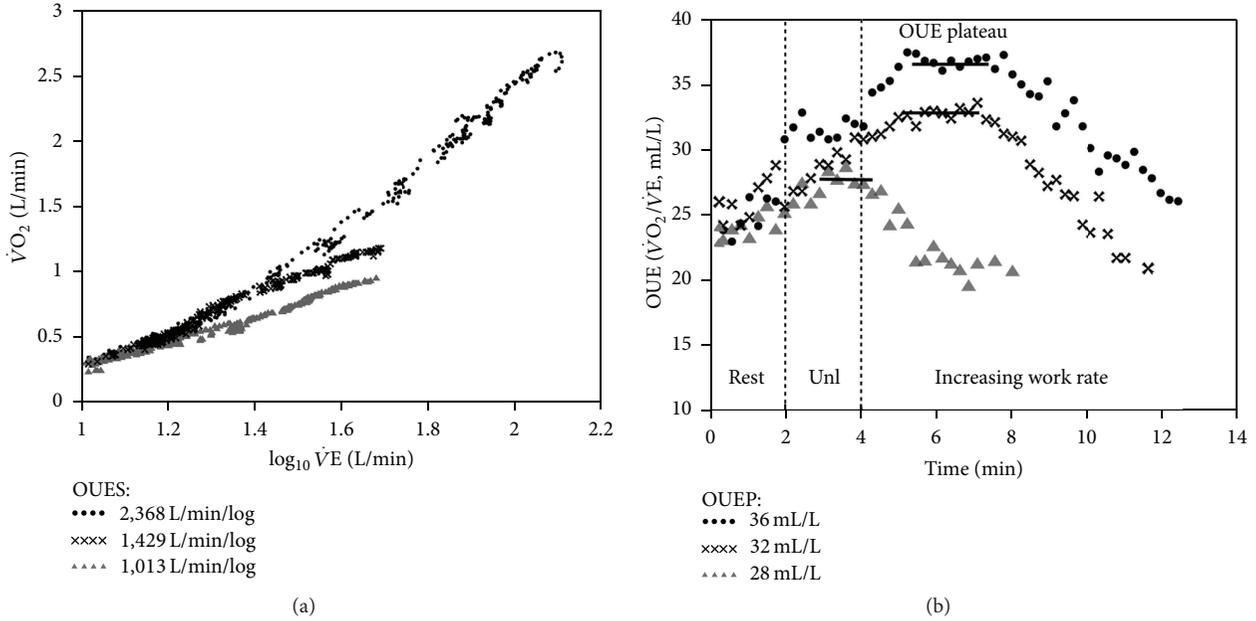


FIGURE 5: Relationship between oxygen uptake (\dot{V}_{O_2}) and minute ventilation (\dot{V}_E) during incremental exercise in a healthy subject (●●●) and patients with mild (××××) and severe (▲▲▲▲) CHF. (a) The slope of \dot{V}_{O_2} upon $\log_{10} \dot{V}_E$ is the oxygen uptake efficiency slope (OUES) 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.

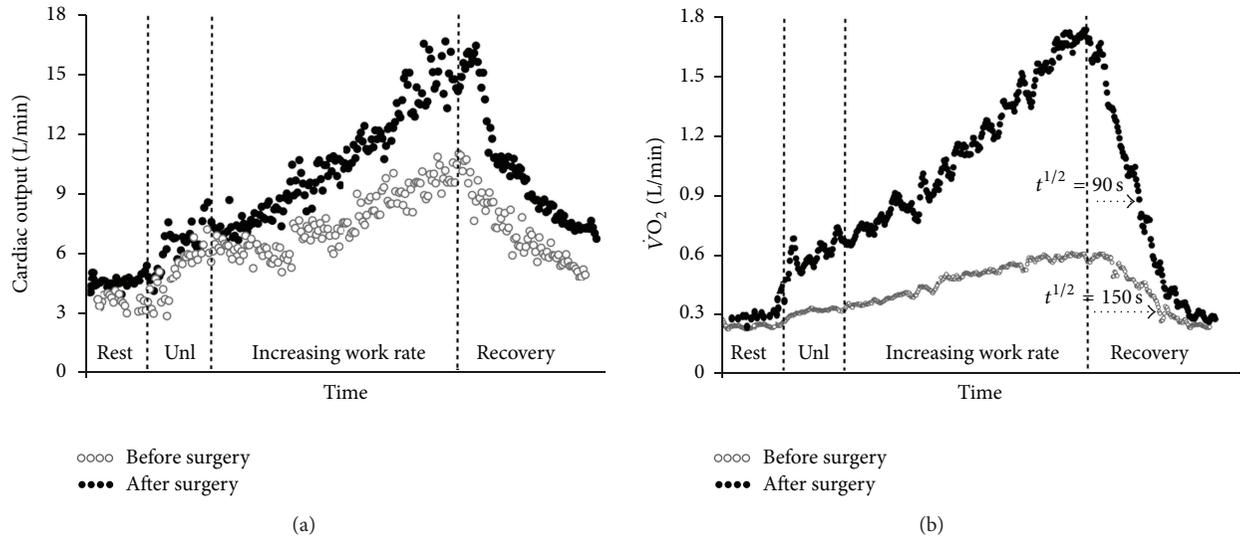


FIGURE 6: Incremental cycle ergometer exercise tests in the same patient of Figure 4 with chronic thromboembolic pulmonary hypertension. After pulmonary endarterectomy (closed symbols), haemodynamic improvement (panel (a)) led to a higher oxygen uptake (\dot{V}_{O_2}) at peak exercise and a faster (lower 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.

sleep apnea [139]. Impairment in cardiovascular responses to exercise as indicated by a delayed recovery of cardiac output was closely associated with slower off-exercise \dot{V}_{O_2} kinetics in CHF [200]. Improvements in O_2 delivery might be expected to speed the rate of O_2 recovery in cardiovascular diseases (Figure 6) [201].

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

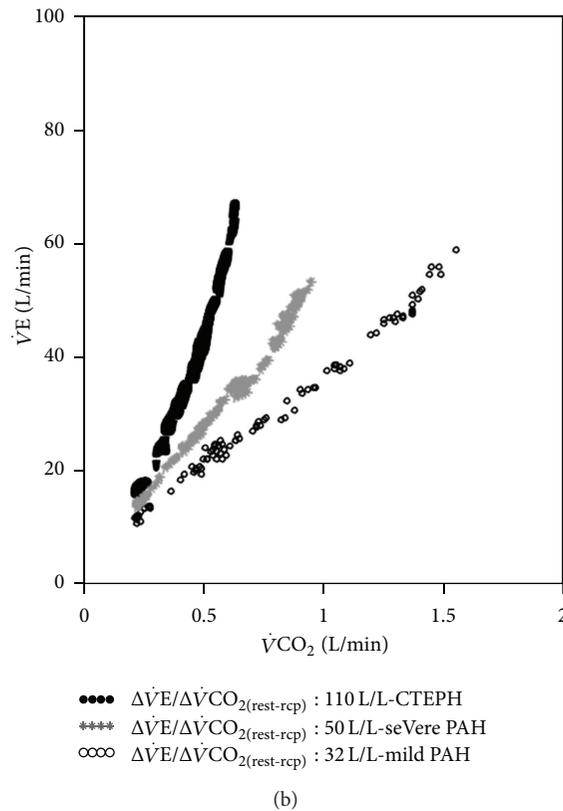
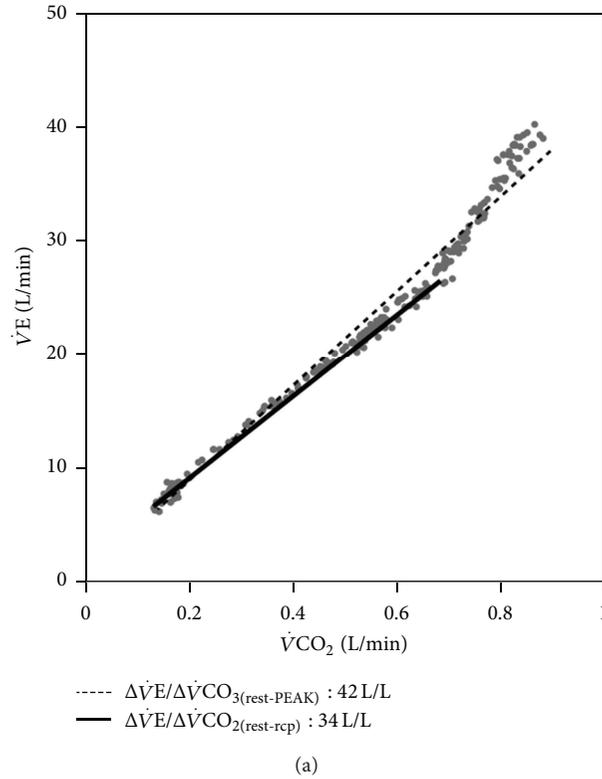


FIGURE 7: (a) Minute ventilation (\dot{V}_E)/carbon dioxide output (\dot{V}_{CO_2}) relationship from the beginning of exercise to the respiratory compensation point (solid line) or up to peak exercise (dashed line) in a patient with CHF. Note that $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-PEAK})}$ is steeper than $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ 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.

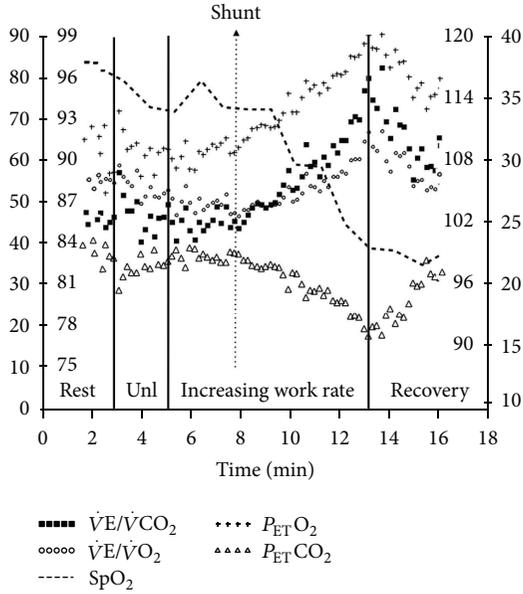


FIGURE 8: Exercise-induced right-to-left shunt as suggested by sudden decrease in oxyhemoglobin saturation by pulse oximetry (SpO_2) and abrupt increases in the ventilatory equivalents for CO_2 and O_2 (\dot{V}_E/\dot{V}_{CO_2} and \dot{V}_E/\dot{V}_{O_2}) associated with a sustained decrease in the end-tidal partial pressure for CO_2 ($P_{ET}CO_2$) with a concomitant increase in $P_{ET}O_2$ 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.

produced CO_2 . Exercise \dot{V}_E for a given \dot{V}_{CO_2} is inversely related to the prevailing level at which P_aCO_2 is regulated (the CO_2 “set-point”) and the dead space (V_D)/tidal volume (V_T) ratio; that is,

$$\frac{\dot{V}_E}{\dot{V}_{CO_2}} = \frac{1}{P_aCO_2 (1 - (V_D/V_T))}. \quad (2)$$

Consequently, the largest \dot{V}_E/\dot{V}_{CO_2} values will be found in those who chronically hyperventilate (low CO_2 “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}_{CO_2} 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 appropriated description of a greater-than-expected ventilatory response to metabolic demand [205].

3.1.2. Technical Considerations. There are a number of alternatives to express the \dot{V}_E - \dot{V}_{CO_2} relationship during progressive exercise: (1) as a ratio (\dot{V}_E/\dot{V}_{CO_2}) at peak exercise, at the VT (Figure 1(b)), and as the lowest (nadir) value and (2) as a slope of \dot{V}_E versus \dot{V}_{CO_2} from the beginning of exercise to the RCP ($\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$) (Figure 2(c)) or, alternatively, up to peak exercise ($\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-PEAK})}$) (Figure 7) [25, 26, 207].

Sun et al. reported that the $\dot{V}_E/\dot{V}_{CO_2(\text{nadir})}$ had the least variability with the advantage that choosing the lowest value does not require VT identification [26]. However, \dot{V}_E/\dot{V}_{CO_2} might not decline at all during early exercise in some patients with severe cardiopulmonary disease (Figure 8) which might preclude LT identification. P_aCO_2 is relatively constant up to the RCP, and, as described (2), a steeper-than-normal $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ can be explained by a higher V_D/V_T and/or a low CO_2 set point. $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-PEAK})}$ is expected to be even steeper than $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ (Figure 7(a)) because the former adds a component of hyperventilation to lactic acidosis and/or to other sources of \dot{V}_E stimuli at near maximum exercise [26, 207]. It should be emphasized, however, that there are interpretational pitfalls of using $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-PEAK})}$ as a single linear characterization of a relationship which is characteristically curvilinear (Figure 7). $\dot{V}_E/\dot{V}_{CO_2(\text{nadir})}$ is equal to $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ when the slope has an y -intercept of zero. However, $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ has a positive y -intercept in normal subjects [208] which explains why $\dot{V}_E/\dot{V}_{CO_2VT}$ is usually greater than the slope. $\dot{V}_E/\dot{V}_{CO_2VT}$ will also exceed the slope if the VT is a low value (i.e., in less fit subjects) [10]. On the other hand, a very steep $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ would produce a negative y -intercept thereby making it greater than $\dot{V}_E/\dot{V}_{CO_2VT}$ [205].

3.1.3. Interpretative Issues. $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ 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 $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ across all age ranges (Figure 3(c)) [10, 11]. There is plenty of evidence that $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ 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}_{O_2} peak. The prognostic value in CHF persisted in patients on β -blockers [99, 100]. Interestingly, $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-PEAK})}$ has been found better than $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})}$ to predict 1-year cardiac mortality and hospitalization in these patients [207]. As expected, composite scores adding $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ to other cardiopulmonary variables improved even further their prognostic value [211]. A single study found that coexistence of COPD tends to “normalize” $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ in CHF patients which casts doubt on its prognostic usefulness in this specific subpopulation [214].

In patients with PAH, $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ and \dot{V}_E/\dot{V}_{CO_2} (at rest, VT, and peak) are higher compared to CHF [215]. $\dot{V}_E/\dot{V}_{CO_2VT} > 37$ plus $P_{ET}CO_2VT < 30$ mmHg increased the probability of pulmonary vascular disease [111]. In those with idiopathic PAH, higher $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ and \dot{V}_E/\dot{V}_{CO_2} (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

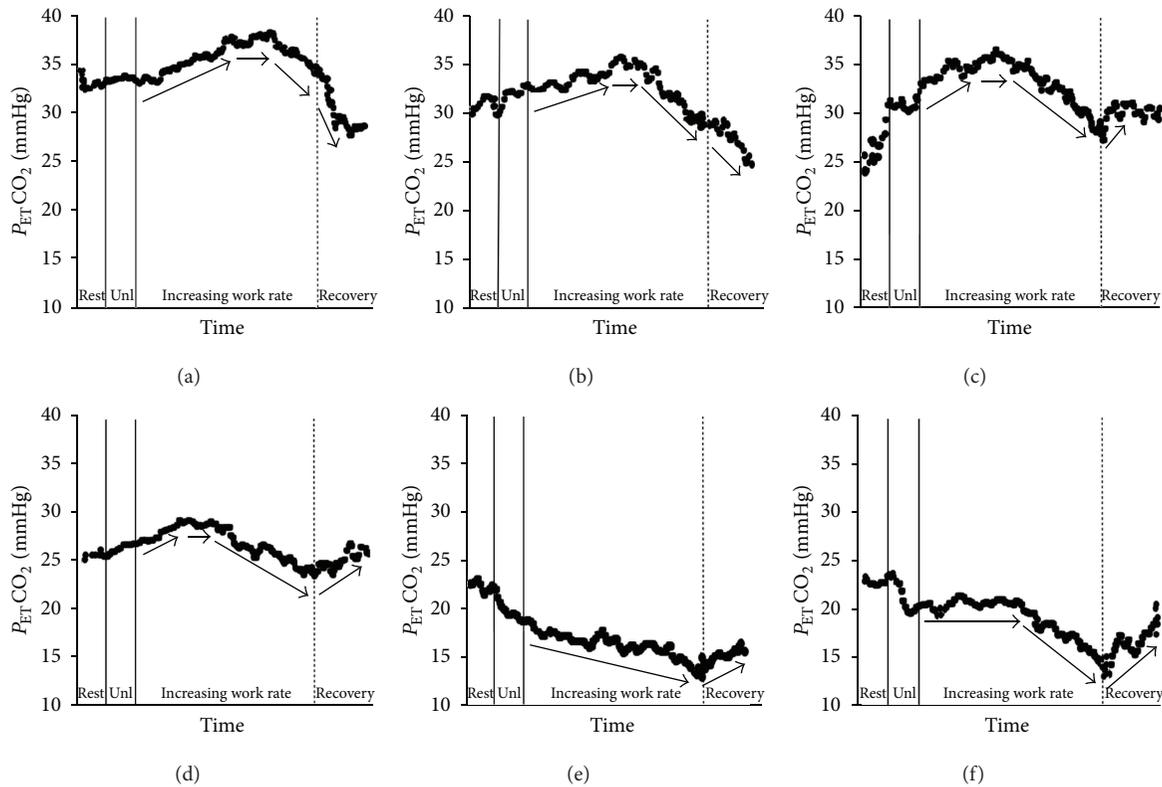


FIGURE 9: Time course of end-tidal partial pressure for carbon dioxide ($P_{ET}CO_2$) during incremental exercise and early recovery in a healthy control (panel (a)) and five patients with pulmonary arterial hypertension of progressing severity (panels (b) to (f)). Note that $P_{ET}CO_2$ becomes lower and even fails to increase as disease progresses. Moreover, it frequently increases (instead of diminishing) during recovery. Panel (f), in particular, depicts a severely impaired patient showing abrupt and sustained decrease in $P_{ET}CO_2$ concomitant with the opening of a *forame ovale* (Figure 8). Unl is unloaded pedaling.

of excess exercise ventilation in PAH hold the same prognostic importance as in CHF, Deboeck et al. recently described that $\dot{V}_E/\dot{V}_{CO_{2VT}}$ (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, $\Delta\dot{V}_E/\Delta\dot{V}_{CO_{2(rest-RCP)}} > 34$ 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 $\dot{V}_E/\dot{V}_{CO_{2VT}}$ would be rarely associated with increased V_D/V_T whereas the opposite would be likely at very high $\dot{V}_E/\dot{V}_{CO_{2VT}}$. In fact, Roman and coworkers recently described that when $\dot{V}_E/\dot{V}_{CO_{2VT}}$ 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 $\dot{V}_E/\dot{V}_{CO_{2VT}}$ was ≥ 39 . Unfortunately, intermediate values were not useful to dis-

criminate the underlying mechanisms. Interestingly, 95% of the patients with an obstructive ventilatory defect ($FEV_1/FVC < 0.7$) and $\dot{V}_E/\dot{V}_{CO_{2VT}} \geq 39$ had increased V_D/V_T [217].

3.2. End-Tidal Partial Pressure for CO_2

3.2.1. Physiological Background. Expired CO_2 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 CO_2 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., V_T) and the duration of the exhalation. $P_{ET}CO_2$ reflects poorly P_aCO_2 , (ideal alveolar) as there are significant regional variations in alveolar P_{CO_2} (P_ACO_2) and \dot{V}_A -to-perfusion ratios—even in normal subjects [2, 16]. It should also be recognized that $P_{ET}CO_2$ becomes systematically greater than P_aCO_2 during incremental exercise as the first is the peak of the intrabreath oscillation of P_ACO_2 and P_aCO_2 measured in peripheral arterial blood is an average of the oscillation over several breaths [2, 16].

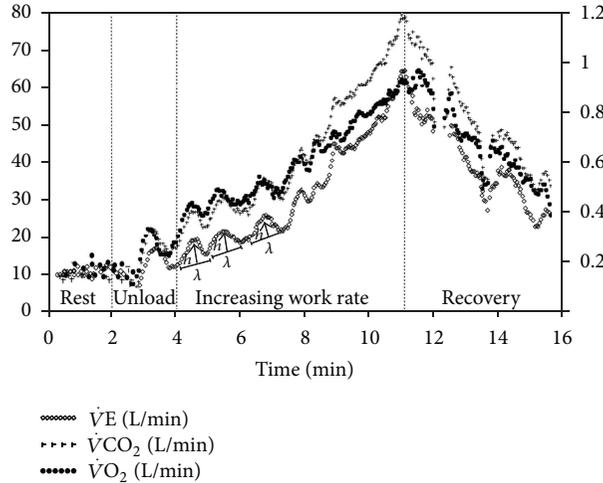


FIGURE 10: Exertional oscillatory ventilation (EOV) during incremental CPET in a 56-yr-old male with severe CHF. EOV was defined by regular (standard deviation of three consecutive cycle lengths (λ) within 20% of their average) and ample (minimal h of 5 L/min) cycles of ventilatory (\dot{V}_E) oscillations [27]. A similar oscillatory pattern is also seen in oxygen uptake (\dot{V}_{O_2}) and carbon dioxide output (\dot{V}_{CO_2}).

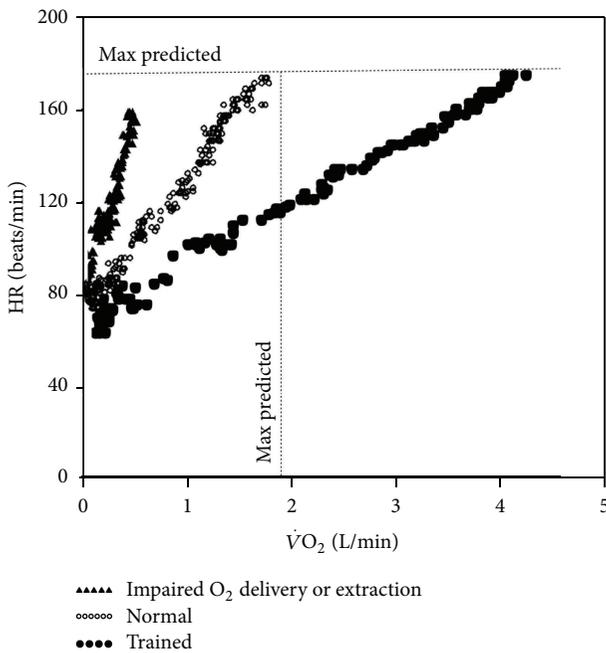


FIGURE 11: Heart rate (HR) response as a function of \dot{V}_{O_2} in 3 males of same age: a patient with abnormal O_2 delivery and/or extraction (severe pulmonary arterial hypertension, $\Delta HR/\Delta \dot{V}_{O_2} = 158$ beats/L), a normal sedentary subject ($\Delta HR/\Delta \dot{V}_{O_2} = 65$ beats/L), and a triathlete ($\Delta HR/\Delta \dot{V}_{O_2} = 26$ beats/L).

3.2.2. *Technical Considerations.* $P_{ET}CO_2$ increases from rest to LT (which is proportional to decrease in \dot{V}_E/\dot{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 1(b) and 9(a)). As mentioned, P_aCO_2 underestimation by $P_{ET}CO_2$ is roughly proportional to V_D/V_T ; consequently, computing V_D/V_T using $P_{ET}CO_2$ instead of P_aCO_2 overestimates V_D/V_T in normal subjects and underestimates it in patients [218].

3.2.3. *Interpretative Issues.* $P_{ET}CO_2$ differs from P_aCO_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 $P_{ET}CO_2$ is complex in the absence of P_aCO_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 [111]. There is now established evidence that $P_{ET}CO_2$ at rest [112–114], LT [115], and peak exercise [116] are valuable for prognosis estimation and disease severity assessment in CHF [219, 220]. Low $P_{ET}CO_2$ values have also been found in PAH (see also later) [97, 111, 117, 118]. Decreased $P_{ET}CO_2$ 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 $P_{ET}CO_2$ and cardiac output [120]. In addition to reduced cardiac output, an augmented ventilatory drive may also account for a reduction in $P_{ET}CO_2$ whereas altered breathing pattern seems to have a minor role in CHF [204].

$P_{ET}CO_2$ is typically lower in PAH than CHF [111, 219]. In fact, Yasunobu and co-workers suggested that observation of an unusually low $P_{ET}CO_2$ 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 [111]. $P_{ET}CO_2$ 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 $P_{ET}CO_2$ changed parallel to P_aCO_2 , a hyperbolic relationship between

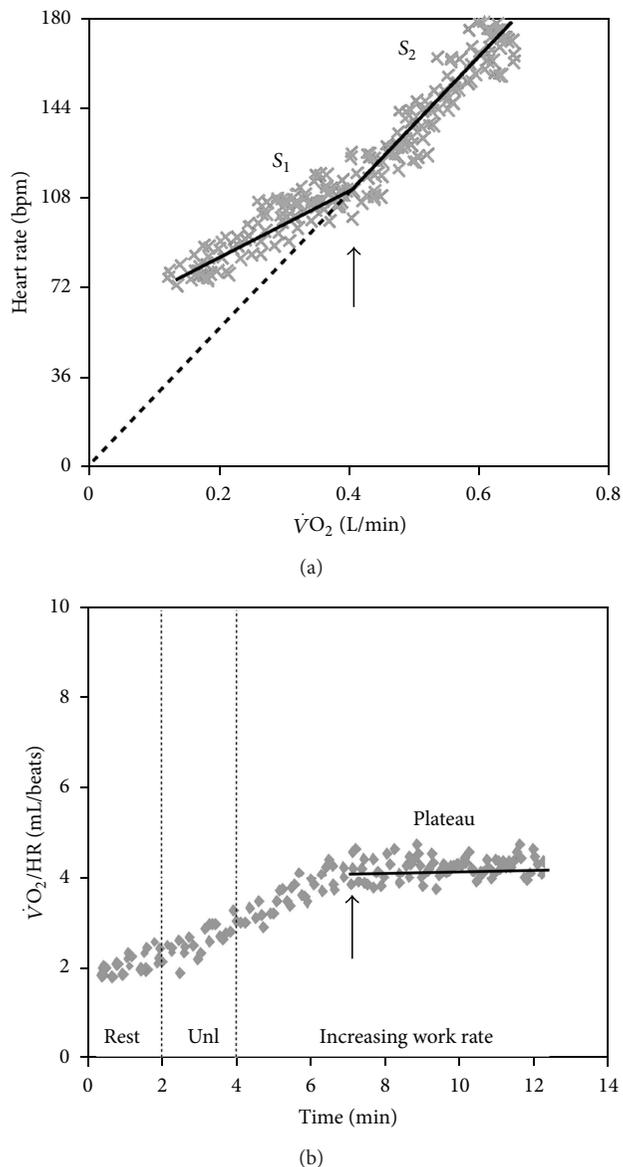


FIGURE 12: Change in Δ heart rate (HR)/ Δ oxygen uptake (\dot{V}_{O_2}) (arrow) slope (arrow) during incremental CPET in a patient with severe cardiovascular limitation to exercise (panel (a)). Note that this led to a plateau in O_2 pulse (\dot{V}_{O_2}/HR ratio) as the y -intercept becomes zero; that is, the relationship passes through its origin (panel (b)). Unl is unloaded pedaling.

\dot{V}_E/\dot{V}_{CO_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. 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_aCO_2 and the apneic (or hypoventilatory) threshold [27, 122, 123, 225–235].

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 \dot{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 \dot{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 or 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. Δ Heart Rate (HR)/ Δ Oxygen Uptake (\dot{V}_{O_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

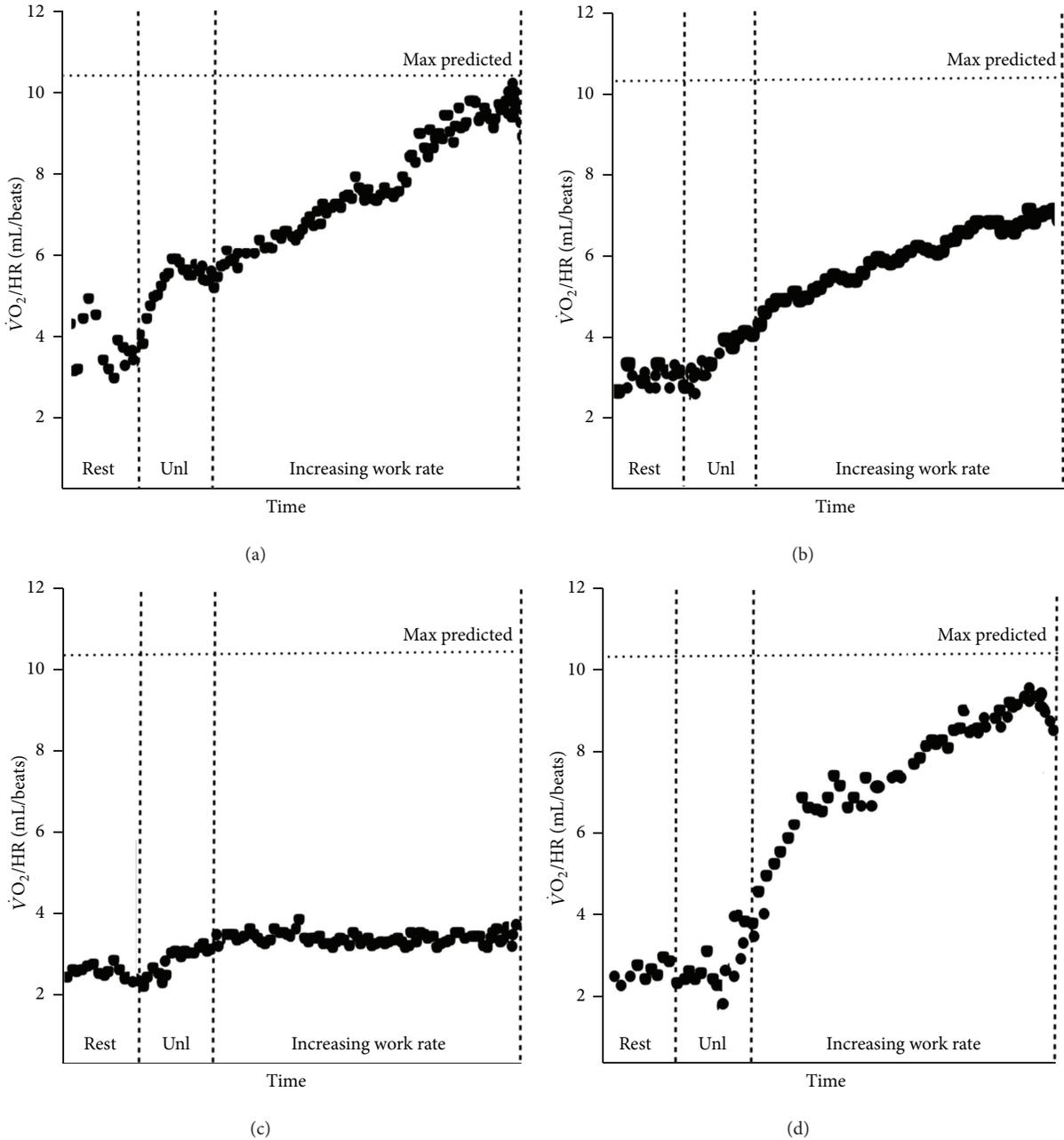


FIGURE 13: $\dot{V}O_2$ pulse ($\dot{V}O_2/HR$) as a function of time during incremental exercise. (a) Curvilinear increase up to a normal predicted value in a healthy subject; (b) abnormally low peak values due to ventilatory limitation and early exercise cessation in a patient with COPD; (c) failure to increase and early plateau in a patient with end-stage pulmonary arterial hypertension; (d) decrease at near maximum exercise in a patient with concomitant electrocardiographic abnormalities indicative of coronary artery disease. Unl is unloaded pedaling.

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,

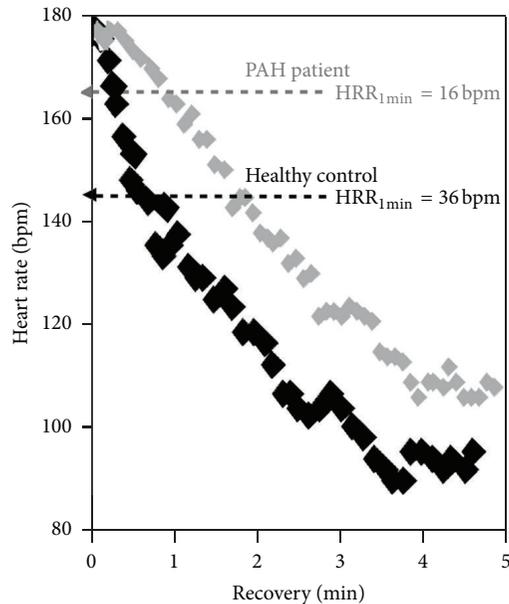


FIGURE 14: Heart rate (HR) response after incremental exercise in a healthy control and a patient with pulmonary arterial hypertension (PAH) of same age and gender (both females aged 31). Note the delayed HR recovery (HRR) up to the 5th minute after-exercise in the patient compared to the control. $HRR_{1\min} \leq 18$ bpm after cycle ergometer exercise test has recently been found an independent predictor of mortality in these patients [28].

the slope should be calculated only over the initial linear phase response (Figure 2(b)). As detailed later, pronounced changes in linearity may hold important clinical implications.

4.1.3. Clinical Usefulness. $\Delta HR/\Delta \dot{V}_{O_2}$ increases with age being consistently higher in females than males (Figure 3(b)) [10]. As expected, cardiovascular and muscular diseases which are known to impair O_2 delivery and/or utilization have been found to increase both the slope and the intercept of the $\Delta HR/\Delta \dot{V}_{O_2}$ relationship [127–130]. Some specific conditions, however, may prevent HR to increase even in the presence of disease: (a) patients under β -blocker therapy [248], (b) ischemic involvement of the sinus node artery [249], and (c) advanced CHF [250]. The so-called O_2 pulse (\dot{V}_{O_2}/HR ratio) is a commonly used derivation of $\Delta HR/\Delta \dot{V}_{O_2}$. As the primary \dot{V}_{O_2} -HR relationship has a negative y -intercept, O_2 pulse increases hyperbolically [16] towards an asymptotic value at end-exercise (Figure 13(a)) which might reflect the SV response [131]. However, all pathologic conditions known to increase $\Delta HR/\Delta \dot{V}_{O_2}$ (including desaturation, anemia, and impaired O_2 extraction) will also diminish peak O_2 pulse. Moreover, early exercise termination due to symptom limitation (including breathlessness in patients with COPD) (Figure 13(b)) and/or submaximal effort would decrease peak O_2 pulse in the absence of cardiovascular limitation. In these cases, however, a normal $\Delta HR/\Delta \dot{V}_{O_2}$ is reassuring. A more clinically useful pattern of response relates to abrupt increases in $\Delta HR/\Delta \dot{V}_{O_2}$ slope

to an extent that the relationship goes through its origin or becomes with a negative y -intercept; that is, O_2 pulse turns flat (Figure 12) or even decreases (Figure 13(d)). This suggests that the HR response became the sole mechanism for cardiac output increase due to a severely impaired SV response. In practical grounds, there is limited evidence that as myocardial perfusion is reduced in patients with coronary artery disease, there is reversible left ventricle dysfunction thereby steepening $\Delta HR/\Delta \dot{V}_{O_2}$ (Figure 12(a)) and flattening (Figure 12(b)) (or even decreasing) (Figure 13(d)) O_2 pulse [88, 132, 133].

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 sympathetic 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 \dot{V}_{O_2} [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 1: Clinical usefulness and suggested cutoffs of selected dynamic responses to rapidly incremental CPET.

Variable	Clinical usefulness	Cutoffs/patterns of abnormality
Metabolic		
Estimated lactate threshold (LT)	(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]	(i) \dot{V}_{O_2} LT < 40% predicted \dot{V}_{O_2} peak [2] (ii) Influenced by age, gender, and fitness [4, 7, 42, 76]
$\Delta\dot{V}_{O_2}/\Delta$ work rate (mL/min/W)	(i) Indicative of impaired O_2 delivery and/or utilization [77–81] (ii) Adjunct for the diagnosis of myocardial ischemia [82–88]	(i) <lower limit of normality (<8.5 mL/min/W) [4, 8] (ii) Decrease in slope (or plateau) as exercise progresses [77–81]
\dot{V}_{O_2} efficiency slope (OUES)	(i) Functional impairment and prognosis in CHF [18, 89–94] (ii) Response to interventions in CHF [95] (iii) More sensitive to training than the $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2}$ slope in CHF [96]	Mortality in CHF <1.05 L/min/log (L/min) or <65% predicted [89]
\dot{V}_{O_2} efficiency plateau (OUEP)	Functional impairment and prognosis in CHF [89]	Mortality in CHF <25 mL/L or <65% predicted [89]
Ventilatory		
Excess exercise ventilation	(i) Prognosis in PAH [97, 98] and CHF, even under β -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]	<age—and gender-specific lower limits of normality [10, 11] Mortality in CHF $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})} \geq 34$ [108] $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-PEAK})} \geq 45$ [109] Mortality in PAH $\dot{V}_E/\Delta\dot{V}_{CO_2\text{nadir}} \geq 52$ [97] $\dot{V}_E/\dot{V}_{CO_2} \text{ LT} \geq 54$ [98] $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})} \geq 62$ [98] $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-PEAK})} \geq 48$ [97] Postoperative complications of lung resection $\Delta\dot{V}_E/\Delta\dot{V}_{CO_2(\text{rest-RCP})} \geq 34$ [110]
End-tidal partial pressure for CO_2 ($P_{ET}CO_2$)	(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 forame ovale in PAH [119] (v) Responsive to drug therapy in PAH [105] and CHF [101] (vi) Responsive to exercise training [120]	Diagnosis of PVD [111] “likely” = ≤ 30 mmHg at the LT “very likely” = ≤ 20 mmHg at the LT progressive reductions as exercise increases sudden increase with exercise cessation Mortality in CHF ≤ 33 mmHg at rest [112, 114] ≤ 36 mmHg at the LT [115] < 31 mmHg at peak [116]
Exertional oscillatory ventilation	(i) Indicative of worsening clinical status, severe hemodynamic dysfunction, and reduced functional capacity in CHF [121–126] (ii) Responsive to interventions in CHF [101]	Three or more regular \dot{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]
Cardiovascular		
Δ Heart rate/ $\Delta\dot{V}_{O_2}$ (beat/L)	(i) Indicative of abnormal cardiovascular response to exercise [127–130] (ii) Adjunct for the diagnosis of myocardial ischemia [88, 131–133]	<age—and gender-specific lower limits of normality [9, 10] Changes in linearity with increases in steepness [88, 132, 133]

TABLE 1: Continued.

Variable	Clinical usefulness	Cutoffs/patterns of abnormality
Heart rate recovery (HRR) (beats/min)	(i) Prognosis in asymptomatic subjects referred for exercise testing [134], CHF [135], PAH [28], Type 2 diabetes [136], and COPD [137] (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] (iii) Responsive to aerobic training in CHF, COPD, obstructive sleep apnea, and systemic lupus erythematosus [146–149]	Mortality in patients referred for exercise testing Treadmill, cooldown: $HRR_{1\ min} \leq 12$ [134, 150, 151]
		Treadmill, no cooldown: $HRR_{1\ min} \leq 18$ [135] $HRR_{2\ min} \leq 22$ [152]
		Treadmill, no cooldown: $HRR_{2\ min} \leq 42$ [153]
		Mortality in CHF Treadmill, cooldown: $HRR_{1\ min} < 6.5$ [154]
		Treadmill, no cooldown: $HRR_{1\ min} \leq 12$ [155]
		Bike, cooldown: $HRR_{1\ min} < 17$ [156]
		Mortality in PAH Bike, cooldown: $HRR_{1\ min} \leq 18$ [28]
		Mortality in COPD Bike, cooldown: $HRR_{1\ min} \leq 14$ [137]
		Mortality in Type 2 diabetes Treadmill, cooldown: $HRR_{1\ min} < 12$ $HRR_{2\ min} < 28$ [136]

\dot{V}_{O_2} : oxygen uptake; \dot{V}_{CO_2} : carbon dioxide output; \dot{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/\dot{V}_T : Dead space to tidal volume ratio
 \dot{V}_A : Alveolar ventilation
 \dot{V}_E : Minute ventilation

\dot{V}_E/\dot{V}_{O_2} : Ventilatory equivalent for O₂
 \dot{V}_E/\dot{V}_{CO_2} : Ventilatory equivalent for CO₂
 \dot{V}_{O_2} : Oxygen uptake
 VT: Ventilatory threshold
 WR: Work rate.

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Review Article

Inspiratory Capacity during Exercise: Measurement, Analysis, and Interpretation

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Cardiopulmonary exercise testing (CPET) is an established method for evaluating dyspnea and ventilatory abnormalities. Ventilatory reserve is typically assessed as the ratio of peak exercise ventilation to maximal voluntary ventilation. Unfortunately, this crude assessment provides limited data on the factors that limit the normal ventilatory response to exercise. Additional measurements can provide a more comprehensive evaluation of respiratory mechanical constraints during CPET (e.g., expiratory flow limitation and operating lung volumes). These measurements are directly dependent on an accurate assessment of inspiratory capacity (IC) throughout rest and exercise. Despite the valuable insight that the IC provides, there are no established recommendations on how to perform the maneuver during exercise and how to analyze and interpret the data. Accordingly, the purpose of this manuscript is to comprehensively examine a number of methodological issues related to the measurement, analysis, and interpretation of the IC. We will also briefly discuss IC responses to exercise in health and disease and will consider how various therapeutic interventions influence the IC, particularly in patients with chronic obstructive pulmonary disease. Our main conclusion is that IC measurements are both reproducible and responsive to therapy and provide important information on the mechanisms of dyspnea and exercise limitation during CPET.

1. Introduction

Cardiopulmonary exercise testing (CPET) is increasingly recognized as an important clinical diagnostic tool for assessing exercise intolerance and exertional symptoms, and for objectively determining functional capacity and impairment [1]. CPET is particularly well suited for understanding factors that may limit or oppose (i.e., constrain) ventilation in the face of increasing ventilatory requirements during exercise both in research and clinical settings. Traditionally, ventilatory reserve has been evaluated by examining the relationship between peak exercise ventilation (V_E) and the measured (or estimated) maximal voluntary ventilation (MVV). Thus, an increased ratio (e.g., $V_E/MVV > \sim 85\%$) occurring at

a relatively low work rate, in the setting of an adequate cardiovascular reserve, strongly suggests that ventilatory factors are contributing to exercise limitation [1]. However, MVV may not accurately reflect sustainable peak V_E in some individuals since respiratory muscle recruitment patterns, operating lung volumes, breathing pattern, and respiratory sensation are distinctly different during brief bursts of voluntary hyperpnea compared with the hyperpnea of exercise [2]. Moreover, the ventilatory reserve provides little information on the factors that limit or constrain further increases in V_E [3] or, indeed, the concomitant sensory implications. It is increasingly clear that perceived intolerable respiratory discomfort may limit exercise even before physiological maxima are reached and needs to be considered in CPET interpretation.

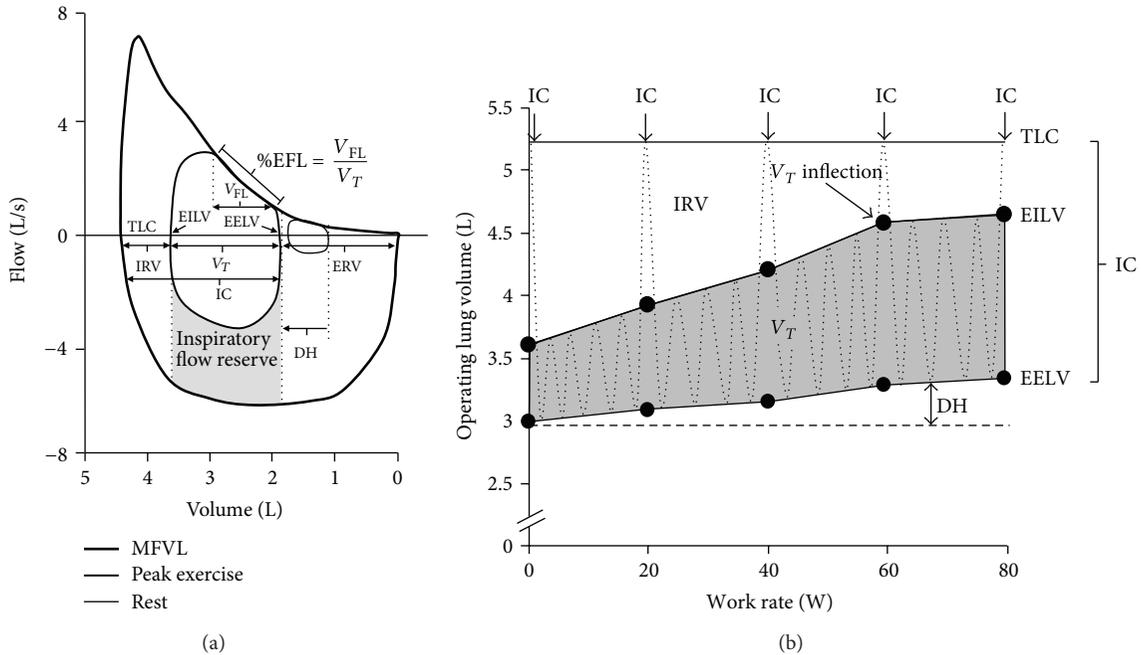


FIGURE 1: (a) Example of a resting and peak exercise tidal breath superimposed within a maximum flow-volume loop (thick black line). Modified from [3]. The position of the tidal breaths along the x-axis is based on the measurement of end-expiratory lung volume (determined from inspiratory capacity maneuvers). (b) Operating lung volume plot versus cycle work rate. Inspiratory capacity maneuvers are performed at rest (0 W) and every 20 W throughout exercise. TLC, total lung capacity; IRV, inspiratory reserve volume; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; V_T , tidal volume; IC, inspiratory capacity; V_{FL} , volume of the tidal breath that is flow limited on expiration; %EFL, percentage of expiratory flow limitation; ERV, expiratory reserve volume; MFVL, maximum flow-volume loop; DH, dynamic hyperinflation.

More detailed assessments during CPET can provide additional valuable information regarding the presence of respiratory mechanical constraints to ventilation. For example, Johnson et al. [3] have advocated the flow-volume loop analysis technique for estimation of both inspiratory and expiratory flow reserves during exercise in health and in cardiopulmonary disease. This approach has proven clinical utility: it permits the estimation of expiratory flow limitation, the extent of dynamic hyperinflation, and tidal volume (V_T) constraints [3] (Figure 1(a)). However, it is important to consider the potential confounding effects of thoracic gas compression and bronchodilation when using this technique [4]. Another refinement in the assessment of mechanical volume constraints is the portrayal of changes in operating lung volumes (V_T , end-expiratory lung volume (EELV), end-inspiratory lung volume (EILV), and inspiratory reserve volume (IRV)) as a function of time, V_E , work rate or oxygen uptake (V_{O_2}) during exercise (Figure 1(b)). This approach has the advantage of graphically displaying the time course of change in all of the relevant operating lung volumes throughout exercise relative to total lung capacity (TLC). This analysis of operating lung volumes, in conjunction with breathing pattern and dyspnea intensity ratings, allows a comprehensive evaluation of ventilatory abnormalities during exercise and their contribution to exercise limitation in the individual patient. Both of these approaches are critically dependent on an accurate measurement of inspiratory capacity (IC) to track

changes in EELV. EELV can also be measured using gas dilution techniques [5], respiratory inductance plethysmography [6], or optoelectronic plethysmography [7]. However, these technically demanding methods are expensive, they require specialized training, and they are rarely used in clinical settings. The simplest and most widely accepted method for measuring EELV during exercise is to have individuals perform serial IC maneuvers at rest and throughout exercise [4, 8–12]. A number of software options are now available on various commercial metabolic measurement systems to facilitate such measurements during CPET.

The IC, the maximal volume of air that can be inhaled after a quiet breath out, is a relatively simple measurement and it does not require any specialized equipment since all metabolic systems are able to measure lung volume. Despite the simplicity of this measurement, the IC provides valuable information on the ventilatory response to exercise; it is often used as a primary or secondary endpoint in clinical trials [13–15]; and it correlates well with several important outcome parameters such as peak V_{O_2} [16, 17] and carbon dioxide retention during exercise [18]. When expressed relative to TLC, the resting IC is an independent risk factor for mortality [19] and acute exacerbation [20] in patients with chronic obstructive pulmonary disease (COPD). Progressive reductions in the resting IC with increasing COPD severity have also been shown to be associated with important mechanical constraints on V_T expansion and the development of dyspnea

TABLE 1: Consequences of dynamic hyperinflation.

Negative consequences of dynamic hyperinflation
(i) Increased elastic and threshold loading on the inspiratory muscles
(ii) Increased work and O ₂ cost of breathing
(iii) Functional inspiratory muscle weakness and possible fatigue
(iv) Mechanical constraint on tidal volume expansion
(v) Early ventilatory limitation to exercise
(vi) Increased neuromechanical uncoupling of the respiratory system
(vii) CO ₂ retention and possibly arterial hypoxemia
(viii) Potential adverse cardiovascular consequences
(ix) Increased dyspnea and exercise intolerance

For a more detailed review on the consequences of dynamic hyperinflation, see O'Donnell and Laveneziana [21].

during exercise [12]. In addition, dynamic lung hyperinflation, defined as the temporary and variable increase of EELV above the resting value, can contribute importantly to dyspnea and exercise intolerance in patients with chronic lung disease [17]. Other important consequences associated with dynamic hyperinflation include (1) increased elastic and threshold loading on the inspiratory muscles resulting in an increased work and O₂ cost of breathing; (2) V_T constraints resulting in early mechanical ventilatory limitation; (3) functional inspiratory muscle weakness and possible fatigue; (4) CO₂ retention and arterial O₂ desaturation; (5) adverse effects on cardiac function (see Table 1 and [21]). Dynamic hyperinflation can be tracked as a progressive reduction in IC during exercise. Despite the well-known association between static and dynamic IC and its role in the genesis of dyspnea and exercise intolerance, there are no specific guidelines or recommendations on how to adequately perform, analyze, and interpret the IC, particularly during exercise. Given the valuable clinical and research insight that this measurement can provide, a standardized approach to this method is warranted. Accordingly, the purpose of this paper is to critically evaluate the method of measuring IC during exercise. Specifically, we will address issues related to methodological assumptions and reproducibility of the IC, how to perform the maneuver, and how to analyze and interpret IC data. This paper will also briefly address typical IC responses to exercise in health and disease. We will evaluate the utility of assessments of dynamic operating lung volumes and breathing pattern to assess mechanical constraints to ventilation and discuss the effects of various therapeutic interventions on the IC at rest and during exercise in patients with COPD.

2. Assumptions and Reproducibility

Accurate assessment of EELV (calculated as TLC minus IC) is directly dependent on the stability of TLC throughout exercise and the ability of the individual to maximally inflate their lungs during the IC maneuver. Thus, if TLC is constant,

then any change in IC will reflect the inverse change in EELV. Constancy of TLC has been demonstrated during exercise in healthy individuals [22] and in patients with COPD [23]. It also appears that individuals with COPD are able to maximally activate their diaphragm during inspiratory efforts to TLC [24, 25], even when dyspneic at peak exercise [24]. Yan et al. [26] determined the reliability of IC measurements in individuals with COPD during incremental cycle exercise by comparing esophageal pressure at peak inspired plateau volume during serial IC efforts. These authors demonstrated consistent peak esophageal pressures throughout exercise despite changes in IC. They concluded that TLC did not change and that the IC was reliable for assessing changes in EELV during exercise. This conclusion is supported by other studies which have shown high reproducibility of the IC [10, 27] and its responsiveness to change during exercise following different forms of therapy [28–32]. O'Donnell et al. [33] recently extended these observations by examining reproducibility of the IC at rest and during cycle exercise in large multicentre clinical trials. These authors demonstrated high reproducibility of the IC at rest, isotime, and at peak exercise (intraclass correlation $R \geq 0.87$). Reproducibility data of IC measurements during treadmill exercise or walk tests have not been published to date.

To our knowledge, no information is available about the reliability of IC measurements to track operating lung volumes in other clinical populations. For example, reductions in IC during exercise have been reported in obesity [34], congestive heart failure [35, 36], pulmonary arterial hypertension [37], and cystic fibrosis [38]. Since inspiratory muscle weakness may be present to a variable degree in some, if not all, of these conditions, the assumption that IC reduction during exercise represents an increase in EELV must be made with caution. Accurate interpretation of IC behaviour in these circumstances requires the concomitant assessment of respiratory muscle function and peak inspiratory pressures during the IC maneuver.

3. Measurement of IC

3.1. Technical Considerations. The ability to accurately evaluate IC during exercise requires the measurement of bidirectional flow using flow sensing devices, which is then integrated to calculate volume. Metabolic carts that only measure inspiratory flow are inappropriate for measuring IC. This is because many individuals will alter their breathing pattern prior to performing an IC maneuver. Specifically, they either decrease or increase their expired volume immediately prior to the IC resulting in an underestimation or overestimation of IC, respectively (Figure 2). Depending on the measurement tool and method of delivery of instructions, there can also be anticipatory changes in breathing pattern that can increase the variability of premaneuver EELV. It is therefore essential that inspiratory and expiratory volumes be continuously monitored so that alterations in EELV can be identified and accounted for (see Section 4).

An important technical consideration when measuring bidirectional flow/volume is that signal “drift” occurs with all flow sensing devices. Drift may occur as a result of

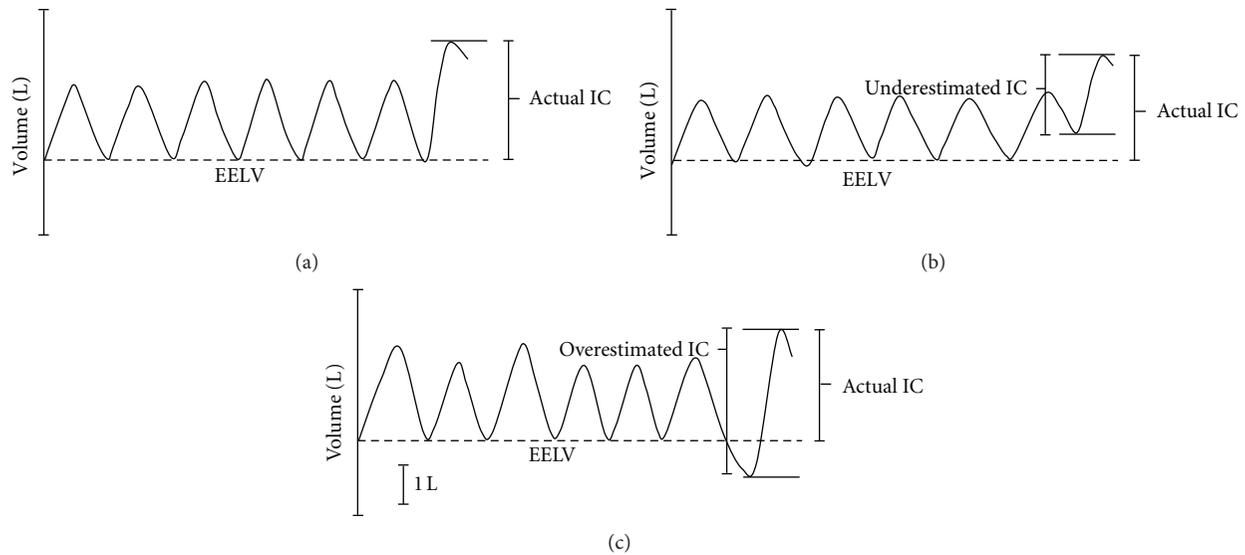


FIGURE 2: Three examples of inspiratory capacity (IC) maneuvers performed during exercise. (a) Correctly performed maneuver where the individual initiates the IC maneuver at the appropriate end-expiratory lung volume (EELV), denoted by the dashed line. (b) Individual initiating the IC maneuver prior to reaching the appropriate EELV. The absolute volume of the IC breath will be underestimated if it is not anchored to the appropriate EELV. (c) Individual initiating the IC maneuver after surpassing the appropriate EELV. The absolute volume of the IC breath will be overestimated if it is not anchored to the appropriate EELV.

electrical changes over time, nonlinearities in the flow sensing device, and physiological changes such as temperature, gas density, and humidity [39]. Drift must therefore be accounted for prior to analysis of the IC maneuver [3, 27]. Most commercially available breath-by-breath metabolic systems that offer exercise flow-volume analysis software account for thermodynamic drift by correcting both the inspiratory and expiratory flow/volume signals to BTPS conditions. The tester should be able to view the volume-time plot in real-time during the maneuvers to monitor changes in breathing pattern and drift. Real-time assessments of changes in EELV using tidal flow-volume plots are also popular but, in our experience, may be more difficult than volume-time plot analysis.

There is limited information regarding standards for intermaneuver reproducibility of resting IC measurements. The American Thoracic Society and European Respiratory Society Task Force [40] simply states that there should be at least three acceptable maneuvers and that the mean coefficient of variation for IC is $5 \pm 3\%$ in patients with chronic airflow obstruction, based on the work of Pellegrino et al. [41]. Although they suggest that the two largest acceptable values of other spirometric values (forced vital capacity (FVC) and forced expiratory volume in 1 second) should be within 0.15 L of each other, or within 0.10 L if FVC is ≤ 1.0 L, they do not provide specific criteria for IC. The American Association for Respiratory Care suggests that IC measurements should agree within 5% or 60 mL of the mean (whichever is larger) [42]. However, the 5% or 60 mL cutoff may be too stringent for resting IC measurements. If patients are unable to achieve reasonable reproducibility at rest, then it is unlikely that they will be able to accurately perform IC measurements during exercise.

3.2. Exercise Protocols. A wide range of protocols on both treadmills and cycle ergometers have been used for the evaluation of IC during exercise, including constant work rate tests [14, 43, 44] and incremental tests [9, 17, 28, 45]. There does not appear to be a major difference in IC values when comparing treadmill versus cycle exercise [46, 47], at least in patients with COPD. The duration of each exercise stage can vary for incremental exercise tests depending on the population and the purpose of the study (e.g., 1–3 minute stages). The main consideration when selecting exercise protocols, particularly for incremental tests, is to use stepwise increases in work rates. Ramp tests, where the work rate incrementally increases every 1–2 seconds, are probably inappropriate for measuring IC due to the inability to establish stable ventilations. IC maneuvers are typically performed during the final 30 seconds of each exercise stage when V_E is assumed to be reasonably stable.

3.3. Performing the IC Maneuver. The IC maneuver involves a maximal inspiration from a stable EELV to TLC. Despite the relative simplicity of this technique, several steps must be taken to ensure optimal performance by the individual. Like any volitional test, we have to assume that individuals are able to give a true maximal effort for the IC value to be accurate. Careful and consistent instructions are critically important and testers must be appropriately trained in explaining the maneuver to the individual. Individuals should be given sufficient time to practice the maneuvers at rest and during exercise for familiarization purposes. It is important to first explain the maneuver in general terms to the individual and to heavily emphasize the importance of fully inflating their lungs. It is then recommended that the tester demonstrate the test with an emphasis on the volitional nature of the

maneuver. The following is an example of general instructions: *“During the resting period and once during every stage of exercise, we are going to ask you to take a deep breath in until you are completely full. To do this, you will finish your normal breath out and then proceed to fill up your lungs quickly and without hesitation until you are as full as possible. When you are certain you can’t get any more air in then you can go back to normal breathing.”*

When the individual is breathing on the mouthpiece at rest and their breathing pattern is stable, then the following (or similar) instructions should be given to prompt the initiation of the IC maneuver: *“at the end of a normal breath out, take a deep breath all the way in until you are completely full.”* During the IC maneuver, the tester should give verbal encouragement (e.g., *“in in in...”*). The tester should also encourage the individual to avoid holding their breath during the maneuver. Ideally, the tester should be able to view the volume-time trace and/or the flow-volume loop tracing during and after the maneuver. If the individual does not initiate the IC at a stable EELV then it is recommended that the tester reexplain what is meant by *“at the end of a normal breath out.”* Doing this during the familiarization period is most appropriate. There is a natural tendency for some individuals to “cheat” immediately before performing the IC maneuver by taking a smaller or larger tidal breath out than the previous stable breaths as shown in Figure 2. Giving the individual visual feedback on their test at rest or even drawing out an example during the familiarization period may help some individuals better understand what is meant by *“at the end of a normal breath out.”*

It is also important to note that some individuals take several more breaths before performing the maneuver once the prompt is given by the tester. Some of these individuals significantly change their breathing pattern (rate and depth) as an anticipatory response to performing the IC. In some cases, individuals will even alter their cadence if they are on the cycle ergometer. In these instances, it should be encouraged that the individual not “over-think” the test and try to perform the IC as soon as they are given the prompt to do so. The alternative is to tell the individual when to perform the IC (i.e., *“at the end of this (the next) breath out, take a deep breath all the way in until you are completely full”*). In rare instances where individuals struggle with both of these approaches, the tester may consider telling them to maximally inspire without any warning. This approach requires careful monitoring of flow and volume tracings and/or watching the individual’s breathing rhythm. As soon as the tester sees that the individual is about to take a breath in, they can quickly tell them to maximally inflate their lungs: *“all the way in on this breath – in in in...”* However, this approach is extremely difficult if breathing frequency is very high. The ideal situation is to have the instructions and method standardized for all individuals. However, alternative approaches must be used if the individual has difficulty following instructions or has major alterations in breathing pattern when given the prompt to perform the IC.

It should be noted, however, that if the breathing pattern alterations immediately prior to the IC maneuver are relatively minor, then the data can still be used as long as

the baseline EELV is adjusted according to the stable breaths prior to the IC. It is therefore critical that there is stable breathing for at least 4 breaths prior to the IC. This is not a problem for many individuals (particularly during exercise), but some individuals find the mouthpiece uncomfortable and they will often cough, swallow, or clear their throat. For these individuals, it may be appropriate to remind them to avoid coughing or swallowing when stable breathing patterns are most important for data collection.

Obtaining a reliable IC at peak exercise can also be a challenge. The most accurate peak exercise IC is that obtained immediately prior to exercise cessation. Performing the peak exercise IC several breaths into recovery is usually not appropriate given that the breathing pattern typically changes immediately upon reducing the work rate and since IC may quickly return to resting levels after exercise cessation. This can be challenging if the individual terminates exercise suddenly. Accordingly, we recommend that testers give the following instructions during the preexercise resting period: *“The goal is for you to exercise as long as you can until you feel like you can’t go any longer. When you feel like you have about 10 seconds left, give us a warning wave with your hand so that we can get you to perform the last breathing maneuver.”* We recommend giving them a reminder when the exercise test is becoming more difficult using the following (or similar instructions): *“as a quick reminder, when you feel like you can’t go any longer, just give us a 10 second warning wave.”* Then immediately say: *“you’re still looking really strong though so keep going for as long as you can.”* This motivational statement is important because some individuals will use the 10 second warning reminder as an invitation to stop exercising. As soon as the individual gives the warning wave, provide verbal encouragement: *“you’re almost there...only a few seconds left...keep going.”* Once enough tidal breaths are recorded, have the subject perform the IC and then immediately reduce the exercise load.

4. Analysis of IC

The first step in analyzing IC data is to ensure that drift in the volume-time trace has been adequately corrected [3, 27]. The tester then needs to decide if the IC maneuver should be accepted or rejected. The following general guidelines should be used to establish if the IC should be rejected.

- (i) *Number of Premaneuver Tidal Breaths Available for the Assessment of EELV.* It is recommended to have a minimum of 4 stable breaths prior to the IC maneuver in order to accurately establish the baseline EELV (Figure 2). The best approach is to continuously monitor volume so that all breaths are captured. However, some commercially available systems that offer IC modules only permit data collection for a defined time period (e.g., 30 seconds). This 30-second time limit may be inappropriate, particularly if breathing frequency is very low.
- (ii) *Variability of EELV Prior to the IC Maneuver.* Too much variability in EELV could be due to anticipatory changes in breathing pattern and/or excessive drift

due to moisture accumulation in the flow sensor and/or air leaks at the mouth/nose. Anticipatory changes in breathing pattern can be identified during the test by the tester. With adequate instruction and practice by the individual, this problem can generally be avoided. Excessive signal drift due to imperfect correction of inspiratory and expiratory flow signals to BTPS conditions, or due to moisture accumulation, may be difficult to correct and may result in spurious IC values. Leaks at the mouth can also be avoided by reminding the individual to ensure that they have a good seal around the mouthpiece throughout the test.

- (iii) *Adequacy of Inspiratory Effort.* Accurate assessment of inspiratory effort can be accomplished by simultaneously measuring peak inspiratory esophageal pressure during the IC maneuver [26, 48]. If peak inspiratory pressures during exercise are similar to the pressures obtained repeatedly at rest during the IC maneuver, then it is safe to assume adequate effort. However, esophageal pressure measurements are invasive and not necessary for most clinical- and research-based exercise tests. Quantification of effort without esophageal pressure can be difficult. However, providing verbal encouragement during the IC maneuver and emphasizing the volitional nature of the test during the instruction period can be helpful to ensure adequate effort. Finally, simple observation of the individual during the IC maneuver will often allow the tester to determine if the effort was appropriate.

If a test is deemed adequate for analysis (i.e., stable premaneuver breathing pattern, stable premaneuver EELV, and good inspiratory effort to TLC), then the tester can establish the baseline EELV. The volume during the IC breath minus the baseline EELV value represents the IC volume (Figure 2). Establishing the baseline EELV can be automated or manually determined. Manual adjustment is offered on some commercially available systems (i.e., by dragging a horizontal line on the volume-time plot or a vertical line on the flow-volume plot to the appropriate EELV). This approach is subjective and could be affected by tester bias. Thus, for research-related testing, it is appropriate for the tester to be blinded to the experimental conditions in order to avoid introducing possible bias into the analysis.

4.1. Measurements Derived from IC Maneuvers. Table 2 shows the range of variables that can be derived from IC measurements collected at rest and during exercise, and the various ways in which these variables can be expressed. For example, dynamic hyperinflation can be evaluated as the difference between the IC at rest and during exercise (ΔIC). The same value will be obtained if you take the difference between EELV at rest and during exercise. These approaches provide information regarding the magnitude of dynamic hyperinflation at a single time point during exercise. An alternative to evaluating dynamic hyperinflation at one time point is to examine the slope relating the full range of IC values to V_E at rest and throughout exercise [10, 49] (Figure 3).

TABLE 2: Data derived from IC maneuvers.

Variable	Formula	Units
ΔIC	$IC - IC_{rest}$	L
IC/TLC	$(IC/TLC) \times 100$	%
IC/VC	$(IC/VC) \times 100$	%
IRV	$IC - V_T$ or $TLC - EILV$	L, %TLC, %TLC _{pred}
V_T/IC	$(V_T/IC) \times 100$	%
EELV	$TLC - IC$	L, %TLC, %TLC _{pred} ,
<i>Surrogates for EELV:</i>		
	FVC - IC	%FVC, %FVC _{pred} , %VC,
	VC - IC	%VC _{pred}
EILV	$EELV + V_T$	L, %TLC, %TLC _{pred} , %FVC, %FVC _{pred} , %VC, %VC _{pred}
EFL	$(V_{FL}/V_T) \times 100$	%

IC: inspiratory capacity; ΔIC : change in inspiratory capacity from rest; TLC: total lung capacity; VC: vital capacity; IRV: inspiratory reserve volume; V_T : tidal volume; EILV: end-inspiratory lung volume; TLC_{pred}: predicted total lung capacity; EELV: end-expiratory lung volume; FVC: forced vital capacity; FVC_{pred}: predicted forced vital capacity; VC_{pred}: predicted vital capacity; EFL: expiratory flow limitation; V_{FL} : volume of tidal breath that is flow limited on expiration (see Figure 1(a)).

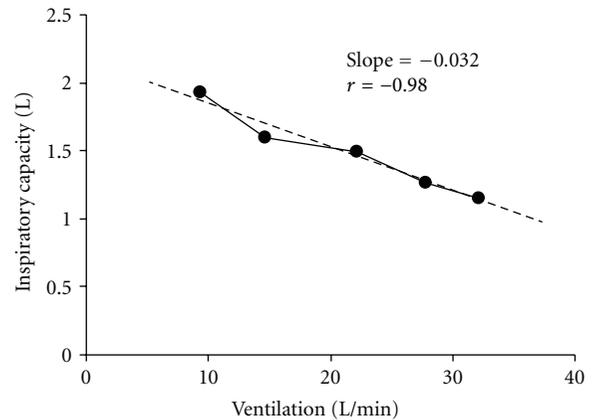


FIGURE 3: Dynamic hyperinflation can be evaluated as the linear slope relating inspiratory capacity and minute ventilation [49]. Dynamic hyperinflation is typically assessed at a single time point during an exercise test. The slope method accounts for all inspiratory capacity measurements during an exercise test and takes into account possible changes in ventilation that can occur with various interventions (e.g., hyperoxia, heliox, bronchodilators, exercise training, etc.).

This approach takes into account all data points and any changes in V_E that might occur with different interventions (e.g., hyperoxia and exercise training). However, the slope approach to analysis may not be appropriate in all cases since changes in IC may not always change linearly with V_E .

Operating lung volumes can provide valuable insight into the respiratory response to exercise. Similar to the flow-volume loop approach (Figure 1(a)), operating volume plots (Figure 1(b)) allow the researcher or clinician to examine the EELV and EILV, the magnitude of dynamic hyperinflation, the presence of V_T constraints, and the inspiratory

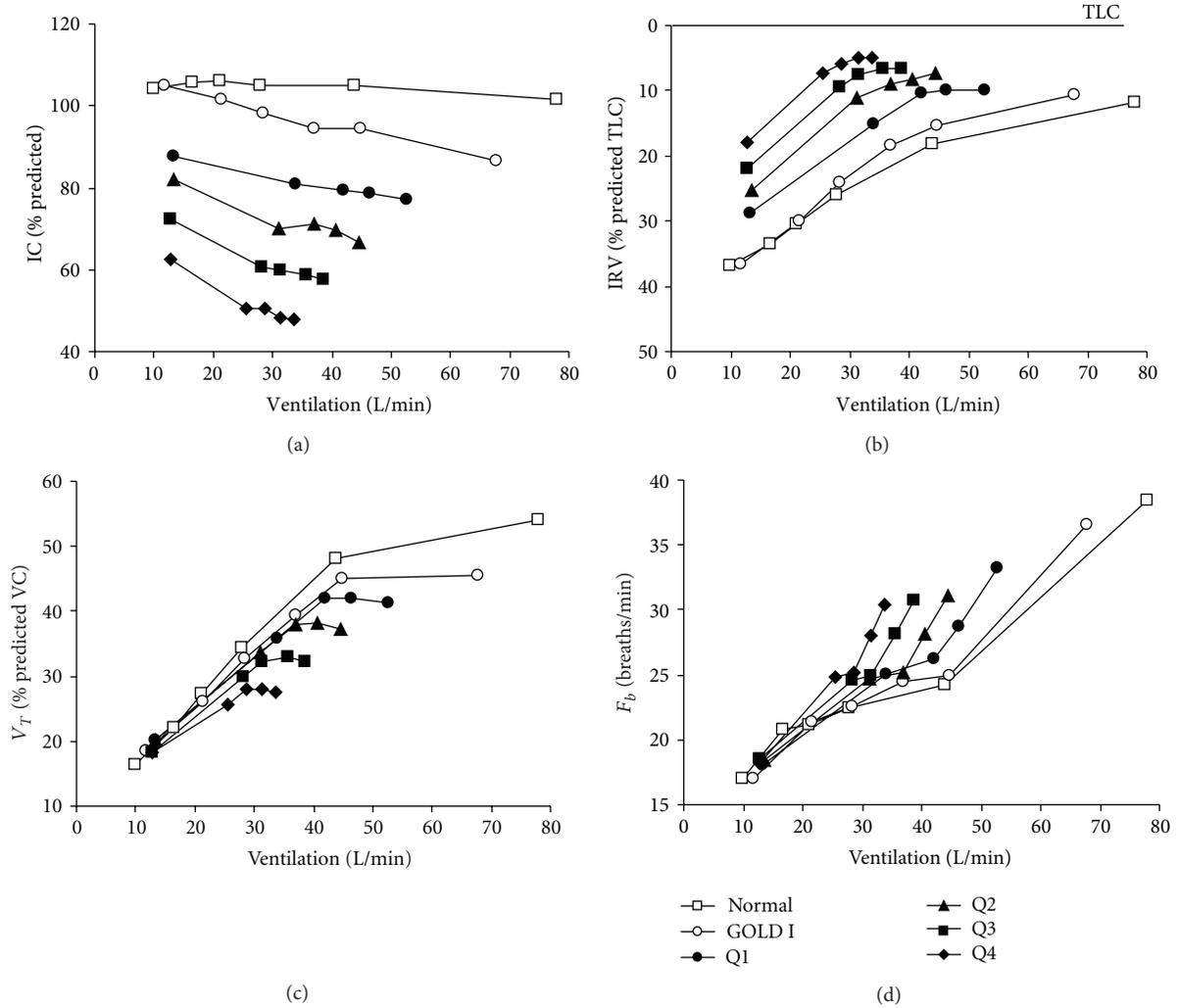


FIGURE 4: Inspiratory capacity (IC), inspiratory reserve volume (IRV), tidal volume (V_T), and breathing frequency (F_b) responses versus minute ventilation during constant work rate exercise across the continuum of health and COPD severity. The IC at rest and throughout exercise progressively decreases with advancing disease. Note the clear inflection (plateau) in the V_T -ventilation relationship, which coincides with a simultaneous inflection in the IRV-ventilation relationship. After this point, further increases in ventilation are accomplished by accelerating F_b . Data from Normal subjects and GOLD stage I (i.e., mild COPD) are from Ofir et al. [61]. Quartiles (Q) of COPD severity are based on forced expiratory volume in 1 second (FEV_1) expressed as percent predicted (ranges: Q1 = 54.5–85.1; Q2 = 43.8–54.1; Q3 = 34.9–43.6; Q4 = 16.5–34.9) from O’Donnell et al. [12]. VC, vital capacity; TLC, total lung capacity; GOLD, Global Initiative for Obstructive Lung Disease.

and expiratory reserve volumes. Accurate measurement of operating volumes in absolute terms (litres) is dependent on the measurement of TLC. However, some laboratories are only capable of measuring FVC (or vital capacity (VC)). In these cases, a surrogate for EELV can be calculated as the difference between the FVC (or VC) and IC. While this value is inaccurate in absolute terms, it still allows one to examine the pattern of change in operating volumes [9, 50, 51]. How an investigator chooses to express their operating volumes (litres, %TLC, %TLC_{pred}, etc.) depends on their preference, the nature of their clinical/research question, and whether or not there are group comparisons involved. For example, if a comparison is made between healthy individuals and patients with lung disease, then expressing the data as a percentage of predicted TLC may give more insight into the effects

of disease (e.g., static lung hyperinflation) than if the data are expressed as a percentage of the measured TLC, which could be abnormal. Regardless of the approach, the pattern of change in EELV and EILV will be the same. Combining operating lung volume data with breathing pattern responses (e.g., V_T and breathing frequency) permits a more comprehensive evaluation of ventilatory limitation during exercise (Figure 4).

5. Interpretation of IC Measurements

5.1. Typical Responses in Health and Disease. In the untrained healthy individual, systemic O_2 transport, and not the ventilatory system, is the proximate limiting factor for maximal

V_{O_2} . The majority of studies in health have demonstrated that EELV decreases (IC increases) during most exercise intensities [50, 52–54] while a few have shown that it remains relatively constant [22, 55]. Those studies that demonstrated a decrease in EELV also showed considerable interindividual variability with some individuals decreasing EELV only at the highest exercise levels [54]. However, in most individuals, the changes are progressive with increasing exercise intensity. Typically, V_T expands to reach its maximal value at ~70% of the IC (i.e., when dynamic IRV is 0.5–1 L below TLC). In many untrained healthy individuals, this usually occurs near the limits of tolerance close to peak V_E ; a discreet inflection or plateau in the V_T/V_E relation may not be discernible. In health, expiratory muscle recruitment during exercise results in reductions of EELV, which allow V_T to expand within the linear portion of the respiratory system's pressure-volume relation. Thus, earlier encroachment of EELV on the upper "stiffer" portion of this relation is avoided. In addition, vigorous expiratory muscle contraction stores energy in the chest wall, which is released during early inspiration, thereby assisting the inspiratory muscles [56, 57]. This strategy, together with breathing pattern adjustments, allows healthy individuals to increase V_E during exercise (up to 20 times resting values) without experiencing significant respiratory discomfort.

This effective strategy to optimize respiratory muscle function and respiratory sensation during exercise in health is undermined in a number of clinical conditions characterized by airway dysfunction. In these situations, lung emptying is compromised by mechanical time constant (product of resistance and compliance) abnormalities in heterogeneously distributed alveolar units. Under these circumstances, the time available during spontaneous expiration is insufficient to allow EELV to decline to its natural relaxation volume, resulting in gas trapping or dynamic lung hyperinflation. Thus, a failure to decrease EELV, or an actual increase in EELV during exercise, has been shown in conditions where there is a combination of expiratory flow limitation and increased ventilatory requirements (e.g., natural aging, COPD, and cystic fibrosis). In healthy elderly individuals, changes in the lung connective tissue matrix result in increased lung compliance, which predisposes these individuals to expiratory flow limitation and gas trapping at higher ventilations during exercise [45, 58]. The ability to reduce EELV during exercise is also limited in individuals with a reduced resting expiratory reserve volume and EELV; in such patients, resting pulmonary function tests are otherwise normal (e.g., obesity [34], pregnancy [59], and in some patients with pulmonary arterial hypertension [37]). It should be noted that in these conditions, the resting IC is preserved, or actually increased, and the negative mechanical and sensory consequences of dynamic hyperinflation are likely to be less pronounced than when the resting IC is diminished.

The regulation of EELV in patients with chronic lung disease can be remarkably different from their healthy counterparts. In COPD, the resting IC, an indirect marker of lung hyperinflation, is an important predictor of peak V_E during symptom-limited exercise [16, 17, 60]. The lower the IC, the lower the V_E at which V_T reaches its plateau (or maximal

value) having reached the minimal dynamic IRV [12]. At this point, there is a corresponding increase in breathing frequency. The effect of declining IC on breathing pattern and ventilatory capacity across the continuum of health and COPD is illustrated in Figure 4. Note that significant dynamic hyperinflation is detectable even in patients with milder COPD [61, 62]. The majority (80%–85%) of patients with moderate-to-severe COPD increase EELV (decrease IC) relative to resting values, even during submaximal exercise intensities [17, 33, 63, 64]. It is unclear why a minority of patients with COPD do not dynamically hyperinflate during exercise, but it may be related, at least in part, to having a lower resting IC [17, 64]. Smaller studies using optoelectronic plethysmography have identified varied behaviour of end-expiratory chest wall motion during exercise and have designated subgroups of COPD as nonhyperinflators ("euvolumics") [7], and "early" and "late" hyperinflators [65]. The physiological consequences of dynamic hyperinflation are briefly summarized in Table 1 [21].

The sensory consequences will vary with the resting IC as this will determine the V_E at which the V_T reaches its maximal value. This V_T inflection, or plateau, which occurs at an IRV of 0.5–1.0 L below TLC (Figure 4), is an important mechanical event during exercise in COPD. This event marks the beginning of an ever widening disparity between central neural drive and the mechanical/muscular response of the respiratory system (i.e., neuromechanical uncoupling) [66]. At this point, dyspnea intensity escalates sharply towards intolerable levels and the distressing sensation of "unsatisfied inspiration" displaces "increased breathing effort" as the dominant qualitative descriptor [67]. Recent studies have suggested that dyspnea intensity during exercise in COPD is more closely associated with the increase in EELV (or the decrease in dynamic IRV) than with the increase in EELV, *per se* [64].

6. Effects of Selected Therapeutic Interventions on IC

6.1. Bronchodilators. Bronchodilators act to reduce airway smooth muscle tone, improve airway conductance, and accelerate the time constants for lung emptying of heterogeneously distributed alveolar units. Bronchodilators of all classes have consistently been shown to increase the resting IC in patients with COPD by an average of ~0.3 L (or 15%) (for review see [21]). This improvement reflects a decrease in resting lung hyperinflation and is associated with improvements in dyspnea and exercise endurance time [10, 14, 43, 68, 69]. Combining a long-acting anticholinergic with a long-acting β_2 agonist may also have additive effects on improving IC [70]. The combination of an inhaled corticosteroid with a bronchodilator has also shown beneficial effects on resting IC compared with placebo [71].

The effects of bronchodilators and various forms of combination therapy also increase IC during exercise [10, 14, 43, 68, 69]. This increase in IC reflects a reciprocal decrease in EELV (Figure 5(a)) and, thus, it is commonly thought that pharmacotherapy reduces dynamic

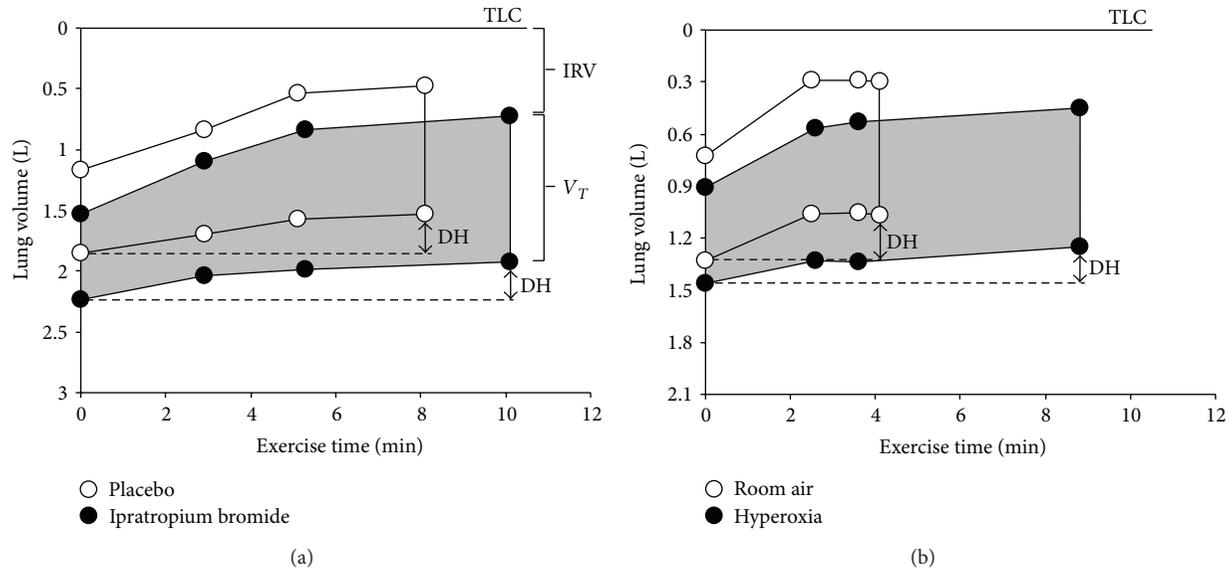


FIGURE 5: Operating lung volume plots during constant work rate cycle exercise in COPD patients following acute high-dose anticholinergic therapy versus placebo (a) and hyperoxia versus room air (b). The operating lung volumes (i.e., end-expiratory and end-inspiratory lung volumes) were reduced at rest (0 min) following anticholinergic therapy and resulted in a downward shift in operating lung volumes throughout exercise. The magnitude of dynamic hyperinflation at peak exercise (calculated as the difference in EELV from resting values) did not change following bronchodilation. The magnitude of dynamic hyperinflation was also similar at peak exercise (~ 0.2 L) during hyperoxia compared with room air in hypoxemic patients with COPD. Data for these graphs are based on previously published studies from our laboratory [43, 74]. IRV, inspiratory reserve volume; V_T , tidal volume; DH, dynamic hyperinflation; TLC, total lung capacity.

hyperinflation. However, bronchodilators, alone or in combination with inhaled corticosteroids, rarely reduce the absolute magnitude of dynamic hyperinflation that occurs acutely during exercise. In fact, the magnitude of dynamic hyperinflation either remains the same or may worsen slightly reflecting the higher ventilations that can be achieved during exercise as a result of the bronchodilation [43, 69, 72]. The reason for this misconception is based on the fact that we do not currently have an established operational definition of dynamic hyperinflation. Traditionally, dynamic hyperinflation is defined as an increase in EELV (or decrease in IC) relative to *resting* values. The reason pharmacotherapy does not reduce dynamic hyperinflation, based on this definition, is because the resting EELV (and IC) also improves with bronchodilation. In other words, bronchodilator treatment or combination therapy simply cause a parallel downward shift in the EELV over the course of the exercise test reflecting the reduction in resting (static) lung hyperinflation (Figure 5(a)). Regardless of the terminology, we can confidently say that improving airway function with pharmacotherapy has beneficial effects on IC at rest, and therefore during exercise. This increase in IC delays the onset of critical ventilatory constraints to ventilation. Improvements in dyspnea and exercise tolerance are closely related with release of V_T restriction and enhanced neuromechanical coupling of the respiratory system [66].

6.2. Oxygen. A number of studies have shown improvements in exercise performance and reductions in exertional dyspnea in response to hyperoxic breathing in patients with COPD

[31, 73–75]. The underlying mechanisms of dyspnea relief and enhanced exercise performance with hyperoxia are controversial [73, 76–78] but are likely related, in part, to lower ventilatory requirements [31, 74, 77] due to reduced chemoreceptor drive [73, 75]. Given that dynamic hyperinflation is largely determined by V_E , it seems intuitive that hyperoxic breathing would improve the IC during exercise and, thus, reduce the magnitude (or delay the onset) of dynamic hyperinflation. However, the interrelationship between possible reductions in dynamic hyperinflation and improvements in dyspnea and exercise endurance with hyperoxia has been difficult to establish. O'Donnell et al. [74] evaluated the effects of hyperoxic breathing during exercise in hypoxemic COPD patients and demonstrated a significant delay in dynamic hyperinflation during exercise compared with room air. However, the magnitude of dynamic hyperinflation at peak exercise was unaffected by hyperoxia (Figure 5(b)), which is consistent with the recent work of Eves et al. [79]. It should be noted that the beneficial effects of delaying dynamic hyperinflation and reducing operating lung volumes during hyperoxic exercise may be less pronounced in normoxic or mildly hypoxemic COPD patients [72, 77].

A study by Somfay et al. [31] evaluated the dose-response effects of hyperoxia on operating lung volumes during exercise in normoxic COPD patients and in healthy controls. Their study demonstrated consistent increases in IC as the fraction of inspired O_2 increased from 0.21 to 0.50 with no further improvements thereafter in the COPD patients (no effect was observed in the healthy controls). The improvement in dyspnea with hyperoxia was correlated with changes in both EELV and EILV. However, this relationship has not

been found in more recent studies [72, 80]. Collectively, these studies suggest that hyperoxia consistently reduces V_E and dyspnea and improves exercise tolerance in patients with COPD. Most studies show some favourable effect of hyperoxia on IC during submaximal exercise but responses are highly variable and are likely dependent on the baseline level of respiratory impairment (e.g., resting level of hyperinflation, airway obstruction, and hypoxemia; hyperinflator versus nonhyperinflator during exercise, etc.) [72, 74, 77, 80].

6.3. Exercise Training. Well-designed exercise training interventions as part of a pulmonary rehabilitation program can improve exercise performance to a greater extent than other available treatment interventions for patients with COPD [81]. One of the primary mechanisms by which exercise training can improve exercise capacity is through a reduction in ventilatory stimulation due to lower levels of lactic acidosis (and V_{CO_2}) for any given exercise intensity [82]. The reduction in ventilation following exercise training seems to be mediated primarily through a reduced breathing frequency [83, 84]. This permits greater time for expiration between breaths, and, like other interventions that reduce ventilation (e.g., oxygen), this should have some favourable effects on IC during exercise. However, the impact of exercise training on IC behaviour during cycle exercise has been both modest and inconsistent across studies and it is clear that improvement in IC during exercise is not obligatory to achieve important improvements in the intensity and affective domains of dyspnea following exercise training [83–88].

7. Conclusion

Calculation of the peak exercise V_E to MVV ratio has traditionally been used to evaluate ventilatory reserve during CPET. This provides an estimate of demand versus capacity but gives little information on the source or nature of the ventilatory impairment. The resting IC provides valuable information on potential ventilatory capacity during exercise. A low IC increases the likelihood of critical dynamic mechanical constraints at relatively low exercise intensities, thus limiting further increases in ventilation. Examination of the IC, IRV, and breathing pattern at a standardized time or ventilation during exercise gives important insight into the individual's prevailing mechanical abnormalities and the mechanisms underlying dyspnea and exercise limitation. This detailed approach to CPET interpretation can also give valuable insight into the mechanisms of dyspnea relief and exercise performance improvements following various therapeutic interventions. The wealth of data derived from IC measurements also allows detection of physiological impairment in dyspneic patients with near-normal spirometry (e.g., mild COPD, pulmonary arterial hypertension, obesity, etc.) and may prompt specific treatment interventions to improve exercise tolerance. Collectively, the valuable information gained from the IC and derived physiological parameters provide a solid rationale for their regular inclusion during standard CPET for both clinical and research purposes.

Conflict of Interests

J. A. Guenette, R. C. Chin, J. M. Cory, and K. A. Webb have no conflict of interests to report. D. E. O'Donnell has received research funding via Queen's University from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Novartis, Nycomed, and Pfizer, and has served on speakers bureaus, consultation panels and advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Nycomed, and Pfizer.

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Review Article

Responsiveness of Various Exercise-Testing Protocols to Therapeutic Interventions in COPD

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Exercise intolerance is a key element in the pathophysiology and course of Chronic Obstructive Pulmonary Disease (COPD). As such, evaluating exercise tolerance has become an important part of the management of COPD. A wide variety of exercise-testing protocols is currently available, each protocol having its own strengths and weaknesses relative to their discriminative, methodological, and evaluative characteristics. This paper aims to review the responsiveness of several exercise-testing protocols used to evaluate the efficacy of pharmacological and nonpharmacological interventions to improve exercise tolerance in COPD. This will be done taking into account the minimally important difference, an important concept in the interpretation of the findings about responsiveness of exercise testing protocols. Among the currently available exercise-testing protocols (incremental, constant work rate, or self-paced), constant work rate exercise tests (cycle endurance test and endurance shuttle walking test) emerge as the most responsive ones for detecting and quantifying changes in exercise capacity after an intervention in COPD.

1. Introduction

Chronic airflow limitation is the defining physiological feature of Chronic Obstructive Pulmonary Disease (COPD) whose main symptom is dyspnea. Exercise intolerance is another major consequence of COPD, leading to a sedentary life style and poor quality of life [1, 2]. In fact, exercise intolerance is central to the progression of the downward spiral of COPD [3]. Considering the key role of exercise intolerance in the pathophysiology and course of COPD, the evaluation of exercise tolerance should now be included in the assessment of this disease [4], especially for the evaluation of the response to pharmacological and nonpharmacological interventions [5–7]. Also, the heterogeneity in the mechanisms of exercise intolerance in COPD highlights the importance of comprehensive exercise testing, assessing all systems potentially involved [8].

Exercise testing is currently included in the follow-up of chronic diseases like COPD. Exercise testing can be used to document the severity of pulmonary disease, the functional impact of altered respiratory function and to better

understand the pathophysiological mechanisms involved in exercise intolerance; this refers to the discriminative characteristic of the test. Exercise testing can also be used to quantify the impact of an intervention to improve exercise tolerance [9, 10] or dyspnea [11, 12] and in the preoperative and pre rehabilitation assessments of patients, corresponding to the evaluative characteristic of the test. A third characteristic corresponds to the reproducibility of the test. Each exercise testing presents different levels of responsiveness, according to their methodology advantages and disadvantages relative to these characteristics. The main focus of the present paper is to review the responsiveness of various exercise testing protocols that are used to assess the effects of pharmacological (bronchodilation) and nonpharmacological (exercise training, surgery) interventions on exercise capacity in COPD.

We will first discuss the concept of the minimal important difference (MID) since its understanding is crucial to place the magnitude of improvement in exercise tolerance following a given intervention into perspective. Then, the specifics of each testing protocol will be presented including the advantages and disadvantages of each individual

protocol regarding their properties. This will be followed by a nonsystematic review of the published results related to the testing protocol under consideration. Finally, the main physiological mechanisms explaining the differences in responsiveness across the exercise protocols will be briefly explained. The exercise protocols will be classified into three categories depending on the workload characteristic (incremental or constant) of the exercise protocols and the self-paced methodology.

2. The Concept of the Minimal Important Difference

It is now appreciated that statistical and clinical significances are not synonymous and that the interpretation of clinical trials should be done from a broader perspective taking into account both aspects (statistical and clinical) of the treatment effect. The minimal important difference (MID) is a concept defined as “the smallest difference in score of a domain of interest that patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management” [13]. Conceptually, the MID provides guidance to help determining whether a given change in a clinical outcome is associated with meaningful improvement for the patient. What is considered meaningful is typically assessed using questionnaires or perception scales (e.g., the 7-point Likert scale).

Three different methods can be used for the determination of MID values [14]: (i) the distribution (statistical) approach which is an estimate based on the distribution around the mean of the scores of the measure of interest in an untreated population (usually half the standard deviation of the changes in the variable of interest [15]); (ii) the anchor (external measure) approach which is an estimate based on the comparison of scores of the measure of interest to other outcome measures (the anchors) for which a MID has been previously determined; and (iii) the opinion approach which gathers opinions of experts, patients, and health-care practitioners about what should be considered as a meaningful change.

Each method could lead to various values and there is no single best methodology for the determination of a valid MID estimate. Therefore, it is recommended to combine them since one can gain confidence in the MID estimation if different methodologies provide similar estimates. Strictly speaking, the current methodologies available to assess the MID provide an estimation of the perception threshold and under most circumstances, it remains to be determined if this perception threshold is important for the patients. One important limitation of the MID concept is that MID values are not relevant for the interpretation of individual results. In fact, MID values are often considered as a “cut-off” threshold for a dichotomous categorization of individual results (“responder” or “non-responder” individuals) after an intervention. However, a misinterpretation could appear by considering any individual showing an improvement after intervention greater than MID as a “responder”, whereas

the natural individual variability could already exceed the MID value in the absence of an intervention [16]. This phenomenon highlights the limitation of applying MID values obtained by group data to the interpretation of individual results [16, 17] and therefore requires other tools for the interpretation of individual responses to intervention. Significant effort have been put forward to clarify what should be considered as a meaningful difference in power, duration and distance achieved with therapy during several exercise testing procedures over the past 15 years. Collectively, this work is of great assistance in the interpretation of the changes in exercise tolerance seen with interventions. The respective MID values for each different exercise testing protocol presented in this paper are provided in Table 1.

3. Incremental Exercise Tests

Based on the progressive increase of the exercise intensity in a short time duration, incremental exercise testing protocols (also called CardioPulmonary Exercise Testing when coupled with physiological measurements; CPET) are currently considered as the “Gold Standard” method for the evaluation of the degree of exercise limitation and to investigate the mechanisms of exercise limitation. These protocols can be performed on a cycle or a treadmill. They are often used to quantify the changes in exercise tolerance after an intervention [4]. Incremental exercise tests are relatively accessible for the evaluation of COPD patients but, when coupled to physiological measurements, they require expensive equipment, which needs regular maintenance and calibration and qualified staff to overview the tests [9].

3.1. Incremental Maximal Cycling Exercise Test. Incremental maximal cycling exercise is modestly responsive to rehabilitation, reflecting that the major benefit of exercise training is not to improve peak exercise capacity [18]. Lacasse et al. [19] reported a mean pooled effect of 8.4 Watts (95% CI: 3.4 to 13.4) in peak exercise work rate across 18 studies of pulmonary rehabilitation, an improvement that is in the range of the MID for this parameter. Reviewing the impact of exercise training on peak exercise capacity, Butcher and Jones [20] reported a 7% to 35% improvement of baseline peak exercise capacity. More recently, in a systematic review designed to compare interval and continuous training, Beauchamp et al. [21] showed an increase in peak exercise capacity of 11 Watts (95% CI: 9 to 13) and 10 (95% CI: 8 to 11) for interval and continuous training respectively. Although the available data suggest that CPET is responsive to demonstrate improvements following pulmonary rehabilitation, this exercise protocol is not the most sensitive tool to evaluate the impact of exercise training (see below).

Bronchodilation, a first-line therapeutic option for the management of the COPD, may improve exercise capacity by reducing expiratory flow limitation and air trapping [22]. The effect of short-acting bronchodilators on peak exercise capacity was evaluated in several studies [23–27]. In some of these studies, the improvement in peak exercise work rate was statistically significant but of uncertain clinical significance

TABLE 1: Characteristics of exercise testing protocols in COPD.

Characteristics	Incremental exercise tests			Constant work load exercise tests			Self-paced tests		
	Incremental cycle exercise	Incremental treadmill exercise	ISWT	CET	ESWT	Constant work rate treadmill test	3-min walk and step test	6MWT	6MST
Reproducibility	+	?	?	+++	+	?	+	+	+
Discriminative properties	+++	?	?	?	?	?	?	+++	?
Responsiveness	±	?	±	+++	++	?	?	±	?
MID values	+5-10 W [40, 41]	?	+48 m [42]	+100-200 s [10, 43]	+65 s or +95 m [7]	?	?	+25-54 m [17, 40, 44]	?

With ISWT: Incremental Shuttle Walking Test, CET: Cycle Endurance Test, ESWT: Endurance shuttle Walking Test, 6MWT: 6-minute walking test, 6MST: 6-minute stepper test; +, ++ and +++: positive result, ±: controversial result, ?: no data in the literature; W: watts, m: meters and s: seconds.

as the average improvement ranged from 3 to 7 watts [23, 26, 27] while in others, no significant effect of short-acting bronchodilators on peak exercise capacity were demonstrated [6, 25]. The impact of long-acting beta-2-agonist on peak exercise capacity is in the same order of magnitude [24, 25].

To summarize, incremental exercise testing protocols show a consistent responsiveness to interventions such as rehabilitation or bronchodilation but the magnitude of improvement is small. The modest responsiveness of the incremental exercise testing protocol can be easily understood when considering that peak exercise performance does not dramatically change with interventions, even in the healthy population, and that the spectrum of changes is much greater for endurance exercise capacities than for peak exercise capacities [18]. Furthermore, the absence of a well defined MID value could be a negative point for the responsive characteristic of this type of protocol. Despite this limitation for the assessment of response to therapy, incremental exercise testing is clinically useful in the exploration of the mechanisms of exercise limitation and as discriminative tools in the assessment of patients with COPD.

3.2. Incremental Maximal Exercise Test on Treadmill. Incremental maximal exercise tests can also be performed on treadmill. The rationale for doing so is to better mimic daily activities of COPD patients, even if the pattern of walking is different on treadmill than in daily conditions [28]. Only few studies used this methodology to assess patients with COPD [29, 30], and to the best of our knowledge, none used incremental treadmill exercise for assessing the impact of an intervention (pulmonary rehabilitation or bronchodilation).

3.3. Incremental Shuttle Walking Test. The ISWT is responsive to exercise training. Griffiths et al. [31] reported an increase in ISWT walking distance, ranging from 140 metres to 211 metres following a 6-week rehabilitation program for the rehabilitation group, a value that is clearly above the MID for this variable. Singh et al. [32] also reported significant improvement in the distance walked during the ISWT but to a lesser extent (+58 metres after a 7-week training program). However, the responsiveness of the ISWT to pulmonary rehabilitation is not universal. One randomized controlled trial aiming to determine the effect of creatine supplementation as an adjunct therapy to exercise training on functional exercise capacity in patients with COPD reported only a modest improvement in ISWT distance of 36.8 metres (95% CI: 17.6 to 56.1) for “Creatine and exercise training” group and of 24.3 metres (95% CI: 7.7 to 40.9) for “exercise training alone” group [33]. This improvement of ISWT distance is consistent in magnitude with the findings of Revill et al. [34], who reported a 37-metre improvement in the distance walked during the ISWT after a 7-week pulmonary rehabilitation.

The incremental shuttle walking test has been also used to evaluate the effects of bronchodilation on exercise capacity in COPD. In general, bronchodilation alone has only a modest impact on ISWT performance, with studies reporting smaller gains in walking distance than the proposed MID value for this exercise testing protocol. Twelve weeks of treatment

with formoterol (a long-acting β_2 -agonist) or ipratropium (a short-acting anticholinergic), compared to placebo, did not improve ISWT walking distance in patients with moderate to severe COPD [35, 36]. Other bronchodilation studies reported statistically significant results but the clinical significance of the findings are questionable. For example, a single dose of procaterol (a short-acting β_2 -agonist) was associated with a modest 37-meter improvement in ISWT walking distance [37]. The administration of salmeterol (a long-acting β_2 -agonist) during 52 weeks improved the ISWT walking distance by 30 metres (95% CI: 0 to 60) compared to placebo [38]. The use of once-daily inhaled tiotropium (a long-acting anticholinergic) in a 12-weeks multicentre randomized trial also induced a statistically significant increase of ISWT distance by 33 ± 12 metres (10.8%) on day 42 and by 36 ± 14 metres (11.8%) on day 84 compared with placebo [39].

To summarize, incremental walking shuttle test only presents a modest responsiveness to interventions, with the exception of exercise training for which some studies are positive [31, 32]. The improvement in ISWT walking distance reported in bronchodilation studies is usually within the MID value for this variable.

Based on the findings that we have reviewed, incremental exercise protocols (incremental cycle or treadmill exercise tests and ISWT) are not the ideal methodology to assess response to interventions because of questionable responsiveness. These tests are more appropriate in the evaluation of peak exercise capacity and/or the prescription of training programs. Incremental cycling exercise tests, when performed with cardiopulmonary monitoring, can also be used to investigate the physiological response to exercise. Although similar measurements could also be obtained during the ISWT with portable exercise system, this may be more challenging in walking subjects (see Table 1).

4. Constant Work Rate Exercise Protocols

The use of constant work rate exercise tests to quantify the effects of an intervention is increasingly popular due to several advantages of this methodology. Constant work rate endurance protocols are based on externally imposed and constant cycling or walking cadence that the patient has to maintain until exhaustion. The primary endpoint of these protocols is thus the endurance time (or the distance which is a product of the speed and time). These tests are usually performed at a high fraction of peak exercise capacity typically representing 75–85% of peak cycling work rate or 80% of the estimated peak VO_2 during the incremental shuttle walking test. An implication (and a disadvantage of this) is that the constant work rate protocols have to be performed with the knowledge of the peak cycling or walking capacity. These tests address the fact that increasing endurance capacity is a more natural outcome of exercise training than increasing walking speed during self-paced walks.

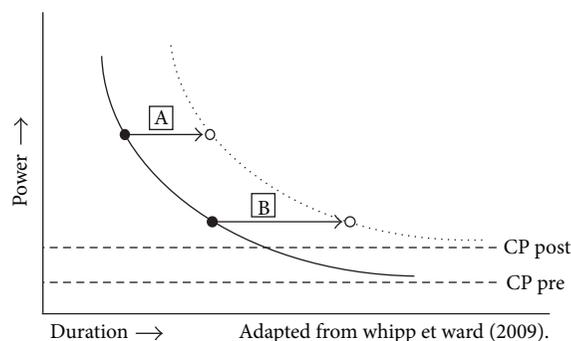
4.1. Cycling Endurance Test (CET). The CET is generally considered to be more responsive for detecting acute and

long-term improvement in functional capacity after pulmonary rehabilitation than the 6MWT [45–47]. Cambach et al. [45] investigated the effects of exercise training on exercise capacity in a cross-over study design. They reported an overall increase in cycling endurance time of ~7 min with exercise training in comparison to the control intervention. Porszasz et al. [48] reported a ~176% increase (from 6.6 min before training to 18.2 min after training) in endurance time in CET after endurance training. Laviolette et al. [10] reported, just after a 6–12 week rehabilitation program, a mean increase of 198 seconds of the endurance time measured during a CET performed at 80% peak work capacity. The improvement in constant work rate endurance time with pulmonary rehabilitation was maintained one year after the rehabilitation program, albeit to a smaller magnitude (137 seconds for endurance time in comparison with baseline values).

Cycle endurance tests have also been widely used for the evaluation of bronchodilation on exercise tolerance in COPD [22, 23, 49–57]. On average, the improvements seen with pharmacotherapy are smaller than with pulmonary rehabilitation. In most short-acting bronchodilation studies, the improvement in endurance time during CET is within the proposed MID for this parameter [23, 54, 58] although one study is positive both from a clinical and statistical point of view [59]. The impact of long-acting bronchodilator on endurance time during CET appears to be superior to that of short-acting bronchodilators with several investigators reporting improvements in endurance time following long-acting bronchodilation ranging from 90 to 236 seconds [22, 49–52]. This may have to do with the increased efficacy of long-acting bronchodilators but also with the longer duration of the treatment period. Some investigators did not succeed in showing benefits of long-acting bronchodilators on exercise tolerance during CET. These studies were generally relatively small and may have lacked statistical power [55, 56].

In summary, cycle endurance tests are considered as a responsive tool for evaluating the effectiveness of a pharmacological or nonpharmacological intervention in COPD population. Based on these findings, the CET exercise protocol should be viewed as more responsive than incremental cycle exercise test or the 6 min walking distance tests in the evaluation of response to therapy in COPD.

One limitation of the CET is that the physiological significance of a given improvement in endurance time after an intervention may be difficult to interpret. This has to do with the power/duration relationship properties that dictate that the endurance time varies exponentially with variations in the workload (or power) that is used during the test [60] and therefore explain the disparity among studies that used singles bouts of endurance test for the evaluation of the effectiveness of an intervention [61]. For example, let us consider the Figure 1 the power/duration relationship before (black circles) and after an intervention (white circles). Assuming that this intervention leads to an increase in critical power corresponding to an upward shift of this parameter (the power or workload for which exercise can be tolerate for very long period of time), the implication is a rightward shift of power/duration relationship, toward higher exercise durations for a given power [61].



A: increase of 100 s

B: increase of 200 s

FIGURE 1: The impact of the power/duration relationship on the exercise endurance response following an intervention. With CP: critical power pre- or postintervention, considered as the asymptote of the power/duration relationship.

From this figure, it can be appreciated that the choice of the power (relative to critical power) at which the test is performed at baseline (CP pre) influences the magnitude of improvement in endurance time seen after the intervention (CP post), and this, for the same degree of physiological improvement [61]. For example, in situation A, performed at a high power output relative to CP pre, the intervention induces an increase of 100 seconds of the CET endurance time. If we consider situation B for which the preintervention endurance time is larger (due to a smaller power output relative to CP pre), the gain in endurance time is now 2-fold higher than with situation A, and this for the same degree of physiological improvement. Therefore, the magnitude of improvement in CET endurance time is dependent on the baseline pretreatment value (i.e., the longer the pretreatment endurance time, the larger the postintervention improvement). Thus, any increase in endurance time to constant load exercise must be interpreted with caution regarding the physiological benefits that have accrued from the intervention, unless the pre- and postintervention power/duration characteristics are also reported [60]. Despite the importance of the power/duration relationship characteristics and its impact on the magnitude of improvement after an intervention, there is no consensus on the intensity to use for the realization of CET. Further investigations are required for the determination of the optimal intensity and therefore offering a standardization which is required for studies comparisons.

4.2. Endurance Shuttle Walking Test (ESWT). The endurance shuttle walk test was developed by Revill et al. and these authors firstly reported the responsiveness of the ESWT to pulmonary rehabilitation [34]. In this study, pulmonary rehabilitation induced a significant improvement amounting to 160% of the ESWT duration after a 7-week pulmonary rehabilitation program (corresponding to an increase of 334 metres). The corresponding improvement in ISWT distance was 32%. Eaton et al. [62] reported a 302-metre increase in ESWT distance after a similar intervention (corresponding

to a 92% increase) compared to a 17% improvement (47 m) in the 6MWD. These results highlight the fact that the ESWT may be more responsive to pulmonary rehabilitation than incremental protocols or the 6MWT [62], explaining the growing popularity of the ESWT, and more generally of any constant work rate exercise protocols.

Our group confirmed the responsiveness of the ESWT to detect improvement in walking endurance with various therapies [63, 64]. For example, a 117-second (or 160 metres) increase in endurance time was reported with a single inhalation of salmeterol compared to placebo [63] and a 132-second increase in endurance time was seen after 3 weeks of tiotropium [64]. Thus, similarly to what was reported in pulmonary rehabilitation studies, the ESWT appears to be more responsive than the 6MWT for detecting improvement of exercise tolerance after bronchodilation. This form of exercise is also more relevant to daily activities than cycling exercises [65].

4.3. Constant Workrate Treadmill Exercise Test. Constant workrate treadmill exercise test addresses the challenge of the requirement of a corridor to perform the ESWT. This form of exercise has been used in a clinical trial of pharmacotherapy in COPD [66]. The results from this study have been presented in the form of an abstract and full results are in preparation for publication.

4.4. 3 Minute Constant Workrate Walking and Stepping Test. A 3 min constant rate shuttle and 3 min constant rate stepping test have recently been developed. These two protocols have been specifically designed to evaluate the effects of therapies on exertional dyspnea, the most prominent symptom in patients with COPD [12, 67]. These tests have the advantage of not requiring an incremental exercise test before their performance since the walking or stepping cadence used during the test is not dependant on peak exercise performance [12, 67]. Their short duration and little requirement for equipment make them suitable for the use in the primary care setting. However, in the study of Perrault et al. [12], multiple bouts of exercise have been performed, limiting the use of such methodology in the primary care setting. Therefore, further studies are required in the future for developing an algorithm which can allow to determine the optimal walking or stepping rate required for inducing a sufficient breathing stimulus and thus reducing the number of exercise bouts. The responsiveness of the 3 min constant rate shuttle walking test to demonstrate reduction in dyspnea following acute bronchodilation has recently been demonstrated in a small clinical trial [67]. Similar results for the 3 min constant rate stepping protocol await confirmation. A MID for these two 3 min exercise protocols has not been determined.

The results concerning the responsiveness of the various exercise protocols to interventions are summarized in Figure 2.

In summary, constant work rate exercise protocols appear to be highly responsive to pulmonary rehabilitation and bronchodilation. The magnitude of improvements seen with these protocols after the intervention is well above the MID

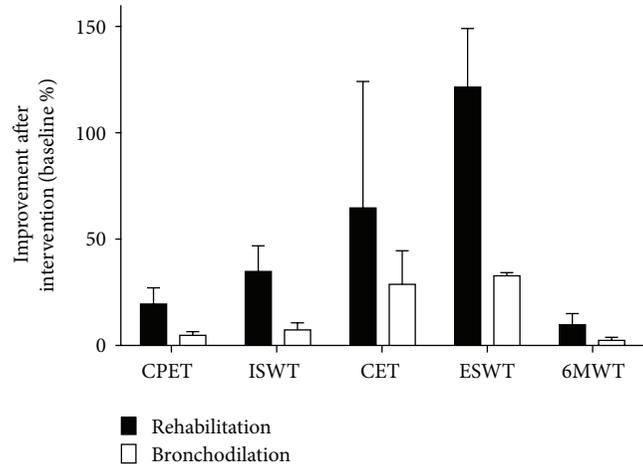


FIGURE 2: The impact of interventions on the exercise performance following testing methodologies in COPD population. With CPET: CardioPulmonary Exercise Test, ISWT: Incremental Shuttle Walking Test, CET: Cycle Endurance Test, ESWT: Endurance Shuttle Walking Test and 6MWT: 6 minute Walking Test. The percentages of improvement have been calculated, for each exercise protocol, by using the references quoted in the manuscript. All the others tests present in Table 1 (incremental treadmill exercise, constant work rate treadmill test, 3 min walk and step tests, and 6 minute stepper test) are not shown as there is nonexistent or insufficient data in the literature.

values, meaning that the observed improvement should be perceived as beneficial by most of the patients. Therefore, this type of testing protocol appears to be an excellent evaluating tool.

5. Self-Paced Exercise Tests

Due to the constraints relative to incremental exercise testing protocols and for being more representative of the daily activities performed by COPD patients, field tests have been developed in order to propose more simple tools for the evaluation of exercise capacity. The self-paced walking test, particularly the six-minute walking test, is the most popular field test when it comes to the evaluation of patients with COPD.

5.1. Self-Paced Walking Tests. Because of its widespread and ease of application, several pulmonary rehabilitation studies used the 6MWT distance as the main outcome. In a meta-analysis including 11 trials, Lacasse et al. [68] reported a mean treatment effect of 55.7 metres (95% CI: 27.8 to 92.8 metres) between treatment and control groups. In the 2006 updated version of this meta-analysis that involved 16 trials, the common effect for the six-minute walk was 48 metres, with 95% CI: 32 to 65 metres [19]. Similar values have been reported in one study aiming to compare interval and continuous exercise training, with an improvement of 48 metres (95% CI: 29 to 68 metres) after interval training and of 42 metres (95% CI: 25 to 59 metres) after continuous training [21]. Despite its popularity, one study reported that the 6MWT is

not the most responsive exercise tool to assess the effects of pulmonary rehabilitation in COPD [10]. This study highlights the fact that 6–12 weeks of pulmonary rehabilitation induce an improvement of the walk distance of 25 ± 52 metres (which is under the MID value). Moreover, the authors report that, among the population under consideration, only 27% of the patients reported an improvement higher than the MID value [10]. In summary, although the 6MWT is responsive to exercise training, it may not be the most responsive test to quantify the exercise-enhancing effects of this intervention.

There is lack of consensus about whether the MID for the 6MWT (and, as a matter of fact, for other exercise protocols) should be expressed in absolute or relative terms. In two studies, the MID value was reported as a percentage of baseline walk distance, ranging from 10% to 14% of the baseline 6 min walk distance [44, 69]. In the field of COPD however, most investigators prefer to report the MID in absolute values assuming that there is a fixed MID value across the range of baseline exercise performance. This practice is also justified based on the fact that an absolute value may be a more sensitive indicator than a relative value [69] and that MID expressed in % baseline value does not necessarily provide a better estimate than the absolute value [7].

The 6MWT has been used to evaluate the effects of bronchodilation in COPD. The overall conclusion is that the 6MWT has a low responsiveness in this setting since most of the studies reported improvement in 6MWD that are well below the MID value for this intervention, ranging from 20 to 42 m with short-acting β_2 -agonist [6, 70, 71], from 6 to 39 metres with short-acting anticholinergics [6, 23], from 21 to 54 metres with long-acting β_2 -agonist [72–74] and around 10 m with long-acting anticholinergics [75]. The lack of responsiveness of the 6MWT could be due to the presence of a ceiling effect with this test. Although this hypothesis is appealing, it was not supported by the findings of Pepin et al. [76] showing that patients with a high baseline walking distance did not show lesser gains in 6MWD than patients with lower performances. Another hypothesis concerns the intrinsic design and characteristic of the 6MWT, which has a fixed duration and a self-imposed pace. Under this situation, the only way to improve the walking distance is to increase the walking speed, something that patients are not typically inclined to do. In fact, patients are likely to tend to repeat the same performance after bronchodilation. This idea is supported by Pepin et al. [76] who reported similar cardiorespiratory kinetics and walking speeds during two separate 6MWT, one being performed after placebo and one after a bronchodilator, confirming that patients tend to reproduce the same walking pattern and to choose similar comfortable walking speed during repeated walking tests, irrespective of the administration of a bronchodilator.

Others interventions have been tested with self-paced walk tests. Inhaled corticosteroids induce an improvement of the walk distance (+33 metres or +8%) [77]. Diaphragmatic strength training [74], lung volume reduction surgery [78] and supplementary oxygen [79] have also been shown to improve walk distance after intervention by 50 to 95 metres (or from 20% to 36%). For these three studies, it is likely that the gains in the 6MWT distance were clinically relevant.

In summary, the current information of the 6MWT indicate that this methodology is not the most responsive to evaluate the effects of interventions (pulmonary rehabilitation or bronchodilation) on exercise tolerance in patients with COPD. However, it is well accepted that self-paced walk tests present a good discriminative capacity for the estimation of the severity of the disease and a good predictive value in estimating vital prognosis [80, 81].

5.2. Self-Paced Stepping Test. With the idea of avoiding the need for a corridor and to reproduce stair climbing, an important daily physical task, some authors have developed a 6 min stepping version of the walking protocol [82]. This protocol consists of asking patients to step up and down for as much as possible during a fixed duration of 6 minutes [82]. Little information is available for this specific field test because it has only been recently developed. No MID values are currently available for this test. The responsiveness of the 6 minute stepper test has not been evaluated in the COPD population; the sensitivity of the stepper test being inferred from comparisons of the performance during this test in two COPD versus healthy individuals [82]. Rammaert et al. [83] used the 6 min stepper test for the evaluation of home-based pulmonary rehabilitation in idiopathic pulmonary fibrosis and reported a significant improvement of the number of steps performed after 6 minute of exercise, suggesting that the 6 min stepper test is responsive to rehabilitation. However, this finding could be specific to pulmonary fibrosis and the responsiveness in COPD population needs to be confirmed.

6. Physiological Mechanisms Underlying the Responsiveness of Exercise Protocols to Interventions

Aerobic training, alone or in conjunction with strengthening exercises, induces structural changes and adaptations in cardiovascular and muscular systems. These adaptations mainly concern the improvement of oxygen delivery and uptake at exercising muscle level, with adaptations reflecting an increase of muscle capillaries and a conversion from fast fibre type (type II) to slow fibre type (type I), which indicates an increased oxidative capacity of the muscle [84, 85]. As result of these adaptations, the muscle metabolism will be modified promoting the use of the aerobic pathway instead of the glycolytic pathway [86, 87]. One implication of these muscle physiological adaptations will be a reduced tendency toward limb muscle fatigue [88]. The preferential use of aerobic metabolic pathway will also have consequences at the central component of exercise limitation by reducing the ventilatory requirements for a given exercise level [86, 89–91]. The reduced ventilation, along with a slower and deeper breathing pattern [89], will be associated with a decrease of dynamic hyperinflation and dyspnea [48, 92, 93].

The mechanisms of improved exercise tolerance with bronchodilation are different than with exercise training. The use of bronchodilators increases airways calibre, improves

expiratory flow rates and, as a consequence, decreases hyperinflation at rest and during exercise [22]. Breathing at lower operative lung volumes will allow larger expansion in tidal volume (V_T), a major determinant of exercise tolerance in COPD [94]. This ability to expand V_T reflects lesser mechanical ventilatory constraints in relation to the increased resting and exercising inspiratory capacity and inspiratory reserve volume [49, 95]. From the patient perspective, breathing at lower operative volumes, farther from total lung capacity, has a tremendous impact of the perception of dyspnea [95].

Physiological factors could also explain the different levels of responsiveness of the different tests for the detection of the effectiveness of an intervention (see Figure 2). The better sensibility of walking to detect improvement of exercise tolerance after an intervention could be explained by the fact that walking induces less quadriceps fatigue than during cycling [96]. Leg fatigue is a phenomenon that prevents bronchodilation to fully translate into better exercise capacity [96, 97]. On the other hand, exercise desaturation is more common during walking than cycling [98–100]. This could be viewed as a potential disadvantage of walking protocols since severe hypoxemia could diminish the ability of bronchodilation to improve exercise capacity. Although the ESWT and 6MWT both involve walking they do not share similar responsiveness. This difference in evaluative properties between the two walking protocols is in part related to their design, the main point being that the 6MWT is self-paced and the ESWT externally paced. Therefore, the improvement of the exercise performance for the two tests does not involve the same mechanisms. 6MWT requires the patient to increase his walking speed while the ESWT requires the patient to increase endurance time. Considering the fact that patients tend to reproduce the same walking pattern during 6MWT [76], increasing walking speed with intervention appears more difficult to achieve than walking for a longer period of time at a predetermined cadence.

7. Conclusion

This paper focuses on the responsiveness of various exercise testing protocols currently available for the evaluation of exercise tolerance in COPD. It emerges that constant-load endurance tests are generally more responsive for detecting improvement on exercise tolerance after an intervention than incremental exercise tests protocols or self-paced walk tests. However, each test has its own discriminative and evaluative properties (see Table 1) as well as their specific methodological features. As such, the choice of the most appropriate exercise test methodology should be determined according to the objective of the measurement.

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Research Article

A Multivariable Index for Grading Exercise Gas Exchange Severity in Patients with Pulmonary Arterial Hypertension and Heart Failure

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Patients with pulmonary arterial hypertension (PAH) and heart failure (HF) display many abnormalities in respiratory gas exchange. These abnormalities are accentuated with exercise and track with disease severity. However, use of gas exchange measures in day-to-day clinical practice is limited by several issues, including the large number of variables available and difficulty in data interpretation. Moreover, maximal exercise testing has limitations in clinical populations due to their complexity, patient anxiety and variability in protocols and cost. Therefore, a multivariable gas exchange index (MVI) that integrates key gas exchange variables obtained during submaximal exercise into a severity score that ranges from normal to severe-very-severe is proposed. To demonstrate the usefulness of this index, we applied this to 2 groups (PAH, $n = 42$ and HF, $n = 47$) as well as to age matched healthy controls ($n = 25$). We demonstrate that this score tracks WHO classification and right ventricular systolic pressure in PAH ($r = 0.53$ and 0.73 , $P \leq 0.01$) and NYHA and cardiac index in HF ($r = 0.49$ and 0.74 , $P \leq 0.01$). This index demonstrates a stronger relationship than any single gas exchange variable alone. In conclusion, MVI obtained from light, submaximal exercise gas exchange is a useful approach to simplify data interpretation in PAH and HF populations.

1. Introduction

The lungs are linked hemodynamically in series with the heart, share a common surface area, are exposed to similar intrathoracic pressure changes during breathing, compete for intrathoracic space, and receive nearly 100% of the cardiac output. Receptors in the heart influence breathing patterns, while neural pathways in the lungs in turn may influence cardiac function (e.g., heart rate). Small increases in metabolic demand (e.g., exercise) enhance these cardiopulmonary interactions. Thus it is no surprise that diseases that primarily influence the lungs or the heart significantly impact the other organ system [1, 2]. This can be especially observed in patients with pulmonary arterial hypertension (PAH) where right heart failure evolves and in patients with left heart failure (HF) where significant changes occur in lung mechanics, ventilatory control, and ultimately in respiratory gas exchange. In both these patient groups gas exchange abnormalities are often present at rest, but are accentuated with the challenges of exercise. Thus,

noninvasive measures of cardiopulmonary gas exchange obtained during exercise have become a relatively common means to assess disease severity, prognosis, and response to therapy. However, despite the large availability of data confirming the utility of exercise gas exchange measures during exercise in these patients groups and the quickly improving and simplified approaches to testing, noninvasive respiratory gas exchange remains relatively poorly understood and underutilized in day to day clinical practice [3].

There have been a number of impediments to more extensive utilization of exercise respiratory gas exchange. This includes issues such as the large number of variables that are produced from typical commercially based systems, the somewhat broad range of normal values (influenced by age, gender, fitness, obesity, anxiety, body size, etc.), comorbidities that may influence the data, the complexities and expense that have been associated with comprehensive clinically based cardiopulmonary exercise testing, and difficulties and anxieties associated with maximal testing of often brittle patient populations [4].

TABLE 1: Model showing individual variables (individual variable index, IVI) that make up the multivariable scoring system. Normal values from literature with delta representing a risk cutoff for each IVI. (MVI = CUM IVI/6).

	Rest PetCO ₂	ΔPetCO ₂	SaO ₂	OUES	V _E /VCO ₂ slope	P _{CAP}	
Normal value	40	3.6	94	1.6	26	400	
Delta	5	1.8	4	0.24	7	40	
Severity: IVI scores	Measured	Measured	Measured	Measured	Measured	Measured	CUM IVI
Normal: 0	40	3.6	94	1.6	26	360	0.00
Normal-mild: 1	35	1.8	90	1.36	33	320	6.00
Mild-moderate: 2	30	0	86	1.12	40	280	12.00
Moderate-severe: 3	25	-1.8	82	0.88	47	240	18.00
Severe-very severe: 4	20	-3.6	78	0.64	54	200	24.00

However, noninvasive commercially available gas exchange systems have been developed that are simpler, self-calibrating, with a lighter, less complicated patient interface [5]. In addition, it is becoming clear that gas exchange data other than peak oxygen consumption (VO_{2max} or VO_{2peak}) that can be obtained from light or submaximal exercise (e.g., V_E/VCO_2 slope, OUES, and PetCO₂) as a slope or change from rest may be as good or in some cases more prognostic, reproducible, and sensitive than those obtained from maximal exercise testing and provoke less patient anxiety at reduced cost [6]. We have previously demonstrated that blending simpler devices with minimized, and submaximal protocols is well liked by patients, with the gas exchange data adequately separating both PAH and HF patients from healthy populations and according to disease severity [7–9].

To further simplify cardiopulmonary gas exchange for clinical use in the PAH and HF populations, we are further proposing a multivariable index (MVI) that takes into account the key gas exchange variables obtained during exercise that have been shown to be associated with these disease entities. The value of a multivariable index, or score, has been previously suggested and should have the following characteristics [10]: (1) utilizes variables that have been well documented in the literature for their normative ranges and prognostic value, (2) utilizes variables that have been associated with other clinical identifiers (e.g., disease classifications or common clinical metrics such as right heart pressures or cardiac index), (3) utilizes a model that can easily be adjusted as literature evolves, and (4) provides a simple conceptual framework for scoring that is similar to clinically intuitive scoring methods (e.g., WHO or NYHA classification), but provides a continuous variable which is more sensitive to changes in disease pathophysiology or to therapy than typical, more subjective scoring systems. This approach to creating a novel noninvasive gas exchange severity score from submaximal data for both PAH and HF is described and tested in these patient groups. We previously reported a gas exchange scoring system specific for PAH; however, we suggest this current more comprehensive and systematic approach provides a clearer framework for tracking PAH patients, appears to track disease status in the HF population, and provides a modifier for exercise induced PH [11–13].

2. Methods

2.1. Development of the Multivariable Index (MVI) for Scoring Gas Exchange Data. Based on previously reported data from our laboratory as well as others, we identified 6 variables that have been shown to track disease severity and/or prognosis in PAH and in the HF populations which can be obtained from rest and light, submaximal exercise [8–10, 13–18]. Many of these variables have published cut off values or ranges that are associated with higher risk [16, 19]. This includes (1) the ventilatory equivalents for carbon dioxide production (V_E/VCO_2) or breathing efficiency [19], (2) the oxygen uptake efficiency slope (OUES) [17], (3) oxygen saturation (SaO₂) [20], (4) the resting PetCO₂ [21], (5) the change in PetCO₂ with exercise, and (6) a calculated gas exchange variable as an index for pulmonary capacitance (P_{CAP}) which is the oxygen pulse multiplied by PetCO₂ ($O_{2pulse} \times PetCO_2$) that tracks invasive measures of pulmonary capacitance [13] and a modifying variable based on the slope of change in the inflection of PetCO₂ from rest to light exercise [12]. This final modifier has been suggested to reflect more severe exercise-induced changes in pulmonary vascular pressure and/or potential shunting through a PFO or intrapulmonary shunts due to high pressures [12]. There is some redundancy purposefully built into the MVI for variables most strongly associated with clinical measures, but yet retaining the ultimate goal of a single score that quantifies the severity of derangement in gas exchange rather than a formal surrogate to these other clinical markers. In fact, we would propose that in many cases that gas exchange data from light exercise may give a more important measure of integrated central hemodynamic function than the more commonly used “gold standards” for assessing and quantifying disease severity.

Table 1 describes the variable set used, the normal values [3, 4, 22, 23], and the delta value or the difference between the normal value and the risk cutoff point. In the lower table, the rows under “measured” are measured values of the variable in that column ranging in severity from normal to severe-very severe. The first column is individual variable index (IVI) score following severity, and the last column is cumulative IVI scores in a row. It is noted that some variables vary directly in severity from low to high (e.g., V_E/VCO_2 slope) and some variables vary in severity inversely from high to low (e.g., OUES). In this manner, if the measured = NV

TABLE 2: Baseline multivariable index (MVI) scoring system.

CUM IVI	MVI = CUM IVI/6	Range	Severity	NYHA
0.00	0.00	<1	Normal	n/a
6.00	1.00	1 and <2	Normal-mild	I
12.00	2.00	2 and <3	Mild-moderate	II
18.00	3.00	3 and <4	Moderate-severe	III
24.00	4.00	≥ 4	Severe-very severe	IV

TABLE 3: MVI scoring system weighted for P_{CAP} .

CUM IVI	MVI = CUM IVI/7	Range	Severity	NYHA
0.00	0.00	<1	Normal	n/a
7.00	1.00	1 and <2	Normal-mild	I
14.00	2.00	2 and <3	Mild-moderate	II
21.00	3.00	3 and <4	Moderate-severe	III
28.00	4.00	≥ 4	Severe-very severe	IV

TABLE 4: MVI scoring system weighted for the slope of change and magnitude of change in PetCO_2 (indicative of exercise induced PH).

MVI_{PH}	Modifier
≥ 0	0.00
<0 and > -5	0.50
≥ -5 and > -10	0.75
≤ -10	1.00

(normal value), the value of the $\text{IVI} = 0$. If the measured equals the risk cutoff point, the value of $\text{IVI} = 1$. IVIs that result in MVIs greater than 4.0 are scored as severe-very severe. Hence, MVI is cumulative IVI divided by 6. Normal subjects have MVI values less than 1.0, and it can be seen that the 6 variable MVI values closely resemble the NYHA classification system as shown in Table 2.

2.2. Seven Variable Model with Weighting. Another feature of the MVI classification system is the ability to impart a greater weight to IVIs . It is proposed that this feature would allow for the evolution of disease specific MVIs . For this paper, the individual IVI for P_{CAP} was “double counted.” This metric was double weighted due to the ability of it to track pulmonary vascular capacitance, an important metric in gas exchange severity in both HF and PH. Therefore, the MVI was then obtained by dividing the cumulative IVI by 7, rather than 6 for the unweighted MVI . The effect of doing so can be observed in Table 3.

2.3. Additional Modifiers. The MVI classification system also has the ability to apply modifiers. It has been demonstrated in the literature that an abrupt fall PetCO_2 (steep slope) with exercise is itself a gauge of severity of PH [12]. We therefore increased the MVI score by values proportional to the magnitude and slope of change in PetCO_2 during

exercise (see Table 4). Adding the modifier for the PetCO_2 patterns increased the severity score for individual subjects without altering the MVI scale range. In addition, adding the MVI_{PH} modifier to the MVI score consistently improved the correlations between the index and other clinical variables in both PAH and in the HF populations.

3. Results

3.1. Testing the Model in Patient Groups. We examined the use of the final MVI score ($\text{CUM IVI}/7 + \text{additional modifier}$) in three populations from previously published studies (Table 5) [9, 24, 25]. This included patients with primarily PAH and classic systolic HF along with healthy subjects of similar age ranges. The PAH patients were recruited with known pulmonary hypertension through our PH clinic and performed a light submaximal 3 min step test after collecting 2 min of resting data, while the HF patients performed submaximal cycling ergometry (similar levels of perceived exertion). Control subjects performed a combination of the light step testing and submaximal cycle ergometry. Both patient groups had a range of disease severity levels and were typically on standard therapy. Breath by breath gas exchange data were collected for all populations using the Shape Medical Systems, Inc., simplified gas exchange system, and slopes (e.g., $V_E/V\text{CO}_2$) were determined by linear regression. Thirty second averages were used to calculate MVI variables.

The ranges for MVI for each database are illustrated in Figure 1(a) (PAH) and Figure 1(b) (HF). When compared to the WHO or NYHA classification for the respective patient cohorts, (Figures 2(a) and 2(b)), it can be seen that the clinical classification results in “data aliasing” versus the MVI score which gives a continuous variable. Figures 3 and 4 give examples of individual PAH and HF patients over the range of scores obtained by the final MVI model. This also includes a healthy normal individual. Figure 5 shows the ranges of MVI scores for the control, PAH, and HF populations. It should be noted that the patient populations presented have benefited from medical therapy, and thus overlap exists across populations.

Figure 6 shows an example of a PH patient and an HF patient before and after intervention (medication titration in the PH patient and cardiac resynchronization therapy in the HF patient). Both patients demonstrated benefits in clinical measures (RVSP , CI , and 6 min walk in PH patient and NT Pro BNP , NYHA class, and LVEF in the HF patient), with improvements in the MVI score. We also examined the overall relationship between the MVI score to RVSP and WHO classification in PAH (Figures 7(c) and 7(d)) and CI and NYHA class in HF (Figures 7(a) and 7(b)). The MVI demonstrated a good relationship with clinical indices, (e.g., WHO class and RVSP in PAH $r = 0.53$ and 0.73 , resp., and NYHA and CI in HF $r = 0.49$ and 0.74 , resp.; $P \leq 0.01$). The score was more highly correlated with the physiological measures versus the more subjective functional classifications. Individual correlations for the components of the MVI score with CI and RVSP are provided in Table 6. PetCO_2 , OUES , $V_E/V\text{CO}_2$ slope, and P_{CAP} all demonstrated significant relationships with CI in HF and RVSP in PAH

TABLE 5: Subject characteristics.

	Controls	PAH	Heart failure
Number (% female)	25 (80%)	40 (80%)	45/(13%)
Age (years)	51 ± 15	50 ± 13	54 ± 8
Height (cm)	167.8 ± 8.2	167.7 ± 7.0	174.9 ± 8
Weight (kg)	70.1 ± 12.7	75.8 ± 16.5	86.6 ± 16.3
HF etiology			
Ischemic/dilated (<i>n</i>)			23/22
NYHA Class (I/II/III/IV)			5/7/23/10
LVEF (%)	61 ± 7	64 ± 7.3	20 ± 6
NT Pro BNP/BNP		770 ± 1239	852 ± 2341
Cardiac index	3.0 ± 0.3	3.1 ± 0.7	1.9 ± 0.6
PAH etiology			
Idiopathic	—	25 (63%)	
Hereditary	—	4 (10%)	
Associated with diet drug use	—	2 (5%)	
Portopulmonary hypertension	—	1 (2%)	
Associated with connective tissue disease	—	8 (20%)	
Functional class (WHO) (I/II/III/IV)	—	7/20/11/2	
RV pressure (mmHg)	26 ± 4	76 ± 23	49 ± 18

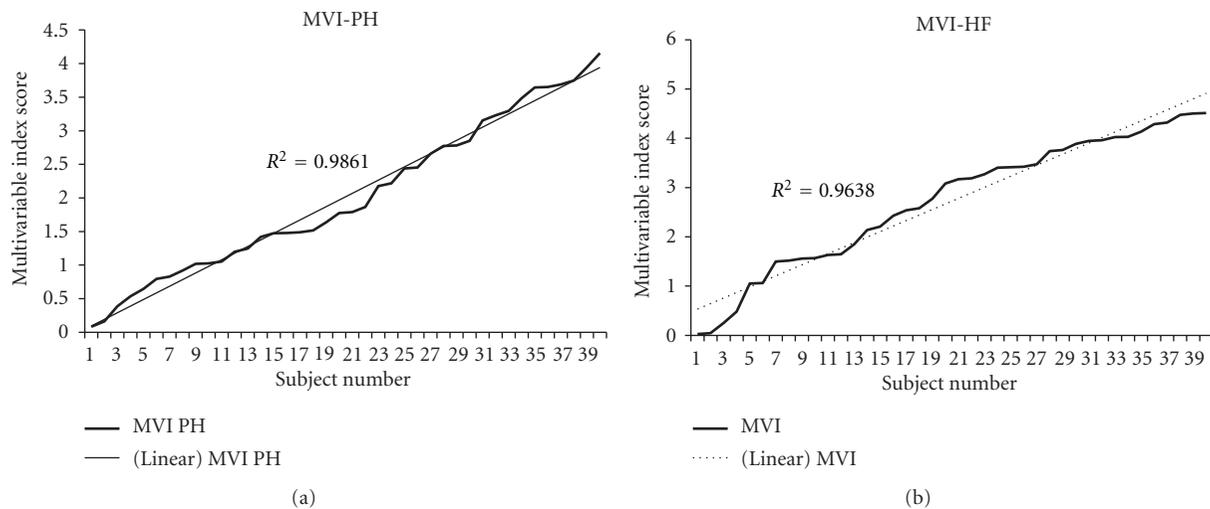


FIGURE 1: MVI score sorted and plotted for each subject for PAH and HF populations showing the score to be a continuous variable.

patients with less significant relationships between these gas exchange measures and NYHA or WHO classification. Modest improvements over the majority of variables were observed using the MVI score.

4. Discussion

4.1. Summary of Pertinent Findings. We propose a comprehensive multivariable index (MVI) scoring system to quantify gas exchange severity from light submaximal exercise data specific to populations with pulmonary vascular disease and demonstrate its utility in patients with PAH and systolic heart failure. The MVI allows a simple approach to integrating important gas exchange variables into a single conceptual score designed to track disease severity. The score

is further weighted towards variables that reflect more severe hemodynamic derangement during exercise and is based on exercise loads that are commonly experienced by patients in daily activities. This score while designed to reflect gas exchange abnormalities and not necessarily other clinical tracking variables shows a modest association with clinically used classification schemes as well as catheter or echo-based measures.

4.2. Rationale and Goals for Designing a MVI Scoring System for Exercise Gas Exchange in Chronic Disease. While methods for capturing noninvasive gas exchange during exercise have evolved to simple breath by breath systems, little advancement has been made in simplifying the approach to interpretation and applying this to clinical populations.

TABLE 6: Relationship of individual gas exchange measures with CI and RVSP in HF and PAH, respectively.

	HF cardiac index	NYHA	PAH RVSP	WHO
Rest PetCO ₂	0.52	0.47	0.39	0.12
ΔPetCO ₂	0.42	0.23	0.62	0.55
SaO ₂	0.05	0.23	0.47	0.15
OUES	0.66	0.40	0.46	0.47
V _E /VCO ₂ slope	0.53	0.34	0.63	0.51
P _{CAP}	0.69	0.40	0.58	0.41
MVI score	0.74	0.49	0.73	0.53

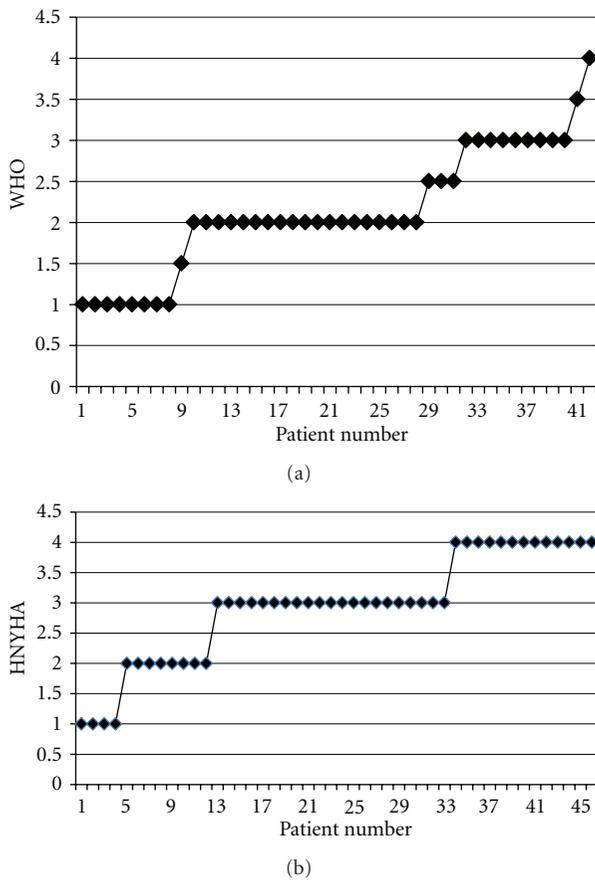


FIGURE 2: WHO classification for PH group and NYHA classification for HF group.

As a result, noninvasive measures of gas exchange during exercise remain underutilized in clinical practice [3, 4, 22]. A large number of variables are quantified during a typical test that include measures of breathing pattern, breath timing intervals, and gas exchange measures. Most established clinical exercise laboratories tend to focus on maximal testing and the classic assessment of peak oxygen consumption (VO_{2peak}). However, there are a number of limitations in this type of assessment. This includes issues regarding patient anxiety with maximal testing-balance problems

and uncertainties in their ability to push themselves to a true maximum. There is a need for more comprehensive monitoring equipment with the risks of maximal testing, often the need for multiple personnel for testing (increasing the cost), different use of protocols across centers as well as stopping criteria (making it hard to compare data), and the modest variability in the VO_{2peak} obtained. Over the last decade or more, it has become clear that a number of submaximal responses to exercise are as or more predictive for morbidity and mortality in the HF population, and many of these noninvasive submaximal measures are slopes or changes from rest and thus relatively insensitive to intensity of exercise, and in many cases being more reproducible [6]. Metrics that have been shown to be highly prognostic and sensitive to disease severity include the ventilatory efficiency, the oxygen uptake efficiency slope, the absolute or change in PetCO₂, the change in O_{2pulse}, (oxygen saturation, SaO₂) [8–10, 13–18].

Ventilatory efficiency has been linked to high dead space ventilation, due mostly to a more rapid shallow breathing pattern, combined with a greater relative hyperventilation. It increases progressively with disease severity in both PAH and HF [8, 9, 26]. PetCO₂ appears to track the rise in pulmonary vascular pressures with exercise, especially in PAH patients, likely not only due to both a pressure-induced increase in ventilation, but also due to increasing ventilation and perfusion inhomogeneities in the lungs and is typically inversely related with V_E/VCO₂ slope suggesting that in general they provide similar information [8, 9, 12]. Oxygen pulse (VO₂/HR) is essentially the stroke volume multiplied times oxygen extraction, but appears to track stroke volume relatively well [13]. Using invasive or technical echocardiography-based measures, various techniques have been used to quantify a value representing pulmonary vascular capacitance (change in stroke volume relative to change in pulmonary pressures), which has been shown to be predictive of mortality in the PAH population [27, 28]. We previously compared a noninvasive estimate of pulmonary capacitance based on the equation (O_{2pulse}, as an estimate of stroke volume) × (PetCO₂, as an estimate of pulmonary vascular pressure) to catheter based measures obtained during exercise and found a strong relationship in the HF population [13]. The gas exchange derived P_{CAP} also demonstrated a relatively strong relationship with our clinical metrics in this study with only modest improvements using the complete MVI score. However, many gas exchange variables tend to change in concert, and in particular measures of PetCO₂ and/or V_E/VCO₂ slope appear to be the variables that are most highly associated with clinical metrics and are counted or weighted heavily in the MVI scoring system, while at the same time allowing for other variables (e.g., SaO₂) to contribute in a positive or negative way to the final score. In addition, such an approach to amalgamating variables tends to reduce noise. Thus the MVI score is weighted heavily towards factors which elevate dead space ventilation, inhibit a rise in stroke volume, cause a more rapid, and shallow breathing pattern and to a lesser extent cause oxygen desaturation with exercise (e.g., shunt, low VA/Qc regions, and diffusion limitation). We also amplify the

	Normal	Normal-mild	Mild-moderate	Moderate-severe	Severe-very severe
Age (yr)	58	58	52	50	48
Weight (kg)	72	74	82	66	79
BNP		327	617	829	2100
Rest PetCO ₂ (mmHg)	29.2	34.2	41.3	31.5	28.4
Delta PetCO ₂ (mmHg)	5.1	-0.8	-4.1	-0.7	-5.5
SaO ₂ (%)	95	91	95	97	94
OUES	2.1	1.5	1.1	0.7	0.8
V _E /VCO ₂ slope	29.9	35.1	36	35.5	56.5
P _{CAP}	388	362	274	159	135
CUM IVI 7	0.17	7.44	13.69	20.42	28.2
CUM IVI/7	0.02	1.06	1.96	2.92	4.03
Modifier	0	0	0.25	0.25	0.5
MVI	0.02	1.06	2.21	3.17	4.53

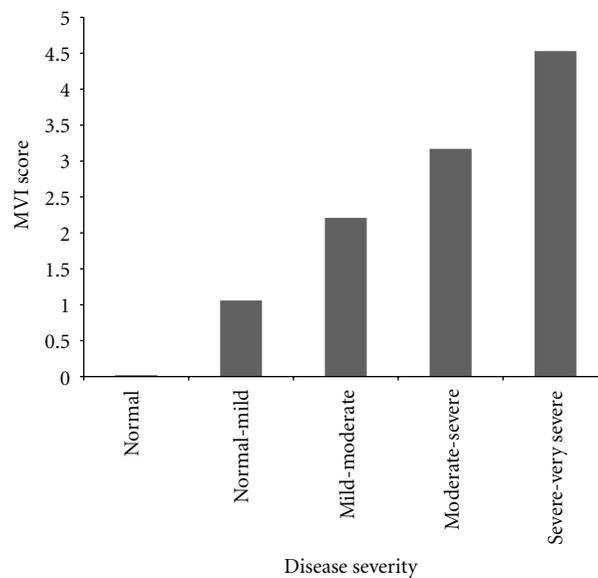


FIGURE 3: Final model with examples of HF patients according to gas exchange severity.

negative score if the rate of change in PetCO₂ with exercise is excessive.

4.3. Need for a Multivariable Gas Exchange Severity Score and Taking an Intuitive versus Statistical Approach. The MVI score demonstrates a modest improvement in the association with clinical measures over any single variable. However, while the score was purposefully weighted to track disease severity in the PAH and HF populations, the original intent was to create a gas exchange severity score and thus to some extent to be independent of other clinical measures. Thus, while one would expect the MVI score to generally track other clinical or physiological measures associated with disease severity, one would not necessarily expect a strong relationship with these clinical measures for a variety of reasons. For example, in some PAH patients, creating artificial shunts may reduce symptoms, but at the same time cause greater gas exchange abnormalities with exercise, making the gas exchange severity score worse. Therefore we chose to take an intuitive approach rather than a statistical

approach to create the scoring system, as the score should be able to serve as an independent way to track disease and because there is no perfect gold standard for which to develop the statistical approach. In addition, other measures such as NYHA or WHO classification remain quite subjective.

Other problems exist with the current “gold standards,” including a large variability in both echocardiogram and catheter-based measures, and both measures tend to have a number of limitations and often assumptions, particularly when cardiac hemodynamics are assessed during exercise. Thus our goal was to develop a comprehensive and adaptable gas exchange severity score based on the literature that is not dependent on maximal exercise values and provides an independent value for grading and tracking disease relative to other clinical measures.

4.4. Implications for the Future of Exercise Gas Exchange in Select Populations. With simplified techniques for quantifying gas exchange and the growing awareness that values

	Normal	Normal-mild	Mild-moderate	Moderate-severe	Severe-very severe
Age (yr)	52	41	57	44	53
Weight (kg)	77	68	73	66	76
BNP		103	518	918	3056
Rest PetCO ₂ (mmHg)	34.2	37.3	30.2	34.9	29.1
Delta PetCO ₂ (mmHg)	3.7	-0.8	2.2	-1.8	-7.3
SaO ₂ (%)	95	91	91	93	90
OUES	1.71	1.53	1.08	0.78	1.15
V _E /VCO ₂ slope	29.4	35.1	33.7	36.2	61.0
P _{CAP}	396	362	226	242	166
CUM IVI 7	1.1	7.1	15.5	17	27.7
CUM IVI/7	0.16	1.02	2.21	2.43	3.96
Modifier	0	0	0	0.75	1
MVI	0.16	1.02	2.21	3.18	4.96

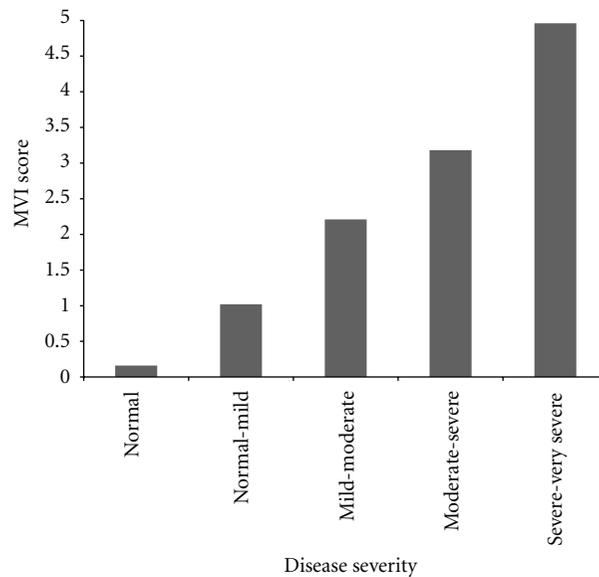


FIGURE 4: Final model with examples of PAH patients according to gas exchange severity.

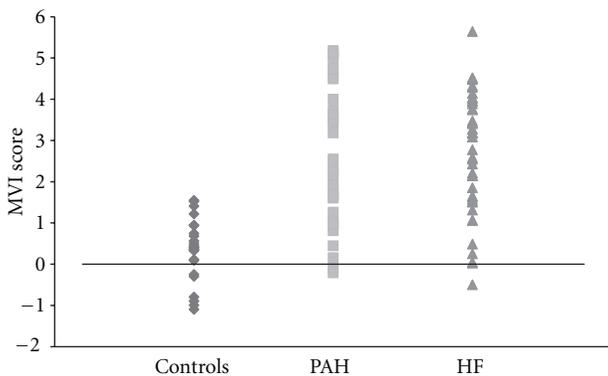


FIGURE 5: Range of MVI scores for patient groups and controls.

obtained with light submaximal exercise are as prognostic as maximally obtained values in several populations, cardiopulmonary gas exchange could be easily adapted to many clinical areas as more of a “vital sign” rather than the more comprehensive and elaborate approach to testing

that has classically been used, particularly in the HF and PH populations where ischemia detection is not a primary end point. Adding a gas exchange severity score to this simplified approach for screening and tracking patients further simplifies testing and reduces the need for specific expertise in cardio respirator physiology. We would propose that having a scoring system such as the MVI would allow a more comprehensive metric than “VO_{2peak}” and a scaling system that is more similar to other scoring systems (e.g., NYHA or WHO classification) that are familiar to clinical experts.

4.5. Limitations. We have created a gas exchange severity score that is weighted towards abnormalities in gas exchange found in HF and PAH. We have not specifically tested this in large populations with multiple comorbidities (e.g., COPD), and thus its utility in these patient groups would need to be determined. However, the MVI system is easily adaptable to other patient groups and changed or weighted towards additional variables that are more specific to a given population.

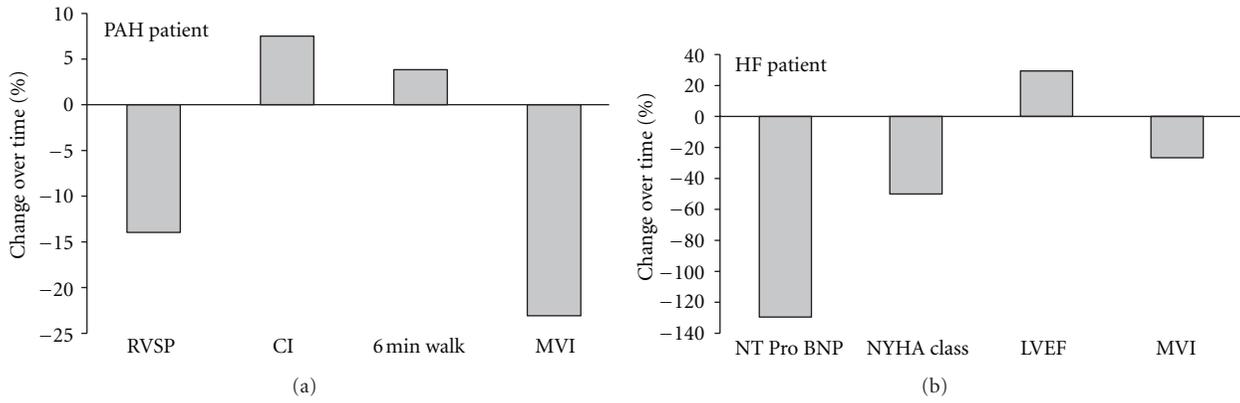


FIGURE 6: Tracking disease status over time, (a) PAH patient 3 mo. after treatment demonstrating modest improvements in clinical measures and the MVI score, (b) HF patients 3 mo. after CRT device implantation demonstrating similar directional changes in MVI score with clinical metrics.

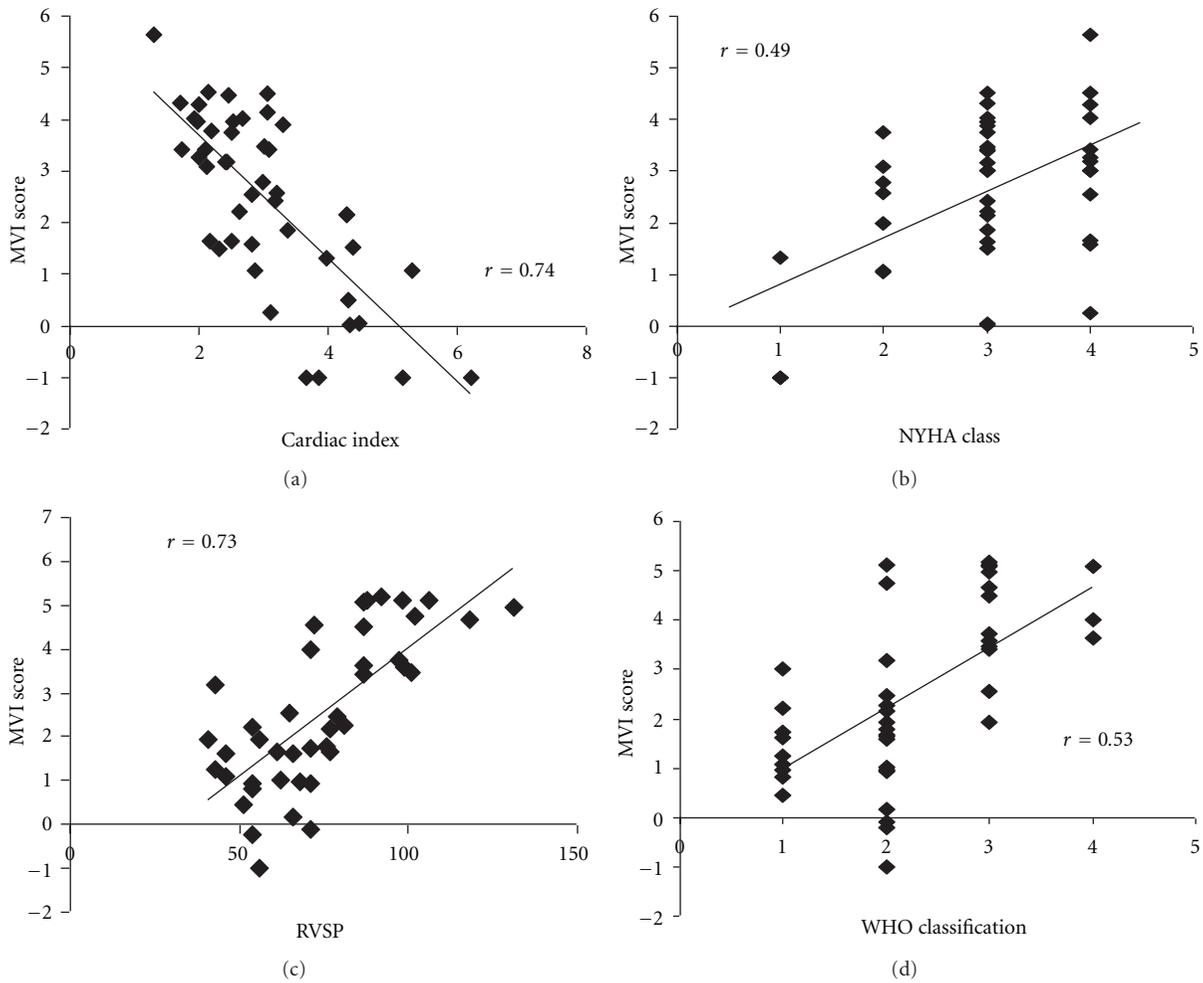


FIGURE 7: Relationships of MVI score with clinical parameters.

5. Conclusions

Measures of cardiopulmonary gas exchange with exercise have previously been underutilized due to their complexity and difficulty in interpretation. The MVI gas exchange severity score provides a simple means to rapidly assess disease risk and response to therapy in HF and PH patients and provides an overall assessment of integrative cardiac hemodynamics. The score reduces the complications of having to understand a large number of variables, eliminates the need for interpretation, accounts for variables with multiple directional changes, avoids noise that can be created by one value being abnormal versus the other values, and provides an easily identifiable numbering scheme for physicians to track.

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Review Article

Lungs in Heart Failure

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Lung function abnormalities both at rest and during exercise are frequently observed in patients with chronic heart failure, also in the absence of respiratory disease. Alterations of respiratory mechanics and of gas exchange capacity are strictly related to heart failure. Severe heart failure patients often show a restrictive respiratory pattern, secondary to heart enlargement and increased lung fluids, and impairment of alveolar-capillary gas diffusion, mainly due to an increased resistance to molecular diffusion across the alveolar capillary membrane. Reduced gas diffusion contributes to exercise intolerance and to a worse prognosis. Cardiopulmonary exercise test is considered the “gold standard” when studying the cardiovascular, pulmonary, and metabolic adaptations to exercise in cardiac patients. During exercise, hyperventilation and consequent reduction of ventilation efficiency are often observed in heart failure patients, resulting in an increased slope of ventilation/carbon dioxide (VE/VCO_2) relationship. Ventilatory efficiency is as strong prognostic and an important stratification marker. This paper describes the pulmonary abnormalities at rest and during exercise in the patients with heart failure, highlighting the principal diagnostic tools for evaluation of lungs function, the possible pharmacological interventions, and the parameters that could be useful in prognostic assessment of heart failure patients.

1. Introduction

Not only heart is involved in chronic heart failure but also lung, kidney, peripheral and respiratory muscles, chemoreceptors, neurohormonal mechanisms, mitochondria, all play a major role in determining the complex clinical syndrome of chronic heart failure. Indeed, energy deficit is a relevant contributor to the development of cardiac and skeletal myopathy. In heart failure several functions of muscle bioenergetics are altered such as oxygen availability, substrate oxidation, ATP production by the mitochondria, and transfer to contractile apparatus [1]. Notably, the clinical syndrome of heart failure is characterized by symptoms apparently unrelated or partially related to the heart, such as fatigue, dyspnea, anxiety, and exercise intolerance.

Dyspnea, either at rest or during exercise, is one of the main symptoms in heart failure. Indeed, the most often used heart failure grading methodology, the NYHA classification, is based on dyspnea. Dyspnea is the result of a neurological reconstruction of an abnormal physiological condition characterized by hyperventilation and by high ventilation to metabolic demand ratio. This leads to a reduced ventilatory efficiency, which is physiologically defined as the amount of ventilation needed to eliminate a given amount of CO_2 . The excess of ventilation is due to an increase of dead space/tidal volume (VD/VT) ventilation and of ventilatory drive from peripheral chemo- and ergoreceptors. The reduced ventilatory efficiency during exercise is used more and more as a prognostic marker in heart failure. In addition, an improvement of the efficiency of ventilation is among the goals

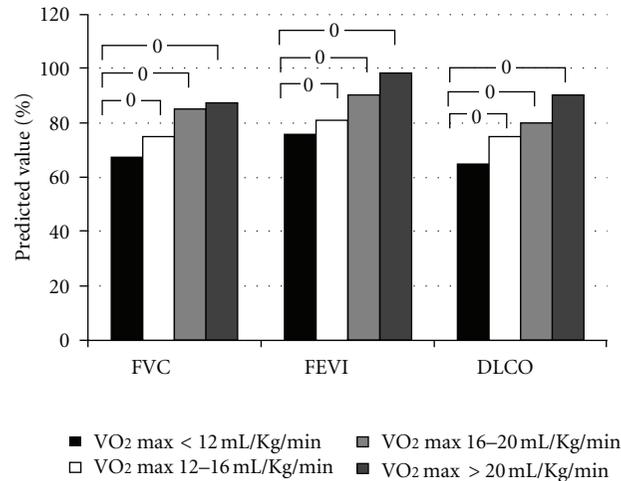


FIGURE 1: Lung function at rest in 190 heart failure patients in stable clinical condition. Patients were grouped according to exercise capacity. From left to right: peak $\text{VO}_2 < 12 \text{ mL/min/kg}$ (black bars), peak $\text{VO}_2 = 12\text{--}16 \text{ mL/min/kg}$ (white bars), peak $\text{VO}_2 = 16\text{--}20 \text{ mL/min/kg}$ (grey bars), and peak $\text{VO}_2 > 20 \text{ mL/min/kg}$ (dashed bars). FVC: forced vital capacity; FEV1: forced expiratory volume 1 second; DLCO: lung diffusion for carbon monoxide. Data from [8, Table 1].

of heart failure therapy. The following review will examine the role of different mechanisms underlying ventilatory efficiency evaluated with spirometry, lung gas diffusion measurement, and cardiopulmonary exercise test in heart failure patients.

2. Lung Abnormalities at Rest

Pulmonary abnormalities are part of the heart failure syndrome, as both lung mechanics and alveolar-capillary gas exchange are impaired [2–5]. In heart failure, pulmonary abnormalities may be due to respiratory comorbidities but also to heart failure itself. Therefore, standard spirometry and resting lung diffusion for carbon monoxide (DLCO) [6] provide an integrated evaluation of the respiratory function and should be performed in all heart failure patients. Moreover, it may be useful to split DLCO into its two sub-components either using the classic Roughton and Forster method or nitric oxide lung diffusion. Accordingly, D_m , the resistance to molecular diffusion of carbon monoxide across the alveolar-capillary membrane, and V_{cap} , the resistance to carbon monoxide binding to hemoglobin, the so-called pulmonary capillary blood volume, can be calculated [7].

2.1. Spirometry. Spirometry is the preliminary pulmonary function test to assess respiratory mechanics.

Wasserman et al. [5] showed in a large multicenter study that, at rest, forced expiratory volume in the first second and vital capacity are either normal or proportionately reduced in heart failure. More recently, Agostoni et al. [8] demonstrated that pulmonary function at rest is usually normal in patients with moderate heart failure, while a restrictive lung disease is observed in 50% of patients with severe heart failure (Figure 1). Cardiac enlargement in heart failure appears to be involved in causing restrictive lung pattern [4, 9]. Indeed, a negative correlation between cardiac size, as analyzed by

the cardiothoracic index at chest X-ray, and lung function parameters, including alveolar volume, has been described [4]. Notably, Palermo et al. [10] showed that, in heart failure, pulmonary function varies in relationship with the position of the body, being worst in the lateral decubitus. The larger the heart, the greater the difference in lung function between the sitting position and the lateral decubitus. Moreover, McCormack [11] showed that the restrictive lung disease secondary to severe heart failure seems to be completely reversible after cardiac transplantation, with an increase in forced vital capacity after transplantation, directly correlated with the decrease in cardiac volume.

2.2. Lung Diffusion. Alterations of respiratory mechanics and of gas exchange capacity are strictly related in heart failure patients. Reduction in the pulmonary DLCO is well documented in heart failure [3, 13–15]. The acute pathogenetic mechanisms of lung diffusion abnormalities in heart failure are related to interstitial edema, alveolar-capillary membrane hydrostatic injury, and altered alveolar fluid clearance. These mechanisms result in a remodeling process that causes a persistent reduction in alveolar-capillary membrane conductance and lung diffusion capacity. Indeed, Mettauer et al. [16] demonstrated that DLCO is only partially restored after cardiac transplantation. DLCO improves less in patients with long standing heart failure. This implies that in heart failure the alveolar-capillary membrane undergoes changes that are only partially reversible with heart failure treatment [17].

Reduced D_m is the main component of impaired pulmonary gas transfer in heart failure [18]. Puri et al. [18] demonstrated that D_m decreases and V_{cap} increases in relationship with the severity of the disease. The V_{cap} increase was interpreted as a compensatory mechanism aimed, by pulmonary vessel recruitment, at preserving alveolar-capillary diffusion. V_{cap} tends to increase in patients with stable heart failure, but could decrease in the advanced stages [19]. Agostoni et al. [8] showed that in severe heart

failure in stable clinical condition there are few alveolar-capillary units at work (low alveolar volume), characterized by greater efficiency (high D_m/V_{cap} ratio) compared to alveolar-capillary units in intermediate chronic heart failure severity. However, the physiological mechanism behind this phenomenon is still undefined. Indeed, V_{cap} is related to the amount of hemoglobin participating in gas exchange, which, on its turn, depends from hemoconcentration, cardiac output, and the amount of capillary vessels in the ventilated airways. The latter is related to pulmonary venous pressure.

In heart failure, the alveolar-capillary membrane surface area available for gas exchange is reduced and partially responsible for low D_m . Furthermore, D_m reduction remains even after correction for alveolar volume (D_m/VA) [18]. In fact, D_m is affected by several factors including interstitial edema that increases the distance between alveolar gas and red blood cells, fibrosis, inability to further activate the pump mechanism at the alveolar surface which enhances chlorine and sodium transport [20], and peribronchial edema that may reduce ventilation to some lung units. Moreover, there is a strict correlation between hemodynamics and D_m , as proven by the observation that D_m decreases after infusion of a small amount of saline (150 mL) [21] or after exercise [22, 23].

Nevertheless, we must underline that, albeit several heart failure models have been prepared to study the correlation between increased congestion of lung interstitial space and pulmonary function, a reliable model of lung function abnormalities mimicking those present in heart failure does not exist. Studies in healthy humans [24–26] demonstrated a reduced vital capacity, forced expiratory volume, and total lung capacity with a preserved DLCO after a rapid increase fluid content. This observation is consistent with some clinical findings. For instance, ultrafiltration, which acutely reduces the congestion of lung interstitium, improves lung mechanics but not DLCO in heart failure [17, 27].

DLCO is a limiting factor for exercise performance [28, 29], which improves (below sea level, as in the Dead Sea) or worsens at different altitudes more in heart failure patients with reduced DLCO compared to subjects with a normal DLCO [30, 31]. DLCO and D_m abnormalities have a relevant prognostic capacity in heart failure [32], although we do not know whether an improvement of DLCO with treatment is associated with an improvement of prognosis.

More recently, a new biomarker of alveolar-capillary membrane damage has been described [33, 34]. Increased circulating plasma levels of surfactant protein B have been reported in heart failure patients with a good correlation with heart failure severity. The mature form of surfactant protein B plays a crucial role in the formation and stabilization of pulmonary surfactant film. The level of surfactant protein B correlates with lung diffusion as well as peak $\dot{V}O_2$ and ventilation versus $\dot{V}CO_2$ production (VE/VCO_2) slope [34]. The clinical applicability of this biomarker is unclear at present.

3. Lung Abnormalities during Exercise

Cardiopulmonary exercise test (CPET) with incremental increases in workload is considered as the “gold standard”

when studying the cardiovascular, pulmonary, and metabolic adaptations to exercise in cardiac patients.

Traditionally, ventilatory limitation to exercise is assessed by measuring the breathing reserve calculated as the difference between minute ventilation at peak exercise and maximal voluntary ventilation or some estimate of the maximal voluntary ventilation (typically the forced expiratory volume in the first second multiplied by 35 or 40). Any difference >15 L/min or breathing reserve >20 – 40% is interpreted as consistent with exercise not being limited by ventilation [35]. In normal individuals, there is a progressive increase of ventilation (VE) during exercise, due to both VT and respiratory rate increase. The increase in VT mainly occurs at the beginning of exercise, whereas respiratory rate typically increases more toward peak exercise.

CPET reveals an increased VE, at comparable levels of effort, in heart failure patients with respect to age-matched normal individuals [36]. At a given work rate, heart failure patients show a higher VE than normal subjects, the result of an exaggerated respiratory rate response, and a truncated VT response [5] (Figure 2).

Ventilatory response may be abnormal during exercise despite normal breathing reserve as showed in different settings and in heart failure patients [12, 37, 38]. Lung hyperinflation and expiratory flow limitation can cause fatigue of the inspiratory muscles; therefore, it becomes clear that breathing reserve is insufficient for a comprehensive and precise assessment of the contribution of the respiratory system to physical exercise in physiologic and disease conditions. Indeed, diminished respiratory muscle strength has been demonstrated in heart failure patients. Mouth inspiratory and expiratory pressures are reduced in heart failure compared to normal subjects, and they seem to be correlated with exercise capacity [39]. Moreover, inspiratory muscle strength has independent prognostic value in heart failure. The results of trials with inspiratory muscle training [40] indicate that this intervention improves exercise capacity and quality of life in heart failure. Some benefit from muscle training may be accounted for by the attenuation of the inspiratory muscle metaboreflex. Furthermore, inspiratory muscle training results in improved cardiovascular responses to exercise. These findings suggest that routine screening for intercostal muscle weakness is advisable in patients with heart failure and specific inspiratory muscle training and/or aerobic training are of practical value in the management of these patients.

More detailed information about ventilatory abnormalities during exercise in heart failure is provided by analysis of the spontaneous expiratory flow-volume loop relative to the maximal forced curve. Expiratory flow limitation is reached when the right upper corner of the flow-volume loop curve is very close to the maximal flow volume curve registered at rest. When this happens, subjects stop the effort or proceed through the exercise but the flow volume curve shifts to the left, away from the functional residual capacity, in a region where the cost of breathing increases. Johnson et al. [41] and Agostoni et al. [12] showed that in heart failure, because of lung stiffness, the spontaneous flow-volume loop reaches the maximal flow-volume loop and the expiratory flow

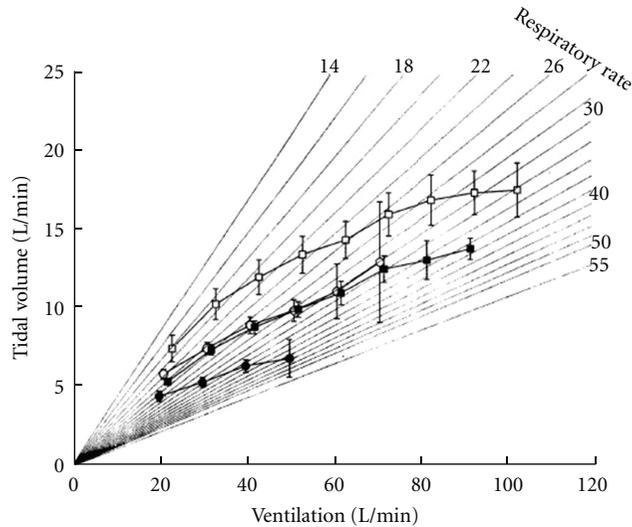


FIGURE 2: Tidal volume versus ventilation in patients with severe heart failure (peak $\text{VO}_2 < 12 \text{ mL/min/kg}$, black circles), moderate to severe heart failure (peak $\text{VO}_2 12\text{--}16 \text{ mL/min/kg}$, black squares), moderate (peak $\text{VO}_2 > 16 \text{ mL/min/kg}$, empty circles), and normal subjects (empty squares). From [5]. Reproduced with permission.

reserve is dramatically reduced, requiring an increase in end-inspiratory lung volume. An increase in end-inspiratory lung volume raises work of breathing and decreases inspiratory endurance time [41]. In addition, after exercise in healthy subjects, the maximal flow-volume loop is increased due to bronchodilation induced by exercise; this is not the case in heart failure [42]. Figure 3 describes an example of flow-volume curves' behavior during exercise in a normal subject and in a heart failure patient. Moreover, Bussotti et al. [43] showed that maximal flow-volume loops maneuver does not interfere with the main functional parameters used for the interpretation of CPET. Consequently, with a single CPET both flow-volume curve and ventilation efficiency (VE/VCO_2 slope) can be evaluated.

3.1. Ventilation versus VCO_2 . In normal subjects the relation of VE versus VCO_2 is characterized during CPET progressive work load increase by three linear relationships. The three slopes are progressively steeped. This is due to the change in the functional parameters governing the VE versus VCO_2 relationship and specifically VO_2 , VCO_2 , and pH [44]. Clinically the VE versus VCO_2 slope is measured from the first minute after the beginning of loaded pedaling to the end of isocapnic period (Figure 4), albeit some authors [45] suggest to measure the slope obtained considering the entire exercise as a single linear relationship. Differently the VE/VCO_2 ratio declines at the beginning of exercise, reaches a plateau, and increases in the last part of exercise, when metabolic acidosis becomes unbuffered. In heart failure exercise is characterized by hyperventilation, which is likely due to several causes, including alteration of lung mechanics, reduced lung diffusion, increased CO_2 production due to early lactic acidosis, increased VD , decreased ventilatory efficiency, and overactive reflexes from metaboreceptors, baroreceptors, and chemoreceptors. In other words, in heart

failure patients, besides abnormalities in the lung, either due to mechanics or to gas exchange, also ventilatory control is altered. The latter is likely a part of deranged cardiorespiratory reflex control. Indeed, a direct link between exercise hyperventilation and impaired reflexes which control heart rate and blood pressure has been convincingly proposed [46] providing the physiological base of the link between hyperventilation and poor prognosis in heart failure. Ventilatory efficiency is best defined by the relationship of the amount of ventilation required to eliminate a given amount of CO_2 . Efficiency of ventilation can be expressed as a slope of the VE/VCO_2 relationship or as VE/VCO_2 ratio measured either at the anaerobic threshold or as the lowest value recorded during exercise. The modified alveolar equation [44] concisely describes the determinants of the steepness which VE rises with respect to VCO_2 :

$$\frac{\text{VE}}{\text{VCO}_2} = \frac{K}{[\text{PaCO}_2 \times (1 - \text{VD}/\text{VT})]}, \quad (1)$$

where $[K/\text{PaCO}_2 \times (1 - \text{VD}/\text{VT})]$ is the slope, K is constant to adjust for standard temperature pressure dry and body temperature pressure saturated and to convert fractional concentrations to pressures, PaCO_2 is partial pressure of CO_2 in arterial blood, and VD/VT is the fraction of VT that goes to VD . This equation is linear over a wide range of exercise. Figure 4 describes a theoretical example of VE/VCO_2 slope in a normal subject and in a patient with heart failure. If PaCO_2 is driven down by a high ventilatory drive from peripheral chemoreceptors or by ergoreceptors in skeletal muscles, the slope of the VE/VCO_2 will increase as well as if VD/VT is high. Little is known about chemosensitivity in heart failure. It has been documented that central hypercapnic chemosensitivity is enhanced in patients with heart failure with central sleep apnea [47]. Chua et al. [48] demonstrated that there is increased hypoxic and central hypercapnic

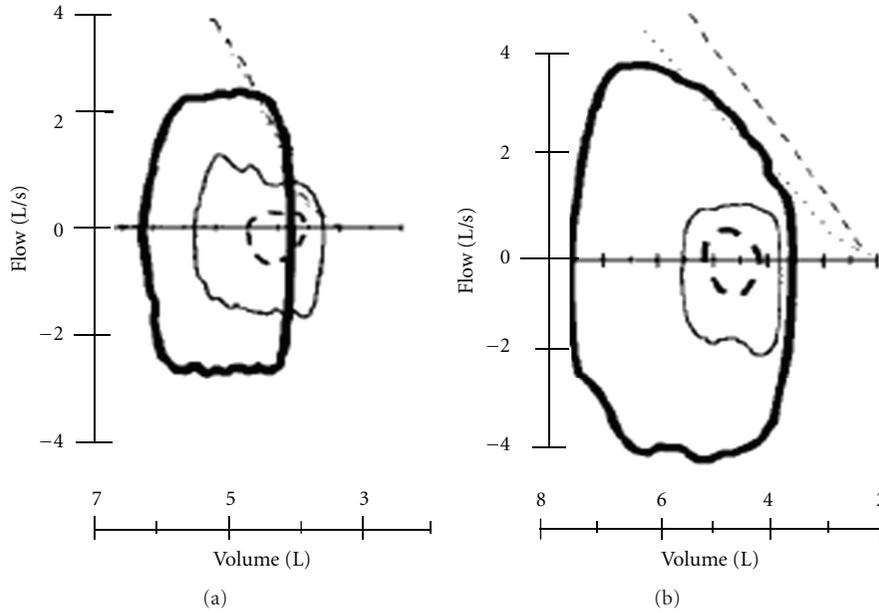


FIGURE 3: Tidal flow-volume loops at rest (dashed lines) at 40% of maximal ventilation (thin solid lines), and at maximum exercise (thick solid lines) in typical heart failure (a) and normal (b) subjects. The 2 oblique lines on flow-volume loops are partial forced expiratory flows recorded at rest (dotted line) and at maximum exercise (dashed line). From [12].

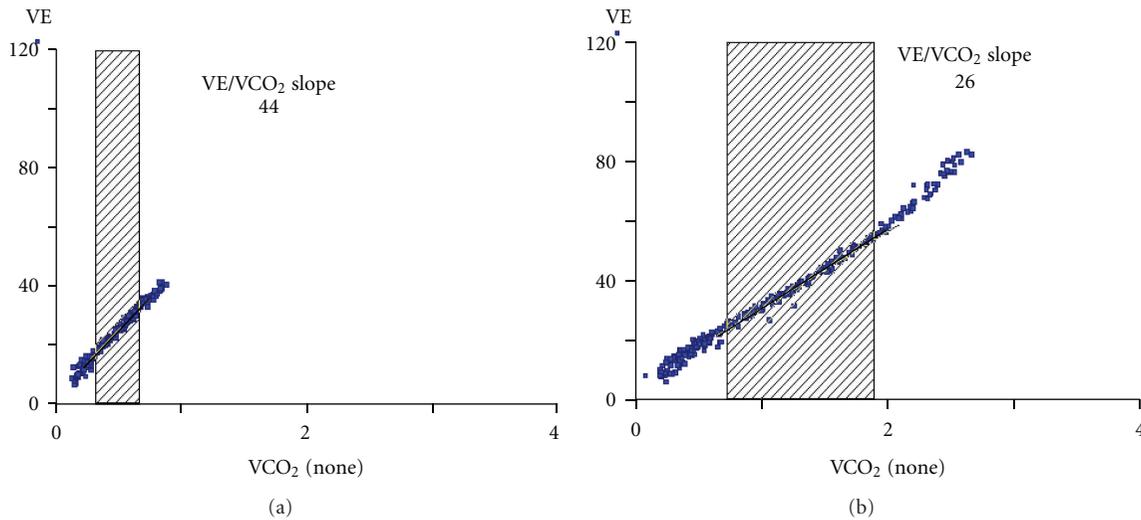


FIGURE 4: VE/VCO_2 slope in an heart failure patient (a) and an healthy control (b).

chemo-sensitivity in patients with heart failure, and that its suppression with dihydrocodeine is associated with a reduction of exercise ventilation, an improvement in exercise tolerance, and a decrease in breathlessness [49]. Piepoli et al. [50] showed that muscle reflex (ergoreflex) has an important effect on the ventilatory responses to exercise in heart failure compared to control subjects, and that training may reduce this exaggerated ergoreflex activity, thereby improving the response to exercise. The increase in reflex sensitivity may serve as a compensatory mechanism producing an increase in ventilatory response during exercise and thereby preserving blood gas homeostasis, also maintaining arterial oxygen

concentration. Studies analyzing the effect of drugs interfering with chemo-sensitivity are on-going, and no data are available at present.

In normal subjects, VE/VCO_2 relationship, for incremental exercise, is normally linear up to the “respiratory compensation point,” when ventilatory compensation begins in response to metabolic (lactic) acidosis. Over the linear phase of the VE/VCO_2 relationship, below the respiratory compensation point, the profile of VE/VCO_2 closely reflects that of VD/VT , providing information on ventilatory efficiency. In heart failure, hyperventilation is associated with an increased VD/VT and VCO_2 and a lower $PaCO_2$ when

compared to similar normal subjects at a similar percent of VO_2 peak [5]. Patients with heart failure often have a reduced tidal volume at heavy exercise [5], which would increase the VD/VT ratio; however, Buller and Poole-Wilson [51] showed that the increased ventilatory response to exercise in patients with heart failure is largely caused by mechanisms other than increased ventilation of anatomical VD [51]. In heart failure patients, in the absence of coexisting lung disease, this pattern of a high VD/VT ratio with normal arterial blood gases suggests that nonuniformity of ventilation/perfusion (V/Q) ratios in the lung is more likely caused by increased non-uniformity of perfusion than of ventilation [52]. A totally different behavior of the VE/VCO_2 relationship is likely when respiratory comorbidities, such as emphysema, are present [53, 54].

The normal VE/VCO_2 at the nadir is between 25 and 35. Normal values for these ventilatory equivalents with an end-tidal of CO_2 (PetCO_2) of approximately 40 mmHg suggest a normal VD/VT and uniform matching of V/Q [44].

In recent years, the VE/VCO_2 slope has gained notoriety in the heart failure population as an outstanding prognostic marker. Several studies report the VE/VCO_2 slope to be prognostically superior to peak VO_2 to predict mortality [55–60]. Arena et al. [55] built a classificatory system based on exercise VE/VCO_2 slope to stratify the risk of major cardiovascular events in heart failure. Corrà et al. [56] used VE/VCO_2 slope (with a cutoff >34) for efficient prognostic stratification in patients with moderate to severe heart failure (defined as VO_2/kg peak 10–18 mL/kg/min). Ponikowski et al. [60] showed that, even in heart failure patients with normal exercise performance and peak $\text{VO}_2 >18$ mL/kg/min, abnormal exercise ventilation significantly discriminates survival. Guazzi et al. [61] suggested that the VE/VCO_2 slope has a remarkable value for risk stratification even in patients with diastolic heart failure.

Another way to assess ventilation during exercise is to analyze the relationship between end-tidal CO_2 pressure (PetCO_2) and VE during the isocapnic buffering period [44, 62]. At sea level, during isocapnic buffering period, there is a straight relationship between CO_2 set point and ventilation. PetCO_2 , equivalent to PaCO_2 , during the isocapnic buffering period, is around 40 mmHg in normal subjects, higher in athletes [63] and lower in heart failure patients. Guazzi et al. [64] suggested that a low peak PaCO_2 (and consequently a low peak PetCO_2 and an elevated VD/VT) is a strong independent predictor of mortality in stable heart failure, and that a low peak PaCO_2 is the most significant determinant of the prognostic value of a steep VE/VCO_2 slope. Another ventilation-related index with a prognostic value in heart failure is Oxygen Uptake Efficiency Slope (OUES). OUES is derived from the relation between oxygen uptake (VO_2 L/min) and VE (L/min) during incremental exercise. OUES is determined by the linear relation of VO_2 (y -axis) versus the logarithm of VE (x -axis) during exercise [65].

The following equation was used to determine the relation between VO_2 and VE :

$$\text{VO}_2 = a \log \text{VE} + b. \quad (2)$$

The differential of this equation by VE yields is

$$\frac{d\text{VO}_2}{d\text{VE}} = \frac{a(1/\log 10)}{\text{VE}}, \quad (3)$$

where a is the constant that represents the rate of increase in VO_2 in response to VE . We define the constant “ a ” as the OUES. Baba et al. [65] emphasized the value of OUES as a submaximal, effort-independent, and objective parameter to estimate cardiorespiratory functional reserve, and they reported that OUES strongly correlates with VO_2 max ($r = 0.941$).

Myers et al. [66], when defining a CPET score for predicting outcomes in heart failure, considered OUES to be a stronger predictor of risk than peak VO_2 . Davies et al. [67] claimed OUES as a prognostic marker in heart failure patients. Sun et al. [68] have recently described the Oxygen Uptake Efficiency highest Plateau (OUEP, i.e., oxygen uptake/ventilation = VO_2/VE) as the best single predictor of early death (six months), in a cohort of 508 patients with low ejection fraction ($>35\%$), with an Odds ratio for mortality of 13. When OUEP is combined with periodic breathing, the Odds ratio increases to 56.

3.2. Periodic Breathing. Periodic breathing is a ventilatory pattern, which is present in some heart failure patients both at rest and during exercise. Exercise-induced periodic breathing has been defined by Kremser et al. [69] as the presence of cyclic fluctuation of VE lasting longer than 66% of the exercise, with an amplitude of more than 15% of the average value at rest. It can be observed during the entire exercise or it disappears after a few minutes. The origin of periodic breathing is still unclear and several mechanisms have been proposed, mainly grouped into ventilatory (instability in the feedback ventilatory system) and hemodynamic (pulmonary blood flow fluctuations). Agostoni et al. [70], showed that, adding 250 and 500 mL of dead space, respectively, periodic breathing disappears earlier during exercise and suggested that low tidal volume and carbon dioxide apnea threshold are important contributors to periodic breathing. Schmid et al. [71] supposed that periodic breathing in heart failure might potentiate the negative effects of low cardiac output and high ventilation on exercise performance, and they concluded that the presence of periodic breathing negatively influences the exercise performance of heart failure patients, likely because of an increased cost of breathing. Indeed, periodic breathing disappearance during exercise showed to be associated with a more efficient oxygen delivery in most cases. Regardless, periodic breathing is associated with a worse prognosis [64, 72] in heart failure and reflects disease severity [73].

4. Therapeutic Interventions

Several reports showed that the respiratory system can be one of the targets for proper heart failure treatment. On this regard, several therapeutic interventions affect the ventilatory abnormalities both at rest and during exercise in heart failure patients. Indeed, ACE-inhibition improves pulmonary diffusion in heart failure [74]. ACE-inhibition could

improve pulmonary hemodynamic, remove interstitial fluid and pulmonary vasoconstriction, and improve DLCO. The effect of ACE-inhibitors is counteracted by aspirin, suggesting that bradykinin metabolism has a role, and bradykinin is likely to participate to abnormal alveolar capillary gas diffusion regulation in heart failure. Most importantly the studies on ACE-inhibitors, with and without aspirin, showed a direct effect of these drugs on lung gas diffusion, in the absence of a hemodynamic effect [74]. Agostoni et al. [75] showed that spironolactone improves gas diffusion through the lungs in stable heart failure patients with impaired DLCO, possibly through a reduction of pulmonary fibrosis.

Also Beta-blockers affect DLCO diffusion. Beta-receptors in the lung are located on the alveoli, mainly Beta2-receptors, and on the airways (mainly Beta1-receptor). Carvedilol reduces DLCO, due to a reduction of membrane diffusion [62], while Bisoprolol does not modify DLCO [76]. Carvedilol and Bisoprolol have a different pharmacological action, blocking both Beta1- and Beta2-receptors (Carvedilol) or selectively Beta1-receptor (Bisoprolol). The pharmacological action of Beta-blockers can explain the different actions on DLCO diffusion. Carvedilol improves clinical conditions, without affecting exercise performance. Carvedilol, but not Bisoprolol, reduces hyperventilation through exercise [77], as shown by a lower VE/VCO₂ slope, consequent to an increase in the arterial CO₂ set point [62, 78]. The improvement of the clinical conditions of heart failure patients treated with Carvedilol could be associated with reduction of the inappropriately elevated ventilation levels observed during exercise and consequently dyspnea.

A direct effect of Carvedilol on chemoreceptors activity has been recently suggested [79]. This reduction of hyperventilation during exercise is present both in normoxia (equivalent to sea level) and in hypoxia (equivalent to 2,000 m altitude). The reduction of hyperventilation by Carvedilol has a negative influence on arterial PO₂ during exercise at a simulated altitude of 2,000 m [78].

In conclusion, lung abnormalities have a major role in heart failure syndrome. Indeed, lung abnormalities influence the clinical setting being dyspnea, a frequently reported heart failure symptom, affecting exercise performance, providing a tool to grade heart failure severity and to predict its prognosis, and finally being the target of therapy with several drugs commonly used in heart failure.

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Review Article

Mechanisms of Physical Activity Limitation in Chronic Lung Diseases

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In chronic lung diseases physical activity limitation is multifactorial involving respiratory, hemodynamic, and peripheral muscle abnormalities. The mechanisms of limitation discussed in this paper relate to (i) the imbalance between ventilatory capacity and demand, (ii) the imbalance between energy demand and supply to working respiratory and peripheral muscles, and (iii) the factors that induce peripheral muscle dysfunction. In practice, intolerable exertional symptoms (i.e., dyspnea) and/or leg discomfort are the main symptoms that limit physical performance in patients with chronic lung diseases. Furthermore, the reduced capacity for physical work and the adoption of a sedentary lifestyle, in an attempt to avoid breathlessness upon physical exertion, cause profound muscle deconditioning which in turn leads to disability and loss of functional independence. Accordingly, physical inactivity is an important component of worsening the patients' quality of life and contributes importantly to poor prognosis. Identifying the factors which prevent a patient with lung disease to easily carry out activities of daily living provides a unique as well as important perspective for the choice of the appropriate therapeutic strategy.

1. Exercise Intolerance

Exercise intolerance is a condition where the individual is unable to perform physical exercise at the intensity or for the duration that would be expected of someone in his or her age and general physical condition. When this inability is caused by impaired function of one or more of the major physiological systems, namely the respiratory, the cardiovascular, and the peripheral muscle metabolic system, the result is the amplification of the perceptions of respiratory discomfort, either alone or typically in conjunction with peripheral muscle discomfort/fatigue [1]. In patients with chronic lung diseases, dyspnea sensations are exaggerated during exercise secondary to the reduced breathing efficiency that results from the deteriorating ventilatory mechanics on one hand and the increased ventilatory requirement on the other hand (Figure 1).

Respiratory discomfort is typically perceived as the distressing sensation of unsatisfied inspiration because of a mismatch between central neural drive and the respiratory mechanical/muscular response (i.e., the so-called “neuromechanical uncoupling or dissociation”) of the respiratory system [2]. Patients with chronic lung diseases constantly select descriptor clusters that allude to both “increased respiratory work/effort” and “unsatisfied inspiration” upon cessation of physical exercise. Recent theories on the mechanisms of respiratory discomfort have emphasized the central importance of the perception of increased contractile inspiratory muscle effort (dyspnea perceived as “increased respiratory effort”) [3]. In fact, inspired effort and central motor command output are both increased compared to healthy individuals, reflecting the relatively higher ventilation, as well as the increased loading and functional weakness of the inspiratory muscles [4, 5]. Particularly in patients

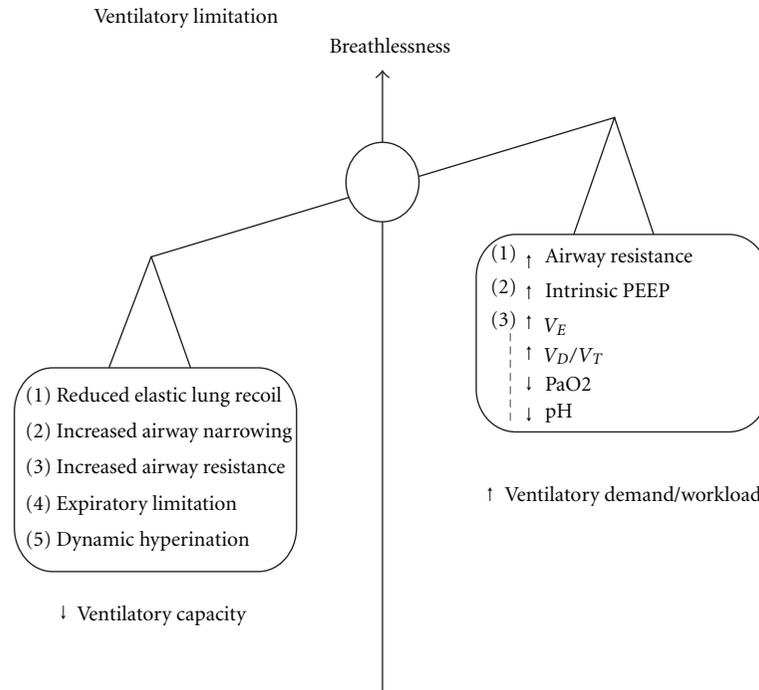


FIGURE 1: Conceptual framework of factors limiting exercise tolerance in COPD. *Mismatch of ventilatory capacity and ventilatory demand/workload.* Ventilatory capacity is reduced in patients with COPD and is thus insufficient to match the ventilatory requirement and increased workload. Such a mismatch leads to intense dyspnea sensations. (PEEP = positive end-expiratory pressure, V_D/V_T = dead space/tidal volume).

with chronic obstructive pulmonary disease (COPD) altered afferent information from activated mechanoreceptors in the overworked and shortened inspiratory muscles, secondary to dynamic lung hyperinflation, may contribute to an increased sense of work or effort, but this remains speculative [6, 7]. It has long been suggested that in these patients, a mismatch between central neural drive and the respiratory mechanical/muscular response (“neuromechanical uncoupling” or dissociation) of the respiratory system, as crudely reflected by the increased effort-displacement ratio, is fundamental to the origin of perceptions of unrewarded inspiratory effort (i.e., “unsatisfied inspiration”) [2, 8].

Peripheral muscle contractile fatigue occurring secondary to a limitation in oxygen supply to, and/or utilization of oxygen by, the mitochondria [9] also constitutes an important factor that limits exercise capacity in patients with chronic lung diseases. This suggestion is further supported by the finding that the degree of exercise-induced quadriceps muscle fatigue in COPD negatively correlates with peak oxygen utilization [10]. A decrease in locomotor muscle force output compared to the predicted normal values has also been reported in patients with interstitial lung disease (ILD) [11] and pulmonary arterial hypertension (PAH) [12].

Accordingly, it is likely that cellular oxygen demand either exceeds the normal maximal oxygen transfer capacity of the oxygen transport chain, (i.e., when maximal oxygen consumption has been truly achieved), or stresses an impaired physiological system (i.e., cardiovascular and/or respiratory) preventing the achievement of a true maximal oxygen

consumption. Hence, the factors that limit physical performance in healthy individuals (i.e., when oxygen demand exceeds the normal maximal oxygen transfer capacity) are different to those (i.e., impairment in oxygen transport) constraining the capacity to perform physical exercise in patients with chronic lung diseases (i.e., ventilatory limitation) [9, 13].

2. Physiological Factors Impairing Physical Activity

Exercise intolerance in patients with chronic lung diseases is multifactorial, involving ventilatory, gas exchange, cardiovascular, and peripheral muscle abnormalities.

2.1. Ventilatory Constraints. During incremental exercise, healthy elderly individuals can sufficiently increase their breathing frequency and their tidal volume to provide up to a 10–15 fold increase in minute ventilation that is essential to clear the carbon dioxide production and meet the increased oxygen demand [14–17]. Under such circumstances, ventilatory function is often not the limiting factor, at least for a wide range of submaximal exercise levels, as minute ventilation (\dot{V}_E) is maintained well below the maximum ventilatory capacity (MVC) [18]. Ventilatory limitation, however, may occur in healthy elderly individuals, particularly women [19] during maximal exercise, as the ratio of \dot{V}_E to MVC (\dot{V}_E/MVC) approaches or even exceeds 85% [20, 21]. While an increased ratio (i.e., >85%) of

peak exercise ventilation to the estimated MVC strongly suggests limiting ventilatory constraints, a preserved peak \dot{V}_E/MVC ratio (i.e., <75% predicted) by no means excludes the possibility of significant ventilatory impairment during intense physical activity [22–26].

Patients with chronic lung diseases are deemed to have ventilatory limitation if, at cessation of exercise, the patient has reached estimated MVC, while at the same time cardiac and other physiological functions are operating below maximal capacity. Hence, attendant respiratory discomfort may limit exercise capacity before actual physiological limitation occurs, and the relative importance of other nonventilatory factors is impossible to quantify with precision. Thus, simultaneous analysis of exercise flow-volume loops at the point of exercise limitation may show marked constraints on flow and volume generation in the presence of an apparently adequate ventilatory reserve as estimated from the peak \dot{V}_E/MVC ratios [22–26]. In a recent study, 14% of a population sample of clinically stable patients with COPD ($n = 105$), with apparent ventilatory reserve at peak exercise (i.e., $\dot{V}_E/\text{MVC} < 75\%$ predicted) had coexisting limiting restrictive ventilatory constraints [i.e., behaved as if they had a restrictive ventilatory defect due to constrained ability to increase V_T when end-inspiratory lung volume (EILV) approached total lung capacity (TLC)] as indicated by an EILV >95% of TLC that is, significantly reduced peak inspiratory reserve volume (IRV) at the same time point [24]. In addition, significant ventilatory constraints may be detected on exercise flow-volume loop analysis, even in patients with mild COPD [22, 25, 26] who have an apparently normal ventilatory reserve at peak exercise, as ascertained again by the peak \dot{V}_E/MVC method. Therefore, the role of exercise flow-volume loop analysis combined with the behavior of dynamically assessed operating lung volumes is crucial in ascertaining the presence or not of significant ventilator constraints in all chronic pulmonary diseases.

In the majority of patients with chronic lung diseases, a disparity is developed between the decreased ventilatory capacity, which is manifested by diminished maximum and sustainable voluntary capacity and eventually by the inability to sufficiently increase minute ventilation during intense physical activities, and the increased ventilatory requirement of exercise [14, 27]. This disparity leads to intense dyspnea sensation that is the symptom limiting physical activity in a large fraction of patients with chronic lung diseases [28, 29]. The factors contributing to decreased ventilatory capacity or increased ventilatory requirement/workload are in brief described below (Figure 1).

2.1.1. Reduced Ventilatory Capacity. Reduced ventilatory capacity during intense physical activity is due to the abnormal respiratory system mechanics and the dysfunction of the respiratory muscles. In patients with chronic lung diseases, the high inspiratory (and expiratory) airway resistance and/or reduced lung compliance (that occurs in ILD and in COPD when breathing on the flat portion of the pressure/volume relationship) can substantially increase the pressure requirement for airflow and thus increase the work of breathing [29–31]. Respiratory muscles are frequently

weakened and unable to endure a given workload adequately due to the presence of hyperinflation and/or intrinsic muscle dysfunction/hypoperfusion.

2.1.2. Ventilatory Demand. Ventilatory demand is increased during intense physical activity owing to gas exchange abnormalities (i.e., worsening of alveolar ventilation/perfusion [\dot{V}_A/Q] mismatch and increased dead space ventilation) which lead to hypoxemia and hypercapnia [20]. The ventilatory demand of exercise is regulated not only by the metabolic rate but also by the arterial carbon dioxide tension (PaCO_2) and the physiological dead space fraction of breath [32]. Metabolic acidosis also increases the ventilatory requirement of intense physical activity [33]. Therefore, in chronic lung diseases, for a given rate of CO_2 output (\dot{V}_{CO_2}) and PaCO_2 , \dot{V}_E is usually increased because of higher dead space ventilation [1] (Figures 2 and 3). Moreover, *ventilatory workload is increased* during exercise because of abnormal dynamic ventilatory mechanics.

In practical terms, during incremental cardiopulmonary exercise testing, exercise intolerance in patients with COPD is typically manifested by reduced peak oxygen uptake (Figure 4(a)) and an early occurrence of the lactate threshold secondary to premature lactic acidosis [14, 33–38]. Early termination of exercise is also accompanied by low peak \dot{V}_E , substantial ventilatory inefficiency (marked by increased ventilatory equivalents for carbon dioxide), and decreased ventilatory reserve (i.e., evident by increased peak \dot{V}_E/MVC).

Typically, minute ventilation increases progressively with increasing exercise intensity in COPD in such a manner that the relationship between ventilation and work rate or oxygen uptake often has a sharper slope when compared to that recorded in healthy age-matched individuals. This is because at a given level of external submaximal intensity, minute ventilation is higher than in healthy subjects owing to increased dead space ventilation (Figure 3(a)). Consequently, at a given work or metabolic rate COPD patients endure a considerably greater work of breathing than their healthy counterparts owing to the higher ventilatory rate *per se* and also to the higher cost per liter of ventilation. The latter is due to the fact that abnormal dynamic ventilatory mechanics of COPD require a greater degree of effort to move a given volume of air.

Expansion of tidal volume is also restricted secondary to the development of dynamic hyperinflation, whereas breathing frequency is increased (Figure 4(b)). Repeated measurements of inspiratory capacity during exercise demonstrate a progressive decrease in this variable indicating that end-expiratory lung volume has been increased [39, 40].

In summary, the deteriorating ventilatory mechanics and the increased ventilatory requirement occurring even during mild to moderate physical exertion in patients with chronic lung diseases worsens breathing efficiency, thereby exaggerating dyspnea sensations.

2.2. Gas Exchange Limitations. Age-related changes in pulmonary circulation would be expected to make elderly individuals more susceptible to gas exchange abnormalities during exercise. However, despite the deterioration in

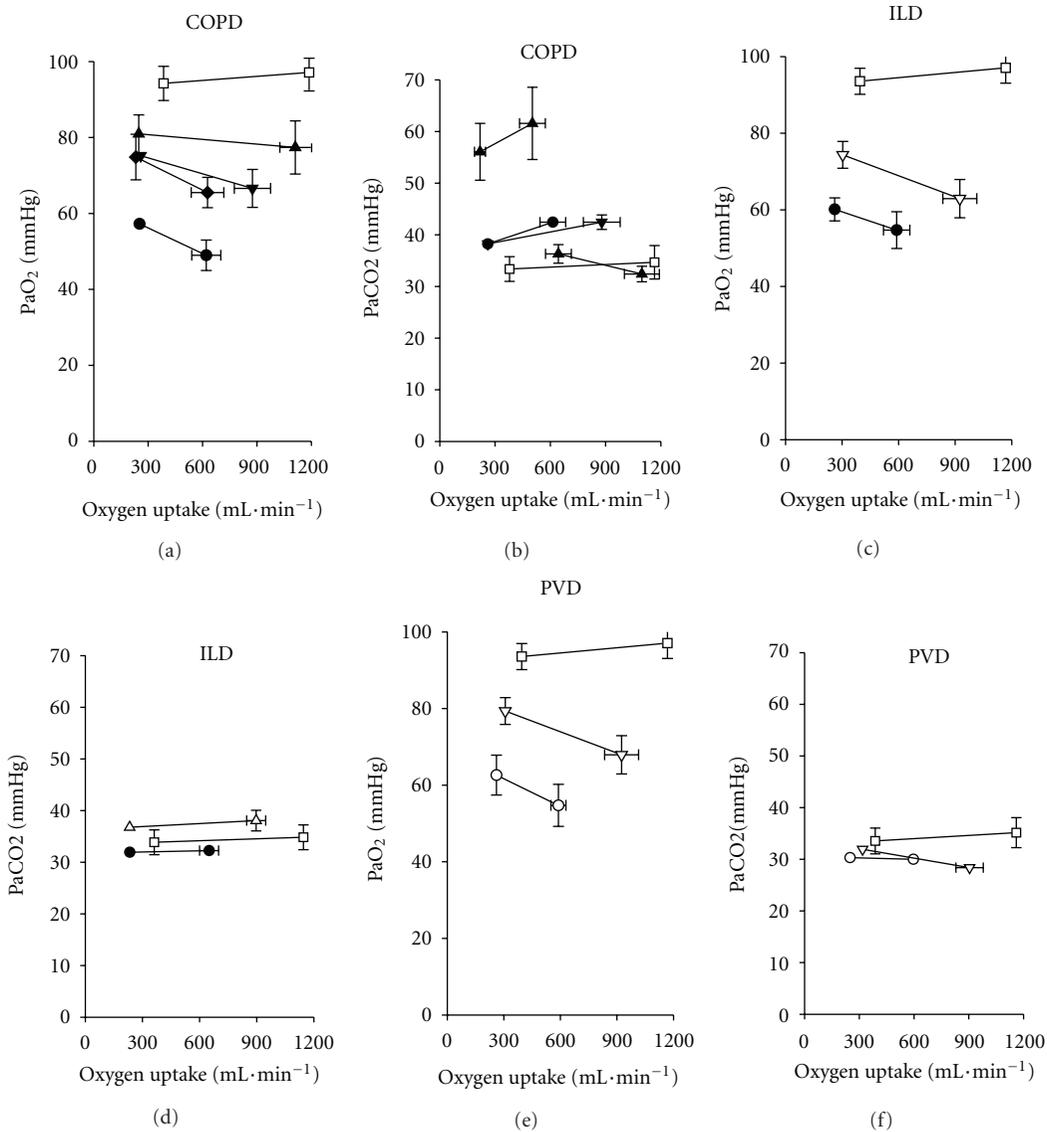


FIGURE 2: Mean arterial oxygen and carbon dioxide tension during exercise in chronic lung diseases. Arterial oxygen tension (PaO_2) and carbon dioxide tension (PaCO_2) as a function of oxygen uptake at rest and during high-intensity exercise in COPD (a and b; range of $n = 7$ to 23); ILD (c and d; range of $n = 8$ to 12); PVD (e and f; range of $n = 7$ to 11). Exercise usually causes PaO_2 to fall in all three diseases. PaCO_2 often rises in COPD but falls or does not change in ILD, PVD, and healthy subjects (\square). With permission from Agustí et al., 1997 [43].

ventilatory reserve with aging, healthy older adults appear able to maintain alveolar ventilation at a level that allows maintenance of arterial blood gases within normal limits, even during heavy exercise [5, 18, 20, 41]. Accordingly, \dot{V}_A/Q remains near unity as both ventilation and perfusion increase several-fold with increasing intensity of physical activity. Moreover, alveolar-capillary diffusion also remains intact, and consequently PaO_2 remains normal, even at a high-intensity physical activity [14, 18, 20] (Figure 2(a)). Furthermore, in healthy elderly individuals, exercise-induced tidal volume (V_T) increase occurs in the setting of relatively fixed anatomic dead space (V_D), so the V_D/V_T ratio decreases such that effective alveolar ventilation increases as a proportion of the increased minute ventilation.

In contrast, gas exchange regulation is impaired in chronic lung diseases that involve the airways, the pulmonary vasculature, and the alveolar-capillary interface to varying degrees thereby producing varying degrees of abnormal \dot{V}_A/Q inequalities, diffusion impairment, and hypoxemia during exercise. In fact, many patients with severe lung disease experience arterial oxygen desaturation during exercise. Furthermore, in Chronic Lung Diseases that affect the pulmonary vasculature, arterial PCO_2 may be higher than in healthy subjects as V_D is increased owing to reduced \dot{V}_A [3, 29, 42, 43] (Figure 2(b)).

Measurement of physiological dead space (V_D physiological) requires the assumption that the PCO_2 of the exchanging (i.e., perfused) alveoli equals PaCO_2 . Normally

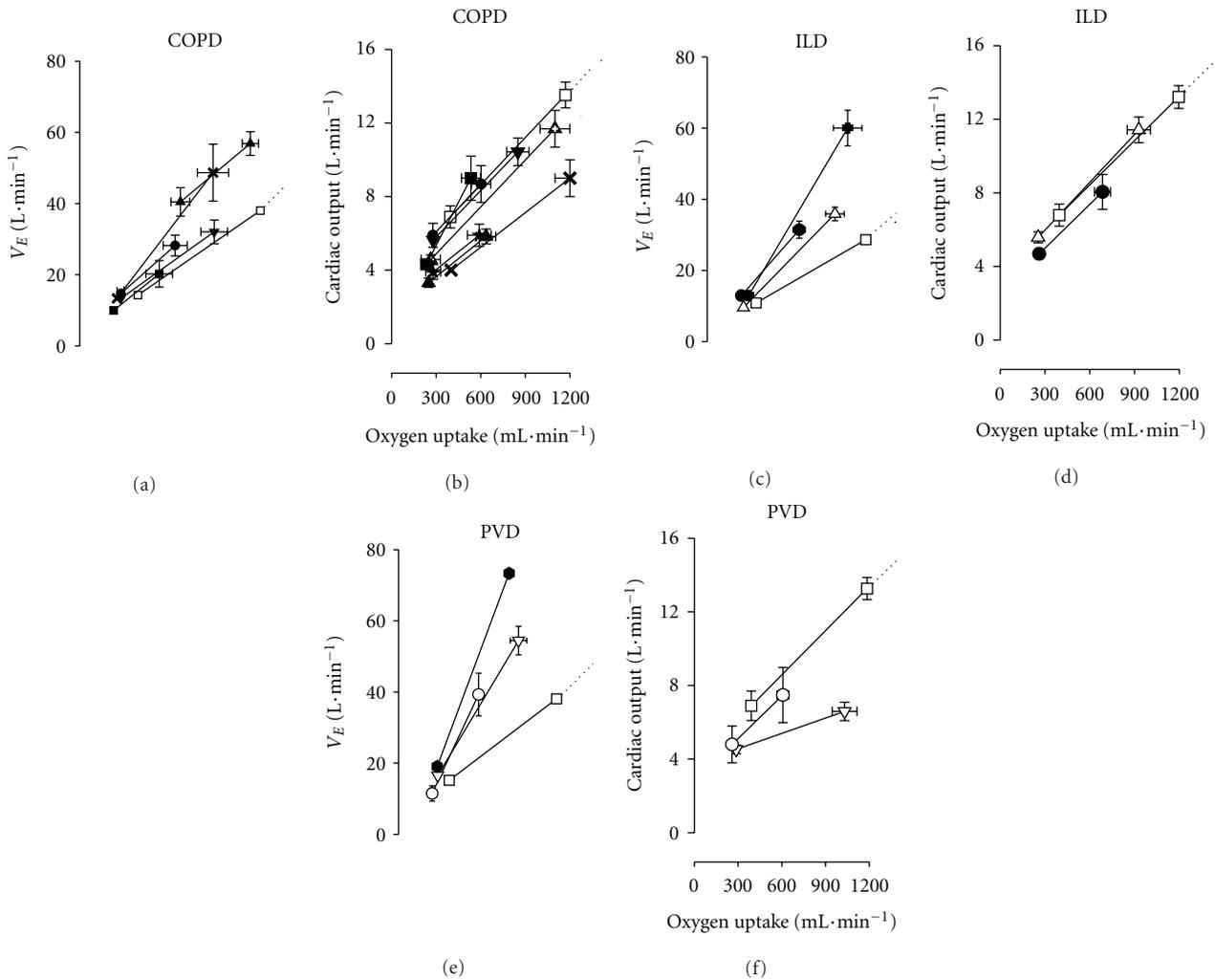


FIGURE 3: Mean minute ventilation and cardiac output during exercise in chronic lung diseases. Minute ventilation (V_E) and cardiac output as a function of oxygen uptake at rest and during exercise in patients with COPD (a and b), ILD (c and d), PVD (e and f), and healthy subjects (\square). Adapted with permission from Agusti et al., 1997 [43].

V_D physiological is approximately equal to anatomical dead space (V_D anatomical) and accounts for about 25%–30% of V_T at rest. It is increased with exercise, consequent to the expanding influence on the conducting airways of the greater transpulmonary pressures. However, as the expansion of the alveolar space is appreciably greater than that of the less distensible conducting airways, V_D physiological/ V_T falls (typically to ~ 0.1 – 0.2 at peak exercise). Naturally, V_D physiological/ V_T is appreciably larger than V_D anatomical in many pulmonary diseases, with V_D physiological/ V_T being as high as 0.5.

Due to the early termination of exercise, peak heart rate is relatively low whilst the heart rate reserve is high. In addition, patients often exhibit arterial hypoxemia (Figure 4(c)) that is manifested by a decrease in arterial oxygen saturation. Furthermore, owing to the reduced alveolar ventilation during exercise, hypercapnia emerges reflecting overt ventilatory insufficiency. In addition, in patients with COPD mechanical factors may substantially constrain the ventilatory response to the metabolically generated CO_2 in such a way that PaCO_2

may not decrease as in normal healthy subjects (i.e., compromised respiratory compensation) [44–47] (Figure 2(b)). Indeed, severe mechanical restriction secondary to dynamic hyperinflation and increased respiratory muscle work in a setting of an increased physiological dead space has been recognised as a contributory factor to hypercapnia in COPD [48].

In summary, during prolonged exercise the aforementioned gas exchange abnormalities worsen the alveolar ventilation/perfusion inequalities further increasing dead space ventilation that in turn leads to hypoxemia and hypercapnia. All these factors contribute to increased ventilatory requirement that in the face of reduced ventilator capacity exaggerate dyspnea sensations, thereby compromising physical capacity.

2.3. Central and Peripheral Hemodynamic Factors. Cardiac output in healthy elderly subjects can increase several-fold in response to exercise [5, 18, 20, 49, 50]. In the majority of healthy elderly subjects, cardiac output is often

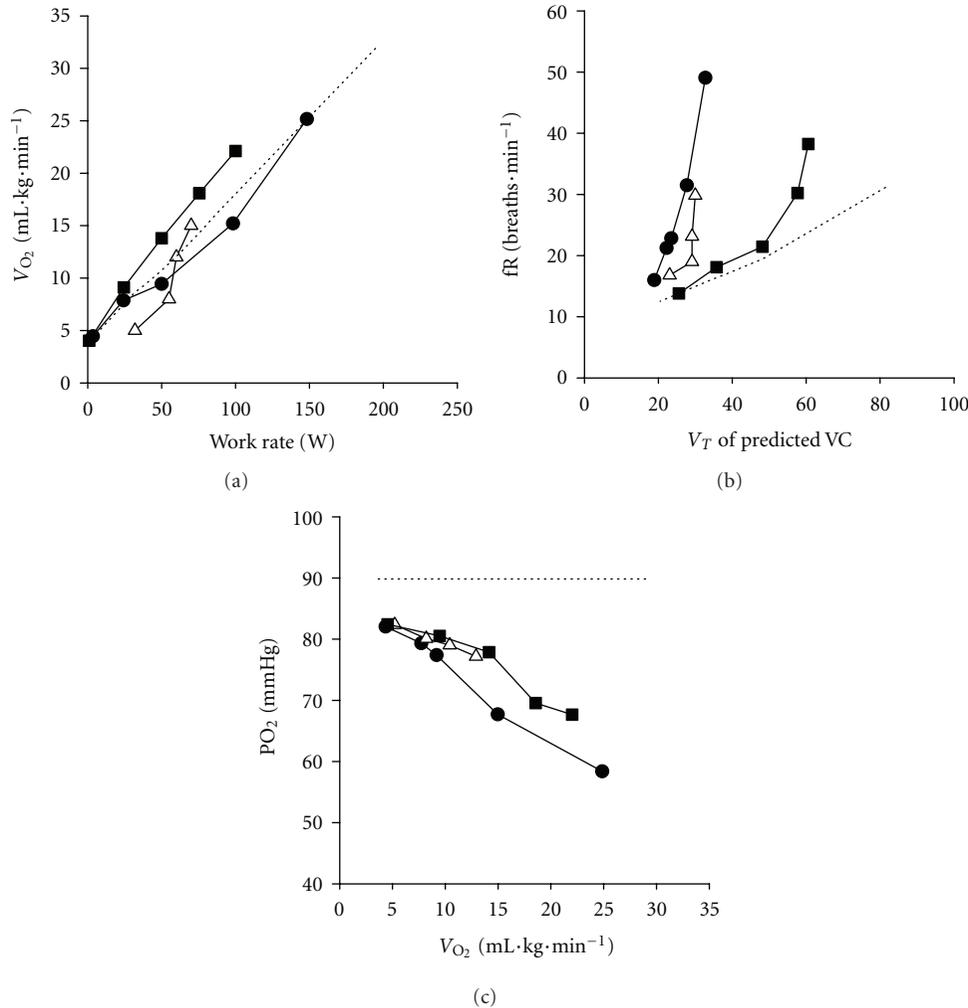


FIGURE 4: Ventilatory and gas exchange responses during incremental exercise in chronic lung diseases. Typical exercise responses in COPD (Δ) interstitial lung disease (ILD: \bullet), PVD (\blacksquare), and healthy age-matched subjects (-----) for (a) oxygen uptake (b) respiratory frequency (fR), and (c) arterial oxygen tension. Responses plotted as a function of oxygen uptake (\dot{V}_{O_2}), work rate, or tidal volume as a % of predicted vital capacity (VC). With permission from O'Donnell et al., 2007 [3–5].

the “rate-limiting step” to exercise, and normal maximal exercise is usually accompanied by a heart rate that often approaches the maximal predicted. In contrast, in chronic lung diseases, the following mechanisms that involve oxygen transport are frequently impaired resulting in reduction of cardiovascular function (Figure 3). Firstly, coexisting right or left ventricular dysfunction can impair physical activity simply because of poor cardiac output capability, which often leads to impaired oxygen delivery and early development of metabolic acidosis. Similarly, functionally important arrhythmias may also impair the normal increase in cardiac output as a function of an increase in work rate [5, 18, 20, 51]. Secondly, in chronic lung diseases, especially in the presence of pulmonary vascular abnormalities, pulmonary hypertension and right ventricular dysfunction may develop [52]. The impaired right ventricle may thus contribute to a limited increase in cardiac output. These phenomena may worsen in the presence of hypoxemia. Hypoxemia can in turn

elevate pulmonary vascular resistance and create pulmonary arterial hypertension with consequent right heart failure [43, 52–58]. The resulting restrained increase in cardiac output, coupled with the low oxygen content, reduces systemic oxygen delivery to all organs of the body, including skeletal muscles. Interestingly, because the work of breathing is often substantially increased in chronic lung diseases, there might also exist a respiratory muscle “steal” of blood flow away from the locomotor muscles, which further compromises peripheral muscle function [59, 60].

In COPD, constant-load exercise tolerance has been documented to largely depend on the imposed workload as the time to the limit of tolerance decreases (similarly to normal subjects) hyperbolically as a function of power output [61]. The hyperbolic shape of the power output-endurance time relationship has been shown to be determined by the dynamics of the ventilatory response toward a reduced and fixed maximum ventilatory ceiling. More

explicitly, for each individual COPD patient there is a so-called “critical power” that represents the highest work rate at which there is sufficient ventilatory reserve. In terms of physiological responses, studies [62, 63] have revealed that in the transition from rest to constant-load exercise, pulmonary oxygen uptake kinetic responses are slower in patients with COPD as compared to age-matched healthy individuals. This sluggishness of oxygen uptake is thought to lead to an early and greater reliance on oxygen-independent metabolic pathways and accumulation of by-products that accelerate the occurrence of muscle fatigability. Along these lines, there is uniform agreement [14, 33–38] that lactic acid production occurs at a very low level of physical activity in COPD (i.e., <40% predicted peak \dot{V}_{O_2}) [27, 60, 64]. In addition, derangements in the diffusive and convective transport of oxygen to skeletal muscle mitochondria have been portrayed as plausible factors to delayed pulmonary oxygen uptake kinetics [62, 63, 65]. Chiappa and colleagues [66] extended those findings by showing that COPD patients also display slower cardiac output kinetics along with faster dynamics of vastus lateralis muscle deoxygenated haemoglobin (an index of muscle microvascular oxygen extraction). These findings have been interpreted to indicate impaired central and peripheral muscle hemodynamic adjustments in COPD compared to healthy subjects [66, 67].

In summary, in chronic lung diseases cardiovascular factors associated with coexisting right and/or left ventricular dysfunction, functional arrhythmias, and various negative cardiopulmonary interactions can impair cardiac function and thus physical activity.

2.4. Skeletal Muscle Abnormalities. Regardless of overt respiratory insufficiency, patients with chronic lung diseases are commonly characterized by reduced physical activity. Inactivity in COPD leads to muscle weakness and altered muscle fibre distribution [68] reflected by high proportion of type I slow twitch fibres which are highly oxidative, low tensioned, and fatigue resistant [12, 69–74]. Reduction in the proportion of oxidative fibres reduces the oxidative potential of the muscles and would make them more vulnerable to fatigue during high-intensity exercise. There is also less capillary density that reduces regional blood flow and oxygen/nutrient delivery. Such structural and metabolic abnormalities of the limb muscles may lead to early lactic acidosis and task failure with exercise [69–73].

In addition, systemic inflammatory mediators, which can profoundly affect skeletal muscle function [44, 75–77] are persistently elevated in chronic lung diseases, thereby accelerating muscle protein degradation [78–85]. This contributes to the loss of muscle mass and the clinical appearance of “muscle wasting” [44, 75–77, 85–87]. Chronic inflammation also increases muscle oxidative stress and increases reactive oxygen species, which directly damage muscle proteins, impair their function, and lead to protein degradation [29, 88–90].

Furthermore, patients with chronic lung diseases [27] are often malnourished. Weight loss occurs in approximately 30% of out-patients with chronic lung diseases [91–96], because of decreased calorie intake and the effects of

chronic inflammation on energy metabolism in general. Reduced protein intake leads to muscle breakdown as muscle proteins and amino acids are utilized for fuel (catabolism). Malnutrition also contributes to reduced muscle enzyme capacity and reduced availability of energy substrates [97–101]. Finally, patients with chronic lung disease may also take corticosteroids, particularly during exacerbations. Corticosteroids can profoundly affect skeletal muscle, as they reduce contractile proteins, increase protein breakdown and turnover, downregulate growth factors, reduce glycolytic activity, and lead to sarcomere and type-II fibre atrophy [102–104].

Accordingly, lower limb muscles in patients with chronic lung diseases are atrophied, weak, fatigable, and metabolically inefficient. These unfavorable muscle characteristics concur to limit exercise capacity, a most debilitating feature in these patients.

In summary, although several mechanisms underlying the development of skeletal muscle dysfunction have been identified (e.g., deconditioning), it is important to further identify the impact of other potential contributors to skeletal muscle dysfunction in chronic lung diseases (such as inflammation, malnutrition, oxidative stress, and inflammation, etc).

2.5. Exercise Intolerance in Chronic Lung Diseases. In patients with COPD, exercise intolerance involves respiratory mechanical, pulmonary gas exchange, hemodynamic and peripheral muscle abnormalities that interfere with the normal in-series system (ventilation, gas exchange, blood flow, hemoglobin, muscle O_2/CO_2 transport, and O_2 utilization/ CO_2 production) upon which exercise depends, thereby ultimately preventing adequate oxygen transfer from the atmosphere to, and/or utilization of oxygen by, the mitochondria. Such abnormalities may occur consequently due to the following reasons: (i) limited ventilatory capacity to suffice the ventilatory requirement, (ii) imbalance between the high blood/oxygen requirement of the locomotor and/or respiratory muscles and the limited blood/oxygen supply to these muscles, and (iii) dysfunction/weakness and reduced oxygen utilization capacity at the level of the peripheral muscles [1–13].

The primary mechanisms limiting exercise tolerance in patients with ILD include the restrictive lung mechanics, pulmonary gas exchange derangements, hemodynamic abnormalities, and peripheral muscle dysfunction [4]. Ventilatory inefficiency occurs secondary to high physiological dead space and arterial hypoxemia and thirdly to premature metabolic acidosis. Likewise, the oxygen cost of breathing per unit ventilation is increased in patients with ILD as the static recoil pressure of the lungs is increased, thereby requiring greater inspiratory muscle activity [43]. Impaired gas exchange occurs as a result of destruction of the pulmonary capillary bed or thickening of the alveolar capillary membrane, causing ventilation/perfusion mismatch, oxygen diffusion limitation, and low mixed venous partial pressure of oxygen. Circulatory limitation resulting from pulmonary capillary destruction and hypoxic vasoconstriction leading to

pulmonary hypertension and cardiac dysfunction also plays an important role in exercise limitation [43].

Relatively reduced lung compliance and inspiratory muscle weakness have been suggested as potential contributing factors of abnormal ventilatory mechanisms in pulmonary vascular diseases. During exercise, there is substantial arterial oxygen desaturation causing widening of alveolar-arterial oxygen tension, reflecting considerable VA/Q inequalities. Circulatory limitation resulting from pulmonary capillary destruction and hypoxic vasoconstriction leading to pulmonary hypertension and cardiac dysfunction also plays an important role in exercise limitation [3, 43].

3. Conclusions

The available literature suggests that in the majority of patients with severe chronic lung disease, primarily ventilatory constraints, resulting from the imbalance between ventilatory demand and capacity, limit physical capacity due to intense dyspnea sensations, whereas to a lesser extent, inadequate energy supply to locomotor muscles and/or locomotor muscle dysfunction limit(s) physical activity performance secondary to locomotor muscle discomfort. In contrast, in many patients with mild and moderate chronic lung disease, both reduced energy supply to locomotor muscles associated with leg discomfort and ventilatory constraints causing breathlessness restrain exercise tolerance.

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Review Article

Assessing Exercise Limitation Using Cardiopulmonary Exercise Testing

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The cardiopulmonary exercise test (CPET) is an important physiological investigation that can aid clinicians in their evaluation of exercise intolerance and dyspnea. Maximal oxygen consumption ($\dot{V}_{O_{2max}}$) is the gold-standard measure of aerobic fitness and is determined by the variables that define oxygen delivery in the Fick equation ($\dot{V}_{O_2} = \text{cardiac output} \times \text{arterial-venous } O_2 \text{ content difference}$). In healthy subjects, of the variables involved in oxygen delivery, it is the limitations of the cardiovascular system that are most responsible for limiting exercise, as ventilation and gas exchange are sufficient to maintain arterial O_2 content up to peak exercise. Patients with lung disease can develop a pulmonary limitation to exercise which can contribute to exercise intolerance and dyspnea. In these patients, ventilation may be insufficient for metabolic demand, as demonstrated by an inadequate breathing reserve, expiratory flow limitation, dynamic hyperinflation, and/or retention of arterial CO_2 . Lung disease patients can also develop gas exchange impairments with exercise as demonstrated by an increased alveolar-to-arterial O_2 pressure difference. CPET testing data, when combined with other clinical/investigation studies, can provide the clinician with an objective method to evaluate cardiopulmonary physiology and determination of exercise intolerance.

1. Introduction

The cardiopulmonary exercise test (CPET) is an important physiological investigation that can aid clinicians in their diagnostic evaluation of exercise intolerance and dyspnea [1, 2]. Although cardiac and pulmonary etiologies are the most common causes for dyspnea and exercise intolerance [3, 4], neurological, metabolic, hematologic, endocrine, and psychiatric disorders can all contribute. The data gathered from a CPET can provide valuable information to differentiate between these causes [5], as progressive incremental exercise testing provides the most comprehensive and objective assessment of functional impairment and yields information about the metabolic, cardiovascular, and

ventilatory responses to exercise. In addition to assisting in the diagnosis of dyspnea and exercise intolerance, CPETs can be used for a broad range of other applications such as determining disease severity, exercise prescription for rehabilitation, assessing the effectiveness of pharmacological agents, or in the assessment for lung transplant (see Table 1).

Algorithms exist to help identify CPET patterns of known clinical diagnosis [6], and typical clinical responses have been detailed previously [1]. However, in order for clinicians to interpret CPET results, a thorough understanding of the cardiopulmonary responses to exercise is needed. The purpose of this paper is to provide the clinician with an overview of the physiological responses to exercise as well as the processes used to evaluate the mechanism(s) for exercise intolerance.

TABLE 1: Indications for cardiopulmonary exercise testing.

Assessment of unexplained dyspnea
Evaluation of disease severity
Development of an exercise prescription for pulmonary rehabilitation
Identification of gas exchange abnormalities
Preoperative assessment:
Lung cancer surgery
Lung volume reduction surgery
Heart or lung transplantation
Evaluation for lung/heart transplantation
Objective evaluation of exercise capacity

2. Cardiovascular Response to Exercise

Maximal oxygen consumption ($\dot{V}_{O_{2max}}$) is a measure of the capacity for aerobic, and exercise is determined by the variables found in the Fick equation:

$$\dot{V}_{O_2} = Q \times (CaO_2 - CvO_2), \quad (1)$$

where Q is the cardiac output (the product of heart rate and stroke volume) and CaO_2 and CvO_2 are the O_2 contents of arterial and mixed venous blood, respectively. From this equation, it is evident that the factors that influence $\dot{V}_{O_{2max}}$ would include cardiac function, oxygen carrying capacity, and the ability of the tissues to extract oxygen.

In healthy subjects, of the variables involved in oxygen delivery, it is the limitations of the cardiovascular system that are most responsible for limiting $\dot{V}_{O_{2max}}$ [7]. Ventilation and gas exchange are usually sufficient to maintain arterial PO_2 (PaO_2), and therefore arterial saturation (SaO_2) and CaO_2 are also maintained up to maximal workload [8]. Numerous studies have shown that $\dot{V}_{O_{2max}}$ can be increased through exercise training [9, 10]. While peripheral adaptation occurs with training that will increase peripheral O_2 extraction [11], the primary mechanism for training-induced improvements in $\dot{V}_{O_{2max}}$ is an increase in cardiac output secondary to an augmented stroke volume response to exercise [12]. Indeed, many studies have shown positive cardiac adaptation with exercise training [13–17]. The increased stroke volume response with exercise results in a reduced submaximal heart rate with exercise training; however, peak heart rate is generally unaffected by training [12]. Experimental studies have demonstrated that improvements in O_2 delivery will positively affect $\dot{V}_{O_{2max}}$. As an example, Stray-Gundersen et al. showed that both peak cardiac output and $\dot{V}_{O_{2max}}$ could be increased by 20% in untrained dogs by performing pericardiectomy [18]. This effect is due to increased ventricular filling and thus an increased cardiac output. Conversely, a reduction in peak cardiac output will lead to a lower $\dot{V}_{O_{2max}}$. This is highlighted by studies in normal humans showing beta blockade reduces $\dot{V}_{O_{2max}}$ by decreasing both maximal heart rate and stroke volume [19]. These examples from experimental studies demonstrate the close link between peak cardiac output and $\dot{V}_{O_{2max}}$ in health.

As \dot{V}_{O_2} increases with incremental exercise, the variables in the Fick equation will eventually reach their upper limits, and as a result, a plateau of the \dot{V}_{O_2} will occur. The plateau in oxygen consumption despite an increase in workload is defined as a person's $\dot{V}_{O_{2max}}$. However, many subjects, particularly clinical patients, do not demonstrate this plateau in \dot{V}_{O_2} [20], for a variety of reasons which may include intolerable symptoms of breathing discomfort (dyspnea), muscular fatigue, chest pain, and so forth, [20, 21]. If a plateau is not seen, then the highest \dot{V}_{O_2} achieved, termed the $\dot{V}_{O_{2peak}}$, is used as an estimate of $\dot{V}_{O_{2max}}$ [20, 22]. These values represent the maximal oxygen consumption and can be expressed in L/min or indexed by body weight and expressed in mL/min/kg [20]. Of note, the best adjustment for body size is not known and many estimations exist [20]. Various reference equations have been provided (see [1] for list) to evaluate $\dot{V}_{O_{2max}}$, and previous guidelines [1] define a $\dot{V}_{O_{2max}} < 85\%$ of predicted as low and abnormal (see later section on evaluating $\dot{V}_{O_{2max}}/\dot{V}_{O_{2peak}}$ for further discussion).

The limitation of the cardiovascular system is well accepted as being the point where healthy subjects reach their $\dot{V}_{O_{2max}}$ [23, 24]. Thus, if a subject reaches their maximum predicted heart rate (HR) for age (i.e., peak HR $> 85\%$ of predicted [1]), it would be reasonable to conclude based on the cardiac response that they have reached their $\dot{V}_{O_{2max}}$. However, this should not be used as a single determinant of $\dot{V}_{O_{2max}}$, as there is considerable between-subject variability in maximal heart rate [25]. As well, clinical conditions and medications, especially beta blocker use, can affect the HR response to exercise [20–22]. Thus, in the setting of a reduced $\dot{V}_{O_{2max}}$ (i.e., $< 85\%$ of predicted [1]), reaching maximal HR suggests maximal subject effort and that a cardiac limitation may exist; however, this must be confirmed by examining additional variables (see later section).

Oxygen pulse is the amount of oxygen consumed by the tissue per heart beat (i.e., $\dot{V}_{O_2}/\text{heart rate}$) [26]. By modifying the variables in the Fick equation, the O_2 pulse is calculated as follows:

$$O_2 \text{ pulse} = \frac{\dot{V}_{O_2}}{HR} = SV \times (CaO_2 - CvO_2). \quad (2)$$

With O_2 pulse, the assumption is that the $a - v$ O_2 difference widens in a predictable manner, and therefore examination of the O_2 pulse can provide information about the stroke volume response to exercise [26]. In the setting of a low $\dot{V}_{O_{2max}}$, a reduced O_2 pulse would indicate a low stroke volume response to exercise. However, as O_2 pulse is calculated using HR, the value is subject to the same assumptions regarding the HR response to exercise, and therefore the considerable between-subject variability in maximal heart rate [25] can translate to substantial variability in O_2 pulse response to exercise.

In summary, the $\dot{V}_{O_{2max}}$ is determined by the variables that define oxygen delivery by the Fick equation. While anything that alters components of the Fick equation can alter $\dot{V}_{O_{2max}}$, studies in health have demonstrated that it is the cardiac output response and more specifically the stroke volume response to exercise that limit $\dot{V}_{O_{2max}}$, and

thus in the normal healthy subject, $\dot{V}_{O_{2\max}}$ is limited by the cardiovascular system.

3. Ventilatory Response to Exercise

As previously mentioned, \dot{V}_{O_2} increases during exercise as governed, by the Fick equation. With increasing O_2 consumption there is an increase in CO_2 production (\dot{V}_{CO_2}). The relationship between $PaCO_2$, \dot{V}_{CO_2} , and alveolar ventilation (\dot{V}_A) is governed by the alveolar ventilation equation [27]:

$$PaCO_2 = \left(\frac{\dot{V}_{CO_2}}{\dot{V}_A} \right) \cdot K. \quad (3)$$

$PaCO_2$ is reported in mmHg (and assumed to be equal to alveolar PCO_2), while both \dot{V}_{CO_2} and \dot{V}_A are reported in L/min [28]. \dot{V}_{CO_2} is always given at $0^\circ C$, 760 mmHg, dry (STPD); \dot{V}_A and $PaCO_2$ are reported under body temperature, ambient pressure and saturated with water vapor (BTPS) [28]. The K is a conversion factor $[(273 + t) \times 760/273]$, where t = body temperature (273 is $0^\circ C$ converted to $^\circ$ Kelvin). K is used to adjust \dot{V}_{CO_2} to body temperature and pressure and is equal to 863 mmHg at sea level and at normal body temperature of $37^\circ C$ [27, 29]. As highlighted in (4) in the following section, \dot{V}_A can be derived from \dot{V}_E (minute ventilation) and \dot{V}_D (physiologic dead space ventilation).

Assuming K does not change with exercise, (3) demonstrates that in order to maintain $PaCO_2$ at normal resting values, \dot{V}_A must increase with exercise because of the increased CO_2 production. Thus in health, the normal response from rest to mild/moderate exercise is an increase in ventilation that is commensurate with metabolic demand (termed exercise *hyperpnea*), and therefore $PaCO_2$ should be unchanged from rest to mild/moderate exercise. Practically, subjects often hyperventilate prior to exercise (or at low levels of exercise in the laboratory), and therefore it is common to see $PaCO_2$ rise to a more normal value with mild/moderate exercise. Once past ventilatory threshold, \dot{V}_A increases disproportionately relative to metabolic demand and $PaCO_2$ drops below resting values (i.e., *hyperventilation*). $PaCO_2$ typically falls to 30–35 mmHg at peak exercise, and a peak $PaCO_2$ of 35–38 mmHg indicates a borderline effective alveolar hyperventilation, while a $PaCO_2$ in excess of 38 mmHg suggests the absence of a compensatory hyperventilatory response [30]. Thus, $PaCO_2$ values obtained with incremental exercise allow for the determination of the adequacy or appropriateness of ventilation during exercise.

End-tidal CO_2 ($PETCO_2$) can be used to estimate $PaCO_2$. At rest $PETCO_2$ is less than $PaCO_2$ (and correspondingly end-tidal O_2 , $PETO_2$ more than alveolar PO_2 , PAO_2) due to dilution of gas from poorly perfused alveoli (i.e., dead space). Using end-tidal values to predict alveolar pressures has the potential of underestimating $PaCO_2$; however, in the healthy lung at rest, dead space is extremely low, and $PETCO_2$ is a good approximation of $PaCO_2$ [28]. With exercise there is an increase in tidal volume (V_T), \dot{V}_{CO_2} and mixed venous CO_2 , such that the within-breath fluctuations of alveolar gas composition are greater [31]. With the rapid

increase in alveolar volume on inspiration during exercise, end-inspiratory PCO_2 is well below the mean alveolar PCO_2 , whereas during expiration, alveolar PCO_2 increases toward mixed venous PCO_2 more rapidly than at rest as the increased CO_2 production of exercise is evolved into a lung volume becoming smaller as expiration continues [32]. The latter factor results in $PETCO_2$ being higher than mean $PaCO_2$ during exercise [33], and therefore $PETCO_2$ has the potential to overestimate $PaCO_2$ at peak exercise. In patients with lung disease who generally have a blunted tidal volume response to exercise, and a relatively low peak metabolic rate, the within-breath fluctuations of alveolar PCO_2 are likely less than what would be seen in health. Rather, a larger issue in lung disease is the increased dead space ventilation and likely underestimation of $PaCO_2$ using $PETCO_2$. Jones et al. developed a prediction equation to calculate $PaCO_2$ from $PETCO_2$ during exercise [$PaCO_2 = 5.5 + (0.90 \times PETCO_2) - (0.0021 \times \text{tidal volume})$] [32]; however, it is worth noting that this equation was developed with subjects exercising up to 50% $\dot{V}_{O_{2\max}}$. Further, it was suggested that the equation should not be used in patients with abnormal pulmonary function nor in children [32]. Thus, there are limitations with using $PETCO_2$ as a prediction of $PaCO_2$ that need to be considered when interpreting CPET data. Arterialized blood can also be used to predict $PaCO_2$ with reasonable accuracy [34, 35] but is practically more difficult as compared to $PETCO_2$.

4. Dead Space Ventilation

As shown in (4), total expired minute ventilation (\dot{V}_E), measured at the mouth, consists of both alveolar ventilation (\dot{V}_A) and physiologic dead space ventilation (\dot{V}_D):

$$\dot{V}_E = \dot{V}_A + \dot{V}_D. \quad (4)$$

Alveolar ventilation is the amount of effective ventilation that participates in gas exchange. Physiological dead space is ventilation that does not participate in gas exchange and consists of anatomical dead space such as the conducting airways, as well as alveolar dead space which are unperfused alveoli. Physiological dead space can be calculated as a fraction of total ventilation using the Enghoff modification [36] of the Bohr [37] dead space equation:

$$\frac{\dot{V}_D}{\dot{V}_E} = \frac{PaCO_2 - PECO_2}{PaCO_2}, \quad (5)$$

where $PECO_2$ represented the mean PCO_2 in the expired air. Examining this equation, dead space ventilation (i.e., \dot{V}_D/\dot{V}_E ratio) would be zero if mean expired PCO_2 was equal to arterial PCO_2 . Conversely, significant dead space results in expiration of gas that is more similar to inspired PCO_2 (i.e., sections of the lung that did not participate in gas exchange and therefore have a $PCO_2 \sim 0$), which has the effect of diluting the expired air and reducing $PECO_2$ relative to $PaCO_2$. Of note, many metabolic carts typically calculate a dead space/tidal volume ratio (V_D/V_T ratio, i.e., dead space per breath), using the same equation as listed in (5). However, these calculations are often based on a $PaCO_2$ that

is predicted from PETCO_2 , and therefore significant caution should be taken in interpreting V_D/V_T values that are not derived using direct PaCO_2 measurement.

5. Breathing Pattern Response to Exercise

The precise matching of alveolar ventilation with metabolic rate during exercise is achieved by increasing minute ventilation. This increase is accomplished by increases in both tidal volume and breathing frequency. The increased tidal volume slightly increases airway dead space, due to tethering effects of the lung parenchyma on airway lumen size. However, the relative tidal volume increase exceeds this effect, and the dead space to tidal volume ratio decreases during exercise from resting values of ~ 0.35 to ~ 0.20 , translating into more efficient ventilation [1]. During low-to-moderate intensity exercise, both tidal volume and breathing frequency increase roughly in proportion to exercise intensity, whereas at higher intensities, tidal volume reaches a plateau and further increases in ventilation are accomplished by increases in breathing frequency alone [1].

Increases in breathing frequency are accomplished by reducing both the inspiratory (T_I) and expiratory times (T_E). However, the ratio of inspiratory time to total breath cycle duration (T_{TOT}), the duty cycle (T_I/T_{TOT}), increases only slightly during exercise (~ 0.40 at rest to ~ 0.50 during high-intensity exercise) [38]. The increase in tidal volume is achieved by reducing the end-expiratory lung volume (EELV) below the functional residual capacity (achieved by activating expiratory muscles) and increasing the end-inspiratory lung volume (see later section on EELV determination) [38]. At lower exercise intensities, increases in ventilation are mostly achieved through tidal volume changes, rather than just increasing breathing frequency, which would increase dead space ventilation and compromise effective alveolar ventilation. To minimize the work of breathing during heavier exercise, tidal volume increases only to $\sim 70\%$ of the vital capacity [39], as above this lung volume, lung compliance decreases markedly and the respiratory pressure production required for a given change in volume is very large, leading to exaggerated respiratory discomfort (i.e., dyspnea) [40].

6. Ventilatory Efficiency

Ventilatory efficiency is typically evaluated by the $\dot{V}_E/\dot{V}_{\text{CO}_2}$ responses to exercise, and as the term implies, it provides information about the effectiveness of minute ventilation for a given metabolic rate. Importantly, ventilatory efficiency has been shown to be decreased in several clinical conditions including chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH) [41, 42], and in heart failure [43]. In patients with PAH [42] and chronic heart failure [43], the $\dot{V}_E/\dot{V}_{\text{CO}_2}$ ratio is predictive of mortality. Importantly, when $\dot{V}_E/\dot{V}_{\text{CO}_2}$ is elevated it is important to understand the underlying physiological mechanism for the increased \dot{V}_E relative to metabolic rate. As shown in (4), \dot{V}_E would be elevated because of an increase in dead space and/or alveolar ventilation. In pulmonary arterial

hypertension, the characteristic response is of pronounced hyperventilation at rest and with incremental exercise likely because of stimulation of receptors in the lung secondary to high vascular pressures [44]. In this condition, the enhanced $\dot{V}_E/\dot{V}_{\text{CO}_2}$ response to exercise is secondary to greater \dot{V}_A as demonstrated by a low PaCO_2 (or PETCO_2) throughout exercise [41, 42]. Patients with chronic heart failure (CHF) also show an exaggerated $\dot{V}_E/\dot{V}_{\text{CO}_2}$ response to exercise [43]; however, PaCO_2 can appear normal in these patients [45], indicating that the increased $\dot{V}_E/\dot{V}_{\text{CO}_2}$ is secondary to enhanced dead space ventilation.

Lung diseases associated with airflow limitation and/or a loss of elastic recoil can lead to altered ventilation/perfusion (\dot{V}_A/\dot{Q}) matching in the lung [46]. As a result of the reduction in \dot{V}_A/\dot{Q} matching, physiological dead space is increased, and therefore V_D/V_T and $\dot{V}_E/\dot{V}_{\text{CO}_2}$ will be increased with incremental exercise as compared to controls [47]. In these patients $\dot{V}_E/\dot{V}_{\text{CO}_2}$ is exaggerated while PaCO_2 is normal or perhaps even elevated, indicating that the increased \dot{V}_E for a given metabolic rate is secondary to increased dead space. This reduction in ventilatory efficiency can further compromise exercise tolerance and potentiate dyspnea in patients with obstructive lung disease as their ventilatory reserve is already reduced, and therefore they have both an inability to increase \dot{V}_E because of airflow limitation, plus a need to have a greater \dot{V}_E for a given metabolic rate because of altered \dot{V}_A/\dot{Q} matching and the associated increased dead space ventilation. These examples highlight how the $\dot{V}_E/\dot{V}_{\text{CO}_2}$ and PaCO_2 responses to exercise can be used to differentiate between pathologies and mechanisms of dyspnea.

7. Ventilatory Reserve

Traditionally, ventilatory reserve has been evaluated by examining how closely the peak minute ventilation on a CPET ($\dot{V}_{E \text{ max}}$) approaches the greatest volume of gas that can be breathed per minute by voluntary effort, termed the maximal voluntary ventilation (MVV). Previous guidelines state that breathing reserve [$\text{BR} = (\text{MVV} - \dot{V}_{E \text{ max}})/\text{MVV} \times 100$] should be $>15\%$ at peak exercise [1]. This method provides a general approximation of ventilatory capacity, with little analysis required. Ventilatory reserve depends on two main factors: ventilatory demand and ventilatory capacity [46, 48]. Ventilatory demand is dependent on metabolic demand, body weight, mode of testing, dead space ventilation as well as neuroregulatory and behavioral factors [48]. Ventilatory capacity is affected by mechanical factors such as airflow limitation and operating lung volumes, ventilatory muscle function, genetic endowment, aging, and disease [48]. Ventilatory capacity can also be affected by bronchoconstriction or bronchodilation [48]. Thus, a reduction in ventilatory reserve may be explained by increased ventilatory demand (such as during heavy exercise in an athlete or with inefficient ventilation) and/or reduced ventilatory capacity (typically due to airflow limitation).

Importantly, there are limitations to determining MVV which can affect determination of ventilatory reserve, and further, there are mechanical differences between voluntary

hyperventilation at rest and exercise-induced hyperpnea. When performing an MVV at rest, subjects often hyperinflate, which can increase work of breathing relative to the same ventilation during exercise [46, 49–51]. In addition, MVV is subject to patient effort, and with poor effort the MVV can be low and the calculated ventilatory reserve falsely reduced. Because of the difficulties in measuring MVV, it is often predicted based on FEV₁ (typically FEV₁ multiplied by 35–40) [48, 52], and as with any prediction equation, there is variance around the accuracy of this prediction. Most importantly, using only the breathing reserve does not provide any information about the mechanism of ventilatory constraint (i.e., is there evidence of expiratory flow limitation or hyperinflation?) [46]. It is for these reasons that examining expiratory flow limitation and operating lung volumes has evolved as the preferred technique to examine a ventilatory limitation to exercise.

8. Expiratory Flow Limitation

To evaluate the degree of ventilatory constraint during exercise, the degree of expiratory flow limitation (EFL) can be examined by plotting the exercise flow-volume loop relative to the maximal flow [46]. This relationship can provide information about the degree of expiratory flow limitation, operating lung volumes, as well as breathing strategies used with incremental exercise. The degree of EFL during exercise has been previously expressed as a percent of V_T that meets or exceeds the expiratory boundary [48, 53, 54]. The presence of EFL promotes dynamic hyperinflation and intrinsic positive end-expiratory pressure with increased work of breathing, functional impairment of inspiratory muscle strength, increased sensations of dyspnea, and adverse effects on hemodynamics [55, 56]. When the degree of expiratory flow limitation becomes significant (>40–50% \dot{V}_T), EELV typically increases [48, 53, 57, 58].

Many of the modern metabolic carts allow for evaluation of EFL by plotting exercise tidal breathing within a maximal flow-volume loop. However, there is no clear consensus regarding the quantification of EFL. Johnson et al. [48] suggested an evaluation criteria regarding EFL and inspiratory capacity (IC); however, this had not been widely adopted clinically. Instead, most typically categorize EFL as an “all or none” criteria. Importantly, it is not unusual for a normal young (<35 yrs) subject of average fitness and no lung disease to have EFL of <25% of V_T at peak exercise [48, 49, 59, 60]. Thus, the clinical significance of some EFL occurring at or close to peak exercise is unclear.

By definition, EFL requires the demonstration of an increase in transpulmonary pressure with no increase in expiratory flow [56]. As well reviewed recently by Calverley and Koulouris [56], the comparison of tidal breathing relative to the maximal flow volume loop has its limitations including (1) thoracic gas compression artifact; to reduce these errors volume should be measured using a body plethysmograph instead of the typical Pneumotach. (2) Incorrect alignment of the tidal breathing curve within the maximal flow-volume loop. (3) The previous volume and time history of a spontaneous tidal breath is different than

the flow-volume curve derived from the maximum forced vital capacity; there is not a single maximum flow volume curve, but rather a family of curves which are dependent on the time course of the preceding forced vital capacity [56, 61–63]. (4) Mechanics and time-constant inequalities are different in tidal versus maximal flow-volume curves. (5) Exercise may cause bronchodilation/bronchoconstriction. (6) The technique requires good patient cooperation/effort. Guenette et al. [64] recently demonstrated that failure to account for gas compression and exercise-induced bronchodilation results in a significant overestimation of EFL. As a result of these limitations, the use of plotting tidal breathing relative to the maximal flow-volume loop to detect/quantify EFL has been questioned [56], although many of these potential limitations can be avoided or minimized with the use of standardized techniques.

As an alternative, the negative expiratory pressure method has been advocated for the detection of EFL. As the name implies, with this technique a small negative pressure (i.e., suction of –3 to –5 cm H₂O) is given during expiration [56]. This method is based on the principle that in the absence of EFL, an increase in the pressure gradient between the alveoli and the mouth would increase flow, whereas with EFL increasing the pressure gradient would not increase flow [56]. This technique has been used during exercise to demonstrate EFL in lung disease [65–67]; however, it does not allow for quantification of severity of EFL and has not been adopted during widespread clinical practice.

9. Inspiratory Capacity

With EFL, expiratory flow rates are independent of expiratory muscle effort and are determined by the static lung recoil pressure and the resistance of the airways upstream from the flow-limited segment [60, 68, 69]. In flow-limited patients, the mechanical time constant for lung emptying is increased in many alveolar units, but the expiratory time available is often insufficient to allow EELV to return to its original values, resulting in gas accumulation and retention (i.e., air trapping) [60]. As demonstrated by (3), the increased CO₂ production with exercise necessitates an increase in \dot{V}_A by increasing V_T and breathing frequency to maintain PaCO₂. However, the increased tidal volume in combination with diminished expiratory time due to increased breathing frequency can cause dynamic hyperinflation in patients with EFL [60]. Thus, the main consequence of expiratory flow limitation during exercise is the development of dynamic hyperinflation (DH) [47, 60].

As reviewed recently by O’Donnell and Lavenziana [60], DH during exercise has several important consequences including (1) a sudden increase in elastic and threshold loads on the inspiratory muscles, leading to increased work and O₂ cost of breathing. (2) Functional inspiratory muscle weakness by shortening the diaphragm muscle length. (3) Reducing the ability of V_T to expand appropriately with exercise, leading to a mechanical limitation of ventilation. (4) Hypoventilation and hypoxemia in more severe patients [70]. (5) Impairment in cardiac function. In COPD patients, $\dot{V}_{O_{2peak}}$ was strongly related to peak tidal volume ($r = 0.68$),

which in turn was strongly related to IC at peak exercise ($r = 0.79$) [71]. These results indicate that DH blunts the tidal volume expansion with incremental exercise, which contributes to exercise intolerance/reduced $\dot{V}_{O_{2peak}}$. Consistent with the consequences of IC listed, the IC during exercise and the rate of change in IC with exercise (i.e., dynamic hyperinflation) are strong determinants of exertional dyspnea and exercise intolerance [71–73].

Dynamic hyperinflation in early exercise may be a compensatory mechanism to increase \dot{V}_E with limited (or minimal) respiratory discomfort [74]; however, with increasing exercise a threshold is reached (around an inspiratory reserve volume of 0.5 L, or within 10% of total lung capacity), where V_T plateaus [60, 74]. At this point the breathing occurs at the least compliant portion of the respiratory system's pressure-volume curve; the diaphragm muscle fibers are maximally shortened, and dyspnea develops at an extremely accelerated rate because of the disparity between the inspiratory effort and tidal volume response [60, 74].

Recent work has shown that below this tidal volume inflection (or plateau), dyspnea increases linearly with workload; however once IC drops below a critical value, dyspnea increases abruptly and becomes the most frequently selected reason for exercise termination regardless of exercise protocol [75]. The rate of dynamic hyperinflation has been shown to be correlated with diffusion capacity (D_{LCO}/\dot{V}_A) [71]. Patients with lower DLCO would be expected to have a greater propensity to expiratory flow limitation because of reduced lung elastic recoil and airway tethering. Patients with a more emphysematous clinical profile (i.e., low DLCO) have been shown to have a greater rate of dynamic hyperinflation, less expansion of tidal volume, greater dyspnea, and lower $\dot{V}_{O_{2peak}}$ as compared to patients with similar airflow obstruction, but normal DLCO [71]. More recent work has shown that in COPD patients it may be the progressive erosion of resting IC with worsening airflow obstruction and hyperinflation that represents the true operating limits for tidal volume expansion from rest to exercise [76]. O'Donnell et al. [76] found that reductions in resting IC were associated with the development of an increasingly shallow, rapid breathing pattern and worsening dyspnea at progressively lower levels of ventilation during exercise. Importantly, regardless of the severity of airflow limitation, once V_T reaches the previously described threshold, there was a steep increase in dyspnea [76]. Other recent work has shown that it may not be the drop in IC but rather a critical reduction in inspiratory reserve volume that causes the plateau in V_T and marked increase in dyspnea [77]. These findings indicate that EFL contributes to DH, and once EELV has increased to a critical value and/or inspiratory reserve volume drops to a critical value, dyspnea is greatly potentiated, resulting in substantial exercise limitation.

Serial inspiratory capacity maneuvers are used during incremental exercise to evaluate EELV/IC progression with exercise. The use of IC to track EELV during exercise is based on the assumption that total lung capacity (TLC) does not change during exercise, and that reductions in IC represent changes in EELV (i.e., $EELV = TLC - IC$) [78, 79]. Inspiratory capacity is determined by the degree of

hyperinflation, inspiratory muscle strength, and the extent of intrinsic mechanical loading on the inspiratory muscles [72]. The IC also provides information regarding the position of the tidal volume on the respiratory system's pressure-volume curve [72]. The lower the IC, the closer towards TLC the subject is breathing, which is the least compliant portion of the respiratory system's pressure-volume curve. Previous work has also shown that IC determination can be reliably obtained during exercise [72, 80]. When performing serial IC measurements with incremental exercise, a good effort is required to inspire up to TLC during each maneuver so as to ensure IC is not becoming falsely reduced because of inadequate inspiration. Esophageal pressure data confirms that peak esophageal pressure (an estimate of effort) does not change with repeated IC measurements, thereby indicating that serial ICs are valid with incremental exercise testing [72, 73, 80]. In addition to IC maneuvers, changes in EELV during exercise can also be tracked with newer methods such as optoelectronic plethysmography or respiratory inductance plethysmography [81, 82]; however, these techniques have not been adopted widely for clinical use.

10. Pulmonary Gas Exchange

Pulmonary gas exchange is typically evaluated by alveolar-arterial oxygen partial pressure difference ($AaDO_2 = PAO_2 - PaO_2$). The stress of exercise on pulmonary gas exchange can be highlighted by the following two equations. For a hypothetical homogeneous lung with no \dot{V}_A/\dot{Q} heterogeneity, the physiological definition of lung diffusion capacity for O_2 (DLO_2) is [28]:

$$DLO_2 = \frac{\dot{V}_{O_2}}{PAO_2 - PcO_2}. \quad (6)$$

PcO_2 is the mean PO_2 passing through the pulmonary capillaries, which cannot be measured and therefore is estimated by arterial blood sampling. Assuming $PcO_2 = PaO_2$ this equation can be rearranged to:

$$AaDO_2 = \frac{\dot{V}_{O_2}}{DLO_2}. \quad (7)$$

This physiological definition demonstrates that with the increased O_2 consumption with exercise, the lung must increase its diffusive capacity in order to limit the increase in $AaDO_2$ [28]. DLO_2 increases with exercise as a result of capillary recruitment, as demonstrated by an increase in diffusion capacity with exercise [83–88]. From this equation it is intuitive as to how exercise may result in impaired gas exchange in patients with lung disease, resulting in decreased $\dot{V}_{O_{2max}}$ and/or increased dyspnea. Patients with a diffusion impairment at rest from thickening of the blood gas barrier, such as in interstitial lung disease, would be expected to show an increase in $AaDO_2$ with exercise, while patients who have an inability to recruit pulmonary capillaries and therefore increase DLO_2 because of capillary destruction (i.e., COPD) would also increase $AaDO_2$ with exercise. Importantly, in addition to the impact on recruitment of diffusion capacity, lung disease can also result in greater \dot{V}_A/\dot{Q} mismatch

which can be exacerbated with exercise, resulting in further deterioration in gas exchange.

In health, most exercising humans show an increase in AaDO₂ with incremental exercise which reaches its peak at $\dot{V}_{O_{2max}}$ [30, 89], but remains within normal limits (i.e., <35 mmHg) [1]. The AaDO₂ appears greatest in endurance athletes, and in severe cases may cause hypoxemia [30, 89], which is somewhat counterintuitive as one would expect endurance athletes to have an excellent cardiopulmonary system. The increase in AaDO₂ with exercise has been an area of physiological interest and is likely explained by a combination of \dot{V}_A/\dot{Q} mismatch [90–92] and diffusion limitation secondarily to reduced red blood cell transit time or the development of interstitial non-clinical edema [90–93] and/or the recruitment of intrapulmonary arteriovenous shunts [94, 95]. Importantly, despite the attention given to pulmonary gas exchange in the research literature, exercise-induced arterial hypoxemia is uncommon in all but the most highly aerobic athletes. Thus, further clinical followup may be warranted in symptomatic non-athletic subjects who demonstrate an exaggerated AaDO₂ (>35 mmHg) and/or decreased PaO₂ with exercise.

As measurement of PaO₂ requires arterial catheterization, most CPET studies are conducted by monitoring arterial saturation by pulse oximetry (SpO₂). While SpO₂ may be appropriate for monitoring, care should be taken when interpreting this data. Firstly, the standard error of estimate for SpO₂ monitors is between 2% and 5% [96–98]. SpO₂ monitors can also bias low when blood flow is reduced, such as what can occur with a finger oximeter while subjects are exercising vigorously on a cycle ergometer. Previous work suggests that an oximeter placed on the forehead provides the most accurate readings [97]. When using SpO₂ to evaluate gas exchange during normoxic exercise, it is important to note that within the typical exercise range, SaO₂ values are on the flat part of the oxygen hemoglobin dissociation curve, and within this range relatively small changes in SaO₂ are associated with large differences in PaO₂. Thus, even small uncertainties in SaO₂ would have a big effect on estimated PaO₂ [97]. SaO₂ is also affected by the temperature and pH changes during exercise, and these alone can result in a SpO₂ decrease of 4%–5% in the absence of any change in PaO₂. Finally, should hypoxemia develop, it is not possible to determine if hypoxemia is secondary to an impairment in gas exchange (i.e., increased AaDO₂) or significant hypoventilation with a corresponding drop in PAO₂ and PaO₂. Previous guidelines [1] define an SpO₂ of 88% during exercise as significant hypoxemia; however, this value does not rule out the development of a significant gas exchange impairment, and therefore temperature-corrected arterial blood gas data should be used if careful gas exchange evaluation is needed.

11. CPET Interpretation

The purpose of the previous sections was to highlight the physiological responses to exercise, and how decrements in cardiopulmonary physiology can lead to dyspnea and exercise intolerance. While a great deal of research has examined

TABLE 2: Contraindications for cardiopulmonary exercise testing.

Acute myocardial infarction
Unstable angina
Unstable arrhythmias
Syncope
Symptomatic severe aortic stenosis
Any acute pulmonary symptom
Any acute infectious process
Inability to comply with testing procedures

cardiopulmonary physiology and exercise, these findings still make it somewhat difficult to integrate all the data obtained in a CPET to provide a clear clinical interpretation of the mechanism(s) contributing to dyspnea/exercise intolerance in symptomatic individuals. Previous position statements have provided insight [1], and the purpose of this section is to provide guidelines to help clinicians evaluate CPET responses. It should be noted that the interpretation strategy described may not apply to all conditions and remains an evolving process. It is also important to appreciate that there are various contraindications to CPET (see Table 2).

12. Determination of Maximal Patient Effort

Prior to full interpretation of a CPET, determination of maximal patient effort is required. Previous guidelines [1] list the following as evidence of maximal patient effort. (1) The patient achieves predicted $\dot{V}_{O_{2peak}}$ and/or a plateau in \dot{V}_{O_2} is observed. (2) Predicted maximal work rate is achieved. (3) Predicted maximal heart rate is achieved. (4) There is evidence of a ventilatory limitation; that is, peak exercise ventilation approaches or exceeds maximal ventilatory capacity. (5) A respiratory exchange ratio (RER, often called respiratory quotient (RQ)) greater than 1.15. (6) Patient exhaustion/Borg scale rating of 9–10 on a 10-point scale.

Importantly, because of the cardiovascular adaptations observed in athletes, these subjects often exceed predicted $\dot{V}_{O_{2max}}$ and predicted maximal work rate even during sub-maximal work, and therefore we would suggest that reaching predicted or $\dot{V}_{O_{2max}}$ or maximum work rate should not be evidence of a maximal effort. Based on this and new research detailed previously on EFL and changes in IC with exercise, we would suggest the following criteria for determination of maximal effort.

Criteria for Maximal Effort

- (1) RER \geq 1.1.
- (2) HR > 90% predicted max.
- (3) Patient exhaustion/Borg scale > 9/10.
- (4) Was there a plateau in \dot{V}_{O_2} ?
- (5) Was there evidence of a ventilatory limitation (breathing reserve <15% and/or significant EFL and/or decrease in IC)?

Importantly, there is no gold standard for evaluating maximal effort [1]. There is currently disagreement as to whether hypoxemia is evidence of a maximal effort. As hypoxemia can develop during submaximal exercise in some patients (e.g., interstitial lung disease), it has been suggested that this is not evidence of a maximal test [1], while others have indicated that hypoxemia is indeed confirmation of a maximal test [99].

With respect to the above-listed criteria, when more criteria are attained during a CPET, there would be more confidence that a maximal patient effort has been obtained. Notably, patients often have difficulty reaching a plateau in \dot{V}_{O_2} , and considering the between-subject variability in maximal heart rate [25], both criteria (2) and (4) are frequently not reached despite maximal effort. Further, while patients may achieve exhaustion with CPET testing (3), their Borg scale may be high, but not exceed a value of “9” on Borg scale as defined by previous guidelines [1]. It is also important to note that in the absence of respiratory disease, criteria (5) is rarely obtained. Conversely, in the presence of a significant ventilatory limitation (5), criteria 1, 2 and 4 may not be achieved despite maximal patient effort. Severe hypoxemia/gas exchange impairment, chest pain, ischemic ECG changes, and decreases in heart rate and blood pressure can occur during submaximal exercise and are not evidence of maximal effort [1], but may be very informative in the interpretation of test results.

13. Evaluation of Peak Oxygen Consumption

As $\dot{V}_{O_{2peak}}/\dot{V}_{O_{2max}}$ is affected by age and sex, conditioning status, and the presence of diseases or medications that can influence its components, accurate interpretation of exercise data requires reference values that are appropriate for each patient (see [1] for a comprehensive list of reference formulas). As with any criteria, the determination of low/abnormal $\dot{V}_{O_{2max}}/\dot{V}_{O_{2peak}}$ is somewhat arbitrary. The American Thoracic Society/American College of Chest Physicians statement on cardiopulmonary exercise testing defines a $\dot{V}_{O_{2max}}/\dot{V}_{O_{2peak}} \leq 84\%$ of predicted as abnormal [1]. When examining long-term survival, subjects with an absolute peak exercise capacity of >8 metabolic equivalents (METs) regardless of age, have improved survival as compared to subjects with a peak workload of 5–8 METs, or below 5 METs [100]. When exercise capacity is expressed as a % of predicted, subjects who attain a $\dot{V}_{O_{2max}}$ of 75%–100% of predicted have lower survival than those who reach $\dot{V}_{O_{2max}} > 100\%$ of predicted, and survival is correspondingly lower for those with a $\dot{V}_{O_{2max}}$ 50 to 74% and those with a $\dot{V}_{O_{2max}} < 50\%$ of predicted, respectively [100]. These findings indicate that a $\dot{V}_{O_{2max}}$ below age-predicted, but still within typical values (i.e., 75%–100% of predicted), is associated with increased mortality and is therefore clinically important.

$\dot{V}_{O_{2peak}}/\dot{V}_{O_{2max}}$ is highly dependent on chronic physical fitness/exercise history and can be increased with exercise training and conversely reduced with inactivity. This is noteworthy when evaluating a previously athletic individual, as in these individuals a $\dot{V}_{O_{2max}}$ of ~100% of predicted may represent a substantial reduction in previous functional

ability. The next section will now review how to determine whether the exercise intolerance can be explained by a pulmonary or cardiovascular limitation to exercise and whether this limitation is physiological (i.e., normal) or pathological.

14. Determining Exercise Limitation

Importantly, the data obtained from a CPET test should not be interpreted in isolation. Rather, the interpretation should be an integration of CPET results with other clinical findings/investigations. In addition to the data directly obtained from the CPET, feedback from the patient, including reason for exercise termination, can be useful in evaluating exercise limitation. Figure 1 provides a guideline for CPET interpretation and classification based on previous work [48, 53, 57, 58, 60, 70, 74].

As detailed previously, $\dot{V}_{O_{2max}}$ is determined by the Fick equation. Increases in cardiac output/blood flow result in increased $\dot{V}_{O_{2max}}$, indicating that the normal person has a cardiovascular limitation to exercise. These subjects would surpass their ventilatory threshold, and therefore the RER would be expected to be >1.1, while HR should approach age-predicted maximum. In these subjects EFL, increases in EELV, and significant gas exchange impairment would not develop with exercise. Subjects who, despite showing a normal pulmonary, cardiovascular and metabolic response to exercise, still have a low $\dot{V}_{O_{2max}}$ would be classified as being deconditioned. In contrast, subjects showing ECG changes with exercise, an exaggerated BP response to exercise, a significant drop in BP or HR with exercise, exaggerated \dot{V}_E/\dot{V}_{CO_2} response with hyperventilation, and a very low $\dot{V}_{O_{2max}}$ would be suggestive of a pathological cardiovascular limitation to exercise. Thus, a cardiovascular limitation to exercise is the interpretation of default; that is, in the absence of any abnormal/pathological response, subjects are limited by their cardiovascular system.

When ventilatory demand is excessive or ventilatory capacity is reduced, a ventilatory limitation to exercise can develop. Ventilatory reserve is related to ventilatory demand, and ventilatory capacity [46, 48]; however because of the difficulties in determining MVV and the lack of information provided about the mechanism of ventilatory constraint, ventilatory reserve in isolation is a more rudimentary evaluation of ventilatory limitation, and determination of EFL and IC is preferable. As mentioned previously, EFL determination also has its limitations, and failure to account for variables such as thoracic gas compression and exercise-induced bronchodilation/bronchoconstriction will result in an overestimation of EFL [64]. Since an EFL < 25% of V_T can occur at maximal exercise in normal subjects [48, 49, 59, 60], it is unlikely that this amount of EFL should be considered abnormal and clinically significant. The development of EFL for >40%–50% V_T is abnormal and can result in an increase in EELV [48, 53, 57, 58]. As EFL contributes to work of breathing and functional impairment of inspiratory muscle strength [55, 56], significant EFL by itself would contribute to perceived dyspnea and exercise intolerance. The development of EFL with a decrease in

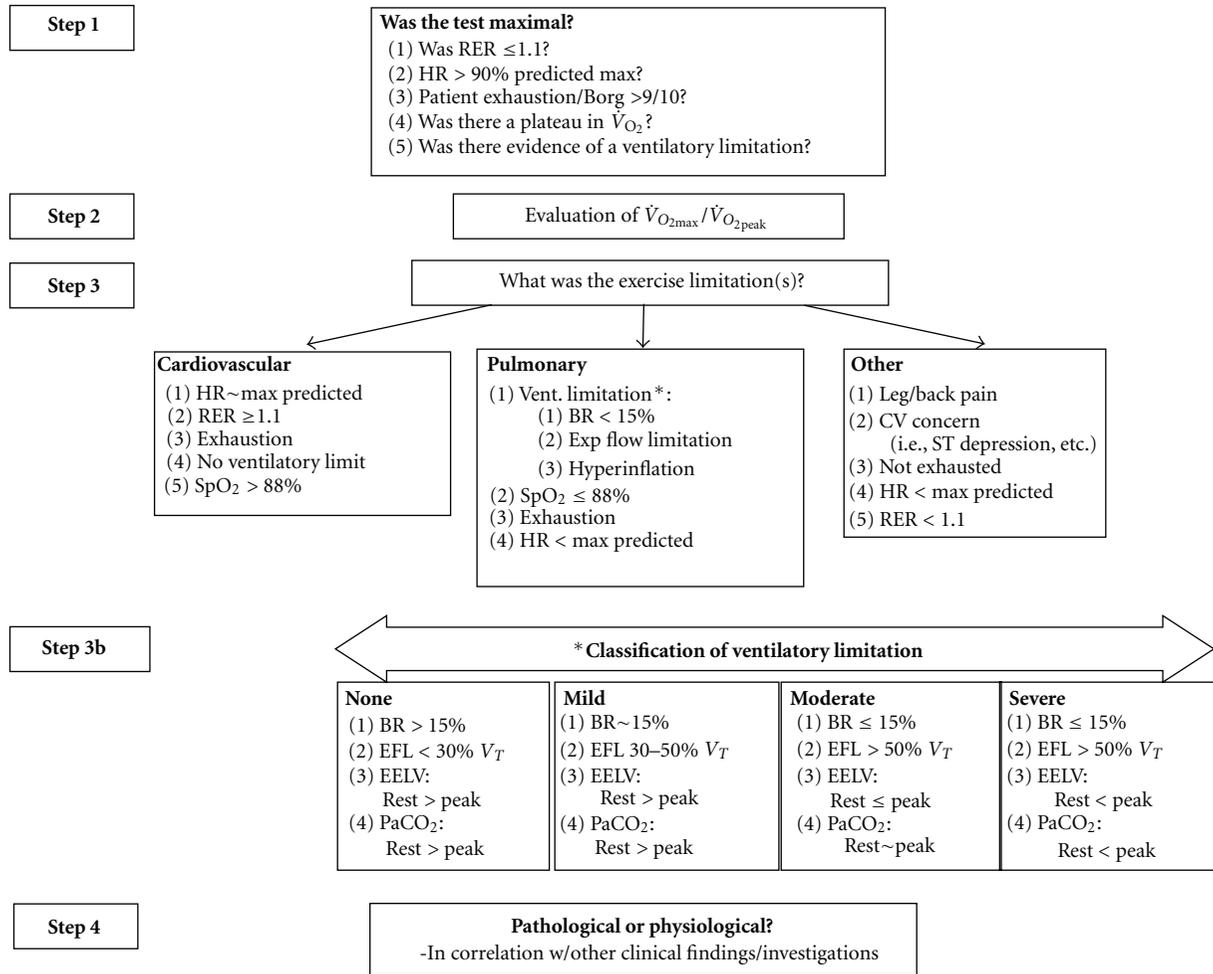


FIGURE 1: Interpretation algorithm for cardiopulmonary exercise testing. This figure provides an outline of a CPET interpretation strategy and suggested classification of ventilatory limitation based on previous work [1, 48, 53, 57, 58, 60, 70, 74]. Importantly, the data obtained from a CPET test should not be interpreted in isolation, but rather results should be integrated with other clinical findings/investigations. RER: respiratory exchange ratio, \dot{V}_{O_2} : oxygen consumption, HR: heart rate, SpO₂: arterial saturation, BR: breathing reserve, CV: cardiovascular, EFL: expiratory flow limitation, V_T: tidal volume, EELV: end-expiratory lung volume, PaCO₂: arterial PCO₂.

IC would represent a more severe respiratory limitation and also result in a plateau in tidal volume expansion and potentiated dyspnea [60, 74]. In the most severe cases, hypercapnea and hypoxemia would develop, as ventilation is insufficient to meet metabolic demand. In many cases, the ventilatory limitation to exercise is so severe that the patient does not reach their ventilatory threshold (i.e., an RER < 1.0 at peak) or age-predicted maximum heart rate. Some subjects demonstrate a reduction in IC with exercise despite normal lung function and no evidence of EFL or any other mechanical limitation. In these situations, behavioral conditions such as anxiety should be considered. See Figure 1 for a suggested classification of ventilatory limitation based on previous work [48, 53, 57, 58, 60, 70, 74].

The pulmonary system can further contribute to exercise intolerance by failing to maintain adequate arterial oxygenation. Previous guidelines indicate a fall in SaO₂ of ≥4%, SaO₂ ≤ 88% or PaO₂ ≤ 55 mmHg is considered clinically significant [1]. As mentioned, SaO₂/SpO₂ evaluated in

isolation does not allow for determination of the underlying mechanism for hypoxemia (i.e., hypoventilation versus gas exchange impairment versus lactic acidosis/hyperthermia).

Poor ventilatory efficiency (i.e., high $\dot{V}_E / \dot{V}_{CO_2}$) can be characteristic of various cardiovascular and pulmonary diseases. Importantly, an abnormal $\dot{V}_E / \dot{V}_{CO_2}$ response may be a signal to obtain arterial blood gases during exercise so that PaCO₂ and dead space ventilation can be directly determined [1]. A high $\dot{V}_E / \dot{V}_{CO_2}$ ratio in isolation may contribute to dyspnea but is not likely to contribute to exercise intolerance by itself. However, with an exaggerated ventilatory response to exercise EFL and an increase in EELV that may develop, and these components would contribute to exercise intolerance.

Other patients may terminate a CPET because of alternate issues such as back pain and knee pain. In addition, the testing staff may terminate the exercise because of safety concerns (ECG changes, altered BP response, etc.). In these situations, the test would be terminated because of

a noncardiopulmonary limitation, and it is unlikely that the patient would have reached maximal patient effort.

As a final step, the clinician should determine whether the limitation to exercise is physiological (i.e., normal) or pathological and needing further followup. By way of example, a subject with a low $\dot{V}_{O_{2peak}}$, but otherwise normal test, would have a physiological cardiovascular limitation to exercise whereby the low $\dot{V}_{O_{2peak}}$ is explained by deconditioning. A subject with a similar $\dot{V}_{O_{2peak}}$, but showing abnormal ECG or BP responses, would have a pathological cardiovascular limitation requiring further followup. A COPD patient who has a low $\dot{V}_{O_{2peak}}$, but otherwise normal test (including a normal ventilatory response to exercise), would have a physiological cardiovascular limitation to exercise whereby the low $\dot{V}_{O_{2peak}}$ is explained by deconditioning. While in contrast, a COPD patient who has a low $\dot{V}_{O_{2peak}}$ but substantial EFL and hyperinflation would have a pathological respiratory limitation to exercise. Respiratory limitations to exercise are typically pathological, except in the case of an athlete with superior cardiovascular function and normal lung function [28]. These athletes can demonstrate EFL, increased EELV and gas exchange impairment; however, this is an example of the cardiovascular system outgrowing the lungs, and not pulmonary pathology [28]. Of note, patients may demonstrate evidence of both a cardiovascular and pulmonary limitation to exercise.

15. Summary

As reviewed in this paper, exercise represents a significant stress to the cardiopulmonary system. With exercise, oxygen delivery and local muscle O_2 extraction must increase appropriately to meet metabolic demand. Ventilation must similarly increase to compensate for the increased CO_2 production and maintain alveolar ventilation, while diffusion capacity must also be augmented to maintain arterial PO_2 . The normal subject has a breathing reserve even at maximal exercise, and therefore expiratory flow limitation and/or hyperinflation should not occur with exercise. In addition, healthy subjects maintain oxygenation up to peak exercise because of an appropriate increase in diffusion capacity. The failure to have an appropriate cardiovascular, ventilatory, or gas exchange response to exercise can result in greater exertional dyspnea and/or exercise tolerance. As outlined in the paper, examining the cardiopulmonary responses to a CPET can provide additional clinical data that is not available through resting tests of lung and cardiac function and can help clinicians determine mechanism(s) for exercise intolerance and/or dyspnea.

Abbreviations

Alveolar PO_2 :	PAO_2
Alveolar ventilation:	\dot{V}_A
Arterial O_2 content:	CaO_2
Arterial PO_2 :	PaO_2
Arterial saturation:	SaO_2
Arterial saturation by pulse oximetry:	SpO_2
Cardiopulmonary exercise test:	CPET

CO_2 production:	\dot{V}_{CO_2}
Diffusion capacity for carbon monoxide:	DLCO
Diffusion capacity for O_2 :	DLO ₂
End-tidal CO_2 :	PETCO ₂
End-tidal O_2 :	PETO ₂
Expiratory flow limitation:	EFL
Expiratory lung volume:	EELV
Expiratory time:	T_E
Heart rate:	HR
Inspiratory capacity:	IC
Inspiratory time:	T_I
Maximal oxygen consumption:	$\dot{V}_{O_{2max}}$
Maximal voluntary ventilation:	MVV
Metabolic equivalents:	METS
Minute ventilation:	\dot{V}_E
Mixed venous O_2 content:	CvO_2
Peak minute ventilation:	\dot{V}_{Emax}
Peak oxygen consumption:	$\dot{V}_{O_{2peak}}$
Physiologic dead space ventilation:	\dot{V}_D
Pulmonary arterial hypertension:	PAH
Tidal volume:	V_T
Total breath cycle duration:	T_{TOT}
Total lung capacity:	TLC
Ventilation/perfusion:	\dot{V}_a/\dot{Q}

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Research Article

Determination of Best Criteria to Determine Final and Initial Speeds within Ramp Exercise Testing Protocols

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This study compared strategies to define final and initial speeds for designing ramp protocols. $V_{O_2 \max}$ was directly assessed in 117 subjects (29 ± 8 yrs) and estimated by three nonexercise models: (1) Veterans Specific Activity Questionnaire (VSAQ); (2) Rating of Perceived Capacity (RPC); (3) Questionnaire of Cardiorespiratory Fitness (CRF). Thirty seven subjects (30 ± 9 yrs) performed three additional tests with initial speeds corresponding to 50% of estimated $V_{O_2 \max}$ and 50% and 60% of measured $V_{O_2 \max}$. Significant differences ($P < 0.001$) were found between $V_{O_2 \max}$ measured ($41.5 \pm 6.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and estimated by VSAQ ($36.6 \pm 6.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and CRF ($45.0 \pm 5.3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), but not RPC ($41.3 \pm 6.2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). The CRF had the highest ICC, the lowest SEE, and better limits of agreement with $V_{O_2 \max}$ compared to the other instruments. Initial speeds from 50%–60% $V_{O_2 \max}$ estimated by CRF or measured produced similar $V_{O_2 \max}$ (40.7 ± 5.9 ; 40.0 ± 5.6 ; $40.3 \pm 5.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ resp., $P = 0.14$). The closest relationship to identity line was found in tests beginning at 50% $V_{O_2 \max}$ estimated by CRF. In conclusion, CRF was the best option to estimate $V_{O_2 \max}$ and therefore to define the final speed for ramp protocols. The measured $V_{O_2 \max}$ was independent of initial speeds, but speeds higher than 50% $V_{O_2 \max}$ produced poorer submaximal relationships between workload and V_{O_2} .

1. Introduction

Exercise capacity is an independent predictor of risk for cardiovascular disease and mortality among asymptomatic and symptomatic individuals [1–3]. Hence the determination of maximal oxygen uptake ($V_{O_2 \max}$) is considered to be one of the most important health-related parameters and has been widely used to evaluate cardiorespiratory fitness in health and illness [4–7].

However, the determination of exercise capacity is closely related to the test protocol employed [8]. An extensive body of evidence has shown that ramp exercise protocols offer advantages over traditional protocols, because the increase in external work occurs in a constant and continuous fashion, and when designing the protocol the rate of increase in workload can be individualized by a previous estimate of maximal exercise capacity [7, 9–12]. This is associated with greater linearity between V_{O_2} and work rate compared to

traditional protocols with large and disproportionate work rate increments [9, 11, 13]. Moreover, ramp protocols induce more uniform hemodynamic and respiratory responses, facilitating the acquisition of information at submaximal intensities, such as the ventilatory threshold [9, 13].

Despite the apparent advantages over traditional exercise testing, standardized criteria to guide the application of ramp protocols remain sparse. For instance, a limitation of ramp protocols is the requirement to estimate maximal exercise capacity from an activity scale and then adjust the ramp rate accordingly [14]. In practical terms, an underestimation of maximal exercise capacity will result in a prolonged total test duration, while an overestimation will result in premature test termination and, therefore, inappropriate test protocol for eliciting a true $V_{O_2 \max}$ [15]. However, there is no consensus in the literature concerning this issue. Available recommendations are generally vague and largely limited to the premise that tests should last between 8 and 12 min [4, 7, 14–17]. The same occurs with regard to the initial work rate of the test—actually we could not find recommendations of standard procedures for its determination [18].

Thus, the first objective of the present study was to compare three nonexercise models to predict maximal exercise capacity as criteria to determine the final speed of maximal treadmill ramp protocols. A second purpose was to investigate how different initial speeds calculated from % $V_{O_2 \max}$ influenced the $V_{O_2 \max}$ measured in the tests.

2. Material and Methods

2.1. Subjects. A group of 117 subjects (47 women) aged between 18 and 51 years (mean: 29.1 ± 7.6 yrs), with no previous experience in high performance physical training, volunteered for the study. Exclusion criteria included a clinical diagnosis of any clinical condition that could limit exercise performance and the use of any medication with potential cardiovascular influence. All participants were fully informed about the procedures and potential risks before giving written consent to take part in the study, which was approved by the local Institutional Research Ethics Committee.

2.2. Procedures. A flowchart of the 1st and 2nd studies is presented in Figure 1, detailing the procedures adopted to determine the workload increments using the nonexercise models (1st study—final speed) and different percent $V_{O_2 \max}$ intensities (2nd study—initial speed).

All 117 subjects enrolled in the first study. After signing the informed consent, the subjects performed the following procedures in a single visit to the laboratory: (a) anthropometric measurements; (b) application of three nonexercise models to estimate $V_{O_2 \max}$ (Veterans Specific Activity Questionnaire (VSAQ), [19, 20]; Rating of Perceived Capacity (RPC) [21]; Questionnaire of Cardio-respiratory Fitness (CRF) [22]); (c) cardiopulmonary exercise testing.

The VSAQ was originally developed by Myers et al. [19, 20] with the specific purpose of individualizing ramp protocols. The VSAQ includes a list of physical activities

with scores ranging from 1 to 13. The responder indicates which of the listed activities would cause fatigue or shortness of breath. Subjects evaluated in the initial studies with the VSAQ had low cardiorespiratory fitness and a high prevalence of overweight/obesity, hypertension, or coronary disease. Even though further studies have demonstrated that the instrument also provided adequate estimation of $V_{O_2 \max}$ in healthy active populations [5, 8], there is a lack of research specifically designed to assess its validity within the application of ramp protocols in healthy subjects. The RPC may be considered a variation of the VSAQ [21], presenting different maximal MET levels (ranging from 1 to 20), which are linked to physical activities of several intensities. Subjects rate their perceived capacity by choosing the most strenuous activity they could sustain for 30 min. However, the RPC has been not validated through direct comparison with exercise capacity using cardiopulmonary exercise testing. The CRF was not specifically developed to design ramp protocols, but it has been extensively applied as a nonexercise model to estimate the maximal cardiorespiratory capacity [22]. It is a progressive scale with scores for the intensity of the activities ranging from 0 to 7. The subjects must select the most appropriate score according to the physical activities performed in the last 30 days. The CRF was selected because of the unusual methodological meticulousness applied to its development. A large sample ($N = 799$) of men and women aged 19 to 79 years was tested. The estimated $V_{O_2 \max}$ was compared to directly measured data, and the questionnaire was cross-validated with another population, which is uncommon in studies assessing such instruments [23, 24].

In the first study, the increase in work rate within the cardiopulmonary exercise test (CPET1) was individualized to elicit each subject's limit of tolerance in 10 min, and treadmill grade was set at 0%. Final and initial speeds were determined using ACSM equations for treadmill running [7], considering the intensities corresponding to the highest $V_{O_2 \max}$ estimated by the non-exercise models (final speed) and 50% of this value (initial speed). The choice of 50% of the estimated $V_{O_2 \max}$ to determine the initial speed was based on a previous pilot study involving 35 subjects. In this pilot study, the initial speed was set at 1/3 of the estimated $V_{O_2 \max}$, which corresponded to a mean speed of $4.3 \text{ km}\cdot\text{h}^{-1}$ and a work rate increase of $0.88 \text{ km}\cdot\text{h}^{-1}$ each minute. The protocols lasted approximately 12 min (11.3 ± 2.2 min) and subjects remained walking, for about 4 min. Thus, an intensity of 50% $V_{O_2 \max}$ would probably shorten the test and increase the time in which the subjects would be actually running.

A subgroup of 37 subjects (17 women; age: 29.1 ± 7.6 yrs) was randomly selected to participate in the second study. These subjects performed three additional cardiopulmonary exercise tests, separated by 72 to 120 h intervals. The increase in work rate and treadmill grade were the same applied in CPET1. In the first test (CPET1bis), the final speed was determined using the best non-exercise model as defined in the first study, and the initial speed set at 50% of this value. The other tests (CPET2 and CPET3) were then performed using the results of CPET1bis as reference. In brief,

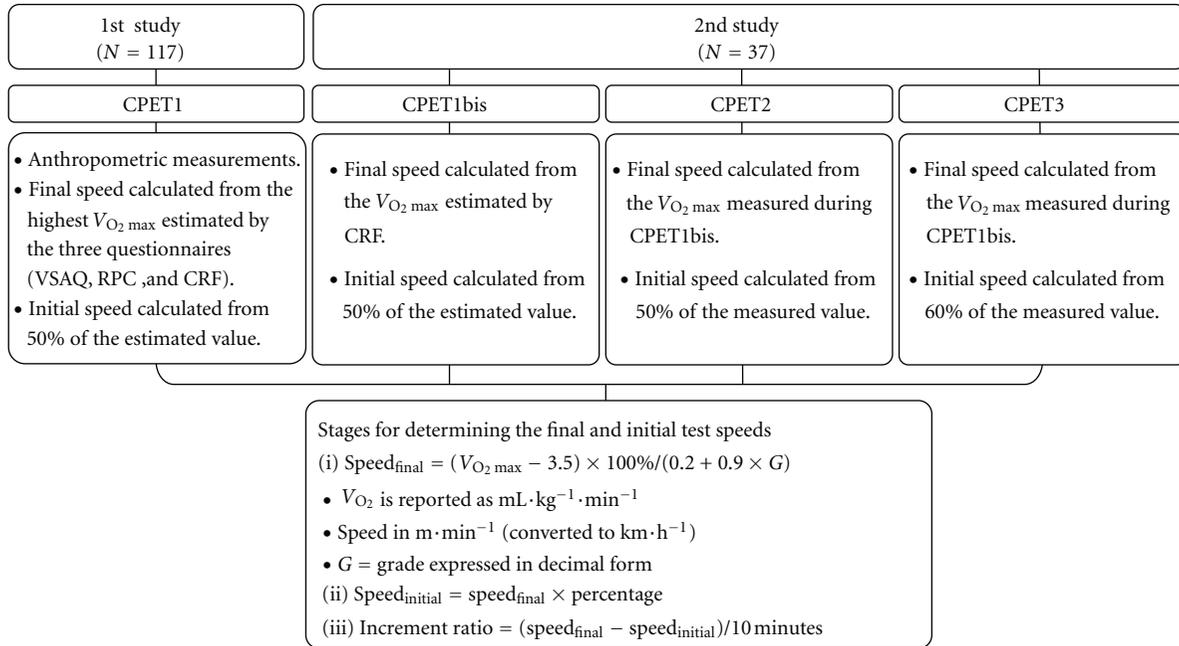


FIGURE 1: Flowchart of the 1st and 2nd studies including the procedures adopted to determine the workload increments, using nonexercise models to estimate $V_{O_2 \max}$ and ACSM running equation to calculate the treadmill speeds. $V_{O_2 \max}$: maximal oxygen uptake; CPET: cardiopulmonary exercise test; VSAQ: Veterans Specific Activity Questionnaire; RPC: Rating of Perceived Capacity; CRF: Questionnaire of Cardiorespiratory Fitness.

the final speed in CPET1bis was estimated from the maximal exercise capacity provided by CRF, whereas in both CPET2 and CPET3 it corresponded to the speed associated with the $V_{O_2 \max}$ assessed in CPET1bis. The initial speeds corresponded to 50% $V_{O_2 \max}$ estimated (CPET1bis), 50% $V_{O_2 \max}$ measured (CPET2), and 60% $V_{O_2 \max}$ measured (CPET3). This approach allowed to observe whether initial speeds ranging from 50 to 60% $V_{O_2 \max}$ (estimated or measured) influenced the results of the tests.

In the first study the CPET1 was applied by a researcher blinded for the results of the non-exercise models. In the second study, the sequence of tests was defined by a counterbalanced crossover design. The participants were blinded for the % V_{O_2} used to establish the initial speeds, and the evaluator was blinded for the purposes of the study.

The cardiopulmonary exercise test protocols were performed using a super-ATL treadmill (Inbramed, Florianopolis, SC, Brazil), and V_{O_2} was averaged and recorded every 30 s. The 30 s time average provided a good compromise between removing noise from V_{O_2} data while maintaining the underlying trend [25]. Data was assessed using a mouthpiece and noseclip. Gas exchange was assessed using a VO2000 analyzer (Medical Graphics, Saint Louis, MO, USA), which was calibrated with a certified standard mixture of oxygen (17.01%) and carbon dioxide (5.00%), balanced with nitrogen. The flows and volumes for the pneumotachograph were calibrated with a 3 L syringe (Hans Rudolph, Kansas, MO, USA). Heart rate was monitored using a Polar S-810 device (Polar, Kempele, Finland). Mean

ambient temperature and relative humidity during testing were $22.4 \pm 1.8^\circ\text{C}$ (range 18–23) and $62.5 \pm 4.1\%$ (range 50–75%), respectively.

The criteria for test interruption followed the recommendations of the American College of Sports Medicine [7]. The test was considered to achieve peak capacity when at least three of the following criteria were observed [26]: (a) maximum voluntary exhaustion as reflected by a score of 10 on the Borg CR-10 scale; (b) $\geq 95\%$ predicted HR max ($220 - \text{age}$) or presence of an HR plateau (ΔHR between two consecutive work rates $\leq 4 \text{ beats} \cdot \text{min}^{-1}$); (c) presence of a V_{O_2} plateau (ΔV_{O_2} between two consecutive work rates $< 2.1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$); (d) respiratory exchange ratio > 1.15 . Participants were verbally encouraged to achieve maximal effort. Holding onto the side or front rails of the treadmill was not permitted.

2.3. Statistical Analyses. Data normality was confirmed by univariate analysis. Therefore the intraclass correlation coefficient (ICC) was used to verify the concordance between the $V_{O_2 \max}$ assessed in CPET1 and the $V_{O_2 \max}$ estimated by the non-exercise models. Limits of agreement and bias for measured and estimated $V_{O_2 \max}$ were determined according to the Bland and Altman method [27]. Intraclass correlation (ICC), R -square coefficients (r^2), and standard errors of estimate (SEE) between actual and estimated $V_{O_2 \max}$ were also calculated.

The $V_{O_2 \max}$ values obtained in CPET1bis, CPET2, and CPET3 were compared by repeated measures ANOVA.

Additionally, linear regression was performed for each subject on each protocol in order to compare the relationships between workload and V_{O_2} , considering data in every 30 s of exercise. Mean \pm SD values of intercepts and slopes were determined for each linear regression model. Student t -tests for paired samples were used to test whether the intercepts and slopes were significantly different from 0 and 1, respectively [12], and to test possible differences between the regression lines, as described in detail elsewhere [28]. The r^2 and SEE for the regression models obtained in all tests were calculated as supplementary criteria to define the best initial speed. Two-tailed statistical significance for all tests was accepted as $P \leq 0.05$. All statistical analyses were performed using Statistica 7.0 (Statsoft, Tulsa, OK, USA) and SPSS 8.0 (IBM, Chicago, IL, USA) statistical analysis software.

3. Results

An achieved statistical power of 0.96 for an effect size of 0.25 was obtained by performing a post hoc power analysis (GPower version 3.0.10, Kiel, University of Kiel, Germany) based on the sample size, P value, number of repeated measures, and groups. Table 1 presents the characteristics of the samples comparing strategies to define final and initial speeds. Table 2 presents values for the assessed $V_{O_2 \max}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) by age and sex groups.

In the first study, mean duration of CPET1 was 13.3 ± 2.1 min for initial and final speeds of $5.9 \pm 0.9 \text{ km}\cdot\text{h}^{-1}$ and $14.7 \pm 2.1 \text{ km}\cdot\text{h}^{-1}$, respectively. Significant differences were detected between $V_{O_2 \max}$ assessed in CPET1 ($41.5 \pm 6.6 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and $V_{O_2 \max}$ estimated from VSAQ and CRF ($V_{O_2 \max}$ VSAQ = $36.6 \pm 6.6 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P < 0.0001$; $V_{O_2 \max}$ CRF = $45.0 \pm 5.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; $P < 0.0001$), but not from RPC ($V_{O_2 \max}$ RPC = $41.3 \pm 6.2 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P = 0.99$).

Figure 2 shows the Bland-Altman analysis, including the limits of agreement for estimated and measured $V_{O_2 \max}$. Table 3 presents values for R -square, SEE, and ICC between $V_{O_2 \max}$ measured and estimated by the questionnaires. The RPC provided the lowest mean difference between $V_{O_2 \max}$ directly assessed in CPET1 and estimated from the questionnaires (RPC = $0.24 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; CRF = $-3.54 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; VSAQ = $4.94 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; $P = 0.05$). However, the CRF exhibited better limits of agreement compared to the other instruments. The higher values obtained for CRF with regard to R -square and ICC were consistent with the results of the Bland-Altman analysis. The SEE between assessed and estimated $V_{O_2 \max}$ was also lower in CRF compared to VSAQ and RPC.

Table 4 shows the distribution of $V_{O_2 \max}$ assessed in CPET1 according to tertiles, as well the percent agreement between estimated and measured $V_{O_2 \max}$ in each tertile. The nonparametric Kendall's tau-b correlation between tertiles was similar across the three questionnaires and measured $V_{O_2 \max}$. However the correlation using the CRF was higher over RPC and VSAQ—the proportion of subjects assigned

in the same tertile category was superior for CRF compared to the other questionnaires, and the distribution was more homogeneous.

With regard to the second study, mean durations of CPET1bis, CPET2, and CPET3 were 13.7 ± 1.8 min, 10.7 ± 1.9 min, and 10.6 ± 0.9 min, respectively. No differences were detected between $V_{O_2 \max}$ assessed in CPET1bis (used as reference to define final and initial speeds in CPET2 and CPET3), CPET2, and CPET3 (CPET1bis = $40.7 \pm 5.9 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; CPET2 = $39.8 \pm 5.6 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; CPET3 = $40.3 \pm 5.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; $P = 0.142$). Mean initial speeds applied in CPET1bis, CPET2, and CPET3 were $5.7 \pm 0.8 \text{ km}\cdot\text{h}^{-1}$, $8.1 \pm 0.9 \text{ km}\cdot\text{h}^{-1}$, and $9.1 \pm 1.1 \text{ km}\cdot\text{h}^{-1}$, respectively. Table 5 shows the relationships between workload and V_{O_2} in the ramp test protocols initiating with speeds corresponding to 50% and 60% $V_{O_2 \max}$ either measured or estimated (slopes, intercepts, R -square, and SEE). CPET1bis showed the closest relationship with the theoretical identity line (slope = 1 and intercept = 0), with the highest R -square and lowest SEE in comparison with CPET2 and CPET3.

4. Discussion

The present study aimed to compare different strategies to define final and initial speeds when designing ramp exercise testing protocols for healthy young populations. Three nonexercise models were employed to estimate maximal cardiorespiratory capacity and therefore the final speed. The choice of VSAQ, RPC, and CRF to estimate the $V_{O_2 \max}$ was due to the fact that these instruments have been frequently applied in previous studies and have been shown to have good potential to estimate the maximal cardiorespiratory capacity in different populations [23, 24]. Two relative intensities (% $V_{O_2 \max}$) using different initial treadmill speeds were tested.

The values obtained for the $V_{O_2 \max}$ assessed in CPET1 are consistent with reference values reported by previous research [4, 7, 14, 16]. Our findings on the ICC, R -square, SEE, and dispersion in the Bland-Altman plot (see Figure 2) suggest that there are advantages in using the CRF to determine the final speed, in comparison with the other instruments. In contrast, the VSAQ had the poorest precision and highest variability with respect to $V_{O_2 \max}$ estimation. In their original study, Myers et al. [19] reported a stronger association between estimated and achieved cardiorespiratory capacity over the present data ($r = 0.79$; SEE = $4.97 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; $P = 0.001$ versus $r = 0.40$; SEE = $7.63 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; $P = 0.0001$, resp.). However, subjects in the two studies differed considerably in terms of clinical and fitness status, which may have contributed to such discrepancy, since poor conditioned individuals are more likely to interrupt earlier the test due to peripheral fatigue. Moreover, Myers et al. [19] did not directly assess the $V_{O_2 \max}$ in their original research. In a later study, these investigators [20] validated the VSAQ measuring $V_{O_2 \max}$ directly in a larger sample ($n = 337$). Subjects had similar characteristics as those in the original study, but the results were more

TABLE 2: Descriptive values for $V_{O_2\max}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) by age and sex groups.

	Age (years)					
	Males ($N = 70$)			Females ($N = 47$)		
	18–29 ($N = 39$)	30–39 ($N = 20$)	>40 ($N = 11$)	18–29 ($N = 32$)	30–39 ($N = 10$)	>40 ($N = 5$)
Mean	46.2	41.1	39.4	39.0	34.3	37.0
SD	5.8	4.4	3.9	5.9	6.3	4.6
Minimum	36.5	32.8	34.0	26.2	25.6	29.5
Maximum	61.5	47.9	44.2	54.8	45.3	40.4

TABLE 3: Mean difference ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), R -square coefficient, standard error of estimate, and intraclass correlation between $V_{O_2\max}$ assessed and estimated by three non-exercise models ($N = 117$).

	Total ($N = 117$)					Males ($N = 70$)					Females ($N = 47$)				
	Mean difference	$V_{O_2\max}$				Mean difference	$V_{O_2\max}$				Mean difference	$V_{O_2\max}$			
		r^2	SEE	ICC	P		r^2	SEE	ICC	P		r^2	SEE	ICC	P
VSAQ	4.94 (11.9%)	0.16	7.63	0.57	<0.0001	-1.81 (-4.1%)	0.05	7.92	0.36	<0.0317	-1.24 (-3.3%)	0.07	7.17	0.42	<0.040
RPC	0.24 (1.0%)	0.09	7.60	0.46	<0.001	3.22 (7.3%)	0.17	1.70	0.58	<0.0001	-3.49 (-9.2%)	0.07	8.35	0.42	<0.035
CRF	-3.54 (-8.5%)	0.53	5.75	0.83	<0.0001	-3.89 (-8.9%)	0.37	6.01	0.76	<0.0001	-2.90 (-7.7%)	0.47	5.36	0.81	<0.0001

VSAQ: Veteran Specific Activity Questionnaire using the following equation: V_{O_2} ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) = $(4.7 + 0.97 (\text{VSAQ}) - 0.06 (\text{age}) \times 3.5)$; for women this value was multiplied by 0.85 [8]; RPC: Rating of Perceived Capacity; CRF: Cardiorespiratory Fitness.

similar to our findings ($r = 0.42$; $\text{SEE} = 9.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; $P = 0.001$).

Maeder et al. [5] compared the $V_{O_2\max}$ obtained in tests using cycle ergometer and treadmill with the exercise capacity estimated by the VSAQ in healthy subjects. The correlations were similar to our data (cycle ergometer: $r = 0.46$ and treadmill: $r = 0.50$; $P < 0.0001$). More recently, Maeder et al. [8] used the VSAQ to select the optimal treadmill ramp protocol in highly trained individuals and reported a similar correlation between estimated and measured $V_{O_2\max}$ ($r = 0.47$), even when using the VSAQ modified nomogram ($r = 0.56$).

Although the VSAQ was developed to facilitate the individualization of ramp protocols, previous research has not ratified this purpose in all populations. Actually, the available evidence does not support its use in determining the final speed within ramp protocols in healthy and well-conditioned populations. Actually the VSAQ has been shown to be more appropriate to estimate the $V_{O_2\max}$ in unfit individuals [20, 29]. The present results confirm this idea. Precision using the VSAQ was lower compared to the other instruments, and the same categorization was obtained in less than 40% of cases. Furthermore, the Bland-Altman plots suggested that in our sample the $V_{O_2\max}$ was systematically overestimated by the VSAQ.

The RPC closely paralleled $V_{O_2\max}$ assessed in CPET1 (mean difference of $0.24 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ or 1%), but exhibited high variability, as evidenced by the Bland-Altman method and SEE ($7.60 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). This variation accounted for the relatively low ICC and R -square values. It is noteworthy that RPC was developed in a sample of 87 young, healthy women (age = 48.4 ± 17.4 years) [21]. However, our experience with this method suggests that strong agreement between estimated and actual $V_{O_2\max}$ can be also obtained in men. Interestingly, although our sample consisted of young

women (age = 28.2 ± 7.0 years), the comparison between $V_{O_2\max}$ directly measured and estimated by RPC showed greater concordance (ICC) and lower variation (SEE) among men versus women (ICC = 0.58 versus 0.42 and SEE = $1.70 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ versus $8.35 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, resp.). A possible explanation for this is that in the original RPC study the $V_{O_2\max}$ was estimated from the work performed on cycle ergometer, and not directly measured. The $V_{O_2\max}$ was estimated using maximal work and body mass, assuming as constants the amount of oxygen required for each Watt of power during ramp cycling ($10.93 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$) and V_{O_2} at rest when sitting on the cycle ($4.3 \text{ mL}\cdot\text{min}^{-1}$). However these unpublished data have been previously determined in a group of healthy men [21], and no information was provided with regard to their possible application in females.

The CRF has been widely used to estimate maximal cardiorespiratory capacity [12, 30–35]. Although it was not originally developed to help designing ramp protocols, our results indicate that it works well for this purpose. The original study by Matthews et al. [22] showed a higher correlation between $V_{O_2\max}$ measured and estimated from CRF than the present study, in a sample of 390 men ($r = 0.82$ versus $r = 0.61$, resp.) and 409 women ($r = 0.83$ versus $r = 0.69$, resp.). However, the SEEs in the total sample ($5.7 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ versus $5.8 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and in gender subgroups (men: $6.3 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ versus $6.0 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; women: $5.0 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ versus $5.4 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) were similar in the two studies. The Bland-Altman analysis showed limits of agreement higher over VSAQ and comparable to RPC, but the CRF had the greatest ICC. In addition, the tertile classifications obtained from CRF were more accurate compared to the other nonexercise models.

Overall, CRF showed higher concordance with measured $V_{O_2\max}$, lower dispersion, and better capacity to discriminate

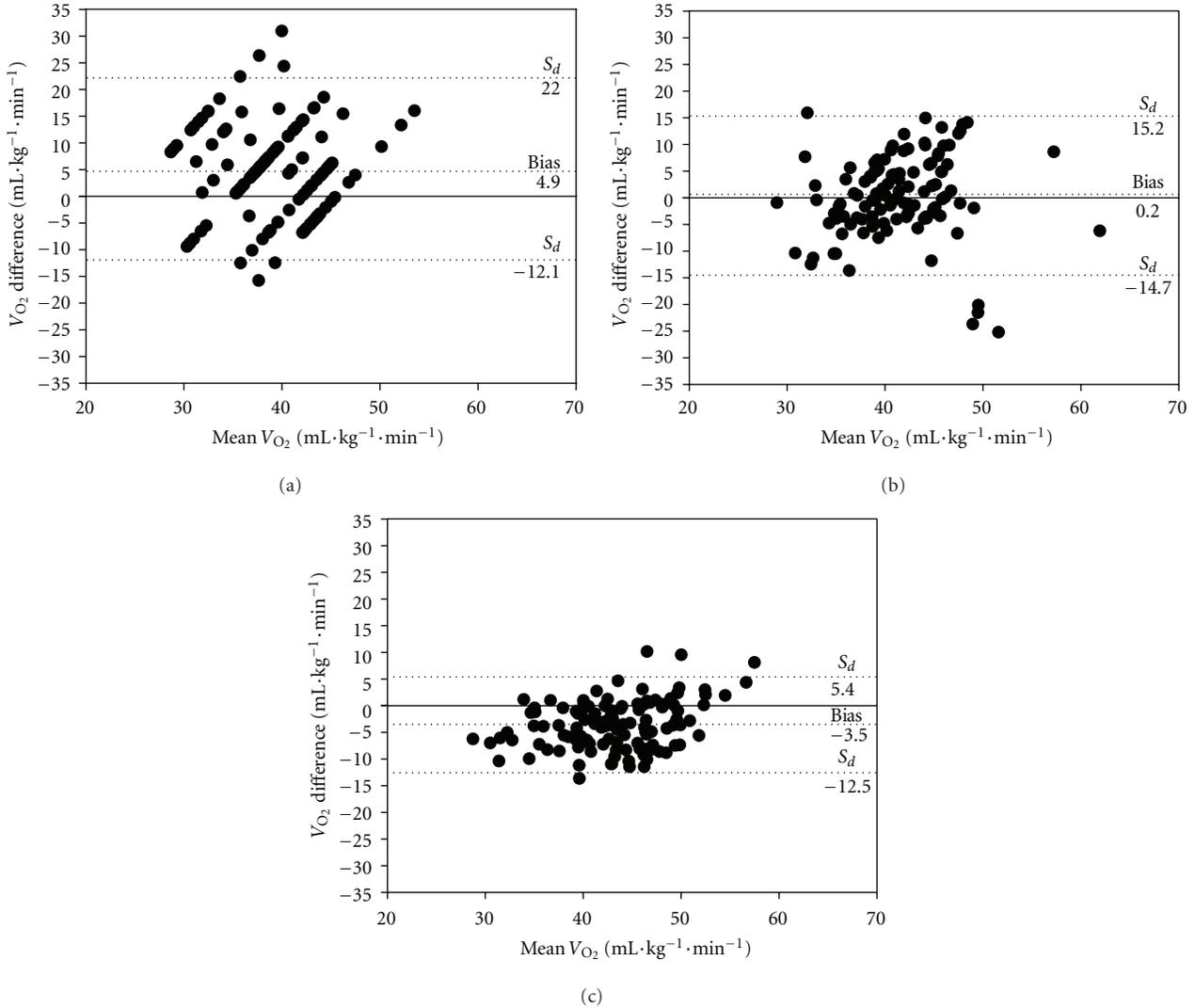


FIGURE 2: Bland-Altman plot for the individual differences between $V_{O_2\max}$ assessed in CPET1 and $V_{O_2\max}$ estimated by VSAQ (a), RPC (b), and CRF (c). The first and third horizontal dashed lines in each graph represent the 95% limits of agreement for VSAQ, RPC, CRF, and VSAQ, corresponding, respectively, to -12.1 to 22.0 (-29.1 to 53.0%); -14.7 to 15.2 (-35.5 to 36.6%); -12.5 to 5.4 (-30.0% to 13.0%). S_d : standard deviation of the differences.

TABLE 4: Percentage of participants ranked in the same tertile, percentage of total agreement, tau-b correlation coefficients between $V_{O_2\max}$ measured and estimated by three non-exercise models (VSAQ, RPC, and CRF) ($N = 117$).

	1st Tertile ($n = 39$)	2nd Tertile ($n = 39$)	3rd Tertile ($n = 39$)	Total ($N = 117$)	R (tau-b)
$V_{O_2\max}$ versus VSAQ	66.66% (26)	5.12% (2)	38.46% (15)	36.75% (43)	0.833
$V_{O_2\max}$ versus RPC	43.58% (17)	25.64% (10)	43.58% (17)	37.60% (44)	0.992
$V_{O_2\max}$ versus CRF	69.23% (27)	41.02% (16)	58.97% (23)	56.41% (66)	0.983

VSAQ: Veteran Specific Activity Questionnaire; RPC: Rating of Perceived Capacity; CRF: Questionnaire of Cardiorespiratory Fitness.

subjects with high and low cardio-respiratory capacity in comparison to VSAQ and RPC. Notably, the CRF may be limited when assessing cardiorespiratory capacity in subjects with $V_{O_2\max} > 55.0 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ [29], which could be a problem when designing ramp protocols in highly fit individuals. However, fewer than 20% of ordinary healthy individuals achieve this level [7]. It therefore seems unlikely

that the final speed would be wrongly determined from inaccurate estimation of $V_{O_2\max}$ estimation, at least in most healthy nonathletic subjects.

In what concerns the second study, the literature is mixed regarding criteria to determine the initial speed for ramp testing [9, 11]. Recommendations from different expert panels are also ambiguous with regard to this issue

TABLE 5: Intercept, slope, R -square (r^2), and standard error of estimate (SEE) for the regression models obtained in ramp protocols initiating with speeds corresponding to 50% of the estimated $V_{O_2 \max}$ (CPET1bis), 50% of the measured $V_{O_2 \max}$ (CPET2), and 60% of the measure $V_{O_2 \max}$ (CPET3).

	Y intercept	Slope	r -Square	SEE ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)
V_{O_2} versus speed in CPET1bis	$-4.882 \pm 2.696^*$	$0.96 \pm 0.027^{\S}$	0.93 ± 0.050	2.14 ± 0.67
V_{O_2} versus speed in CPET2	$-8.270 \pm 6.312^*$	$0.94 \pm 0.029^{\S}$	0.89 ± 0.054	2.19 ± 0.55
V_{O_2} versus speed in CPET3	$-14.666 \pm 8.958^*$	$0.92 \pm 0.036^{\S}$	0.86 ± 0.065	2.48 ± 0.67

* Intercept significantly different from zero ($P < 0.0001$).

\S Slope significantly different from 1.0 ($P < 0.0001$).

[4, 7, 14, 15], and no formal criteria are available on this important aspect of ramp protocols. Our findings suggested that initial speeds within the range corresponding to 50% to 60% $V_{O_2 \max}$ influenced the duration of the test (CPET1bis = 13.7 ± 1.8 min > CPET2 = 10.7 ± 0.9 min \cong CPET3 = 10.6 ± 0.9 min, $P < 0.0001$), but not the achieved $V_{O_2 \max}$ (CPET1bis = 40.7 ± 5.9 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ \cong CPET2 = 40.0 ± 5.6 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ \cong CPET3 = 40.3 ± 5.5 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P = 0.14$). From these results, any initial speed within this range would be appropriate for performing ramp tests. In contrast, the relationship between workload and V_{O_2} among the tests was affected by the initial speed. Considering the identity line as a reference for the ideal regression between workload and V_{O_2} , the current results suggest that higher initial speed produced the lowest R -squares (e.g., poorest adjustment to the identity line) (CPET3—60% $V_{O_2 \max}$ < CPET2—50% $V_{O_2 \max}$ < CPET1bis—50% $V_{O_2 \max}$).

Early research confirms the concept that the initial speed applied does not influence measured $V_{O_2 \max}$. Kang et al. compared three incremental treadmill protocols (Åstrand, Bruce, and Costill/Fox) in 25 sedentary subjects (10 women) [36]. The protocols began with speeds of 9.7 $\text{km}\cdot\text{h}^{-1}$, 2.5 $\text{km}\cdot\text{h}^{-1}$, and 14.4 $\text{km}\cdot\text{h}^{-1}$, respectively, and no differences in $V_{O_2 \max}$ were detected. The relationship between workload and V_{O_2} was not specifically addressed, but the authors considered that this could have been good, at least in the Costill/Fox protocol. The high initial speed significantly shortened the tests (to about 5 min) and precluded the identification of the ventilatory threshold.

In 1991, Myers et al. compared $V_{O_2 \max}$ obtained during ramp and conventional staged protocols (Bruce and Balke modified), which were very different with regard to the combination of initial speed, treadmill grade, and workload increment. The duration of tests was significantly different (Bruce: 6.6 ± 1.5 min versus Balke: 10.4 ± 3.4 min and Ramp: 9.1 ± 1.4 min, $P < 0.05$), with little impact on $V_{O_2 \max}$ (Bruce: 22.3 ± 8.0 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ versus Balke: 21.1 ± 8.0 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and Ramp: 21.0 ± 8.0 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P < 0.05$). However, slopes and SEE for the regression curves between workload and V_{O_2} showed more linear relationships in the ramp protocol (Bruce: slope = 0.62 and SEE = 4.0 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; Balke: Slope = 0.79 and SEE = 3.4 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; Ramp: Slope = 0.80 and SEE = 2.5 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). In other words, differences

in the protocol design may reflect on physiological relationships in submaximal workloads, but not necessarily on the assessed $V_{O_2 \max}$. Our findings seem to ratify this idea.

In conclusion, CRF was superior in comparison with RPC and VSAQ to estimate maximal cardio-respiratory capacity and should be preferred when attempting to determine an appropriate speed for ramp testing. Initial speeds within the range corresponding to 50–60% $V_{O_2 \max}$ estimated or measured did not affect assessed $V_{O_2 \max}$. Nevertheless, speeds higher than 50% $V_{O_2 \max}$ may influence the quality of submaximal relationships between work rate and V_{O_2} . Moreover, higher speeds applied at the beginning of ramp protocols may hinder the performance of subjects with poor fitness levels and compromise test results. This information should be considered when data from exercise testing is used to establish relative exercise intensities for exercise prescription.

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Review Article

Respiratory Consequences of Mild-to-Moderate Obesity: Impact on Exercise Performance in Health and in Chronic Obstructive Pulmonary Disease

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In many parts of the world, the prevalence of obesity is increasing at an alarming rate. The association between obesity, multiple comorbidities, and increased mortality is now firmly established in many epidemiological studies. However, the link between obesity and exercise intolerance is less well studied and is the focus of this paper. Although exercise limitation is likely to be multifactorial in obesity, it is widely believed that the respiratory mechanical constraints and the attendant dyspnea are important contributors. In this paper, we examined the evidence that critical ventilatory constraint is a proximate source of exercise limitation in individuals with mild-to-moderate obesity. We first reviewed existing information on exercise performance, including ventilatory and perceptual response patterns, in obese individuals who are otherwise healthy. We then considered the impact of obesity in patients with preexisting respiratory mechanical abnormalities due to chronic obstructive pulmonary disease (COPD), with particular reference to the effect on dyspnea and exercise performance. Our main conclusion, based on the existing and rather sparse literature on the subject, is that abnormalities of dynamic respiratory mechanics are not likely to be the dominant source of dyspnea and exercise intolerance in otherwise healthy individuals or in patients with COPD with mild-to-moderate obesity.

1. Introduction

The prevalence of obesity is increasing at a remarkable rate in the Western world and this has major negative health and economic ramifications [1, 2]. Obesity is clearly linked to multiple comorbidities and is an independent risk factor for reduced survival [3, 4]. Obesity is also associated with reduced activity levels [5] and this, in turn, is associated with increased risk for comorbidities which include skeletal muscle deconditioning, insulin resistance, and cardiovascular disease [6, 7]. Of interest, obese individuals who remain active appear to have lower morbidity and mortality than normal weight individuals who are sedentary [8]. A better understanding of the nature and source of exercise intolerance in obesity is required if we are to offer more effective treatment for this increasingly common health problem. The mechanisms of activity restriction in obesity are likely

to be multifactorial but the role of respiratory impairment and the associated respiratory discomfort is thought to be important. This paper will focus on the respiratory factors that may influence exercise capacity in individuals with mild-to-moderate obesity based on body mass index (BMI) criteria (mild/class I (30–34.99 kg/m²) and moderate/class II (35–39.99 kg/m²)) [9, 10]. We examine how obesity affects the function of the respiratory system during the physiological stress of exercise in otherwise healthy individuals and in patients with preexisting respiratory impairment from COPD. Our paper does not include consideration of mechanisms of exercise intolerance in obese individuals who seek medical attention because of other symptoms or comorbidities, or in those with morbid obesity (class III (>40 kg/m²)), who may have additional abnormalities of ventilatory control.

2. Challenges in Obesity Research

The accurate interpretation of the existing literature on exercise physiology in obesity presents many challenges, particularly when it involves within-group comparisons of obese subjects or comparisons with age-matched normal weight individuals. While classifications of obesity by BMI are widely accepted, greater anthropometric refinement is needed to better describe obesity “phenotypes” [14]. Thus, studies that exclusively rely on BMI to define obesity can make it difficult to make definitive conclusions regarding physiological effects. Body composition (including fat free mass), fat distribution patterns, and visceral fat can be quantified by DEXA scanning [11], hydrostatic methods [15], and various radiographic imaging and bioimpedance techniques [16]. Information about fat distribution patterns (central versus peripheral) may also be inferred from calculations of waist circumference, height: weight and waist: hip ratios, and among other methods [16, 17].

It has been suggested that the effect of obesity on respiratory mechanics may depend to some extent on adipose tissue distribution patterns, which can vary greatly among individuals with the same BMI [18–21]. However, a recent study by Babb et al. [17] showed that the differences in respiratory mechanics (i.e., reduction in end-expiratory lung volume (EELV)) correlated as strongly with the increase in BMI as with cumulative chest wall fat or regional chest wall fat distribution patterns.

Any study on the effect of obesity on exercise performance should also consider important confounders such as habitual activity levels (which influence fitness levels) and the possible presence of medical comorbidities (musculoskeletal, endocrine, and cardiovascular problems). A final consideration in assessing exercise performance in obesity is the exercise testing modality that is selected. The increased metabolic cost of weight-bearing exercise in obesity (e.g., walking) is amplified for a given external work rate when compared with weight-supported cycle exercise [22]. For this reason, it is possible that the obese subjects may perform better with cycle exercise compared with treadmill exercise tests, which more closely resemble daily activities.

3. Cardiorespiratory Fitness in Obesity

Peak oxygen uptake (VO_2) is widely used as a measure of aerobic capacity and cardiorespiratory fitness. Controversy still exists as to the best way to express peak VO_2 in obesity, that is, in absolute (L/min) or relative (mL/kg/min or mL/kg fat free mass (FFM)/min) terms or as a percentage of predicted normal. Peak VO_2 expressed in relative terms may underestimate cardiorespiratory fitness in comparison with normal weight individuals because of the higher weight denominator in obesity [23]. Lean body mass (or FFM) and skeletal muscle hypertrophy may be increased in the obese as an adaptation to the sustained mass loading effect from excessive adipose tissue [17, 24]. Lorenzo and Babb have recently suggested that peak VO_2 should be expressed as percent predicted, rather than in absolute or relative terms, when assessing cardiorespiratory fitness in obese individuals

[23]. These investigators advocated the use of the predictive VO_2 equations of Wasserman et al. [25] for men and of Riddle et al. [26] for women. In addition to adjusting for age and height, these formulae consider ideal body weight [25, 26] and the increased metabolic cost of unloaded cycle exercise (i.e., 6 mL O_2 /min/kg of excess body weight) [25].

Most studies expressing peak symptom-limited VO_2 in absolute terms or as % predicted have concluded that, contrary to expectations, cardiorespiratory fitness is generally in the normal range in individuals with mild-to-moderate obesity [11, 23, 27–29]. Peak work rate measured during incremental cycle exercise may be diminished or fall within the lower range of normal [11, 25, 30]. Other indices of cardiorespiratory fitness such as peak oxygen pulse, submaximal heart rate responses, and anaerobic/ventilatory threshold are generally within the normal range in moderate obesity [31]. The corollary is that the determinants of peak VO_2 (i.e., cardiac output and the arteriovenous oxygen content difference) are also generally preserved in the obese. Preservation of peak symptom-limited VO_2 also suggests that the respiratory impairment is not a proximate source of exercise limitation in otherwise healthy eucapnic obese subjects (see below).

4. Respiratory Consequences of Obesity at Rest

The mass loading effects of excess adipose tissue on the chest wall and abdomen results in reduced compliance (increased stiffness) of the relaxed respiratory system [32–35]. While early physiological studies emphasized the contribution of reduced chest wall compliance [32], more recent studies in anesthetized subjects highlight the significant contribution of reduced lung compliance [35, 36]. Thus, excessive bibasal airway closure and air trapping [37], diffuse heterogeneous microatelectasis, and relatively increased intrathoracic blood volume [38] collectively increase static lung elastic recoil pressure [34]. The net effect of these obesity-related changes on lung and chest wall compliance is a resetting of the relaxation volume (functional residual capacity (FRC) or EELV) of the respiratory system to a lower volume than predicted in normal weight individuals [9, 29, 36]. Since resting EELV is lower, tidal volume becomes positioned closer to the lower nonlinear and less compliant extreme of respiratory system’s sigmoid-shaped pressure-volume relation. Reduced respiratory system compliance contributes to increased work and oxygen cost of breathing in moderate obesity [39].

The reduced EELV in obesity also means that the airways resistance is proportionately increased [40], in absolute terms [41], reflecting the reduced airway diameter compared with normal weight individuals. It is noteworthy that when the volume differences in health and obesity are accounted for as with measurements of specific airway resistance or specific conductance, this difference in airway resistance disappears [40, 42, 43]. In obesity, closing volume may occur at volumes above the lower EELV [37, 44–46]; thus, significant airway closure and gas trapping may occur in basal lung segments during the quiet tidal breathing cycle. The diminished expiratory reserve volume (ERV) in obesity compared with normal weight individuals means that the

lung volume at the end of quiet tidal expiration (EELV) and following forced expiratory efforts (i.e., residual volume (RV)) are quite similar [9] (Figure 1).

5. Effect of Obesity on Pulmonary Function Measurements

5.1. Lung Volumes and Spirometry. Jones and Nzekwu demonstrated an exponential relationship between increasing BMI and decreasing EELV and ERV in a healthy population [9]: these static volume components show the steepest rates of decline within the overweight and mild obesity categories (Figure 2). The decline in RV with increasing BMI is relatively less than that of EELV [9, 11] and in some studies falls within the normal range [47, 48]. Total lung capacity (TLC) may decline modestly with obesity [9, 28, 49, 50]. RV/TLC may be increased in obesity reflecting air trapping secondary to increased volume-dependent airway closure [9, 41, 51], although Jones and Nzekwu found no significant difference in this ratio between BMI groups [9]. Vital capacity (VC) may decline as BMI increases but generally into the lower normal range [9, 48, 50, 52]. However, the inspiratory capacity (IC) and the IC/TLC ratio increase with increasing the BMI reflecting the relative preservation of TLC in the presence of decreased EELV [9, 53].

Spirometric forced expiratory volume in 1 second (FEV_1), which is strongly influenced by VC, is variably affected by obesity but is usually in the lower range of normal [52, 54–56]. The FEV_1/FVC ratio is generally normal or slightly elevated [20, 40, 41, 54, 55]. Even though plethysmographically-determined airway resistance, when corrected for alveolar volume, is similar in obese and lean individuals, there is evidence of increased peripheral airway resistance in the obese. Thus, expiratory flow rates in the mid-volume VC range may be diminished in obesity reflecting volume-dependent small airway dysfunction [41, 57] (Figure 1). Expiratory flow limitation, as measured by the negative expiratory pressure technique, is present in some patients with moderate and morbid obesity during resting breathing [11, 41, 58]. Positive end-expiratory pressures have been documented in some patients with moderate obesity in the supine posture [56].

5.2. Pulmonary Gas Exchange. The effect of obesity on the diffusing capacity of the lung for carbon monoxide, a measure of the alveolar-capillary surface area for gas exchange, is somewhat variable but the majority of studies report normal values [33, 50, 57, 59, 60]. An increased value may reflect the increased intrathoracic blood volume in obesity [9, 50, 61, 62].

Pulmonary gas exchange at rest is within normal limits in most cases. Ventilation/perfusion (V/Q) inequalities may be presented (i.e., lung units with low V/Q ratios), particularly at the lung bases, and aggravated by gravity-dependent effects in the supine posture [45]. Widening of the alveolar-to-arterial O_2 tension gradient at rest becomes clinically significant, only in those with morbid obesity [63].

5.3. Respiratory Muscle Function. Static strength of the inspiratory and expiratory muscles has generally been reported to be within the normal range in mild-to-moderate obesity [64, 65]. The work of breathing is increased by 3–4 fold in moderate obesity [39] and this, in turn, may serve as an intrinsic stimulus to train the respiratory muscles. Thus, static inspiratory muscle strength may be preserved or even increased, despite the restrictive mechanics of obesity. Less information is available on the mechanical efficiency and endurance of the respiratory muscles in moderate obesity. The finding of an increased O_2 cost of breathing, relative to the mechanical work of breathing, in obesity suggests significant mechanical inefficiency as a result of excessive adipose tissue on the chest wall and abdomen [15, 66]. Respiratory muscle function may be compromised in morbid obesity and, in some studies, improves after bariatric surgery [67]. However, little is known about the effect of weight loss on the respiratory muscle function in the moderately obese.

6. Ventilatory Demand and Dynamic Mechanical Responses during Exercise in Obesity

Ventilatory requirements are increased during exercise reflecting the higher metabolic cost (increased VO_2 and VCO_2) of external work [11, 22, 28, 68–73] (Figure 3). Despite the higher ventilatory demand, there are preliminary data to suggest that there is adequate ventilatory reserve at peak exercise in obese participants [74]. The upward parallel shift in the VO_2 /work rate slope in obesity is explained by the increased metabolic requirements of lifting heavy limbs during cycling [22, 69]. It is likely that VCO_2 for a given power output and therefore, the ventilatory demand is higher during weight-bearing (i.e., walking) than weight-supported cycle exercise [22]. No detailed studies of pulmonary gas exchange using arterial sampling are available in individuals with mild-to-moderate obesity. Noninvasive assessments using end-tidal CO_2 ($etCO_2$) measurements in such individuals suggest that, in contrast to those with morbid obesity [75], the compensatory hyperventilation response at the end exercise is similar to that of normal weight individuals [11]. There is a little evidence to suggest that other factors known to stimulate V_E are more prominent in obesity compared with normal weight individuals, for example, high physiological dead space, critical arterial O_2 desaturation, alterations in the set point for CO_2 , earlier metabolic acidosis (secondary to deconditioning), or increased metaboreceptor stimulation from the active peripheral muscles during exercise.

Operating lung volumes and breathing pattern during cycle exercise are different in obese and normal weight individuals partly reflecting the restrictive mechanical effects of truncal and abdominal obesity [11, 28, 76]. Because EELV (and ERV) is lower at rest and throughout exercise in the obese, there is a propensity for expiratory flow limitation and increased gas trapping during the increased ventilation of exercise [11] (Figure 4). This dynamic increase in EELV may actually convey a mechanical advantage: tidal volume

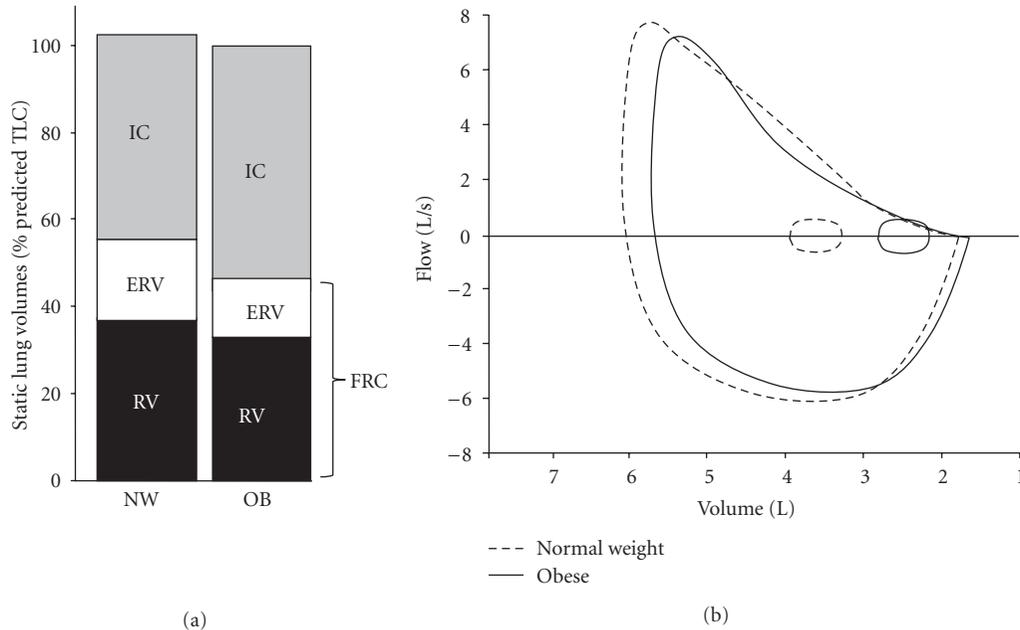


FIGURE 1: (a) Static lung volumes measured by body plethysmography are shown at rest: expiratory reserve volume (ERV) and functional residual capacity (FRC) are decreased, and inspiratory capacity (IC) is increased in the obese (OB) group compared with the normal weight (NW) group of healthy adults. (b) Maximal and tidal flow-volume loops are shown at rest in normal weight (dashed lines) and obese (solid lines) subjects. In obesity, tidal flow-volume loops are shifted rightwards and maximal midexpiratory flow rates may be reduced resulting in greater expiratory flow limitation during resting breathing. RV: residual volume.

becomes positioned on a more compliant portion of the respiratory system's pressure-volume relation, thus avoiding the lower alinear extreme [11]. Moreover, expiratory flow limitation may be attenuated as dynamic EELV approaches the predicted relaxation volume of the respiratory system, that is, "pseudonormalization." The dynamic increase in operating volumes, together with the naturally increased intra-abdominal pressures in obesity [47], may favorably alter the operating characteristics of the diaphragm to enhance its force-generating capacity.

Breathing pattern responses to incremental cycle exercise are usually slightly more shallow and rapid in obese compared with normal weight individuals [11, 28, 71, 77]. The larger resting IC and inspiratory reserve volume (IRV) means that obese subjects can accommodate increases in EELV without end-inspiratory lung volume prematurely encroaching on the TLC; thus, V_T expansion is not more mechanically constrained during exercise compared with normal weight individuals (Figure 4). Adoption of a more rapid, shallow breathing pattern during exercise may simply be a behavioral compensatory adaptation to minimize the elastic work of breathing and attendant unpleasant respiratory sensation [78].

7. Exertional Symptoms in Obesity

Exertional symptoms may, in some cases, limit exercise performance before physiological maxima are reached and must therefore be considered in any assessment of exercise performance [31]. Intensity ratings of perceived respiratory discomfort and leg discomfort have been shown to be

higher for a given external power output during cycle exercise in obese compared with normal weight subjects [11]. This suggests that mass loading of both the respiratory and peripheral skeletal muscles in the obese requires increased motor output (and contractile muscle effort) to drive these two muscle groups in tandem. The increased intensity of breathing discomfort likely reflects the increased chemostimulation and central neural respiratory drive to the respiratory muscles (and increased central corollary discharge to the somatosensory cortex) [79, 80] secondary to the relatively increased VCO_2 for a given power output in obesity (Figure 3) [11, 81]. Babb et al. [71] have shown that increased dyspnea intensity ratings during exercise in a subgroup (37%) of women with moderate obesity was related to increased oxygen cost of breathing, measured during eucapnic voluntary hyperpnea at rest. Pulmonary function, fat distribution, peak VO_2 , and indices of respiratory mechanics, including work of breathing, were not different in the dyspneic and nondyspneic subgroups. The precise mechanistic linkage between increased dyspnea and increased O_2 cost of breathing in this subset of obese women was not determined.

In the study of Ofir et al. [11], the dyspnea intensity/ventilation (V_E) relation during exercise was not affected by obesity, suggesting that mechanical factors are less important in contributing to dyspnea. Thus, if increased mechanical loading of the respiratory muscles in obesity was an important contributor to dyspnea, one would anticipate that dyspnea intensity would be increased for a given V_E [78]. The authors have postulated that the physiological effects of obesity such as adoption of a more rapid, shallow breathing

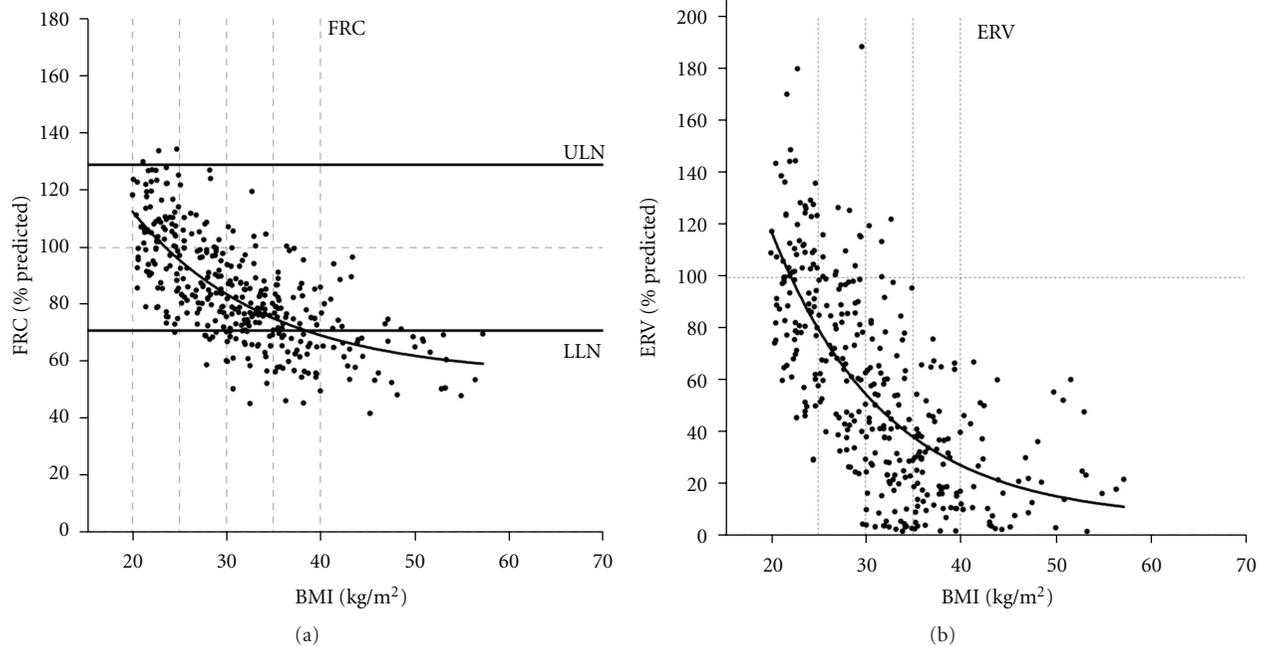


FIGURE 2: FRC and ERV decreased exponentially with increasing BMI in adult patients with normal airway function (for both regressions, $r^2 = 0.49$ and $P < 0.0001$). The horizontal lines for FRC are the average upper limit of normal (ULN) and lower limit of normal (LLN) for men and women, from Jones and Nzekwu [9].

pattern (an appropriate compensation for increased elastic loading), resting IC recruitment, and “pseudonormalization” of EELV may collectively serve to mitigate the expected rise in dyspnea intensity for a given V_E during exercise (Figures 3 and 4). The main conclusion of that study was that the increased dyspnea intensity for a given power output in obese individuals was primarily related to the increased ventilatory requirements and the corresponding increased central neural drive. Obesity-related abnormalities of dynamic respiratory mechanics were thought to be less important.

8. Respiratory Consequences of Obesity in COPD

COPD, a chronic smoking-related disease of the airways, lung parenchyma, and pulmonary vasculature, is also increasing in prevalence worldwide [82]. Obesity and COPD often coexist in an increasing number of patients and this may have major implications for health care utilization [83]. Reported prevalence of obesity in COPD varies from 18% in the Netherlands [84], 25% and 27% in South America [85] and Canada [86], respectively, to as much as 54% in California [87], and may exceed obesity prevalence in the general population [84, 87, 88]. In the general population, obesity is an established risk factor for reduced life expectancy, independent of smoking status [89]. Paradoxically, epidemiological studies have shown that the patients with advanced COPD who are overweight or mildly-to-moderately obese have a survival advantage compared with underweight patients [90–92]. This “obesity paradox” has also been described in other chronic diseases (chronic

heart failure, rheumatoid arthritis, and chronic renal disease) but the protective mechanisms are unknown [93]. It is noteworthy that this reduced risk of mortality was not observed in obese patients with milder COPD [91] and that subgroups of COPD patients with more severe obesity are at a greater risk of death due to respiratory failure than normal weight COPD [94]. At first glance, the imposition of the restrictive mechanical constraints of obesity on patients with preexisting expiratory flow limitation and lung hyperinflation should have detrimental effects on exercise performance, but recent studies suggest that this is not always the case (see below).

9. Effects of Increasing BMI on Resting Pulmonary Function in COPD

In COPD, as in health, there is an exponential relation between increasing BMI and decreases in EELV and ERV [12]. This volume reduction effect occurs across all severity stages of airway obstruction and is seen even as BMI increases from normal weight to the overweight range (Figure 5). TLC and RV are relatively less affected by the increasing weight in COPD [12, 13, 95]. Importantly, as in health, the resting IC (and the IC/TLC ratio) increases in response to increasing BMI across all severity stages, reflecting the greater reduction in EELV relative to TLC. As already mentioned in relation to health [11], recruitment of IC and reduction in operating lung volumes (in absolute terms) are also potentially advantageous from a mechanical standpoint in the obese COPD patient [95]. Moreover, since a higher IC/TLC ratio (>25%) is an established favorable prognostic

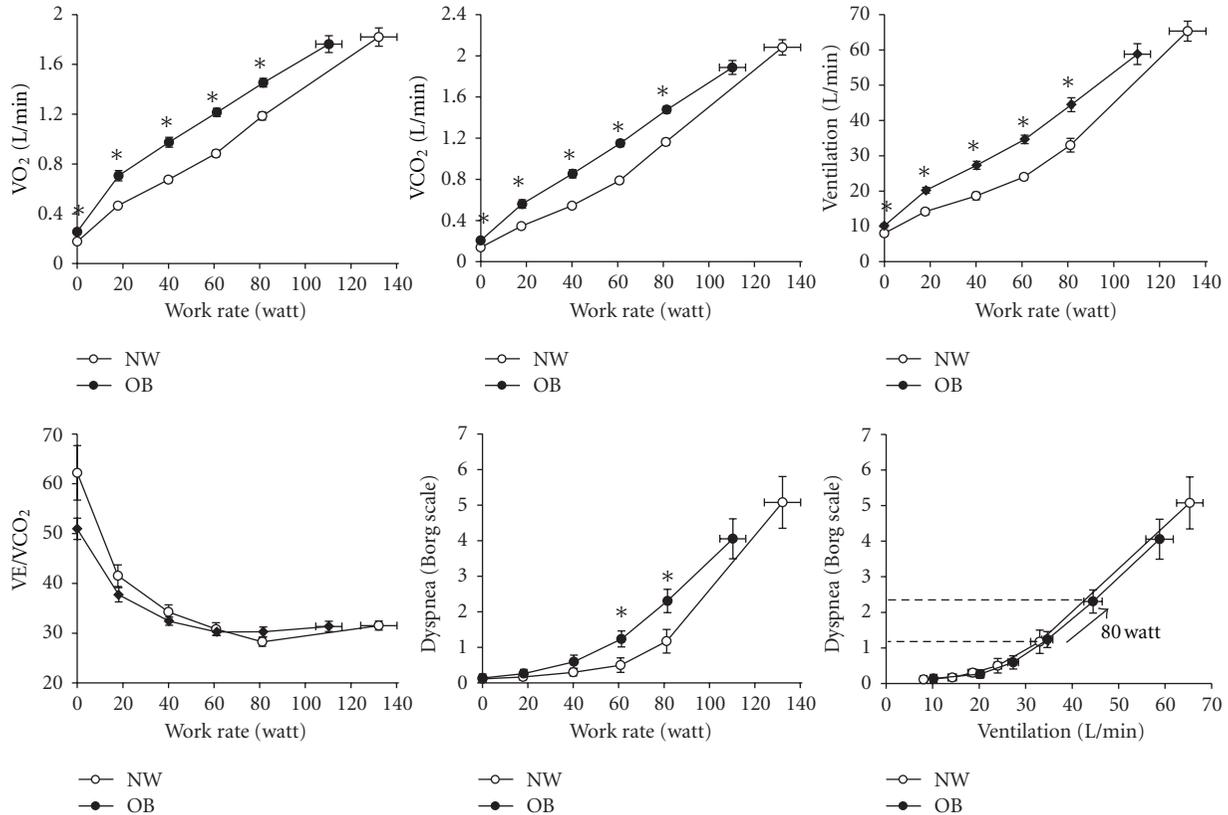


FIGURE 3: Oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (V_E), the ventilatory equivalent for CO_2 (V_E/VCO_2), and dyspnea intensity are shown to be relative to cycle work rate in normal weight (NW) and obese (OB) women. Relationships between dyspnea intensity and ventilation during exercise were similar in OB and NW, thus, increased dyspnea ratings at a given work rate in OB reflected the higher ventilator requirements at that work rate. Values are means \pm SEM. * $P < 0.05$ OB versus NW at a given work rate. Data from Ofir et al. [11].

indicator in COPD, it is interesting to speculate that higher BMI may also be advantageous in this respect [96].

10. Impact of Obesity on Exercise Performance in COPD

As in health, metabolic and ventilatory requirements are elevated for a given power output during cycle exercise in obese compared with normal weight COPD patients [13, 95] (Figure 6). A recent study which compared exercise endurance time during high intensity constant work rate cycle exercise showed no differences between normal weight, overweight, and obese groups of patients with moderate-to-severe COPD [97]. In that study, patients in the overweight and obese groups had a higher peak VO_2 in L/min than normal weight patients. Studies comparing obese with normal weight COPD groups matched for FEV_1 found that peak VO_2 (%predicted based on ideal body weight) during incremental cycle exercise was similar or greater in the obese [13, 95]. Additionally, there was no evidence of CO_2 retention, based on $ETCO_2$ measurements, at the symptom-limited peak of exercise. Thus, contrary to expectations,

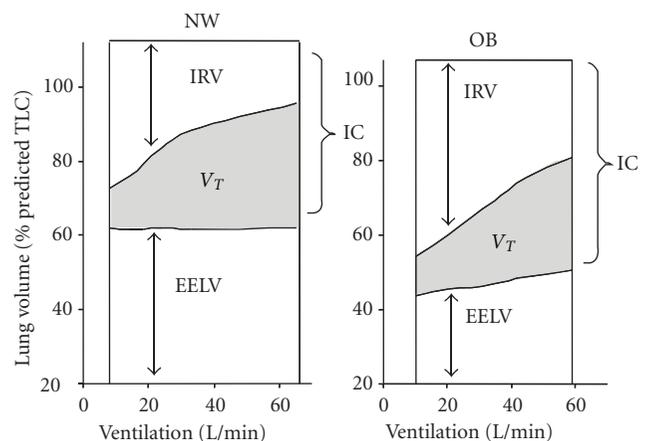


FIGURE 4: Operating lung volumes from rest-to-peak exercise are shown in normal weight (NW) and obese (OB) women. End-expiratory lung volume (EELV) increased by 0.38 L during exercise in OB but did not change in the NW subjects. Inspiratory reserve volume (IRV) was greater at rest and throughout exercise in OB women but was not statistically different at the peak of exercise. TLC: total lung capacity, IC: inspiratory capacity, V_T : tidal volume (shaded area), from Ofir et al. [11].

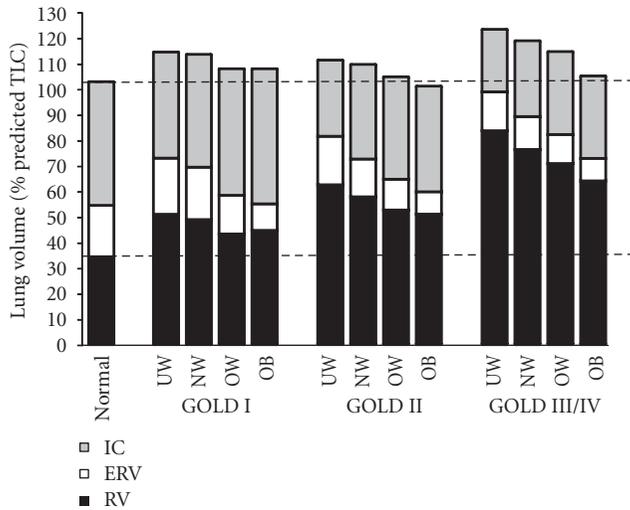


FIGURE 5: Postbronchodilator lung volume components are shown divided by global initiative for chronic obstructive lung disease (GOLD) stage and BMI. The normal column represents measurements from an age-matched healthy, nonsmoker population. UW: underweight; NW: normal weight; OW: overweight; OB: obese; IC: inspiratory capacity; ERV: expiratory reserve volume; RV: residual volume, from O'Donnell et al. [12].

the presence of obesity could not be shown to be a disadvantage, in terms of cycle exercise capacity in COPD [13, 95].

In COPD, the resting IC and IC/TLC ratio are important predictors of peak ventilation during symptom-limited exercise [98–100]. In patients with expiratory flow limitation, the IC represents the operating limits for V_T expansion during physical activity. The greater the resting lung hyperinflation, the lower the IC and, therefore, the lower the ventilation at which V_T reaches its plateau (or maximal value) having encroached on the minimal dynamic IRV [101]. The V_T/V_E plateau, or inflection point, occurs at an IRV of 0.5–1.0 L below TLC and is an important mechanical event during exercise in COPD. This event marks the beginning of an ever widening disparity between central neural drive and the mechanical/muscular response of the respiratory system, that is, neuromechanical uncoupling [102]. At this point, dyspnea intensity escalates sharply towards intolerable levels and the distressing sensation of “unsatisfied inspiration” displaces “increased breathing effort” as the dominant qualitative descriptor [103]. The increased resting IC and IRV in obese COPD patients may mean that they can exercise to a higher V_E before the V_T inflection or plateau occurs (Figure 7) the escalation of dyspnea to intolerable levels is, therefore, delayed.

In obese COPD, dyspnea intensity ratings were not increased at any given $\dot{V}O_2$ or V_E , compared with FEV₁-matched normal weight COPD patients (Figure 8) [13, 95]. How is it possible for obese patients with COPD to accommodate the relatively higher ventilatory requirements of physical work without experiencing greater respiratory discomfort and earlier exercise limitation than normal

weight COPD patients? Based on small mechanical studies, we have postulated that a number of factors may mitigate the increase in dyspnea intensity for a given V_E in these patients with combined restrictive-obstructive problems [13, 95]. These factors which occur in highly variable combinations include: (1) increased static elastic lung recoil pressure in obese COPD, compared with normal weight COPD, may result in larger increases in the driving pressure for tidal expiratory flows during rest and exercise; (2) increased resting IC and the lower operating lung volumes may convey mechanical advantages for the respiratory muscles, particularly the diaphragm, during exercise; (3) increased intra-abdominal pressures in obesity may also improve diaphragmatic function by forcing a more cephaloid position of this muscle at the onset of inspiration; (4) regional recruitment of lung volume (and hitherto closed airways) secondary to acute increases in EELV during exercise may attenuate the increased resistance as respired flow rates increase; (5) increased dynamic EELV may improve pulmonary gas exchange (as indicated by lower V_E/VCO_2 ratios) to a greater extent than in normal weight COPD patients.

The question arises whether the presumed mechanical advantages of obesity in COPD, which preserve cycle exercise tolerance, are also applicable to weight-bearing exercise. Bautista et al. [104] showed that obese (BMI = 37 kg/m²) patients with COPD had reduced six minute walk distance compared with an FEV₁-matched normal weight COPD. The mechanisms for the poorer walking performance in the obese group were not ascertained: peak $\dot{V}O_2$, V_E , and cardiopulmonary responses during the tests were similar in both groups.

Comparisons of treadmill and cycle exercise in normal weight COPD have shown greater arterial O₂ desaturation and a higher $\dot{V}O_2$ for a given work rate during treadmill compared with cycle exercise [105, 106]. On the other hand, selective stress on the quadriceps muscle during cycling forces an earlier metabolic acidosis with accompanying ventilatory stimulation, which improves pulmonary gas exchange relative to treadmill exercise [105]. These differences in pulmonary gas exchange and in metabolic loading across exercise modalities may be further exaggerated in obese COPD and may influence perceptual responses during exercise, but this remains conjectural. Future treadmill-cycle comparison studies, where the increase in work rate is standardized, are needed to determine if the putative mechanical advantages of obesity in COPD during cycling are also evident during weight-bearing exercise.

11. Summary

The influence of obesity on physiological and perceptual responses to exercise is an important topic, given the ever-increasing, worldwide prevalence of this condition. Contrary to expectation, there is increasing evidence that cardiorespiratory fitness, as assessed by peak symptom-limited $\dot{V}O_2$ (expressed as %predicted using ideal body weight), is generally preserved in otherwise healthy individuals with mild-to-moderate obesity. This preservation of exercise capacity occurs despite the presence of such

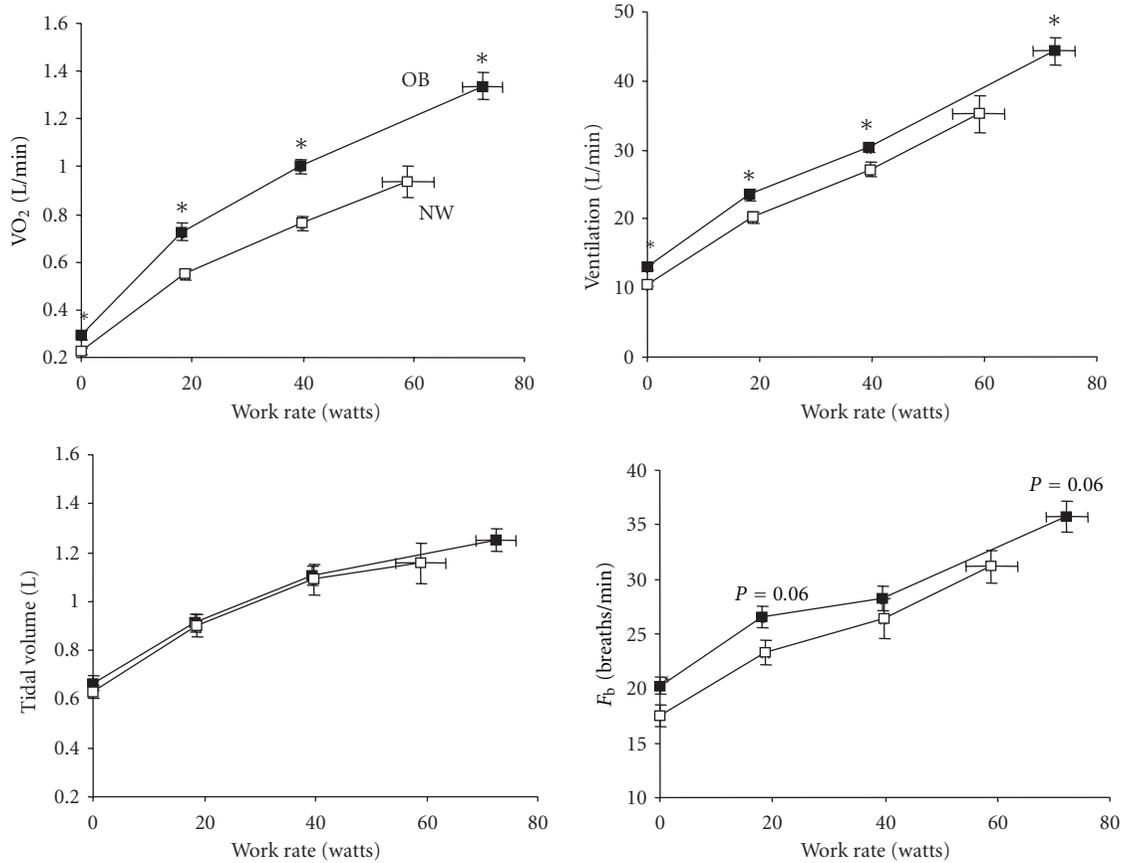


FIGURE 6: Oxygen consumption (VO_2), ventilation, tidal volume, and breathing frequency (F_b) are shown in response to symptom-limited cycle exercise in obese (OB) and normal weight (NW) subjects with COPD. Values are means \pm SEM. * $P < 0.05$ OB versus NW at standardized work rates or at peak exercise, modified from Ora et al. [13].

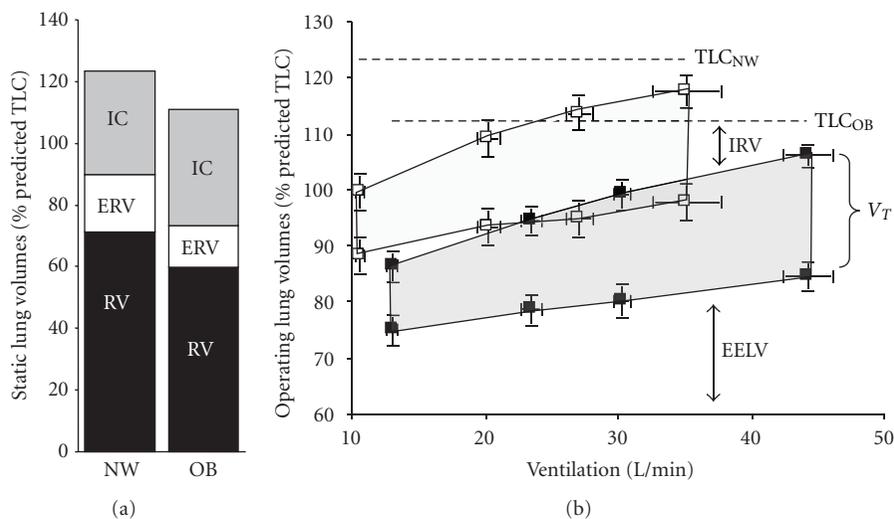


FIGURE 7: (a) Static lung volumes measured by body plethysmography are shown at rest. Expiratory reserve volume (ERV) and functional residual capacity (FRC = ERV + RV) were significantly lower in the obese (OB) group compared with the normal weight (NW) group with COPD. (b) Operating lung volumes (mean \pm SEM) are shown from rest-to-peak exercise in the OB (closed symbols) and NW (open symbols) subjects: end-expiratory lung volume (EELV) was consistently lower at rest and throughout exercise in OB; the OB group reached an EELV at peak exercise that was similar to that of the NW group at the preexercise resting level. IC: inspiratory capacity; IRV: inspiratory reserve volume; V_T : tidal volume (shaded area); RV: residual volume, from Ora et al. [13].

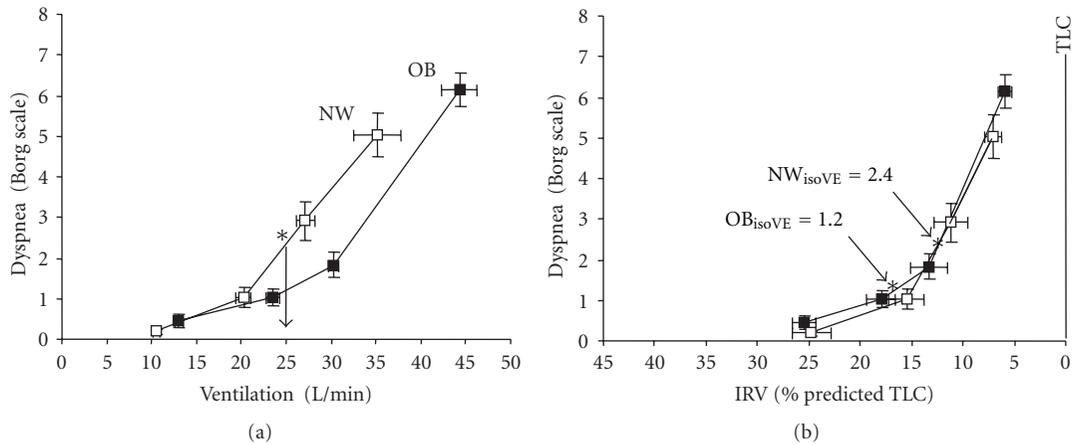


FIGURE 8: (a) Obese (OB) subjects with COPD (closed symbols) had a rightward shift in the dyspnea/ventilation relationship compared with normal weight (NW) subjects with COPD (open symbols). At an isoventilation (V_E) of 25 L/min with arrow, dyspnea intensity was 1.2 versus 2.4 Borg units in OB versus NW (* $P < 0.01$). (b) In both groups, the relationship between dyspnea intensity and inspiratory reserve volume (IRV) (standardized as a % of predicted TLC) were superimposed. At iso V_E , OB subjects were on the flatter part of the dyspnea/IRV relation while NW subjects were on the steeper portion of the curve. Values are means \pm SEM. From Ora et al. [13].

obesity-related factors as mild-mechanical restriction and increased expiratory flow limitation/gas trapping, together with increased metabolic/ventilatory demands during physical exertion. We have argued that an increased IC and compensatory-breathing pattern adaptations may minimize the increased elastic work of the respiratory muscles in obesity. In turn, these factors may mitigate the expected increase in dyspnea intensity for a given ventilation during exercise in the obese. Exertional dyspnea in the obese appears to be closely related to the increased ventilatory demand and higher CO_2 output during physical work.

Similarly, the presence of mild-to-moderate obesity in patients with COPD appears to have little deleterious effect on peak VO_2 . Again, we have proposed that the larger IC and lower operating lung volumes throughout rest and exercise in obese COPD patients (compared with normal weight FEV₁-matched patients) convey a mechanical advantage for the respiratory muscles. This allows obese COPD patients to accommodate the increased ventilatory requirements of a standardized physical task without experiencing greater respiratory discomfort. Collectively, these recent small physiological studies challenge the commonly held belief that critical respiratory mechanical constraints due to obesity importantly contribute to increased dyspnea and exercise intolerance in both health and disease. Future studies are needed to better elucidate the complex and multifactorial nature of daily activity restriction in obesity, particularly the interaction between pulmonary and nonpulmonary factors (e.g., metabolic and musculoskeletal abnormalities) which may be more important than previously realized.

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