CLINICAL CARDIOPULMONARY EXERCISE TESTING

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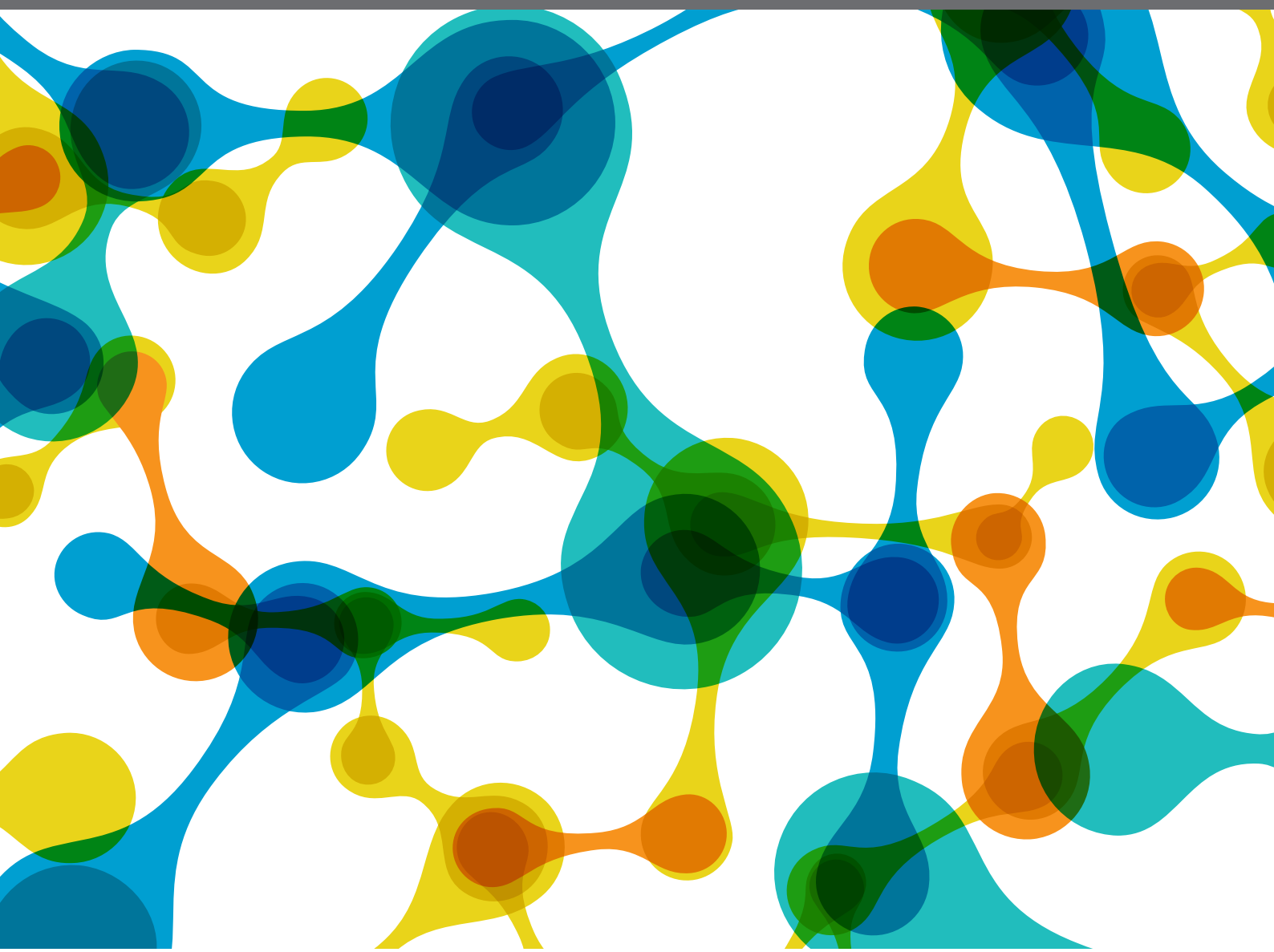

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CLINICAL CARDIOPULMONARY EXERCISE TESTING

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EDITORIAL
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Editorial: Clinical Cardiopulmonary Exercise Testing

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Keywords: cardiopulmonary exercise testing, inspiratory neural drive, dynamic respiratory mechanics, exertional dyspnea, physiological characterization

Editorial on the Research Topic

Clinical Cardiopulmonary Exercise Testing

The value of cardiopulmonary exercise testing (CPET) is well-established as an adjunct to clinical evaluation. Worldwide, exercise "stress" testing is vastly under-utilized, especially for individuals with pulmonary disorders. This is lamentable because modern refinements in the measurements of physiological impairment during CPET have improved our ability to evaluate such patients more comprehensively (Domnik et al.; Phillips et al.; James et al.). Thus, the overarching objective of the current Research Topic series was to review some of these recent advancements in CPET methods and interpretation and to discuss their relevance, in both clinical and research settings, in patients with various respiratory conditions.

Uniquely, CPET can identify specific abnormalities of the integrated metabolic, cardiopulmonary, locomotor muscle, and neurosensory systems, under graded physiologic stress. Based on foundational physiological principles, CPET interpretation has traditionally focused on measuring peak oxygen uptake ($V\dot{O}_2$)—a key metric of exercise performance—and an independent predictor of mortality in various cardio-pulmonary disorders (Killian and Jones, 1984; Jones, 1997; Wasserman et al., 1999, 2012; Jones and Killian, 2000). Traditional interpretative algorithms incorporate quantitative estimates of cardiac and ventilatory reserves, as well as aerobic capacity, to help explain reduced peak $V\dot{O}_2$ in the individual. However, it must be remembered that low peak $V\dot{O}_2$ often reflects intolerable exertional symptoms (e.g., dyspnea and leg discomfort), well before physiological maxima are actually attained (Neder et al.). Thus, measurement of exertional symptoms, using validated scales, is integral to any assessment of exercise capacity (Laviolette and Laveneziana, 2014). Moreover, it is now clear that traditional estimates of breathing and cardiac reserves, based on ratios of peak ventilation and heart rate, to their respective maxima, can sometimes be misleading. Thus, apparent preservation of breathing and cardiac reserves can often obscure important respiratory mechanical constraints and severe dyspnea at relatively low exercise intensities which, in turn, explain low peak $V\dot{O}_2$ (Neder et al.).

Recent experimental work during CPET examined the simultaneous associations between inspiratory neural drive (IND) to the respiratory muscles, dynamic respiratory mechanics and subjective breathing discomfort and has shed light on fundamental mechanisms of exercise limitation in health and various respiratory conditions (Domnik et al.) (Laveneziana et al., 2009, 2011, 2013a,b, 2014, 2015; Laviolette and Laveneziana, 2014; O'Donnell et al., 2017, 2019; Neder et al., 2019; Boucly et al., 2020). In healthy participants, several acute physiological adaptations to the increasing metabolic demand of exercise, ensure admirable preservation of harmonious coupling between increasing IND and the ventilatory response of the dynamic respiratory system,

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such that arterial blood gas and acid-base homeostasis are achieved, and dyspnea is minimized. However, these remarkable, integrated cardio-respiratory adjustments to exercise become variably undermined by the presence of pulmonary diseases, even when resting pulmonary function appears normal. Thus, disease-related disruption of normal cardio-respiratory adaptations to exercise requires large compensatory increases in IND to maintain adequate alveolar ventilation. This, in conjunction with a widening disparity between increasing IND and the abnormal mechanical response of the impaired respiratory system (neuro-mechanical dissociation, NMD) has serious deleterious sensory consequences at higher exercise intensities, leading to premature termination of exercise (Domnik et al.).

Most chronic respiratory conditions are characterized by excessive ventilation for a given metabolic load during exercise, when compared with healthy controls. This ultimately points to increased IND due to multiple physiological perturbations, including: the effect of high physiological dead space, increased respiratory muscle loading, early lactic acidosis, and critical hypoxemia. Additionally, increased sympathetic nervous system activation and altered afferent activity from receptors in the respiratory and locomotor muscles, baroreceptors and chemoreceptors are undoubtedly contributory, but difficult to measure. High ventilatory equivalent for CO_2 (V_E/VCO_2) is linked to increased IND and dyspnea intensity and is common to several respiratory conditions, including chronic obstructive pulmonary disease (COPD) (Phillips et al.), interstitial lung disease (ILD), (Molgat-Seon et al.) and pulmonary arterial hypertension (PAH) (Laveneziana and Weatherald). It is no surprise, therefore, that V_E/VCO_2 is increasingly represented in CPET interpretative algorithms (Phillips et al.). High V_E/VCO_2 nadir (e.g., > 34) generally indicates presence of poor ventilatory efficiency, due to high physiological dead space (and compromised lung CO_2 elimination), alveolar hyperventilation (enhanced chemo-sensitivity) or both. Measurement of arterial partial pressure of CO_2 ($PaCO_2$), and not end-tidal CO_2, (as it may grossly underestimate $PaCO_2$ when physiological dead space is increased), is needed to determine the relative contribution of each to high V_E/VCO_2. As repeatedly highlighted in this series, V_E/VCO_2 must be considered in the context of the prevailing mechanical constraints, which can blunt the normal ventilatory response and compound interpretation. For simplicity, measurement of V_E/VCO_2 *nadir* is the preferred parameter: it generally occurs at relatively low exercise intensities, when arterial O_2 saturation is normal and before the onset of both metabolic acidosis (with ventilatory compensation) and significant restrictive mechanical constraints on tidal volume (V_T) expansion (O'Donnell et al., 2017, 2019; Neder et al., 2019).

Recent refinements in the "non-invasive" assessment of dynamic respiratory mechanics during exercise have increased our ability to ascertain—with reasonable precision—the nature and severity of the physiological impairment in the symptomatic individual (Milne et al.). The combination of operating lung volumes [measured by serial inspiratory capacity (IC) maneuvers] and breathing pattern can help detect important inspiratory mechanical constraints, which are relevant to dyspnea and exercise limitation (Laveneziana et al., 2009, 2011, 2013a,b, 2014, 2015; Laviolette and Laveneziana, 2014; O'Donnell et al., 2017, 2019; Neder et al., 2019; Boucly et al., 2020). This approach is arguably more sensitive than traditional assessments of breathing reserve (V_E/derived maximal ventilatory capacity), especially in milder forms of obstructive and restrictive disorders or other cardio-respiratory conditions (Laveneziana et al., 2009, 2011, 2013a,b, 2014, 2015; Boucly et al., 2020). Additionally, examination of tidal vs. maximal flow-volume loops throughout exercise provides qualitative assessments of inspiratory and expiratory flow reserves. For practical purposes, the IC, and not the vital capacity, represents the true operating limits for V_T expansion in older individuals with common respiratory conditions, especially if expiratory flow limitation is present. Resting IC is variably reduced in both obstructive and restrictive lung disorders (James et al.; Molgat-Seon et al.). The lower the resting IC, the closer V_T is positioned to total lung capacity (TLC) and to the upper extremity of the respiratory system's sigmoidal pressure-volume relation. Thus, as V_T expands to occupy ∼70% of IC and inspiratory reserve volume (IRV) reaches its minimal value, higher IND and breathing effort is needed to achieve a given V_T. This reflects the increased elastance of the respiratory system, when breathing close to TLC. Appearance of the V_T inflection or plateau (minimal IRV), as a function of increasing V_E during exercise, is an important mechanical event and heralds the onset of NMD and an abrupt rise in dyspnea. As resting IC diminishes over time in obstructive and restrictive disorders, critical inspiratory mechanical constraints and onset of dyspnea will occur at progressively lower V_E during exercise (O'Donnell et al., 2017, 2019; Neder et al., 2019).

This series has provided a comprehensive physiological characterization of patients with COPD, ILD, and PAH, (James et al.; Molgat-Seon et al.; Laveneziana and Weatherald) and taught us that exercise response pattern abnormalities are surprisingly similar, despite vastly different pathological origins. For patients referred with unexplained exertional dyspnea, who do not manifest any of the described abnormal patterns during CPET, alternative diagnoses such as dysfunctional breathing of psychogenic origin should be considered (Ionescu et al.). We hope that the pragmatic approach to CPET proposed here will help the clinician to individualize management plans by providing clear answers to a few key questions: *how severe is dyspnea and exercise intolerance in my patient*?; *is ventilatory demand increased and if so, why?*; and *are dynamic mechanical abnormalities present that contribute to poor exercise performance*?

AUTHOR CONTRIBUTIONS

DEO wrote the first draft of the manuscript. All authors were responsible for critically reviewing the manuscript for intellectual content and approved the final version of the manuscript submitted for publication.

REFERENCES

Boucly, A., Morélot-Panzini, C., Garcia, G., Weatherald, J., Jaïs, X., Savale, L., et al. (2020). Intensity and quality of exertional dyspnoea in patients with stable pulmonary hypertension. *Eur. Respir. J.* 55:1802108. doi: 10.1183/13993003.02108-2018

Jones, N. L. (1997). *Clinical Exercise Testing*. Philadelphia, PA: WB Saunders.

Jones, N. L., and Killian, K. J. (2000). Exercise limitations in health and disease. *N. Engl. J. Med.* 343, 632–549. doi: 10.1056/NEJM200008313430907

Killian, K. J., and Jones, N. L. (1984). The use of exercise testing and other methods in the investigation of dyspnea. *Clin. Chest Med.* 5, 99–108. doi: 10.1016/S0272-5231(21)00235-5

Laveneziana, P., Bruni, G. I., Presi, I., Stendardi, L., Duranti, R., and Scano, G. (2013a). Tidal volume inflection and its sensory consequences during exercise in patients with stable asthma. *Respir. Physiol. Neurobiol.* 185, 374–379. doi: 10.1016/j.resp.2012.08.026

Laveneziana, P., Garcia, G., Joureau, B., Nicolas-Jilwan, F., Brahimi, T., Laviolette, L., et al. (2013b). Dynamic respiratory mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Eur. Respir. J.* 41, 578–587. doi: 10.1183/09031936.00223611

Laveneziana, P., Humbert, M., Godinas, L., Joureau, B., Malrin, R., Straus, C., et al. (2015). Inspiratory muscle function, dynamic hyperinflation and exertional dyspnoea in pulmonary arterial hypertension. *Eur. Respir. J.* 45, 1495–1498. doi: 10.1183/09031936.00153214

Laveneziana, P., Montani, D., Dorfmüller, P., Girerd, B., Sitbon, O., Jaïs, X., et al. (2014). Mechanisms of exertional dyspnoea in pulmonary veno-occlusive disease with EIF2AK4 mutations. *Eur. Respir. J.* 44, 1069–1072. doi: 10.1183/09031936.00088914

Laveneziana, P., O'Donnell, D. E., Ofir, D., Agostoni, P., Padeletti, L., Ricciardi, G., et al. (2009). Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. *J. Appl. Physiol.* 106, 1574–1583. doi: 10.1152/japplphysiol.90744.2008

Laveneziana, P., Webb, K. A., Ora, J., Wadell, K., and O'Donnell, D. E. (2011). Evolution of dyspnea during exercise in COPD: Impact of critical volume constraints. *Am. J. Respir. Crit. Care Med.* 184, 1367–1373. doi: 10.1164/rccm.201106-1128OC

Laviolette, L., and Laveneziana, P. (2014). Dyspnoea: a muldimensional and multidisciplinary approach. *Eur. Respir. J.* 43, 1750–1762. doi: 10.1183/09031936.00092613

Neder, J. A., Berton, D. C., Marillier, M., Bernard, A. C., and O'Donnell, D. E. (2019). Inspiratory constraints and ventilatory inefficiency are superior to breathing reserve in the assessment of exertional dyspnea in COPD. *COPD* 16, 174–181. doi: 10.1080/15412555.2019.1631776

O'Donnell, D. E., Elbehairy, A. F., Berton, D. C., Domnik, N. J., and Neder, J. A. (2017). Advances in the evaluation of respiratory pathophysiology during exercise in chronic lung diseases. *Front. Physiol.* 8:82. doi: 10.3389/fphys.2017.00082

O'Donnell, D. E., Milne, K. M., Vincent, S. G., and Neder, J. A. (2019). Unraveling the causes of unexplained dyspnea: the value of exercise testing. *Clin. Chest Med.* 40, 471–499. doi: 10.1016/j.ccm.2019.02.014

Wasserman, K., Hansen, J. E., Sue, D. Y., and Stringer, W. W. (2012). *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. Philadelphia, PA: Lippincott Williams and Wilkins.

Wasserman, K., Hansen, J. E., Sue, D. Y., Stringer, W. W., Sietsema, K. E., Sun, X. G., et al. (1999). *Principles of Exercise Testing and Interpretation*. Baltimore, MD: Lippincott Williams and Wilkins.

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MINI REVIEW
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Measurement and Interpretation of Exercise Ventilatory Efficiency

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Cardiopulmonary exercise testing (CPET) is a method for evaluating pulmonary and cardiocirculatory abnormalities, dyspnea, and exercise tolerance in healthy individuals and patients with chronic conditions. During exercise, ventilation ($\dot{V}_E$) increases in proportion to metabolic demand [i.e., carbon dioxide production ($\dot{V}CO_2$)] to maintain arterial blood gas and acid-base balance. The response of $\dot{V}_E$ relative to $\dot{V}CO_2$ ($\dot{V}_E/\dot{V}CO_2$) is commonly termed ventilatory efficiency and is becoming a common physiological tool, in conjunction with other key variables such as operating lung volumes, to evaluate exercise responses in patients with chronic conditions. A growing body of research has shown that the $\dot{V}_E/\dot{V}CO_2$ response to exercise is elevated in conditions such as chronic heart failure (CHF), pulmonary hypertension (PH), interstitial lung disease (ILD), and chronic obstructive pulmonary disease (COPD). Importantly, this potentiated $\dot{V}_E/\dot{V}CO_2$ response contributes to dyspnea and exercise intolerance. The clinical significance of ventilatory inefficiency is demonstrated by findings showing that the elevated $\dot{V}_E/\dot{V}CO_2$ response to exercise is an independent predictor of mortality in patients with CHF, PH, and COPD. In this article, the underlying physiology, measurement, and interpretation of exercise ventilatory efficiency during CPET are reviewed. Additionally, exercise ventilatory efficiency in varying disease states is briefly discussed.

Keywords: ventilatory efficiency, ventilation, exercise testing, dyspnea, pulmonary gas-exchange

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INTRODUCTION

Cardiopulmonary exercise testing (CPET) is used for clinical evaluation of pulmonary and cardiocirculatory abnormalities, breathlessness (termed dyspnea), and exercise tolerance in patients with chronic conditions (Palange et al., 2007). CPET is a helpful diagnostic tool that can aid clinicians to identify patterns of functional impairment that may not be recognized by resting physiological testing (i.e., pulmonary function test, echocardiogram) and is particularly well suited to understand factors that may lead to pulmonary-related limitations to exercise (Stickland et al., 2012). Further, emerging research suggests that resting physiological tests poorly predict exertional dyspnea and exercise intolerance in clinical populations and that CPET is vital to evaluate causes of previously unexplained dyspnea and exercise intolerance (Elbehairy et al., 2015, 2017; Neder et al., 2016; Boucly et al., 2020).

During exercise, ventilation ($\dot{V}_E$) increases in proportion to metabolic demand [i.e., carbon dioxide production ($\dot{V}CO_2$)] in order to maintain acid-base balance. The response of $\dot{V}_E$ relative to $\dot{V}CO_2$ ($\dot{V}_E/\dot{V}CO_2$), said to reflect ventilatory efficiency (Forster and Pan, 1988), has become a common physiological tool, in conjunction with other key variables such as operating lung volumes and subjective dyspnea ratings, to evaluate exercise responses in patients with chronic conditions. For clinicians to incorporate ventilatory efficiency into CPET interpretation, a thorough understanding of the background physiology of ventilatory efficiency is needed. This article provides a detailed review on the underlying physiology, measurement, and interpretation of exercise ventilatory efficiency during CPET. Additionally, exercise ventilatory efficiency in varying disease conditions is briefly discussed.

Ventilatory Responses During Exercise

Alveolar ventilation ($\dot{V}_A$) represents the ventilation which takes part in gas-exchange. The relationship between $\dot{V}_A$, CO_2 production ($\dot{V}CO_2$), and the partial pressure of alveolar CO_2 (P_ACO_2) is defined by

$$P_ACO_2 = \left(\dot{V}CO_2 / \dot{V}_A\right) \times K \quad (1)$$

where K is a conversion factor (normally = 863) used to adjust $\dot{V}CO_2$ from standard temperature and pressure dry (STPD) to body temperature, ambient pressure, saturated (BTPS). As demonstrated by equation (1), P_ACO_2 is determined by the relative balance of $\dot{V}CO_2$ and $\dot{V}_A$. Due to the difficulty in measuring P_ACO_2, arterial PCO_2 (P_aCO_2) is often used as a surrogate with the assumption that $P_ACO_2 \approx P_aCO_2$ (Enghoff, 1938). Well-matched alveolar ventilation to perfusion is critical to maximize ventilatory efficiency and minimize dead space ventilation (West and Dollery, 1960; West et al., 1964). Although the healthy lung generally has good matching of ventilation to perfusion (West and Dollery, 1960; Whipp and Ward, 1982), a portion of gas remains in the conducting airways and does not participate in gas-exchange, and is termed anatomical dead space. Alveolar dead space represents the fraction of alveoli that are ventilated but not perfused. Dead space ventilation is the sum of alveolar and anatomical dead space, and, thus total minute ventilation is the sum of alveolar and dead space ventilation, as displayed in equation (2):

$$\dot{V}_E = \dot{V}_A + \dot{V}_D \quad (2)$$

Minute ventilation is measured at the mouth with expired gas analysis; however, $\dot{V}_A$ and $\dot{V}_D$ are more difficult to determine. If arterial blood gas and expired gas data are available, it is possible to derive $\dot{V}_A$ from equation (1), or estimate total physiologic dead space as a proportion of tidal volume using Enghoff's modified Bohr equation (Enghoff, 1938):

$$V_D / V_T = \left(P_aCO_2 - P_ECO_2\right) / \left(P_aCO_2\right) \quad (3)$$

In equation (3), P_ECO_2 represents mixed expired partial pressures of CO_2 and V_T is tidal volume. It is often assumed that the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) can be used as a surrogate for P_aCO_2. However, previous research has shown discrepancies between arterial blood-gas derived P_aCO_2 and expired-gas derived $P_{ET}CO_2$ in patients with pulmonary gas-exchange abnormalities (Scheidl et al., 2012; Laveneziana et al., 2014b; Elbehairy et al., 2015). Ventilation-perfusion ($\dot{V}_A/\dot{Q}$) abnormalities (typically alveolar dead space) results in dilution of gas from poorly perfused alveoli, which lowers the end-tidal CO_2 concentration. As a result, $P_{ET}CO_2$ often underestimates P_aCO_2 in patients with increased alveolar dead space such as pulmonary hypertension (PH) and chronic obstructive pulmonary disease (COPD; Scheidl et al., 2012; Laveneziana et al., 2014b; Elbehairy et al., 2015). Because of the potential error in determining P_aCO_2 from end-tidal data, care should be given when interpreting dead space calculated only with end-tidal and mixed expired values.

Based on the equations outlined above, the total ventilatory requirement to remove metabolic CO_2 production ($\dot{V}_E/\dot{V}CO_2$) is elevated in the presence of alveolar hyperventilation and/or high dead space. In conditions of hyperventilation assuming normal dead space, $\dot{V}_E/\dot{V}CO_2$ would be elevated and P_aCO_2 lowered (**Figure 1**). As discussed below, many clinical conditions demonstrate hyperventilation during exercise, secondary to increased afferent feedback (including but not limited to skeletal muscle ergoreceptors, chemoreceptors, and baroreceptors) (Ponikowski et al., 1997, 2001; Scott et al., 2000; Farina et al., 2018). In conditions of increased total physiologic dead space (i.e., high V_D/V_T) during exercise, $\dot{V}_E$ must increase to maintain adequate $\dot{V}_A$ and blood gas homeostasis (i.e., P_aCO_2; **Figure 1**). In addition to classic alveolar dead space (i.e., ventilation with no perfusion), V_D/V_T will be elevated when patients adopt a shallow, tachypneic breathing response. Hyperventilation also results in a rightward shift in the overall $\dot{V}_A/\dot{Q}$ relationship which can directly increase V_D/V_T (West, 1969; Robertson, 2015). In many chronic diseases, both elevated dead space and alveolar hyperventilation coexist (**Figure 1**) and, without measurement of P_aCO_2, it becomes difficult to quantify the contribution of each.

Clinical Significance of Ventilatory Efficiency

It is accepted that perceived dyspnea increases as ventilatory demand rises during incremental exercise, even in healthy individuals (Ofir et al., 2008a,b; Faisal et al., 2015). Ventilatory inefficiency increases the ventilatory demand for a given metabolic load which results in: (1) earlier attainment of critical dynamic mechanical constraint (i.e., critically reduced inspiratory reserve volume) and (2) increased respiratory neural drive, both of which lead to heightened perceived dyspnea and exercise intolerance, even in individuals with relatively preserved airway function (Guenette et al., 2014; Faisal et al., 2016). Multiple studies have linked ventilatory inefficiency to abnormal exertional dyspnea and poor exercise capacity in varying cardiocirculatory and respiratory diseases (Hansen and Wasserman, 1996; Arena et al., 2004; Neder et al., 2015, 2016; Elbehairy et al., 2017; Ewert et al., 2019). Additionally, the elevated $\dot{V}_E/\dot{V}CO_2$ response to exercise is an independent predictor of poor outcomes and mortality in many diseases, including chronic heart failure (CHF), PH, and COPD (Ponikowski et al., 2001; Wensel et al., 2013; Neder et al., 2016). Thus, the clinical utility of assessing ventilatory efficiency during CPET may be helpful to explain reasons for exertional dyspnea and exercise intolerance in various underlying disease states.

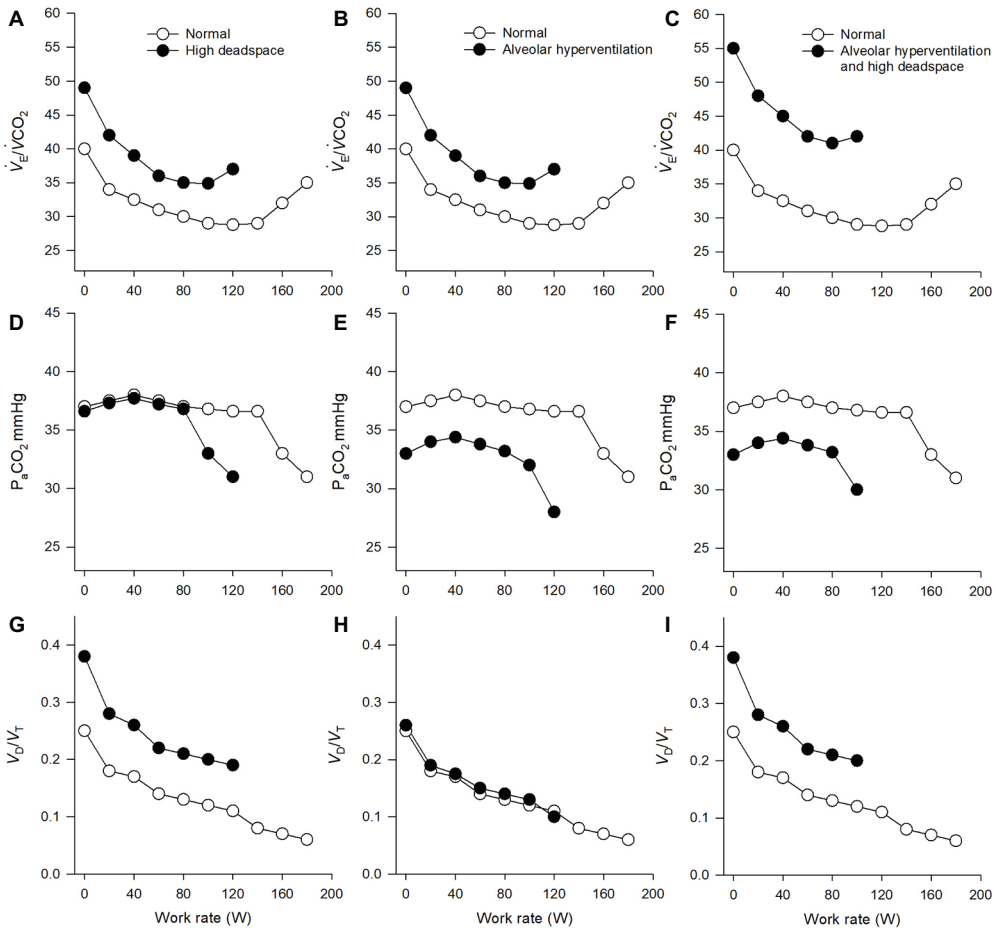

FIGURE 1 | Ventilatory and gas-exchange responses to incremental exercise. The left columns **(A,D,G)** display theoretical normal responses (open circles) and abnormal responses (closed circles). The theoretical abnormal responses demonstrate an elevated ventilatory response to carbon dioxide output ($\dot{V}_E/\dot{V}CO_2$), secondary to elevated dead space (dead space to tidal volume ratio = V_D/V_T) and normal partial pressure of arterial carbon dioxide (P_aCO_2). The middle columns **(B,E,H)** display theoretical normal responses (open circles) and abnormal responses (closed circles). The theoretical abnormal responses demonstrate an elevated $\dot{V}_E/\dot{V}CO_2$, secondary to alveolar hyperventilation (reduced P_aCO_2) but relatively normal dead space. The right columns **(C,F,I)** display theoretical normal responses (open circles) and abnormal responses (closed circles). The theoretical abnormal responses demonstrate an elevated $\dot{V}_E/\dot{V}CO_2$, secondary to a combination of alveolar hyperventilation (reduced P_aCO_2) and elevated dead space.

MEASURING AND INTERPRETING VENTILATORY EFFICIENCY FROM CPET

$\dot{V}_E/\dot{V}CO_2$ is easily included in a standard CPET report; however, careful consideration must be taken when analyzing and interpreting the data. This section describes common methods of reporting ventilatory efficiency from CPET data and technical considerations that may influence interpretation.

$\dot{V}_E$-to-$\dot{V}CO_2$ Slope and *y*-Intercept

During incremental exercise to symptom limitation, the relationship between $\dot{V}_E$ and $\dot{V}CO_2$ can be reported by plotting $\dot{V}_E$ (*y*-axis) relative to $\dot{V}CO_2$ (*x*-axis, **Figure 2**). The $\dot{V}_E$-to-$\dot{V}CO_2$ relationship during exercise can then be determined by analyzing the slope of this regression line (Whipp and Ward, 1982). Previous research has shown that the $\dot{V}_E$-to-$\dot{V}CO_2$ slope lower and upper limits of normal range from approximately 21 to 31 units, respectively (Sun et al., 2002; Naeije and Faoro, 2018). The $\dot{V}_E$-to-$\dot{V}CO_2$ slope is considered one of the most robust indicators of ventilatory efficiency, assuming ventilatory responses are not impaired by abnormal ventilatory mechanics (Neder et al., 2017).

During light to heavy exercise, $\dot{V}_E$ changes as a linear function of $\dot{V}CO_2$. Importantly, at heavy exercise above the respiratory compensation point, $\dot{V}_E$ rises disproportionally to $\dot{V}CO_2$ due to excessive metabolic acidosis. In individuals who tolerate high levels of exercise, an upward inflection in the $\dot{V}_E$ relative to $\dot{V}CO_2$ response would occur at maximal exercise and would inflate the $\dot{V}_E$-to-$\dot{V}CO_2$ slope if all data points are included in analysis. In these cases, determination of the slope of the regression line should exclude the non-linear portion (i.e., data after the respiratory compensation point should be excluded) (Arena et al., 2003; Guazzi et al., 2005).

When analyzing the $\dot{V}_E$-to-$\dot{V}CO_2$ slope in respiratory disease, such as COPD, the interpretation becomes more complex.

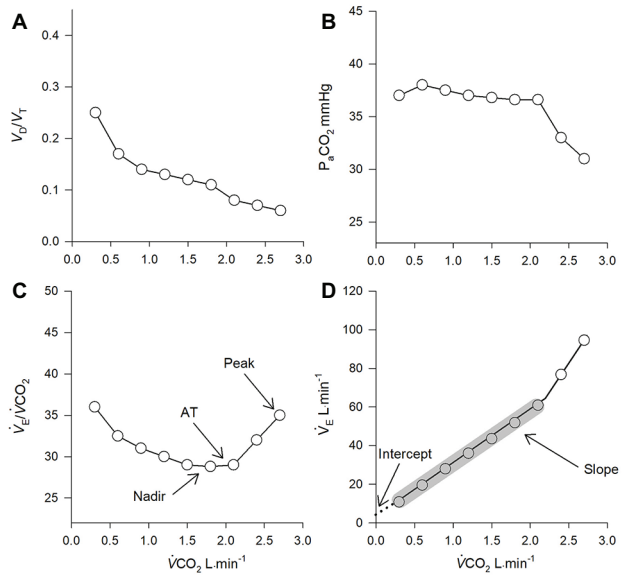

FIGURE 2 | Theoretical gas-exchange **(A, B)** and ventilatory **(C)** responses to incremental exercise. **(D)** represents the ventilatory responses to increasing metabolic demand. P_aCO_2 = partial pressure of arterial carbon dioxide; V_D/V_T = deadspace to tidal volume ratio; $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalent for carbon dioxide; AT = anaerobic threshold. Data points within grey shading represent the values used to calculate the slope of the regression line (note, the final two data points were excluded in the calculation as they occurred after the respiratory compensation point). The dashed line in **(D)** represents linear interpolation to the *y*-intercept.

Respiratory mechanical constraint and airflow limitation are often observed in these patients, which can blunt the rise in ventilation during exercise. As such, the $\dot{V}_E$-to-$\dot{V}CO_2$ slope paradoxically decreases as COPD severity worsens (Neder et al., 2015) (see section COPD Chronic Obstructive Pulmonary Disease). Thus, clinicians must look beyond the $\dot{V}_E$-to-$\dot{V}CO_2$ slope when evaluating ventilatory efficiency from CPET, especially in patients with respiratory mechanical constraints.

In addition to the slope, the *y*-intercept of the $\dot{V}_E$-to-$\dot{V}CO_2$ relationship (i.e., $\dot{V}_E$ when $\dot{V}CO_2 = 0$) can be determined from the same regression analysis (**Figure 2**). An elevated *y*-intercept is indicative of an upward shift in $\dot{V}_E$ for a given $\dot{V}CO_2$ and is considered to be an index of ventilatory efficiency at rest and during light exercise (i.e., at the start of a CPET) (Neder et al., 2015). The *y*-intercept can be a useful tool in the event of a premature test termination, as a maximal effort is not required. Recent research has demonstrated the *y*-intercept may help differentiate CPET patterns between COPD and CHF with overlapping symptoms (i.e., dyspnea and exercise intolerance), as COPD patients consistently demonstrate an elevated *y*-intercept, compared to CHF (Smith et al., 2019).

$\dot{V}_E/\dot{V}CO_2$ Nadir

Generally, in the transition from light to moderate intensity exercise, P_aCO_2 remains constant or slightly increases, while V_D/V_T decreases. As a result, the $\dot{V}_E/\dot{V}CO_2$ ratio is elevated during light exercise at the start of a CPET and progressively decreases in tandem with V_D/V_T to its lowest value (nadir) just prior to the respiratory compensation point (**Figure 2**; Whipp and Ward, 1982). The nadir $\dot{V}_E/\dot{V}CO_2$ is often considered the most accurate assessment of ventilatory efficiency, as it occurs independent of (1) the excess $\dot{V}_E/\dot{V}CO_2$ response to low intensity exercise and (2) metabolic acidosis and respiratory compensation during heavy exercise (Whipp and Ward, 1982). In healthy individuals, the $\dot{V}_E/\dot{V}CO_2$ corresponding to the nadir and the $\dot{V}_E/\dot{V}CO_2$ at anaerobic threshold are often similar (**Figure 2**; Sun et al., 2002). The nadir $\dot{V}_E/\dot{V}CO_2$ increases progressively with age and is abnormally high in cardiocirculatory and respiratory disease (Sun et al., 2002; Ingle et al., 2012; Elbehairy et al., 2015, 2019; Neder et al., 2015; Phillips et al., 2019). Although the nadir $\dot{V}_E/\dot{V}CO_2$ is highly reproducible, it may over-estimate ventilatory inefficiency in individuals with poor exercise tolerance and an excessively short test duration during CPET (Neder et al., 2001).

$\dot{V}_E/\dot{V}CO_2$ at Peak Exercise

At peak exercise, $\dot{V}_E/\dot{V}CO_2$ is often much higher than the nadir value as individuals typically hyperventilate secondarily to excessive metabolic acidosis (**Figure 2**). However, in individuals with poor exercise tolerance who are generally unable to exercise above anaerobic threshold, the nadir and peak exercise $\dot{V}_E/\dot{V}CO_2$ values are often similar (Neder et al., 2015; Phillips et al., 2019). Peak exercise $\dot{V}_E/\dot{V}CO_2$ is considered a poor index of ventilatory efficiency in healthy individuals and in patients who can exercise above the anaerobic threshold (Neder et al., 2017). For these reasons, clinicians should use caution when using peak exercise $\dot{V}_E/\dot{V}CO_2$ values as an index of ventilatory efficiency.

VENTILATORY EFFICIENCY IN VARIOUS CONDITIONS

Healthy Aging

Healthy aging is associated with an increased $\dot{V}_E/\dot{V}CO_2$ (slope and nadir) response to exercise, when compared to younger healthy individuals (Sun et al., 2002; Faisal et al., 2015). The elevated $\dot{V}_E/\dot{V}CO_2$ response is likely due to increased dead space, secondary to age-related reductions in alveolar-capillary surface area, capillary blood volume, and $\dot{V}_A/\dot{Q}$ mismatch (Tenney and Miller, 1956; Raine and Bishop, 1963; Johnson and Dempsey, 1991; Cardus et al., 1997). However, age-related ventilatory inefficiency is generally not a primary cause of exercise limitation in older healthy individuals.

Chronic Heart Failure

Multiple studies have demonstrated that patients with CHF with reduced ejection fraction (HFrEF) have an elevated ventilatory response to exercise, which is a key contributor to exertional dyspnea and exercise intolerance. The elevated $\dot{V}_E/\dot{V}CO_2$ (slope and nadir) is generally ascribed to hyperventilation, secondary to increased afferent feedback from chemoreceptors, baroreceptors, and ergoreceptors (Ponikowski et al., 1997, 2001; Scott et al., 2000). CHF patients typically adopt a rapid-shallow breathing pattern, which would increase

the V_D/V_T ratio and contribute to a greater $\dot{V}_E/\dot{V}CO_2$ (Woods et al., 2010). As described above, part of the increased V_D/V_T in CHF is likely due to the hyperventilation itself, which results in a rightward shift of a normal $\dot{V}_A/\dot{Q}$ distribution to a higher mean $\dot{V}_A/\dot{Q}$ ratio, and greater dead space (Robertson, 2015). The contribution of both hyperventilation (low P_aCO_2) and elevated dead space contributing to an exaggerated $\dot{V}_E/\dot{V}CO_2$ is demonstrated by Johnson (2001) who further analyzed individual CHF exercise data from Franciosa et al. (1984). A low peak P_aCO_2 was associated with a high peak $\dot{V}_E/\dot{V}CO_2$. Of note, a low cardiac index was also associated with a high $\dot{V}_E/\dot{V}CO_2$ (suggesting those with a low cardiac output likely have a higher mean $\dot{V}_A/\dot{Q}$ ratio and thus greater dead space). Finally, a high V_D/V_T ratio was correlated with a high $\dot{V}_E/\dot{V}CO_2$ (Franciosa et al., 1984; Johnson, 2001). When combined, these data suggest both hyperventilation and increased dead space contribute to the increased $\dot{V}_E/\dot{V}CO_2$ during exercise in CHF.

Emerging work has demonstrated ventilatory inefficiency (elevated $\dot{V}_E$-to-$\dot{V}CO_2$ slope) in patients with CHF with preserved ejection fraction (HFpEF; Olson et al., 2016); however, the mechanism(s) for the elevated $\dot{V}_E/\dot{V}CO_2$ is unclear. Patients with HFpEF often have co-existing PH (Lam et al., 2009), which may help explain the elevated $\dot{V}_E$-to-$\dot{V}CO_2$ slope; however, future work is required to better understand the pulmonary gas-exchange abnormalities in this population.

Pulmonary Hypertension

PH is characterized by a heightened ventilatory response to exercise (i.e., elevated $\dot{V}_E$-to-$\dot{V}CO_2$ slope) (Sun et al., 2001; Zhai et al., 2011). Patients with PH demonstrate significant ventilation-perfusion abnormalities, which is evident by an increased mean $\dot{V}_A/\dot{Q}$ ratio, larger than normal arterial-end-tidal PCO_2 differences, and increased dead space (V_D/V_T), all of which contribute to the elevated $\dot{V}_E/\dot{V}CO_2$ response during exercise (Dantzker et al., 1984; Zhai et al., 2011; Laveneziana et al., 2013). Although elevated dead space is generally considered the primary reason for ventilatory inefficiency in PH, previous work has shown that these patients hyperventilate at rest (as demonstrated by a low P_aCO_2) and demonstrate significant hyperventilation during exercise (Laveneziana et al., 2013, 2014a; Farina et al., 2018). Like CHF, patients with PH often have a blunted cardiac output response to exercise. The combination of low cardiac output and hyperventilation would cause a similar upward shift in the mean $\dot{V}_A/\dot{Q}$ ratio as observed in CHF, which may partially explain the elevated dead space typically observed in PH (Dantzker et al., 1984). When combined, it is evident that the increased $\dot{V}_E/\dot{V}CO_2$ response to exercise in PH is explained by both hyperventilation and increased dead space. Readers are referred to a review by Robertson (2015) that provides an excellent summary of current understanding of factors contributing to exercise hyperventilation in patients with cardiocirculatory disease.

Chronic Obstructive Pulmonary Disease

Airflow limitation, secondary to dynamic respiratory mechanical abnormalities, is generally considered the primary cause of exertional dyspnea in COPD. However, emerging research has suggested that ventilatory inefficiency is also a key contributor to dyspnea and exercise intolerance in patients with COPD (Neder et al., 2015; Elbehairy et al., 2019). In a study examining patients with mild COPD, arterial blood gas-derived dead space and $\dot{V}_E/\dot{V}CO_2$ (slope, nadir, and *y*-intercept) were consistently elevated during exercise while P_aCO_2 and alveolar ventilation were similar to age-matched healthy controls (Elbehairy et al., 2015). These data suggest that ventilatory inefficiency during exercise in mild COPD is primarily due to elevated dead space.

With advancing COPD (moderate to very severe), the $\dot{V}_E/\dot{V}CO_2$ response to exercise is more complex. With increasing COPD severity, dead space increases and is markedly elevated in the presence of extensive emphysematous destruction of capillary beds (Rodriguez-Roisin et al., 2009). In these patients, the elevated anatomical and total dead space is further amplified by the adopted rapid and shallow breathing pattern, secondary to severe hyperinflation, critically low inspiratory reserve volume, and limited tidal volume expansion (O'Donnell et al., 2012). Additionally, patients with COPD often become hypoxemic (Stolz et al., 2014), which would stimulate peripheral chemoreceptors and further increase ventilatory drive. The pronounced dead space and reduced P_aO_2 combined with a rapid shallow breathing would result in a substantially elevated $\dot{V}_E/\dot{V}CO_2$ response at rest and during light exercise; however, the pronounced airflow limitation in these patients often results in an inability to increase ventilation appropriately at higher metabolic demands. The net result is that patients with moderate to very severe COPD typically demonstrate an increased $\dot{V}_E$-to-$\dot{V}CO_2$ *y*-intercept and nadir $\dot{V}_E/\dot{V}CO_2$ but low $\dot{V}_E$-to-$\dot{V}CO_2$ slope and $\dot{V}_E/\dot{V}CO_2$ at peak exercise (Neder et al., 2015).

Interstitial Lung Disease

A growing body of research has shown that pulmonary gas-exchange abnormalities and ventilatory inefficiency (i.e., elevated $\dot{V}_E/\dot{V}CO_2$ slope and nadir) are key mechanisms of dyspnea and exercise intolerance in patients with interstitial lung disease (ILD; Faisal et al., 2016; Schaeffer et al., 2018). The increased $\dot{V}_E/\dot{V}CO_2$ during exercise in ILD appears to be due to the combination of increased dead space and hyperventilation (Agusti et al., 1991; Faisal et al., 2016). During exercise in patients with ILD, dynamic restrictive mechanical constraints, secondary to increased lung elastic recoil, increase inspiratory elastic loading, and patients often adopt a more rapid and shallow breathing pattern during exercise to minimize the inspiratory elastic work of breathing (Faisal et al., 2016; Schaeffer et al., 2018). Although the reduction in tidal volume is an effective strategy to minimize the elastic work of breathing during exercise, the compensatory tachypnea increases anatomical dead space and, ultimately, $\dot{V}_E/\dot{V}CO_2$ (Faisal et al., 2016; Schaeffer et al., 2018).

Multiple studies have consistently shown that patients with ILD develop exercise-induced arterial hypoxemia, which would stimulate the peripheral chemoreceptors and increase ventilatory drive, ultimately increasing $\dot{V}_E/\dot{V}CO_2$ (Hamer, 1964; Agusti et al., 1991; Faisal et al., 2016). Patients with ILD, specifically idiopathic pulmonary fibrosis, often have PH which may worsen pulmonary gas-exchange and exacerbate the already elevated

ventilatory response to exercise (Lettieri et al., 2006; Nathan et al., 2007); however, future work is required to better understand how abnormal pulmonary hemodynamics affects pulmonary gas-exchange in this population.

CONCLUSIONS

Measurement of ventilatory efficiency, as determined by the $\dot{V}_E/\dot{V}CO_2$ response to exercise, is an important physiological component, in conjunction with other key variables, to evaluate exercise responses and help explain reasons for exertional dyspnea in different underlying disease states. While measurements of ventilatory efficiency can aid clinicians to interpret CPET results, it is important to understand the strengths and limitations of the various methods of interpreting ventilatory efficiency data and understand the underlying pathophysiology.

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All authors contributed to the article and approved the submitted version.

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REFERENCES

Agusti, A., Roca, J., Gea, J., Wagner, P. D., Zaubet, A., and Rodrigues-Roisin, R. (1991). Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. *Am. Rev. Respir. Dis.* 143, 219–225. doi: 10.1164/ajrccm/143.2.219

Arena, R., Humphrey, R., and Peberdy, M. A. (2003). Prognostic ability of VE/VCO_2 slope calculations using different exercise test time intervals in subjects with heart failure. *Eur. J. Cardiovasc. Prev. Rehabil.* 10, 463–468. doi: 10.1097/01.hjr.0000102817.74402.5b

Arena, R., Myers, J., Aslam, S. S., Varughese, E. B., and Peberdy, M. A. (2004). Peak VO_2 and VE/VCO_2 slope in patients with heart failure: a prognostic comparison. *Am. Heart J.* 147, 354–360. doi: 10.1016/j.ahj.2003.07.014

Boucly, A., Morelot-Panzini, C., Garcia, G., Weatherald, J., Jais, X., Savale, L., et al. (2020). Intensity and quality of exertional dyspnoea in patients with stable pulmonary hypertension. *Eur. Respir. J.* 55:1802108. doi: 10.1183/13993003.02108-2018

Cardus, J., Burgos, F., Diaz, O., Roca, J., Barbera, J. A., Marrades, R. M., et al. (1997). Increase in pulmonary ventilation-perfusion inequality with age in healthy individuals. *Am. J. Respir. Crit. Care Med.* 156, 648–653. doi: 10.1164/ajrccm.156.2.9606016

Dantzker, D. R., D'alonzo, G. E., Bower, J. S., Popat, K., and Crevey, B. J. (1984). Pulmonary gas exchange during exercise in patients with chronic obliterative pulmonary hypertension. *Am. Rev. Respir. Dis.* 130, 412–416. doi: 10.1164/arrd.1984.130.3.412

Elbehairy, A. F., Ciavaglia, C. E., Webb, K. A., Guenette, J. A., Jensen, D., Mourad, S. M., et al. (2015). Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance. *Am. J. Respir. Crit. Care Med.* 191, 1384–1394. doi: 10.1164/rccm.201501-0157OC

Elbehairy, A. F., Faisal, A., Guenette, J. A., Jensen, D., Webb, K. A., Ahmed, R., et al. (2017). Resting physiological correlates of reduced exercise capacity in smokers with mild airway obstruction. *COPD* 14, 267–275. doi: 10.1080/15412555.2017.1281901

Elbehairy, A. F., O'Donnell, C. D., Abd Elhameed, A., Vincent, S. G., Milne, K. M., James, M. D., et al. (2019). Low resting diffusion capacity, dyspnea and exercise intolerance in COPD. *J. Appl. Physiol.* 127, 1107–1116. doi: 10.1152/japplphysiol.00341.2019

Enghoff, H. (1938). Volumen inefficax. Bemerkungen zur frage des schadlichen raumes. *Uppsala Lakarefoeren Fohr* 44, 191–218.

Ewert, R., Ittermann, T., Habedank, D., Held, M., Lange, T. J., Halank, M., et al. (2019). Prognostic value of cardiopulmonary exercise testing in patients with systemic sclerosis. *BMC Pulm. Med.* 19:230. doi: 10.1186/s12890-019-1003-7

Faisal, A., Alghamdi, B. J., Ciavaglia, C. E., Elbehairy, A. F., Webb, K. A., Ora, J., et al. (2016). Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am. J. Respir. Crit. Care Med.* 193, 299–309. doi: 10.1164/rccm.201504-0841OC

Faisal, A., Webb, K. A., Guenette, J. A., Jensen, D., Neder, J. A., O'Donnell, D. E., et al. (2015). Effect of age-related ventilatory inefficiency on respiratory sensation during exercise. *Respir. Physiol. Neurobiol.* 205, 129–139. doi: 10.1016/j.resp.2014.10.017

Farina, S., Bruno, N., Agalbato, C., Contini, M., Cassandro, R., Elia, D., et al. (2018). Physiological insights of exercise hyperventilation in arterial and chronic thromboembolic pulmonary hypertension. *Int. J. Cardiol.* 259, 178–182. doi: 10.1016/j.ijcard.2017.11.023

Forster, H. V., and Pan, L. G. (1988). Breathing during exercise: demands, regulation, limitations. *Adv. Exp. Med. Biol.* 227, 257–276.

Franciosa, J. A., Leddy, C. L., Wilen, M., and Schwartz, D. E. (1984). Relation between hemodynamic and ventilatory responses in determining exercise capacity in severe congestive heart failure. *Am. J. Cardiol.* 53, 127–134. doi: 10.1016/0002-9149(84)90696-9

Guazzi, M., Reina, G., Tumminello, G., and Guazzi, M. D. (2005). Exercise ventilation inefficiency and cardiovascular mortality in heart failure: the critical independent prognostic value of the arterial CO_2 partial pressure. *Eur. Heart J.* 26, 472–480. doi: 10.1093/eurheartj/ehi060

Guenette, J. A., Chin, R. C., Cheng, S., Dominelli, P. B., Raghavan, N., Webb, K. A., et al. (2014). Mechanisms of exercise intolerance in global initiative for chronic obstructive lung disease grade 1 COPD. *Eur. Respir. J.* 44, 1177–1187. doi: 10.1183/09031936.00034714

Hamer, J. (1964). Cause of low arterial oxygen saturation in pulmonary fibrosis. *Thorax* 19, 507–514. doi: 10.1136/thx.19.6.507

Hansen, J. E., and Wasserman, K. (1996). Pathophysiology of activity limitation in patients with interstitial lung disease. *Chest* 109, 1566–1576. doi: 10.1378/chest.109.6.1566

Ingle, L., Sloan, R., Carroll, S., Goode, K., Cleland, J. G., and Clark, A. L. (2012). Abnormalities of the ventilatory equivalent for carbon dioxide in patients with chronic heart failure. *Pulm. Med.* 2012:589164. doi: 10.1155/2012/589164

Johnson, R. L. (2001). Gas exchange efficiency in congestive heart failure. *Circulation* 103, 916–918. doi: 10.1161/01.CIR.103.7.916

Johnson, B. D., and Dempsey, J. A. (1991). Demand vs. capacity in the aging pulmonary system. *Exerc. Sport Sci. Rev.* 19, 171–210.

Lam, C. S., Roger, V. L., Rodeheffer, R. J., Borlaug, B. A., Enders, F. T., and Redfield, M. M. (2009). Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *Circulation* 53, 1119–1126. doi: 10.1016/j.jacc.2008.11.051

Laveneziana, P., Garcia, G., Joureau, B., Nicolas-Jilwan, F., Brahimi, T., Laviolette, L., et al. (2013). Dynamic respiratory mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Eur. Respir. J.* 41, 578–587. doi: 10.1183/09031936.00223611

Laveneziana, P., Montani, D., Dorfmuller, P., Girerd, B., Sitbon, O., Jais, X., et al. (2014a). Mechanisms of exertional dyspnoea in pulmonary veno-occlusive disease with EIF2AK4 mutations. *Eur. Respir. J.* 44, 1069–1072. doi: 10.1183/09031936.00088914

Laveneziana, P., Webb, K. A., Wadell, K., Neder, J. A., and O'Donnell, D. E. (2014b). Does expiratory muscle activity influence dynamic hyperinflation and exertional dyspnea in COPD? *Respir. Physiol. Neurobiol.* 199, 24–33. doi: 10.1016/j.resp.2014.04.005

Lettieri, C. J., Nathan, S. D., Barnett, S. D., Ahmad, S., and Shorr, A. F. (2006). Prevelance and outcomes of pulmonary arterial hypertension in advanced idopathic pulmonary fibrosis. *Chest* 129, 746–752. doi: 10.1378/chest.129.3.746

Naeije, R., and Faoro, V. (2018). The great breathlessness of cardiopulmonary diseases. *Eur. Respir. J.* 51:1702517. doi: 10.1183/13993003.02517-2017

Nathan, S. D., Noble, P. W., and Tuder, R. M. (2007). Idiopathic pulmonary fibrosis and pulmonary hypertension: connecting the dots. *Am. J. Respir. Crit. Care Med.* 175, 875–880. doi: 10.1164/rccm.200608-1153CC

Neder, J. A., Alharbi, A., Berton, D. C., Alencar, M. C., Arbex, F. F., Hirai, D. M., et al. (2016). Ventilatory inefficiency adds to lung function in predicting mortality in COPD. *COPD* 13, 416–424. doi: 10.3109/15412555.2016.1158801

Neder, J. A., Arbex, F. F., Alencar, M. C., O'donnell, C. D., Cory, J., Webb, K. A., et al. (2015). Exercise ventilatory inefficiency in mild to end-stage COPD. *Eur. Respir. J.* 45, 377–387. doi: 10.1183/09031936.00135514

Neder, J. A., Berton, D. C., Arbex, F. F., Alencar, M. C., Rocha, A., Sperandio, P. A., et al. (2017). Physiological and clinical relevance of exercise ventilatory efficiency in COPD. *Eur. Respir. J.* 49:1602036. doi: 10.1183/13993003.02036-2016

Neder, J. A., Nery, L. E., Peres, C., and Whipp, B. J. (2001). Reference values for dynamic responses to incremental cycle ergometry in males and females aged 20 to 80. *Am. J. Respir. Crit. Care Med.* 164, 1481–1486. doi: 10.1164/ajrccm.164.8.2103007

O'Donnell, D. E., Guenette, J. A., Maltais, F., and Webb, K. A. (2012). Decline of resting inspiratory capacity in COPD: the impact on breathing pattern, dyspnea, and ventilatory capacity during exercise. *Chest* 141, 753–762. doi: 10.1378/chest.11-0787

Ofir, D., Laveneziana, P., Webb, K. A., Lam, Y. M., and O'Donnell, D. E. (2008a). Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 177, 622–629. doi: 10.1164/rccm.200707-1064OC

Ofir, D., Laveneziana, P., Webb, K. A., Lam, Y. M., and O'Donnell, D. E. (2008b). Sex differences in the perceived intensity of breathlessness during exercise with advancing age. *J. Appl. Physiol.* 104, 1583–1593. doi: 10.1152/japplphysiol.00079.2008

Olson, T. P., Johnson, B. D., and Borlaug, B. A. (2016). Impaired pulmonary diffusion in heart failure with preserved ejection fraction. *JACC Heart Fail.* 4, 490–498. doi: 10.1016/j.jchf.2016.03.001

Palange, P., Ward, S. A., Carlsen, K. H., Casaburi, R., Gallagher, C. G., Gosselink, R., et al. (2007). Recommendations on the use of exercise testing in clinical practice. *Eur. Respir. J.* 29, 185–209. doi: 10.1183/09031936.00046906

Phillips, D. B., Collins, S. É., Bryan, T. L., Wong, E. Y. L., Mcmurtry, M. S., Bhutani, M., et al. (2019). The effect of carotid chemoreceptor inhibition on exercise tolerance in chronic obstructive pulmonary disease: a randomized-controlled crossover trial. *Respir. Med.* 160:105815. doi: 10.1016/j.rmed.2019.105815

Ponikowski, P., Chua, T. P., Anker, S. D., Francis, D. P., Doehner, W., Banasiak, W., et al. (2001). Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. *Circulation* 104, 544–549. doi: 10.1161/hc3101.093699

Ponikowski, P., Chua, T. P., Piepoli, M., Ondusova, D., Webb-Peploe, K., Harrington, D., et al. (1997). Augmented peripheral chemosensitivity as a potential input to baroreflex impairment and autonomic imbalance in chronic heart failure. *Circulation* 96, 2586–2594. doi: 10.1161/01.CIR.96.8.2586

Raine, J. M., and Bishop, J. M. (1963). A-a difference in O_2 tension and physiological dead space in normal man. *J. Appl. Physiol.* 18, 284–288. doi: 10.1152/jappl.1963.18.2.284

Robertson, H. T. (2015). Dead space: the physiology of wasted ventilation. *Eur. Respir. J.* 45, 1704–1716. doi: 10.1183/09031936.00137614

Rodriguez-Roisin, R., Drakulovic, M., Rodriguez, D. A., Roca, J., Barbera, J. A., and Wagner, P. D. (2009). Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. *J. Appl. Physiol.* 106, 1902–1908. doi: 10.1152/japplphysiol.00085.2009

Schaeffer, M. R., Ryerson, C. J., Ramsook, A. H., Molgat-Seon, Y., Wilkie, S. S., Dhillon, S. S., et al. (2018). Neurophysiological mechanisms of exertional dyspnoea in fibrotic interstitial lung disease. *Eur. Respir. J.* 51:1701726. doi: 10.1183/13993003.01726-2017

Scheidl, S. J., Englisch, C., Kovacs, G., Reichenberger, F., Schulz, R., Breithecker, A., et al. (2012). Diagnosis of CTEPH versus IPAH using capillary to end-tidal carbon dioxide gradients. *Eur. Respir. J.* 39, 119–124. doi: 10.1183/09031936.00109710

Scott, A. C., Francis, D. P., Davies, L. C., Ponikowski, P., Coates, A. J. S., and Piepoli, M. F. (2000). Contribution of skeletal muscle 'ergoreceptors' in the human leg to respiratory control in chronic heart failure. *J. Physiol.* 529, 863–870. doi: 10.1111/j.1469-7793.2000.00863.x

Smith, J. R., Van Iterson, E. H., Johnson, B. D., Borlaug, B. A., and Olson, T. P. (2019). Exercise ventilatory inefficiency in heart failure and chronic obstructive pulmonary disease. *Int. J. Cardiol.* 274, 232–236. doi: 10.1016/j.ijcard.2018.09.007

Stickland, M. K., Butcher, S. J., Marciniuk, D. D., and Bhutani, M. (2012). Assessing exercise limitation using cardiopulmonary exercise testing. *Pulm. Med.* 2012:824091. doi: 10.1155/2012/824091

Stolz, D., Boersma, W., Blasi, F., Louis, R., Milenkovic, B., Kostikas, K., et al. (2014). Exertional hypoxemia in stable COPD is common and predicted by circulating proadrenomedullin. *Chest* 146, 328–338. doi: 10.1378/chest.13-1967

Sun, X. G., Hansen, J. E., Garatachea, N., Storer, T. W., and Wasserman, K. (2002). Ventilatory efficiency during exercise in healthy subjects. *Am. J. Respir. Crit. Care Med.* 166, 1443–1448. doi: 10.1164/rccm.2202033

Sun, X. G., Hansen, J. E., Oudiz, R. J., and Wasserman, K. (2001). Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 104, 429–435. doi: 10.1161/hc2901.093198

Tenney, S. M., and Miller, R. M. (1956). Dead space ventilation in old age. *J. Appl. Physiol.* 9, 321–327. doi: 10.1152/jappl.1956.9.3.321

Wensel, R., Francis, D. P., Meyer, F. J., Opitz, C. F., Bruch, L., Halank, M., et al. (2013). Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. *Int. J. Cardiol.* 167, 1193–1198. doi: 10.1016/j.ijcard.2012.03.135

West, J. B. (1969). Ventilation-perfusion inequality and overall gas exchange in computer models of the lung. *Respir. Physiol.* 7, 88–110. doi: 10.1016/0034-5687(69)90071-1

West, J. B., and Dollery, C. T. (1960). Distribution of blood flow and ventilation-perfusion ratio in the lung, measured with radioactive carbon dioxide. *J. Appl. Physiol.* 15, 405–410. doi: 10.1152/jappl.1960.15.3.405

West, J. B., Dollery, C. T., and Naimark, A. (1964). Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *J. Appl. Physiol.* 19, 713–724. doi: 10.1152/jappl.1964.19.4.713

Whipp, B. J., and Ward, S. A. (1982). Cardiopulmonary coupling during exercise. *J. Exp. Biol.* 100, 175–193.

Woods, P. R., Olson, T. P., Frantz, R. P., and Johnson, B. D. (2010). Causes of breathing inefficiency during exercise in heart failure. *J. Card. Fail.* 16, 835–842. doi: 10.1016/j.cardfail.2010.05.003

Zhai, Z., Murphy, K., Tighe, H., Wang, C., Wilkins, M. R., Gibbs, J. S. R., et al. (2011). Differences in ventilatory inefficiency between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest* 140, 1284–1291. doi: 10.1378/chest.10-3357

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Cardiopulmonary Exercise Testing in Patients With Interstitial Lung Disease

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Interstitial lung disease (ILD) is a heterogeneous group of conditions characterized by fibrosis and/or inflammation of the lung parenchyma. The pathogenesis of ILD consistently results in exertional dyspnea and exercise intolerance. Cardiopulmonary exercise testing (CPET) provides important information concerning the pathophysiology of ILD that can help inform patient management. Despite the purported benefits of CPET, its clinical utility in ILD is not well defined; however, there is a growing body of evidence that provides insight into the potential value of CPET in ILD. Characteristic responses to CPET in patients with ILD include exercise-induced arterial hypoxemia, an exaggerated ventilatory response, a rapid and shallow breathing pattern, critically low inspiratory reserve volume, and elevated sensations of dyspnea and leg discomfort. CPET is used in ILD to determine cause(s) of symptoms such as exertional dyspnea, evaluate functional capacity, inform exercise prescription, and determine the effects of pharmacological and non-pharmacological interventions on exercise capacity and exertional symptoms. However, preliminary evidence suggests that CPET in ILD may also provide valuable prognostic information and can be used to ascertain the degree of exercise-induced pulmonary hypertension. Despite these recent advances, additional research is required to confirm the utility of CPET in patients with ILD. This brief review outlines the clinical utility of CPET in patients with ILD. Typical patterns of response are described and practical issues concerning CPET interpretation in ILD are addressed. Additionally, important unanswered questions relating to the clinical utility of CPET in the assessment, prognostication, and management of patients with ILD are identified.

Keywords: dyspnea, exercise capacity, hypoxemia, idiopathic pulmonary fibrosis, ventilatory limitation

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INTRODUCTION

The term interstitial lung disease (ILD) refers to a large, heterogenous group of conditions that involve variable degrees of fibrosis and/or inflammation of the lung parenchyma (King, 2005). Although the etiology varies across ILD subtypes, the pathogenesis of ILD leads to a host of physiological abnormalities including progressive reductions in lung volumes, pulmonary gas exchange limitations (Chetta et al., 2004; Young and Bye, 2011), decreased cardiovascular function

(Panagiotou et al., 2017) as well as skeletal muscle atrophy and dysfunction (Panagiotou et al., 2016). The pathophysiological features of ILD consistently result in an increased perception of dyspnea, particularly during physical exertion, and reduced exercise tolerance (Collard and Pantilat, 2008; Holland, 2010). Cardiopulmonary exercise testing (CPET) is often considered to be the gold-standard for evaluating exertional dyspnea and exercise intolerance in patients with cardiorespiratory conditions, and provides important information that complements diagnostic investigations performed at rest (Palange et al., 2007). Despite the well-documented application of CPET in other forms of cardiorespiratory disease (American Thoracic and American College of Chest, 2003), its utility in ILD is not well characterized (Bonini and Fiorenzano, 2017); however, a growing body of evidence relating to the pathophysiological responses to exercise in patients with ILD provides new insight into the potential value of CPET in this population.

In this review, we provide a brief summary of recent findings concerning the clinical utility of CPET in patients with ILD. Typical patterns of response and how they differ from those observed in health are described and practical issues concerning the interpretation of CPET variables in ILD are addressed. Given that the focus of this review is on recent findings related to CPET in ILD, the interested reader is directed elsewhere for detailed descriptions of foundational concepts including the pathophysiology of ILD (Parker et al., 2011; Bagnato and Harari, 2015) and the physiological responses to exercise in patients with ILD (Lama and Martinez, 2004; Molgat-Seon et al., 2019).

Physiological Responses to CPET

Functional Capacity

The primary pathophysiological features of ILD have a detrimental impact on the integrative physiological response to exercise. Patients with ILD have reduced functional capacity when compared to healthy individuals, as evidenced by a lower peak power output and oxygen uptake during incremental cycle exercise testing (Wehr and Johnson, 1976; Burdon et al., 1983) as well as a shorter distance achieved during 6-min walk testing (Chang et al., 1999). As is the case in other forms of cardiorespiratory disease, performing CPET in patients with ILD provides a direct assessment of their functional capacity, however, the mechanisms of exercise intolerance in ILD are complex, multifactorial, and variable across patients and ILD sub-types (Holland, 2010; Young and Bye, 2011). The restrictive ventilatory impairment and decreased pulmonary gas exchange efficiency negatively impact the ventilatory response to exercise, while pulmonary vascular destruction and arterial hypoxemia impair the cardiovascular response to exercise. Additionally, ILD may involve skeletal muscle atrophy and dysfunction, which would further decrease exercise capacity (Panagiotou et al., 2016). The abovementioned factors may act individually or synergistically to reduce exercise tolerance (Holland, 2010; Young and Bye, 2011). It is therefore challenging to determine the exact cause of exercise limitation in a given ILD patient. Nevertheless, monitoring the ventilatory, cardiovascular, skeletal muscle, and sensory responses to exercise during CPET in ILD reveals common patterns that differ from those observed in health and can enable clinicians to determine the primary cause(s) of symptom limitation (**Table 1**).

Ventilatory and Pulmonary Gas Exchange Responses

During incremental exercise, minute ventilation ($\dot{V}_E$) must increase in order to meet the demands associated with the rising oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). Similarly, the increase in $\dot{V}O_2$ necessitates a greater rate of oxygen diffusion into the blood in order to maintain arterial oxygen saturation (SaO_2), thereby ensuring adequate oxygen delivery to exercising muscles. In health, the exercise-induced increase in $\dot{V}_E$ is primarily achieved via an expansion of tidal volume (V_T) until it reaches ∼60% of vital capacity (VC). Further increases in $\dot{V}_E$ are then achieved by increasing breathing frequency (f_B). The aforementioned breathing pattern is considered optimal as it minimizes the work of breathing and dead-space ventilation. In patients with ILD, vital capacity (VC) is reduced, which limits their ability to expand V_T and by association, reduces their maximum voluntary ventilation (MVV) (Faisal et al., 2016). Moreover, their lung compliance is decreased, which correspondingly increases the mechanical and metabolic cost of breathing for a given $\dot{V}_E$ (Faisal et al., 2016). For patients with ILD, the higher mechanical and metabolic cost of breathing during exercise may impair ventricular performance, due to the large intrathoracic pressure swings, and may increase the fraction of total cardiac output directed to the respiratory muscles at the expense of locomotor muscle blood flow (Dominelli et al., 2017); however, direct evidence supporting this notion in patients with ILD is currently lacking. Together, the reductions in VC, MVV, and lung compliance alter the ventilatory response to exercise in ILD. At rest, patients with ILD typically have a rapid breathing pattern (i.e., normal V_T and high f_B). During incremental exercise, patients with ILD will initially increase $\dot{V}_E$ by expanding V_T in a similar manner as observed in healthy individuals but will reach a plateau in V_T at a much lower $\dot{V}_E$ and exercise intensity due to their reduced VC. Subsequent increases in $\dot{V}_E$ are then achieved by further increasing f_B. This rapid and shallow breathing pattern implies that the ratio of dead-space volume to V_T (V_D/V_T) is typically high during exercise in patients with ILD. At rest and during exercise at a given absolute intensity, $\dot{V}_E$ is also increased in ILD due to ventilation-perfusion mismatch (Jernudd-Wilhelmsson et al., 1986) as well as increased ventilatory drive resulting from arterial hypoxemia and an early-onset of metabolic acidosis (Van Meerhaeghe et al., 1981), which is evidenced by an elevated $\dot{V}_E/\dot{V}CO_2$ throughout exercise. Thus, some patients with ILD will experience ventilatory limitation during exercise (Marciniuk et al., 1994b), which can be crudely assessed based on whether the ratio of $\dot{V}_E$ and MVV is greater than 85%; however, it is noteworthy that in many cases, patients with ILD will terminate exercise despite having adequate ventilatory reserve (Marciniuk et al., 1994a; Faisal et al., 2016). Lastly, the pathological decrement in pulmonary gas exchange at rest is worsened during exercise, thereby resulting in a progressive decrease in SaO_2, even in those who are not hypoxemic at rest (Young and Bye, 2011). Exercise-induced arterial hypoxemia is a characteristic feature of patients with

TABLE 1 | CPET responses in healthy individuals and how they differ in patients with ILD.

CPET measure	Healthy individuals	ILD
Functional capacity		
$\dot{V}O_2$ max, ml·kg^{-1}·min^{-1}	Typically >85% predicted	Reduced, often <85% predicted
Peak Power Output, W	Typically >85% predicted	Reduced, often <85% predicted
Anaerobic Threshold, %$\dot{V}O_2$ max	Typically >40% of predicted $\dot{V}O_2$ max	Reduced, often <40% predicted $\dot{V}O_2$ max
Ventilatory and pulmonary gas exchange		
f_B, breaths·min^{-1}	Typically <50 breaths·min^{-1} throughout exercise	Increased for a given power output or $\dot{V}_E$, can be >50 breaths·min^{-1} at peak exercise
V_T, l	Typically increases to up 50–60% VC and plateaus	Typically increases to 50–60% VC and plateaus but is reduced for any given $\dot{V}_E$
V_D/V_T	Decreases relative to rest, typically <0.30 at peak exercise	Minimal change from rest and can increase during exercise to >0.30
$\dot{V}_E/\dot{V}CO_2$	Typically <32–34 at or near anaerobic threshold and <36 at peak	Elevated throughout exercise, typically >32–34 at anaerobic threshold and >36 at peak
$\dot{V}_E$/MVV, %	Typically <85% throughout exercise	Variable, but can be >85% at peak exercise
SaO_2	Preserved throughout exercise, similar to resting values	Variable, but typically decrease below resting values
Cardiovascular		
HR, % predicted maximum	Typically >90% of age predicted values at peak exercise	Variable, but will often be below age predicted values at peak exercise
$\dot{V}O_2$/HR, ml·beat^{-1}	Typically >80% of predicted at peak exercise	Reduced, usually <80% of predicted at peak exercise
Symptoms		
Dyspnea	Increases progressively during exercise, usually >5 at peak exercise	Increased for a given power output and $\dot{V}_E$, usually >5 at peak exercise
Leg discomfort	Increases progressively during exercise, usually >5 at peak exercise	Increased for a given power output, usually >5 at peak exercise
Invasive measures		
EMG_{di}, % of maximum	Increases progressively during exercise up to ∼60–70% of maximum	Increased for a given power output and $\dot{V}_E$, similar at peak exercise
PaO_2, mmHg	Relatively stable during exercise, typically <10 mmHg reduction from rest	Typically drops progressively during exercise, >10 mmHg reduction from rest
$P(A\text{-}a)O_2$, mmHg	Increases progressively during exercise, <25 mmHg at peak exercise	Increases progressively during exercise, often >30 mmHg at peak exercise
mPAP– $\dot{Q}$ slope, mmHg·min^{-1}·l^{-1}	<3 mmHg·min^{-1}·l^{-1}	Variable, but can be >3 mmHg·min^{-1}·l^{-1}

EMG_{di}, diaphragm electromyography; f_B, breathing frequency; HR, heart rate; mPAP, mean pulmonary artery pressure; MVV, maximal voluntary ventilation; PaO_2, partial pressure of arterial oxygen; $P(A\text{-}a)O_2$, alveolar-arterial partial pressure of oxygen gradient; $\dot{Q}$, cardiac output; SaO_2, arterial oxygen saturation; $\dot{V}_E$, minute ventilation; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; V_D, dead space volume; $\dot{V}O_2$, oxygen uptake; V_T, tidal volume.

ILD (Agusti et al., 1988). In fact, patients with ILD often exhibit a greater degree of arterial desaturation during exercise than patients with chronic obstructive pulmonary disease (Du Plessis et al., 2017). The importance of assessing the degree of exercise-induced arterial hypoxemia during CPET is highlighted by its association with disease severity and prognosis (Lama et al., 2003; Vainshelboim et al., 2016). Given the limitations associated with pulse oximetry, CPET involving serial assessments of arterial blood gases may be warranted if the main purpose of the test is to determine the adequacy of pulmonary gas exchange (American Thoracic and American College of Chest, 2003). Arterial blood gas sampling enables the assessment of several important parameters, including the partial pressure of arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$), the alveolar-arterial partial pressure of oxygen gradient [$P(A\text{-}a)O_2$], as well as direct measures of SaO_2 and V_D/V_T. The assessment of $P(A\text{-}a)O_2$, which is characteristically widened during exercise in ILD (Agusti et al., 1991) is particularly informative given its correlation with the degree of fibrosis and cellularity obtained from a lung biopsy, as well as its potential prognostic value, at least in idiopathic pulmonary fibrosis (IPF) (Fulmer et al., 1979; Agusti et al., 1994).

Cardiovascular Responses

Despite primarily affecting the lungs, many forms of ILD involve obliteration of the pulmonary capillary bed and remodeling of the pulmonary vasculature (Nathan et al., 2007; Seeger et al., 2013). Depending on the degree of pulmonary vascular involvement, some patients with ILD will have impairments in cardiovascular function that contribute to exercise limitation. In healthy individuals performing incremental exercise, there is a linear increase in cardiac output ($\dot{Q}$) as a function of $\dot{V}O_2$. The exercise-induced increase in $\dot{Q}$ is achieved via a progressive increase in heart rate (HR) and an increase in stroke volume up to approximately 50–60% of maximal oxygen uptake ($\dot{V}O_2$ max), at which point SV plateaus. Patients with ILD are generally capable of increasing $\dot{Q}$ in proportion to $\dot{V}O_2$ during exercise at relatively low intensities; however, at higher exercise intensities, some patients have a diminished rate of increase in $\dot{Q}$ (Bush and Busst, 1988; Degani-Costa et al., 2015), which is presumably

due to a reduction in stroke volume (Degani-Costa et al., 2015). Indeed, patients with ILD typically have a lower oxygen pulse, an indirect marker of stroke volume, during exercise than healthy individuals (Faisal et al., 2016). Thus, patients with ILD often have an abnormal HR response to exercise, whereby HR is higher for a given absolute exercise intensity when compared to their healthy counterparts (Baughman et al., 1984), which may be due to constraints on stroke volume, deconditioning, or both. At peak exercise, HR values in patients with ILD are variable since some patients fail to reach their age-predicted maximum HR due to cessation of exercise prior to reaching their physiological maxima (Faisal et al., 2016), whereas others may have a critically low HR reserve (Schwaiblmair et al., 1996; Baughman et al., 2011). During standard CPET, measures of HR, electrocardiogram parameters, and non-invasive measures of arterial blood pressure are the only available direct cardiovascular measures. However, in cases where there is a high index of suspicion for exercise-induced pulmonary hypertension despite negative tests at rest, invasive CPET with right heart catherization may be warranted in order to directly evaluate the pulmonary vascular response to exercise (Maron et al., 2013). In such cases, some patients may exhibit an exaggerated pulmonary artery pressure response to exercise, whereby a given increase in $\dot{Q}$ results in a greater increase in mean pulmonary artery pressure than in healthy individuals (Degani-Costa et al., 2015). Alternatively, echocardiography may be employed as a non-invasive alternative to cardiac catherization for the assessment of exercise-induced pulmonary hypertension (Himelman et al., 1989; Reichenberger et al., 2009; D'Alto et al., 2011), although echocardiographic data obtained during exercise in patients with ILD is relatively limited.

Skeletal Muscle Responses

It has been suggested that skeletal muscle atrophy and dysfunction may be an important systemic consequence of ILD (Panagiotou et al., 2016). Indeed, the strength of the quadriceps muscles is reduced in patients with ILD when compared to predicted values, and is significantly associated with functional capacity (Nishiyama et al., 2005; Watanabe et al., 2013). If present, skeletal muscle dysfunction would accelerate the onset of metabolic acidosis and skeletal muscle fatigue during exercise. Although standard CPET parameters are not directly indicative of skeletal muscle dysfunction, early termination of a test due to intolerable leg discomfort in the face of significant ventilatory and/or cardiovascular reserves may indicate locomotor muscle dysfunction (Marciniuk et al., 1994a; Nishiyama et al., 2005).

Sensory Responses

For patients with ILD, dyspnea is the most common symptom, particularly upon exertion (Collard and Pantilat, 2008). CPET is often employed to evaluate the mechanisms of unexplained dyspnea in patients with cardiorespiratory disease, including those with ILD (Bonini and Fiorenzano, 2017). During incremental exercise, patients with ILD report higher levels of dyspnea than healthy individuals for a given absolute exercise intensity or $\dot{V}_E$ (O'Donnell et al., 1998; Faisal et al., 2016). The increased dyspnea is thought to reflect the awareness of an increased neural respiratory drive necessitated by the aforementioned pathophysiological alterations in respiratory mechanics and pulmonary gas exchange efficiency (Schaeffer et al., 2018). This notion is supported by the fact that when patients with ILD are given supplemental oxygen during constant-load exercise, the neural respiratory drive to the diaphragm decreases along with their perception of dyspnea (Schaeffer et al., 2017b). Neural respiratory drive to the diaphragm can be estimated during CPET using esophageal electromyography (Faisal et al., 2016; Schaeffer et al., 2018).

Given that ILD primarily affects the lungs, it is logical to assume that ventilatory factors would lead to the increased perception of exertional dyspnea. Indeed, those who experience ventilatory limitation during CPET are more likely to discontinue exercise because of intolerable dyspnea; however, this may not always be the case (Marciniuk et al., 1994a). Patients with ILD who do not exhibit signs of overt ventilatory limitation typically terminate exercise due to intolerable leg discomfort (Marciniuk et al., 1994a), which may be due to attendant hypoxemia, skeletal muscle dysfunction, and/or cardiovascular limitation (Hansen and Wasserman, 1996; Panagiotou et al., 2016). Regardless of the root cause, patients with ILD experience exertional dyspnea and elevated perceptions of leg discomfort during CPET at relatively low exercise intensities. It follows that carefully assessing the perceptual responses to CPET, at rest and throughout exercise, provides important information that can be contextualized with ventilatory, cardiovascular, and metabolic measurements to gain insight regarding the cause of the aforementioned sensations. Additional assessments such as asking patients to report the reason they stopped exercising (i.e., due to dyspnea, leg discomfort, or due to another reason) and evaluating the qualitative descriptors of dyspnea using a validated questionnaire may be helpful in ascertaining the underlying cause of symptom limitation during CPET in ILD (O'Donnell et al., 1998).

Clinical Utility of CPET

It is well established that CPET is a valuable tool for the assessment of patients with several forms of cardiorespiratory disease (Arena and Sietsema, 2011; Bonini and Fiorenzano, 2017). Yet, CPET currently lacks a defined role in ILD management (Bradley et al., 2008; Raghu et al., 2011; Assayag et al., 2018). Nevertheless, recent findings highlight the potential benefits that could be derived from CPET in patients with ILD. Herein, we summarize our current understanding of the clinical utility of CPET in patients with ILD, highlight important findings that outline how the use of CPET in ILD could be expanded, and identify areas where additional research is required.

Current Use of CPET

ILD diagnosis is established by a multidisciplinary team of respirologists, chest radiologists, and lung pathologists based on a combination of clinical information derived from pulmonary function tests, chest imaging, and lung tissue histology (Richeldi et al., 2019). CPET data are not a requirement for a multidisciplinary diagnosis of ILD but may be used to inform patient management. Indeed, there are several reasons for conducting CPET in patients with ILD (**Table 2**; American Thoracic and American College of Chest, 2003). Its most obvious

TABLE 2 | Primary reasons for conducting CPET in patients with ILD.

Reasons for conducting CPET
• Determining the cause(s) of exertional dyspnea
• Assessing functional capacity and the mechanism(s) of exercise intolerance
• Determining the magnitude of exercise-induced hypoxemia
• Establishing a baseline prior to and setting exercise training intensity for pulmonary rehabilitation
• Evaluating the acute and chronic response to pharmacological and non-pharmacological interventions on exercise performance, symptoms, and physiology
• Evaluating pulmonary gas exchange abnormalities
• Patient prognostication
• Determining the presence of co-morbidities
• Evaluation for lung transplantation

and well-established application is in assessing the cause(s) of symptoms such as exertional dyspnea, and objectively evaluating functional capacity (Mezzani, 2017). Determining the intensity at which desaturation occurs may be useful for the prescription of ambulatory oxygen therapy (Palange et al., 2007). Additionally, pulmonary rehabilitation is advocated for some patients with ILD (Assayag et al., 2018) and CPET can be used as a baseline assessment of functional capacity prior to enrollment as well as for precise exercise prescription (Bernard et al., 2014). Repeated CPET also allows clinicians to assess the change in exercise tolerance and exertional symptoms following pulmonary rehabilitation (Tonelli et al., 2017) or other pharmacological and non-pharmacological interventions (Jackson et al., 2010; Blanco et al., 2011; Schaeffer et al., 2017b). Unlike other exercise tests (e.g., 6-min walk test), CPET has the added advantage of being able to identify the physiological mechanisms of improvement. However, it is noteworthy that the minimal clinically-important difference (MCID) for CPET parameters has not yet been established in ILD, which complicates the longitudinal assessment of CPET data.

Important Considerations When Conducting CPET

As is the case with other forms of cardiorespiratory disease, the clinical utility of CPET in ILD depends on the variables measured, the exercise modality used, and how results are interpreted. CPET provides a substantial amount of data that can be used to inform patient management. Depending on the indications for CPET in patients with ILD (**Table 2**), several additional measures may be added to the standard, obligatory measures (i.e., $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, HR, etc.) in order to achieve a particular goal. For example, if the intent is to evaluate the degree of respiratory limitation to exercise, having the patient perform inspiratory capacity maneuvers during exercise may be warranted (Guenette et al., 2013) along with flow-volume loop analyses. Similarly, comprehensively investigating decrements in pulmonary gas exchange efficiency may require arterial blood gas sampling, while determining the degree of pulmonary vascular impairment may necessitate right heart-catherization or echocardiography. In situations where repeated CPET is required, constant-load exercise, rather than incremental exercise, is most sensitive for detecting changes in key physiological and perceptual variables (Puente-Maestu et al., 2016). It is also important to compare sensory and physiological data between repeat CPETs at standardized submaximal measurement times rather than focusing exclusively on peak exercise responses (Schaeffer et al., 2017a). Regardless of the indication for CPET, it is important to define the aim of the test and tailor the method of testing accordingly.

Potential Application of CPET

In comparison to other forms of cardiorespiratory disease, the application of CPET in ILD has been relatively limited (American Thoracic and American College of Chest, 2003; Bonini and Fiorenzano, 2017). However, recent evidence highlights promising areas where pulmonary gas exchange parameters obtained during CPET could improve the management of patients with ILD (Bonini and Fiorenzano, 2017). Pulmonary gas exchange measures during CPET have been used to non-invasively determine whether patients with ILD have pulmonary hypertension. Specifically, patients with ILD who had resting pulmonary hypertension that was confirmed by right heart catheterization had significantly lower partial pressure of end-tidal carbon dioxide and mixed expired carbon dioxide during incremental exercise than those who had no evidence of resting pulmonary hypertension (Armstrong et al., 2013). Thus, CPET may be helpful in revealing possible co-morbidities such as pulmonary hypertension. Another area that has garnered interest is the utility of CPET data to inform ILD prognosis. Pulmonary gas exchange parameters obtained during CPET appear to be superior to resting pulmonary function tests for the prognostication of ILD (Keogh and Crystal, 1980; Miller et al., 1995) and PaO_2 at peak exercise is a significant predictor of survival in IPF (King et al., 2001). The utility of CPET for ILD prognostication may have important implications for the referral of patients for lung transplants (Layton et al., 2017) given that the allocation of lungs is primarily based on 1-year mortality risk (McCurry et al., 2009). However, the notion that CPET parameters have value in the prognostication of ILD remains controversial and requires additional research (American Thoracic and American College of Chest, 2003).

Challenges Associated With CPET Interpretation

The interpretation of CPET data in patients with ILD is challenging for several reasons. First, similar pathological responses may occur in several other forms of disease (e.g., chronic obstructive pulmonary disease, pulmonary hypertension, and chronic heart failure) (Marciniuk and Gallagher, 1994) with these conditions also frequently occurring in patients with ILD. Second, CPET responses can differ substantially across patients given the variable etiology, symptoms, and prognosis of the various ILD subtypes. Finally, in certain cases, patients with ILD may terminate exercise due to factors that are unrelated to their underlying lung disease, such as physical deconditioning or malingering (Marciniuk and Gallagher, 1994). Therefore, it is critical that CPET responses be interpreted in the context of all available information, including whether or not physiological maxima was reached during testing (Younes, 1984).

Considerations for Future Research

The widespread use of 6 min walk tests in ILD highlights the value of using exercise to gain information that can be used to inform the management of patients with ILD (du Bois et al., 2011). Given the host of additional data obtained, it stands to reason that CPET may be even more valuable from a clinical perspective despite its resource intensive nature. Indeed, the potential uses of CPET in ILD are numerous, but additional research is required to promote its widespread use. Most notably, establishing the MCID for CPET parameters in ILD is critical. Future studies should also consider the variability in exercise responses between ILD subtypes and how these differences might provide information to improve patient management. Particular focus should be placed on pulmonary gas exchange responses as they appear to be the most sensitive to the pathophysiological changes associated with ILD.

SUMMARY AND CONCLUSION

The pathophysiology of ILD has a negative impact on the ventilatory, cardiovascular, and skeletal muscle responses to exercise, thereby leading to exertional dyspnea and reduced exercise capacity. CPET is an excellent tool for assessing the severity of exertional dyspnea and mechanisms of exercise limitation in patients with various forms of cardiorespiratory disease; however, its application in ILD has remained limited. A growing body of evidence supports the use of CPET in patients with ILD. CPET is currently used to assess functional capacity, to inform exercise prescription, and to evaluate the effects of various interventions. Recent findings highlight that, in addition to its current uses, CPET-derived measures may help improve the management of patients with ILD. Despite these recent advances, additional research is required in order to confirm the utility of CPET in this population.

AUTHOR CONTRIBUTIONS

All authors contributed to drafting and critically revising the manuscript, approved the final version of the manuscript, and take responsibility for the integrity of its content.

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REFERENCES

Agusti, A. G., Roca, J., Gea, J., Wagner, P. D., Xaubet, A., and Rodriguez-Roisin, R. (1991). Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. *Am. Rev. Respir. Dis.* 143, 219–225. doi: 10.1164/ajrccm/143.2.219

Agusti, A. G., Roca, J., Rodriguez-Roisin, R., Xaubet, A., and Agusti-Vidal, A. (1988). Different patterns of gas exchange response to exercise in asbestosis and idiopathic pulmonary fibrosis. *Eur. Respir. J.* 1, 510–516.

Agusti, C., Xaubet, A., Agusti, A. G., Roca, J., Ramirez, J., and Rodriguez-Roisin, R. (1994). Clinical and functional assessment of patients with idiopathic pulmonary fibrosis: results of a 3 year follow-up. *Eur. Respir. J.* 7, 643–650. doi: 10.1183/09031936.94.07040643

American Thoracic, S., and American College of Chest, P. (2003).). ATS/ACCP Statement on cardiopulmonary exercise testing. *Am. J. Respir. Crit. Care Med.* 167, 211–277. doi: 10.1164/rccm.167.2.211

Arena, R., and Sietsema, K. E. (2011). Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. *Circulation* 123, 668–680. doi: 10.1161/CIRCULATIONAHA.109.914788

Armstrong, H. F., Thirapatarapong, W., Dussault, N. E., and Bartels, M. N. (2013). Distinguishing pulmonary hypertension in interstitial lung disease by ventilation and perfusion defects measured by cardiopulmonary exercise testing. *Respiration* 86, 407–413. doi: 10.1159/000350445

Assayag, D., Camp, P. G., Fisher, J. H., Johannson, K. A., Kolb, M., Lohmann, T., et al. (2018). Comprehensive management of fibrotic interstitial lung diseases: a Canadian Thoracic Society position statement. *Can. J. Respir. Crit. Care Sleep Med.* 2, 234–243. doi: 10.1080/24745332.2018.1503456

Bagnato, G., and Harari, S. (2015). Cellular interactions in the pathogenesis of interstitial lung diseases. *Eur. Respir. Rev.* 24, 102–114. doi: 10.1183/09059180.00003214

Baughman, R. P., Culver, D. A., and Judson, M. A. (2011). A concise review of pulmonary sarcoidosis. *Am. J. Respir. Crit. Care Med.* 183, 573–581. doi: 10.1164/rccm.201006-0865CI

Baughman, R. P., Gerson, M., and Bosken, C. H. (1984). Right and left ventricular function at rest and with exercise in patients with sarcoidosis. *Chest* 85, 301–306. doi: 10.1378/chest.85.3.301

Bernard, S., Ribeiro, F., Maltais, F., and Saey, D. (2014). Prescribing exercise training in pulmonary rehabilitation: a clinical experience. *Rev. Port. Pneumol.* 20, 92–100. doi: 10.1016/j.rppneu.2013.10.005

Blanco, I., Ribas, J., Xaubet, A., Gomez, F. P., Roca, J., Rodriguez-Roisin, R., et al. (2011). Effects of inhaled nitric oxide at rest and during exercise in idiopathic pulmonary fibrosis. *J. Appl. Physiol.* 110, 638–645. doi: 10.1152/japplphysiol.01104.2010

Bonini, M., and Fiorenzano, G. (2017). Exertional dyspnoea in interstitial lung diseases: the clinical utility of cardiopulmonary exercise testing. *Eur. Respir. Rev.* 26:160099. doi: 10.1183/16000617.0099-2016

Bradley, B., Branley, H. M., Egan, J. J., Greaves, M. S., Hansell, D. M., Harrison, N. K., et al. (2008). Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 63(Suppl. 5), v1–v58. doi: 10.1136/thx.2008.101691

Burdon, J. G., Killian, K. J., and Jones, N. L. (1983). Pattern of breathing during exercise in patients with interstitial lung disease. *Thorax* 38, 778–784. doi: 10.1136/thx.38.10.778

Bush, A., and Busst, C. M. (1988). Cardiovascular function at rest and on exercise in patients with cryptogenic fibrosing alveolitis. *Thorax* 43, 276–283. doi: 10.1136/thx.43.4.276

Chang, J. A., Curtis, J. R., Patrick, D. L., and Raghu, G. (1999). Assessment of health-related quality of life in patients with interstitial lung disease. *Chest* 116, 1175–1182. doi: 10.1378/chest.116.5.1175

Chetta, A., Marangio, E., and Olivieri, D. (2004). Pulmonary function testing in interstitial lung diseases. *Respiration* 71, 209–213. doi: 10.1159/000077416

Collard, H. R., and Pantilat, S. Z. (2008). Dyspnea in interstitial lung disease. *Curr. Opin. Support Palliat. Care* 2, 100–104. doi: 10.1097/SPC.0b013e3282ff6336

D'Alto, M., Ghio, S., D'Andrea, A., Pazzano, A. S., Argiento, P., Camporotondo, R., et al. (2011). Inappropriate exercise-induced increase in pulmonary artery

pressure in patients with systemic sclerosis. *Heart* 97, 112–117. doi: 10.1136/hrt.2010.203471

Degani-Costa, L. H., Levarge, B., Digumarthy, S. R., Eisman, A. S., Harris, R. S., and Lewis, G. D. (2015). Pulmonary vascular response patterns during exercise in interstitial lung disease. *Eur. Respir. J.* 46, 738–749. doi: 10.1183/09031936.00191014

Dominelli, P. B., Archiza, B., Ramsook, A. H., Mitchell, R. A., Peters, C. M., Molgat-Seon, Y., et al. (2017). Effects of respiratory muscle work on respiratory and locomotor blood flow during exercise. *Exp. Physiol.* 102, 1535–1547. doi: 10.1113/EP086566

du Bois, R. M., Weycker, D., Albera, C., Bradford, W. Z., Costabel, U., Kartashov, A., et al. (2011). Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am. J. Respir. Crit. Care Med.* 183, 1231–1237. doi: 10.1164/rccm.201007-1179OC

Du Plessis, J. P., Fernandes, S., Jamal, R., Camp, P., Johannson, K., Schaeffer, M., et al. (2017). Exertional hypoxemia is more severe in fibrotic interstitial lung disease than in COPD. *Respirology* 23, 392–398. doi: 10.1111/resp.13226

Faisal, A., Alghamdi, B. J., Ciavaglia, C. E., Elbehairy, A. F., Webb, K. A., Ora, J., et al. (2016). Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am. J. Respir. Crit. Care Med.* 193, 299–309. doi: 10.1164/rccm.201504-0841OC

Fulmer, J. D., Roberts, W. C., von Gal, E. R., and Crystal, R. G. (1979). Morphologic-physiologic correlates of the severity of fibrosis and degree of cellularity in idiopathic pulmonary fibrosis. *J. Clin. Invest.* 63, 665–676. doi: 10.1172/JCI109349

Guenette, J. A., Chin, R. C., Cory, J. M., Webb, K. A., and O'Donnell, D. E. (2013). Inspiratory capacity during exercise: measurement, analysis, and interpretation. *Pulm. Med.* 2013:956081. doi: 10.1155/2013/956081

Hansen, J. E., and Wasserman, K. (1996). Pathophysiology of activity limitation in patients with interstitial lung disease. *Chest* 109, 1566–1576. doi: 10.1378/chest.109.6.1566

Himelman, R. B., Stulbarg, M., Kircher, B., Lee, E., Kee, L., Dean, N. C., et al. (1989). Noninvasive evaluation of pulmonary artery pressure during exercise by saline-enhanced Doppler echocardiography in chronic pulmonary disease. *Circulation* 79, 863–871. doi: 10.1161/01.cir.79.4.863

Holland, A. E. (2010). Exercise limitation in interstitial lung disease - mechanisms, significance and therapeutic options. *Chron. Respir. Dis.* 7, 101–111. doi: 10.1177/1479972309354689

Jackson, R. M., Glassberg, M. K., Ramos, C. F., Bejarano, P. A., Butrous, G., and Gomez-Marin, O. (2010). Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. *Lung* 188, 115–123. doi: 10.1007/s00408-009-9209-8

Jernudd-Wilhelmsson, Y., Hornblad, Y., and Hedenstierna, G. (1986). Ventilation-perfusion relationships in interstitial lung disease. *Eur. J. Respir. Dis.* 68, 39–49.

Keogh, B. A., and Crystal, R. G. (1980). Clinical significance of pulmonary function tests. Pulmonary function testing in interstitial pulmonary disease. What does it tell us? *Chest* 78, 856–865. doi: 10.1378/chest.78.6.856

King, T. E. (2005). Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am. J. Respir. Crit. Care Med.* 172, 268–279. doi: 10.1164/rccm.200503-483OE

King, T. E., Tooze, J. A., Schwarz, M. I., Brown, K. R., and Cherniack, R. M. (2001). Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am. J. Respir. Crit. Care Med.* 164, 1171–1181. doi: 10.1164/ajrccm.164.7.2003140

Lama, V. N., Flaherty, K. R., Toews, G. B., Colby, T. V., Travis, W. D., Long, Q., et al. (2003). Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am. J. Respir. Crit. Care Med.* 168, 1084–1090. doi: 10.1164/rccm.200302-219OC

Lama, V. N., and Martinez, F. J. (2004). Resting and exercise physiology in interstitial lung diseases. *Clin. Chest Med.* 25, 435–453. doi: 10.1016/j.ccm.2004.05.005

Layton, A. M., Armstrong, H. F., Kim, H. P., Meza, K. S., D'Ovidio, F., and Arcasoy, S. M. (2017). Cardiopulmonary exercise factors predict survival in patients with advanced interstitial lung disease referred for lung transplantation. *Respir. Med.* 126, 59–67. doi: 10.1016/j.rmed.2017.03.022

Marciniuk, D. D., and Gallagher, C. G. (1994). Clinical exercise testing in interstitial lung disease. *Clin. Chest Med.* 15, 287–303.

Marciniuk, D. D., Sridhar, G., Clemens, R. E., Zintel, T. A., and Gallagher, C. G. (1994a). Lung volumes and expiratory flow limitation during exercise in interstitial lung disease. *J. Appl. Physiol.* 77, 963–973. doi: 10.1152/jappl.1994.77.2.963

Marciniuk, D. D., Watts, R. E., and Gallagher, C. G. (1994b). Dead space loading and exercise limitation in patients with interstitial lung disease. *Chest* 105, 183–189. doi: 10.1378/chest.105.1.183

Maron, B. A., Cockrill, B. A., Waxman, A. B., and Systrom, D. M. (2013). The invasive cardiopulmonary exercise test. *Circulation* 127, 1157–1164. doi: 10.1161/CIRCULATIONAHA.112.104463

McCurry, K. R., Shearon, T. H., Edwards, L. B., Chan, K. M., Sweet, S. C., Valapour, M., et al. (2009). Lung transplantation in the United States, 1998-2007. *Am. J. Transplant.* 9(4 Pt 2), 942–958. doi: 10.1111/j.1600-6143.2009.02569.x

Mezzani, A. (2017). Cardiopulmonary exercise testing: basics of methodology and measurements. *Ann. Am. Thorac. Soc.* 14, S3–S11. doi: 10.1513/AnnalsATS.201612-997FR

Miller, A., Brown, L. K., Sloane, M. F., Bhuptani, A., and Teirstein, A. S. (1995). Cardiorespiratory responses to incremental exercise in sarcoidosis patients with normal spirometry. *Chest* 107, 323–329. doi: 10.1378/chest.107.2.323

Molgat-Seon, Y., Schaeffer, M. R., Ryerson, C. J., and Guenette, J. A. (2019). Exercise pathophysiology in interstitial lung disease. *Clin. Chest Med.* 40, 405–420. doi: 10.1016/j.ccm.2019.02.011

Nathan, S. D., Noble, P. W., and Tuder, R. M. (2007). Idiopathic pulmonary fibrosis and pulmonary hypertension: connecting the dots. *Am. J. Respir. Crit. Care Med.* 175, 875–880. doi: 10.1164/rccm.200608-1153CC

Nishiyama, O., Taniguchi, H., Kondoh, Y., Kimura, T., Ogawa, T., Watanabe, F., et al. (2005). Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. *Chest* 127, 2028–2033. doi: 10.1378/chest.127.6.2028

O'Donnell, D. E., Chau, L. K., and Webb, K. A. (1998). Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. *J. Appl. Physiol.* 84, 2000–2009. doi: 10.1152/jappl.1998.84.6.2000

Palange, P., Ward, S. A., Carlsen, K. H., Casaburi, R., Gallagher, C. G., Gosselink, R., et al. (2007). Recommendations on the use of exercise testing in clinical practice. *Eur. Respir. J.* 29, 185–209. doi: 10.1183/09031936.00046906

Panagiotou, M., Church, A. C., Johnson, M. K., and Peacock, A. J. (2017). Pulmonary vascular and cardiac impairment in interstitial lung disease. *Eur. Respir. Rev.* 26:160053. doi: 10.1183/16000617.0053-2016

Panagiotou, M., Polychronopoulos, V., and Strange, C. (2016). Respiratory and lower limb muscle function in interstitial lung disease. *Chron. Respir. Dis.* 13, 162–172. doi: 10.1177/1479972315626014

Parker, C. M., Fitzpatrick, M. F., and O'Donnell, D. E. (2011). "Physiology of interstitial lung disease," in *Interstitial Lung Disease*, 5 Edn, eds M. I. Schwarz and T. E. King (Beijing: People's Medical Publishing House), 61–84.

Puente-Maestu, L., Palange, P., Casaburi, R., Laveneziana, P., Maltais, F., Neder, J. A., et al. (2016). Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *Eur. Respir. J.* 47, 429–460. doi: 10.1183/13993003.00745-2015

Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K., et al. (2011). An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am. J. Respir. Crit. Care Med.* 183, 788–824. doi: 10.1164/rccm.2009-040GL

Reichenberger, F., Voswinckel, R., Schulz, R., Mensch, O., Ghofrani, H. A., Olschewski, H., et al. (2009). Noninvasive detection of early pulmonary vascular dysfunction in scleroderma. *Respir. Med.* 103, 1713–1718. doi: 10.1016/j.rmed.2009.05.004

Richeldi, L., Launders, N., Martinez, F., Walsh, S. L. F., Myers, J., Wang, B., et al. (2019). The characterisation of interstitial lung disease multidisciplinary team meetings: a global study. *ERJ Open Res.* 5:00209-2018. doi: 10.1183/23120541.00209-2018

Schaeffer, M. R., Molgat-Seon, Y., Ryerson, C. J., and Guenette, J. A. (2017a). Supplemental oxygen and dypsnoea in interstitial lung disease: absence of evidence is not evidence of absence. *Eur. Respir. Rev.* 26:170072. doi: 10.1183/16000617.0033-2017

Schaeffer, M. R., Ryerson, C. J., Ramsook, A. H., Molgat-Seon, Y., Wilkie, S. S., Dhillon, S. S., et al. (2017b). Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. *Eur. Respir. J.* 49:1602494. doi: 10.1183/13993003.02494-2016

Schaeffer, M. R., Ryerson, C. J., Ramsook, A. H., Molgat-Seon, Y., Wilkie, S. S., Dhillon, S. S., et al. (2018). Neurophysiological mechanisms of exertional dyspnoea in fibrotic interstitial lung disease. *Eur. Respir. J.* 51, 1701726. doi: 10.1183/13993003.01726-2017

Schwaiblmair, M., Behr, J., and Fruhmann, G. (1996). Cardiorespiratory responses to incremental exercise in patients with systemic sclerosis. *Chest* 110, 1520–1525. doi: 10.1378/chest.110.6.1520

Seeger, W., Adir, Y., Barbera, J. A., Champion, H., Coghlan, J. G., Cottin, V., et al. (2013). Pulmonary hypertension in chronic lung diseases. *J. Am. Coll. Cardiol.* 62, D109–D116. doi: 10.1016/j.jacc.2013.10.036

Tonelli, R., Cocconcelli, E., Lanini, B., Romagnoli, I., Florini, F., Castaniere, I., et al. (2017). Effectiveness of pulmonary rehabilitation in patients with interstitial lung disease of different etiology: a multicenter prospective study. *BMC Pulm. Med.* 17:130. doi: 10.1186/s12890-017-0476-5

Vainshelboim, B., Kramer, M. R., Izhakian, S., Lima, R. M., and Oliveira, J. (2016). Physical activity and exertional desaturation are associated with mortality in idiopathic pulmonary fibrosis. *J. Clin. Med.* 5:73. doi: 10.3390/jcm5080073

Van Meerhaeghe, A., Scano, G., Sergysels, R., Bran, M., and De Coster, A. (1981). Respiratory drive and ventilatory pattern during exercise in interstitial lung disease. *Bull. Eur. Physiopathol. Respir.* 17, 15–26.

Watanabe, F., Taniguchi, H., Sakamoto, K., Kondoh, Y., Kimura, T., Kataoka, K., et al. (2013). Quadriceps weakness contributes to exercise capacity in nonspecific interstitial pneumonia. *Respir. Med.* 107, 622–628. doi: 10.1016/j.rmed.2012.12.013

Wehr, K. L., and Johnson, R. L. (1976). Maximal oxygen consumption in patients with lung disease. *J. Clin. Invest.* 58, 880–890. doi: 10.1172/JCI108541

Younes, M. (1984). Interpretation of clinical exercise testing in respiratory disease. *Clin. Chest Med.* 5, 189–206.

Young, I. H., and Bye, P. T. (2011). Gas exchange in disease: asthma, chronic obstructive pulmonary disease, cystic fibrosis, and interstitial lung disease. *Compr. Physiol.* 1, 663–697. doi: 10.1002/cphy.c090012

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REVIEW
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Pulmonary Vascular Disease and Cardiopulmonary Exercise Testing

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Cardiopulmonary exercise testing (CPET) is of great interest and utility for clinicians dealing Pulmonary Hypertension (PH) in several ways, including: helping with differential diagnosis, evaluating exercise intolerance and its underpinning mechanisms, accurately assessing exertional dyspnea and unmasking its underlying often non-straightforward mechanisms, generating prognostic indicators. Pathophysiologic anomalies in PH can range from reduced cardiac output and aerobic capacity, to inefficient ventilation, dyspnea, dynamic hyperinflation, and locomotor muscle dysfunction. CPET can magnify the PH-related pathophysiologic anomalies and has a major role in the management of PH patients.

Keywords: cardiopulmonary exercise testing, dyspnea, prognosis, pulmonary hypertension, dynamic hyperinflation, ventilatory inefficiency

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by anomalies in pulmonary arteries (abnormal proliferation of smooth muscle and endothelial cells) which results in cardiovascular anomalies such as increase in pulmonary vascular resistance (PVR) and finally right ventricular failure (Galie et al., 2015; Humbert et al., 2019; Simonneau et al., 2019). PAH may present with non-specific symptoms and signs such as generalized fatigue, limitation of daily-activities and dyspnea, and this may prevent clinicians from diagnosing it early in the course of PAH and thus most of the time the diagnosis is made at the time of advanced right heart failure. Right-heart catheterization (RHC) is fundamental to confirm the diagnosis of PAH (Simonneau et al., 2019) and recently a new hemodynamic definition of PAH has been proposed (a mean pulmonary artery pressure >20 mmHg instead of previous one ≥ 25 mmHg) based on the analysis of large databases (Kovacs et al., 2017) and a meta-analysis of normal hemodynamics (Kovacs et al., 2009) in order to identify patients with early pulmonary vascular disease (Simonneau et al., 2019).

Cardiopulmonary exercise testing (CPET) is of great interest and utility for clinicians dealing PH in evaluating exercise intolerance and its underpinning mechanisms, accurately assessing exertional dyspnea and unmasking its underlying mechanisms, which are often not straightforward. Previous studies have shown that PAH management at an early stage of the disease translates into better outcomes (Galie et al., 2008; Humbert et al., 2011; Lau et al., 2015). Therefore, it appears crucial to establish early diagnosis and CPET can help clinicians in the differential diagnosis and evaluating prognosis in such an especially fragile population.

PATHOPHYSIOLOGIC RESPONSE-PROFILE TO EXERCISE IN PULMONARY HYPERTENSION

CPET can magnify the PH-related pathophysiologic anomalies and has a major role in the management of PH patients. Pathophysiologic anomalies in PH can widely range from reduced cardiac output and aerobic capacity, to pulmonary gas exchange and ventilatory efficiency anomalies, dyspnea, dynamic hyperinflation and locomotor muscle dysfunction (**Figure 1**).

Pulmonary vascular obstruction along with concurrent increased mean PAP and PVR and reduced pulmonary capillary bed and recruitment give rise to three different pathophysiologic anomalies: (1) ventilation/perfusion (V/Q) inequalities; (2) pulmonary gas exchange anomalies; (3) increased right ventricle (RV) afterload and concomitant reduced left ventricle (LV) filling. These three major pathophysiologic derangements are responsible of characteristic anomalies observed during CPET that can ultimately explain exertional dyspnea and exercise intolerance (**Figure 1**).

V/Q inequalities can manifest with either low V/Q ratios and shunt (right to left shunt through a patent foramen ovale, for example) or high V/Q ratios caused by increased minute ventilation (V'_E) of poorly perfused air spaces (Oudiz et al., 2010) V/Q mismatching can result in hypoxemia (reduced arterial partial pressure of oxygen, PaO_2), high dead space to tidal volume fraction (V_D/V_T) and widening of the alveolar-arterial pressure difference of oxygen [$P(A\text{-}a)O_2$] and of the arterial-end-tidal pressure difference of carbon dioxide [$P(a\text{-}ET)CO_2$]. These anomalies can stimulate an excessive V'_E response to exercise along with altered chemosensitivity and inefficient ventilation mirrored by the increased steepness with which V'_E rises with respect to CO_2 production ($V'CO_2$) (i.e., increased $V'_E/V'CO_2$ slope) (D'Alonzo et al., 1987; Riley et al., 2000; American Thoracic Society, 2003; Velez-Roa et al., 2004; Naeije and van de Borne, 2009; Wensel et al., 2009; Laveneziana et al., 2013b; Farina et al., 2018; Weatherald et al., 2020). Inefficient ventilation and altered chemosensitivity translate into increase ventilatory demand, $V'_E/V'CO_2$ and V_D/V_T, decrease end-tidal pressure of carbon dioxide ($P_{ET}CO_2$) and hypocapnia (reduced arterial partial pressure of carbon dioxide, $PaCO_2$) (Riley et al., 2000; Yasunobu et al., 2005; Zhai et al., 2011; Scheidl et al., 2012; Godinas et al., 2017; Weatherald et al., 2020).

The reduced pulmonary capillary bed and recruitment at rest can be amplified during CPET and translated in pulmonary gas exchange anomalies such as a relative low alveolar-capillary diffusing capacity; this can be mirrored by a reduced diffusing capacity or transfer factor of the lung for carbon monoxide (DLCO or TLCO) at rest and a reduced PaO_2 with enlargement of $P(A\text{-}a)O_2$ during CPET.

Impaired cardiac function (due to increased RV afterload and concomitant reduced LV filling) along with peripheral muscle dysfunction and deconditioning (Bauer et al., 2007; Tolle et al., 2008; Mainguy et al., 2010; Dimopoulos et al., 2013) result in reduced cardiac output and blood flow to the periphery. This translates to reduced oxygen delivery to working locomotor muscles and reduced venous pressure of oxygen (PvO_2), which results in reduced aerobic capacity with attendant reduced anaerobic threshold (AT) and oxygen consumption ($V'O_2$). Reduced oxygen delivery also causes early onset of lactic acidosis and increased $V'CO_2$, which further contributes to the excessive V'_E response to CPET (Nootens et al., 1995; Sun et al., 2001; Deboeck et al., 2004; Hasler et al., 2016; Naeije and Badagliacca, 2017; Weatherald et al., 2018a). The reduced mixed venous O_2 content from altered cardiac output can also contribute and amplify exertional hypoxemia.

Mechanical anomalies on tidal volume (V_T) expansion and dynamic lung hyperinflation can also play a crucial role into the genesis of exertional dyspnea and therefore exercise intolerance (Richter et al., 2012; Laveneziana et al., 2013b, 2015; Manders et al., 2016; Boucly et al., 2020), and can be easily detected during CPET (Laveneziana et al., 2013b, 2015; Boucly et al., 2020).

PERIPHERAL MUSCLE DYSFUNCTION

Deconditioning and peripheral muscle abnormalities are important contributors to exercise intolerance. In chronic heart failure, which shares similar limitations in cardiac output reserve as PAH and CTEPH, oxygen transport and diffusion at the level of skeletal muscle are abnormal (Esposito et al., 2010). Tissue oxygen saturation, oxygen extraction and muscle microcirculatory function may be impaired to an even greater degree in PAH compared with left heart failure (Tolle et al., 2008; Dimopoulos et al., 2013). Peripheral muscle in PAH patients is structurally and functionally abnormal, with a lower relative proportion of type I fibers and reduced quadriceps, forearm, and respiratory muscle strength compared to controls, which may be an important determinant of low peak $V'O_2$ (Bauer et al., 2007; Mainguy et al., 2010).

Respiratory muscle strength has also been shown to be about 40% lower in CTEPH patients (Manders et al., 2016). The mechanism of generalized skeletal muscle dysfunction in PAH may be a result of microcirculation rarefaction and an imbalance in angiogenic factors (Potus et al., 2014). Improvements in exercise capacity with exercise training in individuals with heart failure or peripheral vascular disease (Duscha et al., 2011) have been linked to improvements in skeletal muscle microcirculatory density, capillary-to-fiber ratio and mitochondrial volume (Esposito et al., 2011), which may be mechanisms by which training can improve exercise capacity in stable patients with PAH (Mereles et al., 2006; Ehlken et al., 2016). Peripheral muscle dysfunction is a potential relevant e hidden factor that can worsen the prognosis of PAH patients. Recently, Valli et al. have pointed out that patients with PAH may present with less efficient muscular oxygen utilization than healthy controls. Notably high energy expenditure had a relevant independent prognostic impact (Valli et al., 2019).

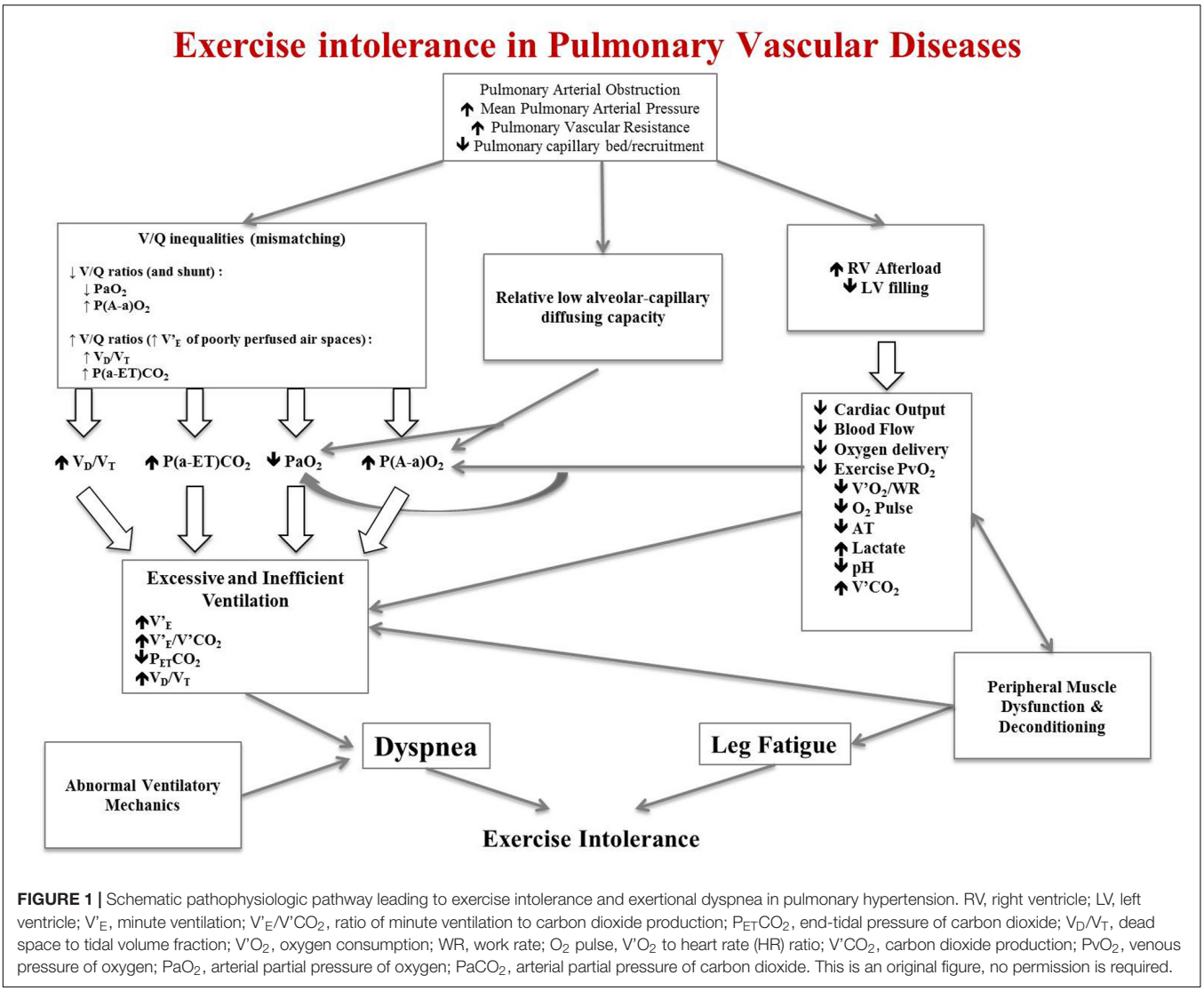

FIGURE 1 | Schematic pathophysiologic pathway leading to exercise intolerance and exertional dyspnea in pulmonary hypertension. RV, right ventricle; LV, left ventricle; V'_E, minute ventilation; $V'_E/V'CO_2$, ratio of minute ventilation to carbon dioxide production; $P_{ET}CO_2$, end-tidal pressure of carbon dioxide; V_D/V_T, dead space to tidal volume fraction; $V'O_2$, oxygen consumption; WR, work rate; O_2 pulse, $V'O_2$ to heart rate (HR) ratio; $V'CO_2$, carbon dioxide production; PvO_2, venous pressure of oxygen; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide. This is an original figure, no permission is required.

TRANSLATING PH-RELATED PATHOPHYSIOLOGIC ANOMALIES INTO CPET VARIABLES: EXPLORING FACTORS EXPLAINING EXERCISE LIMITATION IN PH

One of the indications of CPET is to explore the underlying mechanisms of exertional dyspnea and to detect mechanisms of exercise intolerance. **Table 1** summarizes the main CPET-derived variables defining ventilatory, respiratory mechanical, cardiovascular and pulmonary vascular limitation accompanied or not by gas exchange anomalies to exercise.

Two variables are used to detect exercise intolerance (Radtke et al., 2019) peak $V'O_2$ during an incremental CPET has well defined normal values (Puente-Maestu et al., 2018) and $V'O_2$ at the anaerobic/ventilatory threshold (AT) has the advantage of being an effort independent measure of exercise tolerance (Agusti et al., 1997; ATS/ACCP, 2003; Palange et al., 2007; Puente-Maestu et al., 2016; Huckstepp et al., 2018). The disadvantage is that it relies on pattern recognition for accurate detection (which may differ from operator to operator due to lack of experience or inaccurate detection related to software - never trust software for detecting AT! - or wrong pattern recognition) and some severely impaired PH patients may not be able to attain the AT despite a good effort.

Cardiovascular limitation to exercise is not straightforward and may be defined by certain interrelated variables (**Table 1**). A reduced slope or late plateau of the $V'O_2$ trajectory (i.e., a reduced $V'O_2$/work rate relationship ≤ 8), or plateau (early or late during exercise) of the oxygen pulse ($V'O_2$ to heart rate ratio, i.e., $V'O_2$/HR), or an abnormal HR/$V'O_2$ slope (>50) may be typical (Palange et al., 2018).

Pulmonary vascular limitation to exercise is not straightforward as well and may rely on evidence of increased $V'_E/V'CO_2$ slope and ratio at AT in addition to the above-mentioned anomalies (Weatherald et al., 2018b). Other typical features of pulmonary vascular disease are low levels of

TABLE 1 | Variables defining ventilatory and respiratory mechanical limitation (left panel) accompanied or not by gas exchange anomalies to exercise, and variables defining cardiovascular and pulmonary vascular limitation (right panel) accompanied or not by gas exchange anomalies to exercise.

Ventilatory and respiratory mechanical limitation to exercise	Cardiovascular and pulmonary vascular limitation to exercise
BR < 15–20%	BR > 15–20%
Dynamic Hyperinflation (decrease in IC > 140 mL)	$V'O_2/HR$ < 70%
V_T plateau	$V'O_2$/Work Rate↓
RR > 50–55 breaths/min (if restrictive pattern)	Flat (and declining) V'O2/HR trajectory
V_T = IC or > 60% VC (if restrictive pattern)	Abnormal $HR/V'O_2$ slope (>50)
HR peak < HR predicted	Chronotropic incompetence
EILV >90% TLC at peak exercise	Abnormal blood pressure response to exercise
V_T/IC >70% at peak exercise	ECG abnormalities during exercise
The tidal inspiratory flow >50 to 70% maximal inspiratory flow (in health <50–70%)	
With or without	**With or without**
Gas exchange anomalies:	Gas exchange anomalies:
V_D/V_T ↑	V_D/V_T ↑
$P(A\text{-}a)O_2$ ↑	$P(A\text{-}a)O_2$ ↑
Decrease of PaO_2 ≥ 10 mmHg	Decrease of PaO_2 ≥ 10 mmHg
Decrease of SpO_2 ≥ 5% and/or SpO_2 peak ≤ 88%	Decrease of SpO_2 ≥ 5% and/or SpO_2 peak ≤ 88%
$PaCO_2$ peak > 45–50 mmHg	

BR, breathing reserve; IC, Inspiratory Capacity; VT, tidal volume; RR, Respiratory Rate; VC, Vital Capacity; HR, Heart Rate; EILV, End-Inspiratory Lung Volume; VD/VT, dead space to tidal volume fraction; $P(A\text{-}a)O_2$, alveolar-arterial pressure difference of oxygen;, PaO_2, partial pressure of oxygen; SpO_2, pulse oximetry saturation; $PaCO_2$, arterial partial pressure of carbon dioxide; $V'O_2$, oxygen consumption; $P(a\text{-}ET)CO_2$, arterial-end-tidal pressure difference of carbon dioxide; ↓, reduced; ↑, increased.

$P_{ET}CO_2$ at AT, a V_D/V_T which remains stable or increases or fails to decrease from baseline, a $P(a\text{-}ET)CO_2$ which fails to became negative during exercise and, sometimes, a $P(A\text{-}a)O_2$ which widens on exertion (Weatherald et al., 2020; **Table 1**). Of note, it should be pointed out that the finding of high $V'_E/V'CO_2$ at AT (≥34–35) and low $P_{ET}CO_2$ at AT (≤30 mmHg) without an alternative explanation in patients presenting with unexplained dyspnea and exercise limitation should prompt further diagnostic testing to exclude PAH or CTEPH (Weatherald et al., 2018b) particularly in those patients with risk factors, such as prior venous thromboembolism, systemic sclerosis or a family history of PAH. These gas exchange anomalies are usually not found in patients with pulmonary venous hypertension secondary to cardiac diseases (Weatherald et al., 2018b). Associated low level of hemoglobin will enhance oxygen flow deficiency. Ischemic heart disease or cardiomyopathy may present with electrocardiographic or blood pressure anomalies during CPET (Palange et al., 2018).

Pulmonary gas exchange limitation to exercise is not straightforward as well and may rely on evidence of inefficient carbon dioxide exchange which can be signaled by high V_D/V_T and often by high exercise $V'_E/V'CO_2$ (**Figure 2**) or (alone or in combination with) inadequate oxygen exchange signaled by low PaO_2 or, less directly, by desaturation at pulse oximetry.

Elevated $V'_E/V'CO_2$ (ventilatory inefficiency) and reduced resting $PaCO_2$ (hypocapnia) are frequent in pulmonary vascular disease such as PAH, chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary veno-occlusive disease (PVOD) (Weatherald et al., 2018b) and correlate with negative prognosis (Hoeper et al., 2007; Deboeck et al., 2012; Schwaiblmair et al., 2012; Groepenhoff et al., 2013). Abnormally reduced resting $PaCO_2$ signals augmented chemosensitivity or an abnormal $PaCO_2$ set-point. A low resting $PaCO_2$ predicts a worse prognosis in PAH (Hoeper et al., 2007). However, high V_D/V_T does not cause low resting $PaCO_2$, therefore an altered $PaCO_2$ set-point, increased neural respiratory drive, and/or increased chemosensitivity must explain hypocapnia and consequently, the high $V'_E/V'CO_2$ slope. Several factors such as metabolic acidosis, hypoxemia, baroreceptors in the pulmonary vessels and abnormal activation of the sympathetic nervous system have an influence on the $PaCO_2$ set-point (Wasserman et al., 1975; Whipp and Ward, 1998; Sun et al., 2002; Velez-Roa et al., 2004; Wensel et al., 2004; Laveneziana et al., 2013b; Weatherald et al., 2018c). The evaluation of chemosensitivity and/or the $PaCO_2$ set-point during exercise is difficult and can be problematic. Autonomic dysfunction, increased sympathetic nervous system activity, and an altered CO_2 set-point relate to chemoreflex sensitivity. Recently Farina et al. (2018) performed minute-to-minute blood gas analysis during exercise in 18 patients with pulmonary vascular disease. They run hypoxic and hypercapnic challenge tests to assess peripheral and central chemosensitivity and found an increase in chemoreceptor sensitivity in both PAH and CTEPH that did not correlate (the peripheral chemoreceptor responses to hypoxia and hypercapnia) with any exercise variables. The "non-invasive" evaluation of the $PaCO_2$ set-point during exercise is extremely difficult; one method is to assess the maximal end-tidal CO_2 pressure (maximal $P_{ET}CO_2$) value between the AT and respiratory compensation point where $P_{ET}CO_2$ is constant and, therefore, is supposed to truly reflect the real $PaCO_2$ set-point (Agostoni et al., 2002; Agostoni et al., 2010; Laveneziana et al., 2010). Recently, Weatherald et al. have pointed out that patients with resting hypocapnia (PAH, n = 34; CTEPH, n = 19; PVOD, n = 6) had worse cardiac function and more severe gas exchange anomalies during CPET (Weatherald et al., 2020). High chemosensitivity and an altered $PaCO_2$ set-point were likely explanations for resting hypocapnia and high $V'_E/V'CO_2$ on exertion. The $PaCO_2$ set-point, estimated by the maximal $P_{ET}CO_2$ was the strongest correlate of peak exercise capacity and $V'_E/V'CO_2$, suggesting that this variable could be used as a non-invasive measure of disease severity even during submaximal exercise (Weatherald et al., 2020). Taken together, the results of the two studies from Weatherald et al. (2020) and Farina et al. (2018) imply that hypocapnic patients and/or those with low maximal $P_{ET}CO_2$ during exercise have autonomic dysfunction and a lower CO_2 set-point. Thus, resting $PaCO_2$ or maximal $P_{ET}CO_2$ on exertion could be used to identify patients with probably autonomic dysfunction or to help develop future

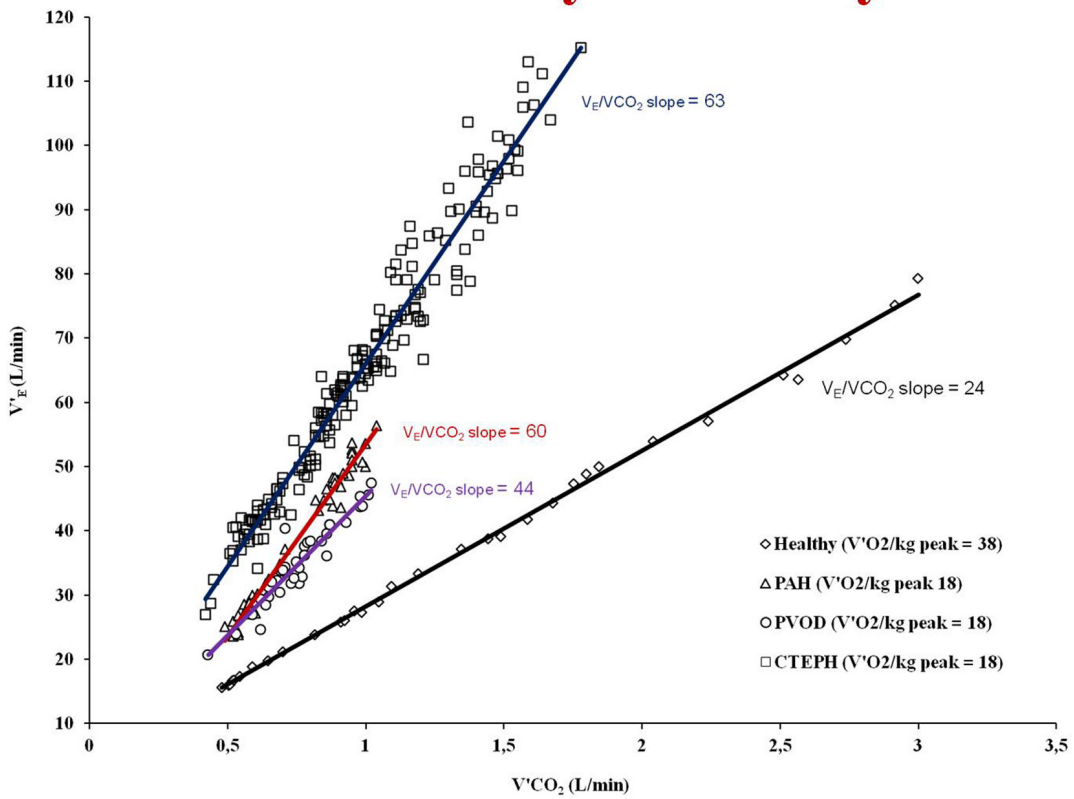

FIGURE 2 | Examples of ventilatory efficiency ($V'_E/V'CO_2$ slope) in a healthy subject with a peak oxygen uptake ($V'O_2$) of 38 mL/Kg/min (black line and rhomboid), in a patient with pulmonary veno-occlusive disease (PVOD) with a peak $V'O_2$ of 18 mL/Kg/min (violet line and circles), in a patient with pulmonary arterial hypertension (PAH) with a peak $V'O_2$ of 18 mL/Kg/min (red line and triangles) and in a patient with chronic thromboembolic pulmonary hypertension (CTEPH) with a peak $V'O_2$ of 18 mL/Kg/min (blue line and squares). This is an original figure, no permission is required.

studies that target the sympathetic nervous system in pulmonary vascular disease.

Ventilatory limitation to exercise can also be detected in some PH patients during CPET (**Table 1**). Beside the well-known breathing reserve, i.e., the comparison of peak V'_E to MVV (maximal voluntary ventilation), other indicators of ventilatory limitation to exercise can be appreciated: constraints on dynamic V_T expansion relative to resting or dynamic decrease in inspiratory capacity (IC) used also to appreciate a critical reduction in inspiratory reserve volume (IRV) (**Table 1**; Laveneziana et al., 2013b, 2015; Boucly et al., 2020). More recently, evidence of ventilatory limitation has been suggested by the occurrence of important expiratory flow limitation (EFL) >25% at peak exercise (Johnson et al., 1999; Palange et al., 2007; Puente-Maestu et al., 2016; Huckstepp et al., 2018) and some other indicators of mechanical ventilatory limitations to exercise such as end-inspiratory lung volume (EILV) >90% TLC alone or in combination with V_T/IC >70% at peak exercise have recently been observed in some patients with pulmonary vascular disease (**Table 1**). **Figure 3** represents the typical exercise response profile of a PAH patient undergoing maximal incremental symptom-limited CPET. **Table 2** summarizes the main alterations that can be observed in patients with pulmonary vascular disease during CPET.

MECHANISMS EXPLAINING EXERTIONAL DYSPNEA IN PH

Exertional dyspnea is most frequent and cumbersome symptom in patients with idiopathic PAH, CTEPH, and PVOD (Laveneziana et al., 2013b, 2014a, 2015; Laviolette and Laveneziana, 2014; Boucly et al., 2020; **Figure 4**).

Although researchers have worked hard to try to explain this symptom, its underpinning mechanisms remain at present not completely understood (Laveneziana et al., 2013b, 2014a, 2015; Laviolette and Laveneziana, 2014; Boucly et al., 2020). Previous research has particularly emphasized the cardio-and-pulmonary-vascular factors contributing to exertional dyspnea (Sun et al., 2001) by pointing out the effects of combined impaired cardiac function and abnormal pulmonary gas exchange on exertion as the result of primary anomalies of pulmonary vessels on the increased ventilatory drive and therefore on the resultant exertional dyspnea (Sun et al., 2001). Nonetheless,

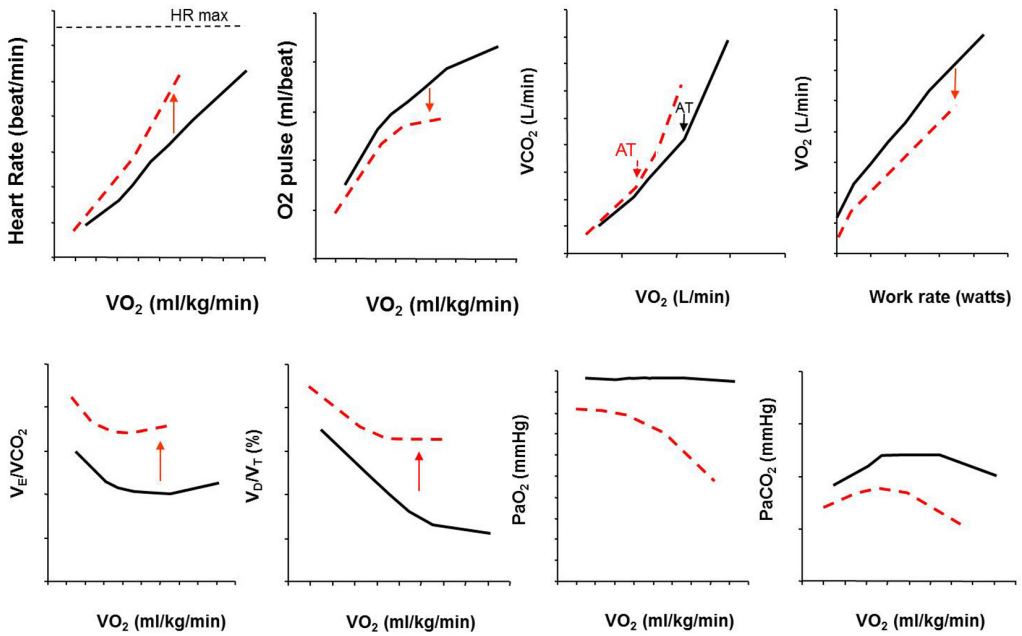

FIGURE 3 | Typical exercise response profile of a PAH patient (red dotted line) compared with healthy control (black line) undergoing maximal incremental symptom-limited CPET. Abbreviations in the text. This is an original figure, no permission is required.

TABLE 2 | Typical CPET anomalies in patients with pulmonary vascular diseases.

		PAH	CTEPH	PVOD
Metabolic and cardiovascular	Peak V'O_2	↓	↓	↓
	V'O_2 at AT	↓	↓	↓↓
	V'O_2/WR	↓	↓	↓
	O_2 pulse	↓	↓	↓
Ventilation and mechanics	Peak V'$_E$	↓	↓	↓
	Breathing Reserve	Normal	Normal	Normal
	Dynamic hyperinflation	Possible	Possible	?
Gas exchange	V'$_E$/V'CO_2 slope	↑	↑↑	↑↑
	V'$_E$/V'CO_2 at AT	↑	↑↑	↑↑
	$P_{ET}CO_2$	↓	↓↓	↓↓
	SaO_2	↓	↓↓	↓↓
	$P_{a-ET}CO_2$	↑	↑↑	↑↑
	$P_{A-a}O_2$	↑	↑↑	↑↑
	V_D/V_T	↑	↑↑	↑↑

CPET, cardiopulmonary exercise testing; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; PVOD; pulmonary veno-occlusive disease; V'O_2, oxygen consumption; AT, ventilator/anaerobic threshold; WR, work rate; O_2 pulse, peak V'O_2 to heart rate ratio at peak exercise; V'E, minute ventilation; V'E/V'CO_2, ratio of minute ventilation to carbon dioxide production (V'CO_2); $PETCO_2$, end-tidal pressure of carbon dioxide; SaO_2, arterial oxygen saturation; PA-aO_2, alveolar-arterial oxygen pressure gradient at peak exercise; Pa-$ETCO_2$, arterial to end-tidal carbon dioxide pressure gradient at peak exercise; VD/VT, physiologic dead space fraction as ratio of dead space (VD) to tidal volume (VT) at peak exercise.

augmented ventilatory drive cannot alone explain the origin of the multifaceted symptom of dyspnea, and other contributions stemming from respiratory and skeletal muscle (dys)function, as well as psychological and emotional status may come into play. Recently, abnormalities of breathing mechanics have been pointed out in some PAH and CTEPH patients during exercise (Richter et al., 2012; Laveneziana et al., 2013b, 2015; Dorneles et al., 2019; Boucly et al., 2020; **Figure 5**) and are likely to precipitate exertional dyspnea in these two populations (Laveneziana et al., 2013b, 2015; Dorneles et al., 2019; Boucly et al., 2020; **Figure 4**).

Now, what kind of abnormalities of breathing mechanics have been observed in PAH and CTEPH patients that can explain, at least in part, dyspnea generated during exertion and during laboratory-based CPET? Without giving to much of details on the underlying mechanisms of the anomalies of breathing mechanics encountered during CPET in PAH and CTEPH patients (which goes outside the scope of this review), we can say that some features are the development of EFL and dynamic lung hyperinflation (indicated by an increased end- expiratory lung volume, i.e., EELV that is mirrored by a decrease of the same amount/proportion in IC on exertion) with concurrent limitation of V_T expansion and attainment of a critical IRV in at least 60% of these patients (Richter et al., 2012; Laveneziana et al., 2013b, 2015; Dorneles et al., 2019; Boucly et al., 2020; **Figure 5**). Of course some considerations must be made here: EFL is most of the time not present at rest and resting IC is preserved (Laveneziana et al., 2013b, 2015; Boucly et al., 2020), even in CTEPH pre and post-pulmonary endarterectomy (Richter et al., 2017); what is evident in 60% of these patients (PAH and CTEPH) is a reduction of the forced expiratory flow at low lung volumes ($FEF_{75\%}$) where V_T occurs; this predisposes to dynamic decrease in IC and limitation of V_T expansion with concomitant attainment of a critical IRV in some of these PAH and CTEPH patients, as

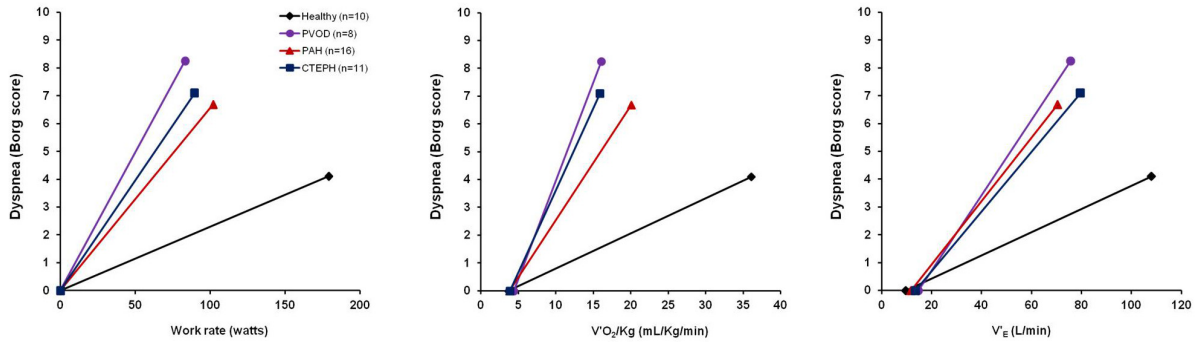

FIGURE 4 | Exertional dyspnea intensity as measured by Borg score is displayed in response to increasing work rate **(left panel)**, increasing oxygen consumption ($V'O_2$/Kg, **mid panel**) and increasing minute ventilation (V'_E, **right panel**) during symptom limited cardiopulmonary exercise testing in 10 healthy subjects (black line and rhomboid), 8 patients with pulmonary veno-occlusive disease (PVOD) (violet line and circles), 16 patients with pulmonary arterial hypertension (PAH) (red line and triangles), 11 patients with chronic thromboembolic pulmonary hypertension (CTEPH) (blue line and squares). The origin of the data provided in Figure 4 is from Laveneziana et al. (2013b, 2014a, 2015), Boucly et al. (2020) and Weatherald et al. (2020).

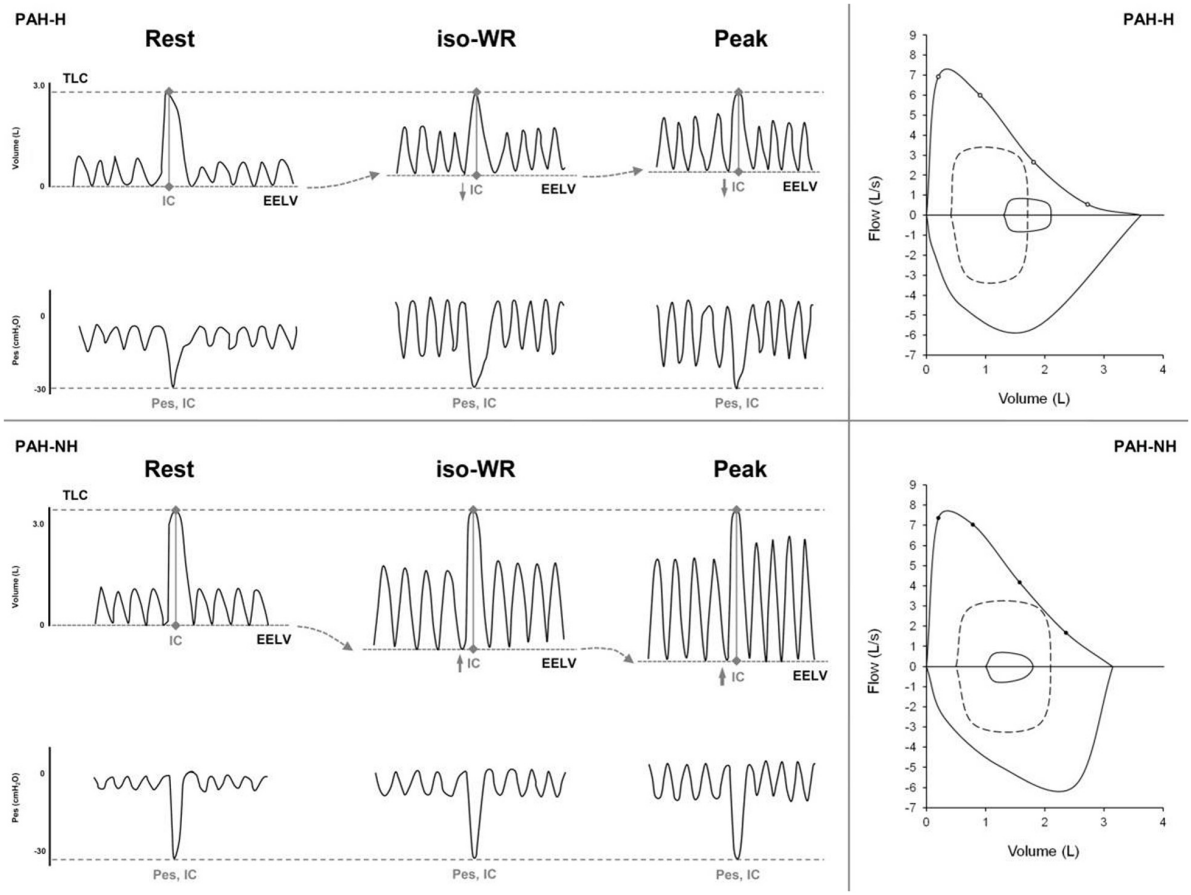

FIGURE 5 | Tracings of lung volume (Volume) and esophageal pressure (Poes) from inspiratory capacity (IC) maneuvers taken during resting breathing, at 60 watts (iso-WR) and peak-exercise from one representative PAH patient who reduced IC (or increased end- expiratory lung volume, i.e., EELV) during exercise [PAH hyperinflator (PAH-H), upper left panel] and one who increased IC (or reduced EELV) [PAH non-hyperinflator (PAH-NH), lower left panel]. Please note that, regardless of changes in IC during exercise, dynamic peak inspiratory Poes recorded during IC maneuvers (Poes, IC) is remarkably preserved in both PAH-H (upper left panel) and PAH-NH (lower left panel). Maximal and tidal flow-volume loops (average data) are shown at rest and at peak- exercise in PAH-H (upper right panel) and PAH-NH (lower right panel). Tidal flow-volume loops are provided at rest (solid line) and at peak-exercise (dashed line). Note a significant decrease in dynamic IC during exercise in PAH-H compared with PAH-NH. TLC, total lung capacity. Reproduced with permission of Laveneziana et al. (2015).

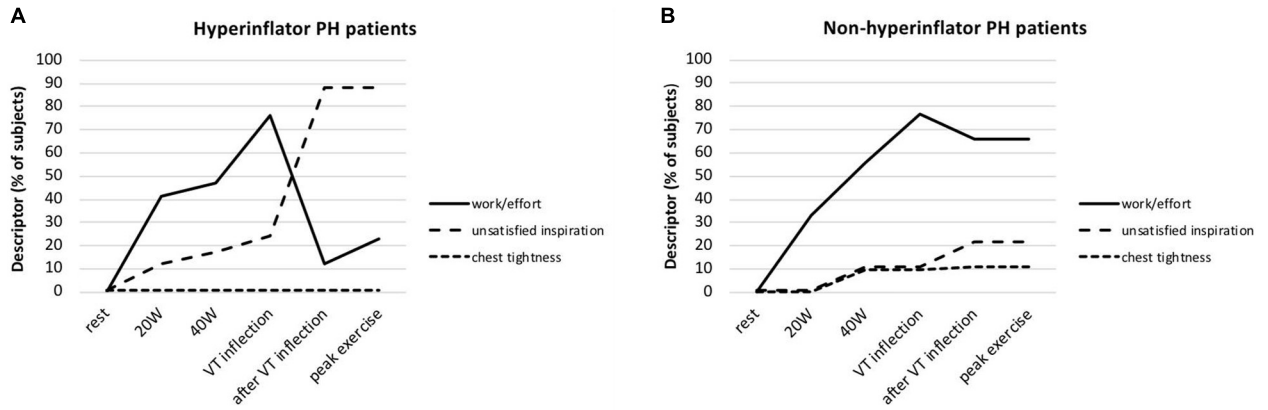

FIGURE 6 | (A) Selection frequency of the three descriptor phrases evaluated during symptom-limited incremental cycle exercise in patients with pulmonary hypertension (PH) who hyperinflate (Hyperinflators) during exercise: increased work/effort, unsatisfied inspiration, and chest tightness. Data are presented as mean at rest, at 20W (iso-WR 1), at 40 W (iso-WR 2), at the tidal volume (VT) inflection point, after the VT inflection point and at peak exercise. **(B)** Selection frequency of the three descriptor phrases evaluated during symptom-limited incremental cycle exercise in patients with pulmonary hypertension (PH) who deflate (Non-hyperinflators) during exercise: increased work/effort, unsatisfied inspiration, and chest tightness. Data are presented as mean at rest, at 20W (iso-WR 1), at 40 W (iso-WR 2), at the tidal volume (VT) inflection point, after the VT inflection point and at peak exercise. Reproduced with permission of Boucly et al. (2020).

it may occur in some patients with asthma (Laveneziana et al., 2006, 2013a), chronic obstructive pulmonary disease (COPD) (Laveneziana et al., 2011, 2014b; Guenette et al., 2012; Soumagne et al., 2016) and chronic heart failure (CHF) (Laveneziana et al., 2009; Laveneziana and Di Paolo, 2019; Smith et al., 2019). The sensory consequence of this is the escalation of dyspnea intensity and the transition in its qualitative description from "work/effort" to "unsatisfied inspiration" (**Figure 6**), as is the case in some asthmatics (Laveneziana et al., 2006, 2013a), and COPD patients (Laveneziana et al., 2011, 2014b; Guenette et al., 2012; Soumagne et al., 2016).

Of note, these particular PAH and CTEPH patients present also with a high level of anxiety which is frequently associated with dyspnea on exertion (Boucly et al., 2020). It should be noted here that 40% of these PAH and CTEPH patients do not manifest decrease in IC (meaning that they deflate normally during exercise), nor limitation of V_T expansion nor attainment of a critical IRV during CPET (Laveneziana et al., 2013b, 2015; Boucly et al., 2020). Dyspnea intensity in this group of PAH and CTEPH is less important than in the other group previously described (Laveneziana et al., 2013b, 2015; Boucly et al., 2020) and its qualitative description remains predominantly the sense of breathing "work/effort" (Laveneziana et al., 2013b, 2015; Boucly et al., 2020; **Figure 6**), as it occurs in healthy subjects on exertion (Laveneziana et al., 2013b, 2014b).

Another important point to bring to reader attention here is whether the dynamic decrease in IC observed during CPET in some PAH and CTEPH patients is truly reflective of dynamic lung hyperinflation or could be related to a dysfunction of inspiratory muscle (weakness or fatigue). The occurrence of fatigue or the overt presence of weakness of inspiratory muscle in PAH patients have been questioned by two studies from Laveneziana et al. (2013b, 2015; **Figure 5**) that have assessed the reliability of IC maneuvers in PH patients by (1) comparing inspiratory esophageal pressure (Poes) values during IC manoeuvers, (2) comparing sniff-Poes values pre- vs. post-exercise in PH patients and (3) comparing TLC pre- vs post-maximal CPET. These studies clearly pointed out that (1) Poes values measured during IC manoeuvers were remarkably preserved during exercise and were independent of exercise intensity and V'_E in PAH (Laveneziana et al., 2015), (2) sniff-Poes values were identical pre- vs. post-exercise in PH patients (Laveneziana et al., 2015) and (3) TLC pre CPET was superimposed to TLC immediately post-exercise in PH patients (Laveneziana et al., 2013b, 2015). Taken together these findings prove that IC maneuvers are reliable (Laveneziana et al., 2013b, 2015) and that inspiratory muscle dysfunction is unlikely to manifest, at least in these stable PAH patients (Laveneziana et al., 2013b, 2015; **Figure 5**).

PROGNOSTIC UTILITY OF CPET

There is good evidence that CPET variables can be used to measure disease severity and are predictive of survival and time to clinical worsening in PAH and CTEPH patients as well as potential treatment targets for PAH patients, with objectives of obtaining peak $V'O_2$ >15 mL.min^{-1}.kg^{-1} or $>$ 65% predicted and a $V'_E/V'CO_2$ slope of <36 (Galie et al., 2015; Puente-Maestu et al., 2016). PAH patients with a peak $V'O_2$ less than 11 mL.min^{-1}.kg^{-1} or a $V'_E/V'CO_2$ slope $\geq$45 are considered high risk with an estimated 1-year mortality of $>$10% according to European Society of Cardiology/European Respiratory Society guidelines (Galie et al., 2015). Peak $V'O_2$ and $V'_E/V'CO_2$ have been associated with survival in several studies including PAH and CTEPH patients (Wensel et al., 2002; Deboeck et al., 2012; Schwaiblmair et al., 2012; Groepenhoff et al., 2013). Wensel et al. (2013) demonstrated that peak $V'O_2$ provides additional prognostic value to resting haemodynamics in patients with PAH. Those with a low $V'O_2$ ($<$46.3% predicted) and PVR $>$16 Wood units had a particularly dismal prognosis, while patients with

peak $V'O_2 \geq 46.3\%$ predicted and a PVR < 11.6 Wood units had >90% 5-year survival. Echocardiographic assessment of RV function in combination with CPET may provide incremental prognostic utility. Badagliacca and colleagues found that RV fractional area change on echocardiogram, in conjunction with the O_2 pulse from CPET, which reflect RV function and stroke volume, were independent predictors of outcome in patients with idiopathic PAH (Badagliacca et al., 2016). Patients with RV fractional area change >26.5% and an O_2 pulse >8.0 mL.beat^{-1} had excellent long-term survival, while PAH patients with RV fractional area change <36.5% and an O_2 pulse <8.0 mL.beat^{-1} had significantly worse survival.

Others have also demonstrated that while $V'_E/V'CO_2$ slope as well as $V'_E/V'CO_2$ peak were associated with survival, once multivariate regression was performed, only ΔO_2 pulse added prognostic value (Groepenhoff et al., 2008). Hemodynamic variables such as PVR and those that reflect right ventricular function (cardiac output, stroke volume, right atrial pressure) are also important predictors of prognosis in PAH (Saggar and Sitbon, 2012; Weatherald et al., 2018a,b; Benza et al., 2019). Wensel et al. evaluated the prognostic value of combining CPET-derived variables with haemodynamic data from RHC (Wensel et al., 2013) they assessed several CPET variables, including $V'_E/V'CO_2$, and found that only peak VO_2, PVR, and HR change during exercise were independently associated with survival. Similarly, another study by Badagliacca et al., found that the only useful CPET parameter independently associated with future clinical worsening was peak VO_2, with $V'_E/V'CO_2$ not adding additional prognostic information (Badagliacca et al., 2019).

CONCLUSION

Cardiopulmonary exercise testing (CPET) is of great interest and utility for clinicians dealing with Pulmonary Hypertension (PH) in several ways such as: helping orienting diagnosis, evaluating exercise intolerance and its underpinning mechanisms, accurately assessing exertional dyspnea and unmasking its underlying often non straightforward mechanisms, generating prognostic indicators. Pathophysiologic anomalies in PH can range from reduced cardiac output and aerobic capacity, to inefficient ventilation, dyspnea, dynamic hyperinflation and locomotor muscle dysfunction. CPET can magnify the PH-related pathophysiologic anomalies and has a major role in the management of PH patients.

AUTHOR CONTRIBUTIONS

PL and JW equally contributed to the writing and revision of the manuscript. Both authors contributed to the article and approved the submitted version.

REFERENCES

Agostoni, P., Apostolo, A., Cattadori, G., Salvioni, E., Berna, G., Antonioli, L., et al. (2010). Effects of beta-blockers on ventilation efficiency in heart failure. *Am. Heart. J* 159, 1067–1073.

Agostoni, P., Guazzi, M., Bussotti, M., De Vita, S., and Palermo, P. (2002). Carvedilol reduces the inappropriate increase of ventilation during exercise in heart failure patients. *Chest* 122, 2062–2067. doi: 10.1378/chest.122.6.2062

Agusti, A. G. N., Anderson, D., Roca, J., Whipp, B., Casburi, R., and Cotes, J. (1997). Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. *Eur. Respir. J.* 10, 2662–2689. doi: 10.1183/09031936.97.10112662

American Thoracic Society (2003). ATS/ACCP Statement on cardiopulmonary exercise testing. *Am. J. Respir. Crit. Care Med.* 167, 211–277. doi: 10.1164/rccm.167.2.211

ATS/ACCP (2003). Statement on cardiopulmonary exercise testing. *Am. J. Respir. Crit. Care Med.* 167, 211–277.

Badagliacca, R., Papa, S., Poscia, R., Valli, G., Pezzuto, B., Manzi, G., et al. (2019). The added value of cardiopulmonary exercise testing in the follow-up of pulmonary arterial hypertension. *J. Heart Lung Transpl.* 38, 306–314. doi: 10.1016/j.healun.2018.11.015

Badagliacca, R., Papa, S., Valli, G., Pezzuto, B., Poscia, R., Manzi, G., et al. (2016). Echocardiography combined with cardiopulmonary exercise testing for the prediction of outcome in idiopathic pulmonary arterial hypertension. *Chest* 150, 1313–1322. doi: 10.1016/j.chest.2016.07.036

Bauer, R., Dehnert, C., Schoene, P., Filusch, A., Bartsch, P., Borst, M. M., et al. (2007). Skeletal muscle dysfunction in patients with idiopathic pulmonary arterial hypertension. *Respir. Med.* 101, 2366–2369.

Benza, R. L., Gomberg-Maitland, M., Elliott, C. G., Farber, H. W., Foreman, A. J., Frost, A. E., et al. (2019). Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. *Chest* 156, 323–337.

Boucly, A., Morelot-Panzini, C., Garcia, G., Weatherald, J., Jais, X., Savale, L., et al. (2020). Intensity and quality of exertional dyspnoea in patients with stable pulmonary hypertension. *Eur. Respir. J.* 55:1802108. doi: 10.1183/13993003.02108-2018

D'Alonzo, G. E., Gianotti, L. A., Pohil, R. L., Reagle, R. R., DuRee, S. L., and Dantzker, D. R. (1987). Comparison of progressive exercise performance of normal subjects and patients with primary pulmonary hypertension. *Chest* 92, 57–62. doi: 10.1378/chest.92.1.57

Deboeck, G., Niset, G., Lamotte, M., Vachiery, J. L., and Naeije, R. (2004). Exercise testing in pulmonary arterial hypertension and in chronic heart failure. *Eur. Respir. J.* 23, 747–751. doi: 10.1183/09031936.04.00111904

Deboeck, G., Scoditti, C., Huez, S., Vachiery, J. L., Lamotte, M., Sharples, L., et al. (2012). Exercise testing to predict outcome in idiopathic versus associated pulmonary arterial hypertension. *Eur. Respir. J.* 40, 1410–1419.

Dimopoulos, S., Tzanis, G., Manetos, C., Tasoulis, A., Mpouchla, A., Tseliou, E., et al. (2013). Peripheral muscle microcirculatory alterations in patients with pulmonary arterial hypertension: a pilot study. *Respir. Care* 58, 2134–2141. doi: 10.4187/respcare.02113

Dorneles, R. G., Plachi, F., Gass, R., Toniazzo, V. T., Thome, P., Sanches, P. R., et al. (2019). Sensory consequences of critical inspiratory constraints during exercise in pulmonary arterial hypertension. *Respir. Physiol. Neurobiol.* 261, 40–47. doi: 10.1016/j.resp.2019.01.002

Duscha, B. D., Robbins, J. L., Jones, W. S., Kraus, W. E., Lye, R. J., Sanders, J. M., et al. (2011). Angiogenesis in skeletal muscle precede improvements in peak oxygen uptake in peripheral artery disease patients. *Arterioscler. Thromb. Vasc. Biol.* 31, 2742–2748. doi: 10.1161/atvbaha.111.230441

Ehlken, N., Lichtblau, M., Klose, H., Weidenhammer, J., Fischer, C., Nechwatal, R., et al. (2016). Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. *Eur. Heart J.* 37, 35–44. doi: 10.1093/eurheartj/ehv337

Esposito, F., Mathieu-Costello, O., Shabetai, R., Wagner, P. D., and Richardson, R. S. (2010). Limited maximal exercise capacity in patients with chronic heart failure: partitioning the contributors. *J. Am. Coll. Cardiol.* 55, 1945–1954.

Esposito, F., Reese, V., Shabetai, R., Wagner, P. D., and Richardson, R. S. (2011). Isolated quadriceps training increases maximal exercise capacity in chronic

heart failure: the role of skeletal muscle convective and diffusive oxygen transport. *J. Am. Coll. Cardiol.* 58, 1353–1362. doi: 10.1016/j.jacc.2011.06.025

Farina, S., Bruno, N., Agalbato, C., Contini, M., Cassandro, R., Elia, D., et al. (2018). Physiological insights of exercise hyperventilation in arterial and chronic thromboembolic pulmonary hypertension. *Int. J. Cardiol.* 259, 178–182. doi: 10.1016/j.ijcard.2017.11.023

Galie, N., Humbert, M., Vachiery, J. L., Gibbs, S., Lang, I., Torbicki, A., et al. (2015). ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the european society of cardiology (ESC) and the european respiratory society (ERS): endorsed by: association for european paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). *Eur. Respir. J.* 46, 903–975. doi: 10.1183/13993003.01032-2015

Galie, N., Rubin, L., Hoeper, M., Jansa, P., Al-Hiti, H., Meyer, G., et al. (2008). Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 371, 2093–2100. doi: 10.1016/s0140-6736(08)60919-8

Godinas, L., Sattler, C., Lau, E. M., Jais, X., Taniguchi, Y., Jevnikar, M., et al. (2017). Dead-space ventilation is linked to exercise capacity and survival in distal chronic thromboembolic pulmonary hypertension. *J. Heart Lung Transpl.* 36, 1234–1242. doi: 10.1016/j.healun.2017.05.024

Groepenhoff, H., Vonk-Noordegraaf, A., Boonstra, A., Spreeuwenberg, M. D., Postmus, P. E., and Bogaard, H. J. (2008). Exercise testing to estimate survival in pulmonary hypertension. *Med. Sci. Sports Exerc.* 40, 1725–1732. doi: 10.1249/mss.0b013e31817c92c0

Groepenhoff, H., Vonk-Noordegraaf, A., van de Veerdonk, M. C., Boonstra, A., Westerhof, N., and Bogaard, H. J. (2013). Prognostic relevance of changes in exercise test variables in pulmonary arterial hypertension. *PLoS ONE* 8:e72013. doi: 10.1371/journal.pone.0072013

Guenette, J. A., Webb, K. A., and O'Donnell, D. E. (2012). Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? *Eur. Respir. J.* 40, 322–329. doi: 10.1183/09031936.00157711

Hasler, E. D., Muller-Mottet, S., Furian, M., Saxer, S., Huber, L. C., Maggiorini, M., et al. (2016). Pressure-flow during exercise catheterization predicts survival in pulmonary hypertension. *Chest* 150, 57–67. doi: 10.1016/j.chest.2016.02.634

Hoeper, M. M., Pletz, M. W., Golpon, H., and Welte, T. (2007). Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension. *Eur. Respir. J.* 29, 944–950. doi: 10.1183/09031936.00134506

Huckstepp, R. T. R., Cardoza, K. P., Henderson, L. E., and Feldman, J. L. (2018). Distinct parafacial regions in control of breathing in adult rats. *PLoS ONE* 13:e0201485. doi: 10.1371/journal.pone.0201485

Humbert, M., Guignabert, C., Bonnet, S., Dorfmuller, P., Klinger, J. R., Nicolls, M. R., et al. (2019). Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur. Respir. J.* 53, 1801887. doi: 10.1183/13993003.01887-2018

Humbert, M., Yaici, A., de Groote, P., Montani, D., Sitbon, O., Launay, D., et al. (2011). Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. *Arthritis Rheum.* 63, 3522–3530. doi: 10.1002/art.30541

Johnson, B. D., Weisman, I. M., Zeballos, R. J., and Beck, K. C. (1999). Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest* 116, 488–503. doi: 10.1378/chest.116.2.488

Kovacs, G., Berghold, A., Scheidl, S., and Olschewski, H. (2009). Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur. Respir. J.* 34, 888–894. doi: 10.1183/09031936.00145608

Kovacs, G., Herve, P., Barbera, J. A., Chaouat, A., Chemla, D., Condliffe, R., et al. (2017). An official European respiratory society statement: pulmonary haemodynamics during exercise. *Eur. Respir. J.* 50, 1700578. doi: 10.1183/13993003.00578-2017

Lau, E. M., Humbert, M., and Celermajer, D. S. (2015). Early detection of pulmonary arterial hypertension. *Nat. Rev. Cardiol.* 12, 143–155.

Laveneziana, P., Agostoni, P., Mignatti, A., Mushtaq, S., Colombo, P., Sims, D., et al. (2010). Effect of acute beta-blocker withholding on ventilatory efficiency in patients with advanced chronic heart failure. *J. Card. Fail.* 16, 548–555. doi: 10.1016/j.cardfail.2010.02.006

Laveneziana, P., Bruni, G. I., Presi, I., Stendardi, L., Duranti, R., and Scano, G. (2013a). Tidal volume inflection and its sensory consequences during exercise in patients with stable asthma. *Respir. Physiol. Neurobiol.* 185, 374–379. doi: 10.1016/j.resp.2012.08.026

Laveneziana, P., Garcia, G., Joureau, B., Nicolas-Jilwan, F., Brahimi, T., Laviolette, L., et al. (2013b). Dynamic respiratory mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Eur. Respir. J.* 41, 578–587. doi: 10.1183/09031936.00223611

Laveneziana, P., and Di Paolo, M. (2019). Exploring cardiopulmonary interactions during constant-workload submaximal cycle exercise in COPD patients. *J. Appl. Physiol. (*1985) 127, 688–690. doi: 10.1152/japplphysiol.00526.2019

Laveneziana, P., Humbert, M., Godinas, L., Joureau, B., Malrin, R., Straus, C., et al. (2015). Inspiratory muscle function, dynamic hyperinflation and exertional dyspnoea in pulmonary arterial hypertension. *Eur. Respir. J.* 45, 1495–1498. doi: 10.1183/09031936.00153214

Laveneziana, P., Lotti, P., Coli, C., Binazzi, B., Chiti, L., Stendardi, L., et al. (2006). Mechanisms of dyspnoea and its language in patients with asthma. *Eur. Respir. J.* 27, 742–747. doi: 10.1183/09031936.06.00080505

Laveneziana, P., Montani, D., Dorfmuller, P., Girerd, B., Sitbon, O., Jais, X., et al. (2014a). Mechanisms of exertional dyspnoea in pulmonary veno-occlusive disease with EIF2AK4 mutations. *Eur. Respir. J.* 44, 1069–1072. doi: 10.1183/09031936.00088914

Laveneziana, P., Webb, K. A., Wadell, K., Neder, J. A., and O'Donnell, D. E. (2014b). Does expiratory muscle activity influence dynamic hyperinflation and exertional dyspnea in COPD? *Respir. Physiol. Neurobiol.* 199, 24–33. doi: 10.1016/j.resp.2014.04.005

Laveneziana, P., O'Donnell, D. E., Ofir, D., Agostoni, P., Padeletti, L., Ricciardi, G., et al. (2009). Effect of biventricular pacing on ventilatory and perceptual responses to exercise in patients with stable chronic heart failure. *J. Appl. Physiol. (*1985) 106, 1574–1583. doi: 10.1152/japplphysiol.90744.2008

Laveneziana, P., Webb, K. A., Ora, J., Wadell, K., and O'Donnell, D. E. (2011). Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *Am. J. Respir. Crit. Care Med.* 184, 1367–1373. doi: 10.1164/rccm.201106-1128oc

Laviolette, L., and Laveneziana, P. (2014). Dyspnoea: a multidimensional and multidisciplinary approach. *Eur. Respir. J.* 43, 1750–1762. doi: 10.1183/09031936.00092613

Mainguy, V., Maltais, F., Saey, D., Gagnon, P., Martel, S., Simon, M., et al. (2010). Peripheral muscle dysfunction in idiopathic pulmonary arterial hypertension. *Thorax* 65, 113–117. doi: 10.1136/thx.2009.117168

Manders, E., Bonta, P. I., Kloek, J. J., Symersky, P., Bogaard, H. J., Hooijman, P. E., et al. (2016). Reduced force of diaphragm muscle fibers in patients with chronic thromboembolic pulmonary hypertension. *Am. J. Physiol. Lung. Cell Mol. Physiol.* 311, L20–L28.

Mereles, D., Ehlken, N., Kreuscher, S., Ghofrani, S., Hoeper, M. M., Halank, M., et al. (2006). Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation* 114, 1482–1489. doi: 10.1161/circulationaha.106.618397

Naeije, R., and Badagliacca, R. (2017). The overloaded right heart and ventricular interdependence. *Cardiovasc. Res.* 113, 1474–1485. doi: 10.1093/cvr/cvx160

Naeije, R., and van de Borne, P. (2009). Clinical relevance of autonomic nervous system disturbances in pulmonary arterial hypertension. *Eur. Respir. J.* 34, 792–794. doi: 10.1183/09031936.00091609

Nootens, M., Wolfkiel, C. J., Chomka, E. V., and Rich, S. (1995). Understanding right and left ventricular systolic function and interactions at rest and with exercise in primary pulmonary hypertension. *Am. J. Cardiol.* 75, 374–377. doi: 10.1016/s0002-9149(99)80557-8

Oudiz, R. J., Midde, R., Hovenesyan, A., Sun, X. G., Roveran, G., Hansen, J. E., et al. (2010). Usefulness of right-to-left shunting and poor exercise gas exchange for predicting prognosis in patients with pulmonary arterial hypertension. *Am. J. Cardiol.* 105, 1186–1191. doi: 10.1016/j.amjcard.2009.12.024

Palange, P., Ward, S. A., Carlsen, K. H., Casaburi, R., Gallagher, C. G., Gosselink, R., et al. (2007). Recommendations on the use of exercise testing in clinical practice. *Eur. Respir. J.* 29, 185–209.

Palange, P. L., Neder, J. A., and Ward, S. A. (2018). *Clinical Exercise Testing. ERS Monograph*. Sheffield: European Respiratory Society.

Potus, F., Malenfant, S., Graydon, C., Mainguy, V., Tremblay, E., Breuils-Bonnet, S., et al. (2014). Impaired angiogenesis and peripheral muscle microcirculation loss contribute to exercise intolerance in pulmonary arterial hypertension. *Am. J. Respir. Crit. Care Med.* 190, 318–328.

Puente-Maestu, L., García de Pedro, J., Troosters, T., Neder, J. A., Puhan, M. A., Benedetti, P. A., et al. (eds) (2018). *Clinical Exercise Testing*. Sheffield: European Respiratory Society, 88–106. doi: 110.1183/2312508X.10011217

Puente-Maestu, L., Palange, P., Casaburi, R., Laveneziana, P., Maltais, F., Neder, J. A., et al. (2016). Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *Eur. Respir. J.* 47, 429–460. doi: 10.1183/13993003.00745-2015

Radtke, T., Crook, S., Kaltsakas, G., Louvaris, Z., Berton, D., Urquhart, D. S., et al. (2019). ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur. Respir. Rev.* 28.

Richter, M. J., Gall, H., Wittkamper, G., Seeger, W., Mayer, E., Ghofrani, H. A., et al. (2017). Inspiratory capacity is not altered in operable chronic thromboembolic pulmonary hypertension. *Pulmon. Circ.* 7, 543–546. doi: 10.1177/2045893217709763

Richter, M. J., Voswinckel, R., Tiede, H., Schulz, R., Tanislav, C., Feustel, A., et al. (2012). Dynamic hyperinflation during exercise in patients with precapillary pulmonary hypertension. *Respir. Med.* 106, 308–313. doi: 10.1016/j.rmed.2011.10.018

Riley, M. S., Porszasz, J., Engelen, M. P., Brundage, B. H., and Wasserman, K. (2000). Gas exchange responses to continuous incremental cycle ergometry exercise in primary pulmonary hypertension in humans. *Eur. J. Appl. Physiol.* 83, 63–70. doi: 10.1007/s004210000240

Saggar, R., and Sitbon, O. (2012). Hemodynamics in pulmonary arterial hypertension: current and future perspectives. *Am. J. Cardiol.* 110, 9S–15S.

Scheidl, S. J., Englisch, C., Kovacs, G., Reichenberger, F., Schulz, R., Breithecker, A., et al. (2012). Diagnosis of CTEPH versus IPAH using capillary to end-tidal carbon dioxide gradients. *Eur. Respir. J.* 39, 119–124. doi: 10.1183/09031936.00109710

Schwaiblmair, M., Faul, C., von Scheidt, W., and Berghaus, T. M. (2012). Ventilatory efficiency testing as prognostic value in patients with pulmonary hypertension. *BMC Pulmon. Med.* 12:23. doi: 10.1186/1471-2466-12-23

Simonneau, G., Montani, D., Celermajer, D. S., Denton, C. P., Gatzoulis, M. A., Krowka, M., et al. (2019). Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur. Respir. J.* 53, 1801913. doi: 10.1183/13993003.01913-2018

Smith, J. R., Johnson, B. D., and Olson, T. P. (2019). Impaired central hemodynamics in chronic obstructive pulmonary disease during submaximal exercise. *J. Appl. Physiol. (*1985) 127, 691–697. doi: 10.1152/japplphysiol.00877.2018

Soumagne, T., Laveneziana, P., Veil-Picard, M., Guillien, A., Claude, F., Puyraveau, M., et al. (2016). Asymptomatic subjects with airway obstruction have significant impairment at exercise. *Thorax* 71, 804–811. doi: 10.1136/thoraxjnl-2015-207953

Sun, X. G., Hansen, J. E., Garatachea, N., Storer, T. W., and Wasserman, K. (2002). Ventilatory efficiency during exercise in healthy subjects. *Am. J. Respir. Crit. Care Med.* 166, 1443–1448. doi: 10.1164/rccm.2202033

Sun, X. G., Hansen, J. E., Oudiz, R. J., and Wasserman, K. (2001). Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 104, 429–435. doi: 10.1161/hc2901.093198

Tolle, J., Waxman, A., and Systrom, D. (2008). Impaired systemic oxygen extraction at maximum exercise in pulmonary hypertension. *Med. Sci. Sports Exerc.* 40, 3–8. doi: 10.1249/mss.0b013e318159d1b8

Valli, G., Palange, P., Badagliacca, R., Papa, S., Poscia, R., and Vizza, C. D. (2019). Exercise energy expenditure in patients with idiopathic pulmonary arterial hypertension: Impact on clinical severity and survival. *Respir. Physiol. Neurobiol.* 264, 33–39. doi: 10.1016/j.resp.2019.04.003

Velez-Roa, S., Ciarka, A., Najem, B., Vachiery, J. L., Naeije, R., and van de Borne, P. (2004). Increased sympathetic nerve activity in pulmonary artery hypertension. *Circulation* 110, 1308–1312. doi: 10.1161/01.cir.0000140724.90898.d3

Wasserman, K., Whipp, B. J., Koyal, S. N., and Cleary, M. G. (1975). Effect of carotid body resection on ventilatory and acid-base control during exercise. *J. Appl. Physiol.* 39, 354–358. doi: 10.1152/jappl.1975.39.3.354

Weatherald, J., Boucly, A., Chemla, D., Savale, L., Peng, M., Jevnikar, M., et al. (2018a). Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. *Circulation* 137, 693–704. doi: 10.1161/circulationaha.117.029254

Weatherald, J., Boucly, A., Launay, D., Cottin, V., Prevot, G., Bourlier, D., et al. (2018b). Haemodynamics and serial risk assessment in systemic sclerosis associated pulmonary arterial hypertension. *Eur. Respir. J.* 52, 1800678. doi: 10.1183/13993003.00678-2018

Weatherald, J., Sattler, C., Garcia, G., and Laveneziana, P. (2018c). Ventilatory response to exercise in cardiopulmonary disease: the role of chemosensitivity and dead space. *Eur. Respir. J.* 51:1700860. doi: 10.1183/13993003.00860-2017

Weatherald, J., Boucly, A., Montani, D., Jais, X., Savale, L., Humbert, M., et al. (2020). Gas exchange and ventilatory efficiency during exercise in pulmonary vascular diseases. *Arch. Bronconeumol.* S0300–S2896:30017-X. doi: 10.1016/j.arbres.2019.12.030

Wensel, R., Francis, D. P., Meyer, F. J., Opitz, C. F., Bruch, L., Halank, M., et al. (2013). Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. *Int. J. Cardiol.* 167, 1193–1198. doi: 10.1016/j.ijcard.2012.03.135

Wensel, R., Georgiadou, P., Francis, D. P., Bayne, S., Scott, A. C., Genth-Zotz, S., et al. (2004). Differential contribution of dead space ventilation and low arterial pCO2 to exercise hyperpnea in patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am. J. Cardiol.* 93, 318–323. doi: 10.1016/j.amjcard.2003.10.011

Wensel, R., Jilek, C., Dorr, M., Francis, D. P., Stadler, H., Lange, T., et al. (2009). Impaired cardiac autonomic control relates to disease severity in pulmonary hypertension. *Eur. Respir. J.* 34, 895–901. doi: 10.1183/09031936.00145708

Wensel, R., Opitz, C. F., Anker, S. D., Winkler, J., Hoffken, G., Kleber, F. X., et al. (2002). Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation* 106, 319–324. doi: 10.1161/01.cir.0000022687.18568.2a

Whipp, B. J., and Ward, S. A. (1998). Determinants and control of breathing during muscular exercise. *Br. J. Sports Med.* 32, 199–211. doi: 10.1136/bjsm.32.3.199

Yasunobu, Y., Oudiz, R. J., Sun, X. G., Hansen, J. E., and Wasserman, K. (2005). End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest* 127, 1637–1646. doi: 10.1378/chest.127.5.1637

Zhai, Z., Murphy, K., Tighe, H., Wang, C., Wilkins, M. R., Gibbs, J. S. R., et al. (2011). Differences in ventilatory inefficiency between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest* 140, 1284–1291. doi: 10.1378/chest.10-3357

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frontiers in Medicine

MINI REVIEW
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Dyspnea and Exercise Limitation in Mild COPD: The Value of CPET

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The majority of smokers with chronic obstructive pulmonary disease (COPD) have mild airflow limitation as determined by simple spirometry. Although small airway dysfunction is the hallmark of COPD, many studies attest to complex heterogeneous physiological impairments beyond increased airway resistance. These impairments are related to inflammation of lung parenchyma and its microvasculature, which is obscured by simple spirometry. Recent studies using advanced radiological imaging have highlighted significant structural abnormalities in smokers with relatively preserved spirometry. These important studies have generated considerable interest and have reinforced the pressing need to better understand the physiological consequences of various morphological abnormalities, and their impact on the clinical outcomes and natural history of COPD. The overarching objective of this review is to provide a concise overview of the importance and utility of cardiopulmonary exercise testing (CPET) in clinical and research settings. CPET uniquely allows evaluation of integrated abnormalities of the respiratory, cardio-circulatory, metabolic, peripheral muscle and neurosensory systems during increases in physiologic stress. This brief review examines the results of recent studies in mild COPD that have uncovered consistent derangements in pulmonary gas exchange and development of "restrictive" dynamic mechanics that together contribute to exercise intolerance. We examine the evidence that compensatory increases in inspiratory neural drive from respiratory control centers are required during exercise in mild COPD to maintain ventilation commensurate with increasing metabolic demand. The ultimate clinical consequences of this high inspiratory neural drive are earlier onset of critical respiratory mechanical constraints and increased perceived respiratory discomfort at relatively low exercise intensities.

Keywords: cardiopulmonary exercise testing, chronic obstructive pulmonary disease, dyspnea, neural drive, respiratory mechanics, gas exchange

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating inflammatory disease of the airways, alveoli, and microvasculature. Patients classified in the mild COPD stage by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria represent the majority of total patients with COPD, with an estimated global prevalence of 7–11% in adults over 40 years of age (1–3). Such patients with mild COPD have an increased risk of morbidity and mortality

compared to healthy non-smokers, and have reduced health-related quality of life (4). The most commonly reported symptom in patients with mild COPD is dyspnea (breathlessness), defined by a 2012 American Thoracic Society (ATS) statement as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (5). Dyspnea is particularly troublesome during exertion in patients with mild COPD, and is often disproportionate to the degree of airflow limitation (6). Further, dyspnea upon exertion has been linked to exercise intolerance in these patients (6, 7). The effective management of this complex and multifactorial symptom, exercise intolerance and the associated poor health status, remains a substantial challenge for caregivers. Interest in systematic evaluation of the heterogeneous physiological derangements of mild COPD has mounted since the discovery of widespread structural abnormalities, quantified by imaging, in large numbers of smokers who have normal spirometry as well as in those who meet GOLD diagnostic spirometric criteria (8, 9). In this context, our understanding of the nature of physiological impairment and its negative consequences (dyspnea and exercise intolerance) in mild COPD has been considerably enhanced by the use of non-invasive cardiopulmonary exercise testing (CPET) using treadmill or cycle ergometry, which allows for the measurement of subjective (i.e., dyspnea measured by Borg scale) and physiologic (breath by breath measures of ventilatory and metabolic) parameters during a standardized physical stimulus or stress (6, 7, 10–12). Conventional CPET is particularly valuable in mild COPD where apparently disproportionate dyspnea and reduced exercise tolerance remain unexplained after routine spirometry. This review will outline evolving concepts of the physiological underpinnings of dyspnea and exercise intolerance in mild COPD, and highlight the clinical utility of CPET.

For the purpose of this review, we propose that mild COPD refer to patients with the following criteria: (1) relevant long-term exposure to tobacco smoke (i.e., current or ex-smoker with significant smoking history), (2) persistent symptoms of dyspnea, cough, and/or sputum production that are not explained by other respiratory disorder, (3) a post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio <0.7, with an FEV_1 $>80\%$ predicted, measured by simple spirometry. Essentially, we focused our review on physiological exercise studies undertaken in smokers meeting GOLD Stage 1B COPD criteria.

EXERTIONAL DYSPNEA IN COPD: CURRENT CONSTRUCTS

Dyspnea is believed to arise from an imbalance between inspiratory neural drive (IND) to breathe and the capacity of the respiratory system to respond (13). This imbalance is variably termed demand-capacity imbalance, efferent-afferent dissociation, neuromechanical, or neuromuscular dissociation. This theory is supported by studies that demonstrate a strong association between the rise in dyspnea intensity during exercise and simultaneous increase in several physiologic ratios (IND, ventilation and muscular effort, all relative to their maximal values) which collectively reflect demand-capacity imbalance of the respiratory system [**Figure 1**; (15–17)]. Together, these studies support the notion that dyspnea increases during exercise as a function of increasing IND (from bulbo-pontine and cortical respiratory control centers) in the face of an ever-decreasing capacity of the respiratory system to appropriately respond, because of significant mechanical constraints.

MECHANISMS OF INCREASED INSPIRATORY NEURAL DRIVE IN MILD COPD

Recent studies in mild COPD have shown that dyspnea during exercise is associated with disproportionately increased IND (as measured by diaphragm electromyography, EMGdi) compared with healthy controls [**Figure 1A**; (7)]. The abnormally high IND in mild COPD is mainly attributed to: (1) reduced ventilatory efficiency during exercise (i.e., increased ventilation relative to carbon dioxide production, V_E/VCO_2), and/or (2) progressive expiratory flow limitation (EFL) and abnormal dynamic breathing mechanics (6, 10, 11).

Pulmonary Gas Exchange Abnormalities

The increased IND during exercise in COPD patients is the result of variable perturbation of both chemical and respiratory mechanical factors (18, 19). In both health and COPD, IND increases as carbon dioxide output (VCO_2) increases during exercise in response to greater energy expenditure and metabolic demand (20). Thus, exercise hyperpnea is closely linked to pulmonary CO_2 gas exchange. Tobacco-related injury of the lung parenchyma, small airways, and microvasculature in mild COPD leads to heterogeneous ventilation-perfusion mismatch and significant abnormalities in pulmonary gas exchange (11, 21–23). In mild COPD during exercise, V_E/VCO_2, physiological dead space (V_D), the dead space to tidal volume ratio (V_D/V_T), and alveolar ventilation (V_A) are elevated when compared with health (11). When combined with EFL, these elevated ventilatory requirements lead to accelerated progression of dynamic mechanical constraints, dyspnea and reduced exercise tolerance (10, 11). Additionally, the associated tachypnea and shallow breathing pattern further increase the dead space to tidal volume ratio (V_D/V_T) (11).

Recently, attenuated pulmonary capillary perfusion has been demonstrated at rest and during exercise in mild COPD (11, 21, 24, 25). Indeed, several studies utilizing various radiological imaging techniques have confirmed important structural and functional abnormalities of the small airways and microvasculature in smokers with normal spirometry and in patients with mild COPD (8, 9, 23, 26). Quantitative high-resolution computed tomography (CT) imaging has shown that patients with mild COPD can have significant emphysema, pulmonary gas trapping, small airway thickening, and vascular abnormalities (8). Studies using contrast-enhanced MRI have provided evidence of significant pulmonary capillary perfusion abnormalities suggesting tobacco smoke-induced vasculopathy

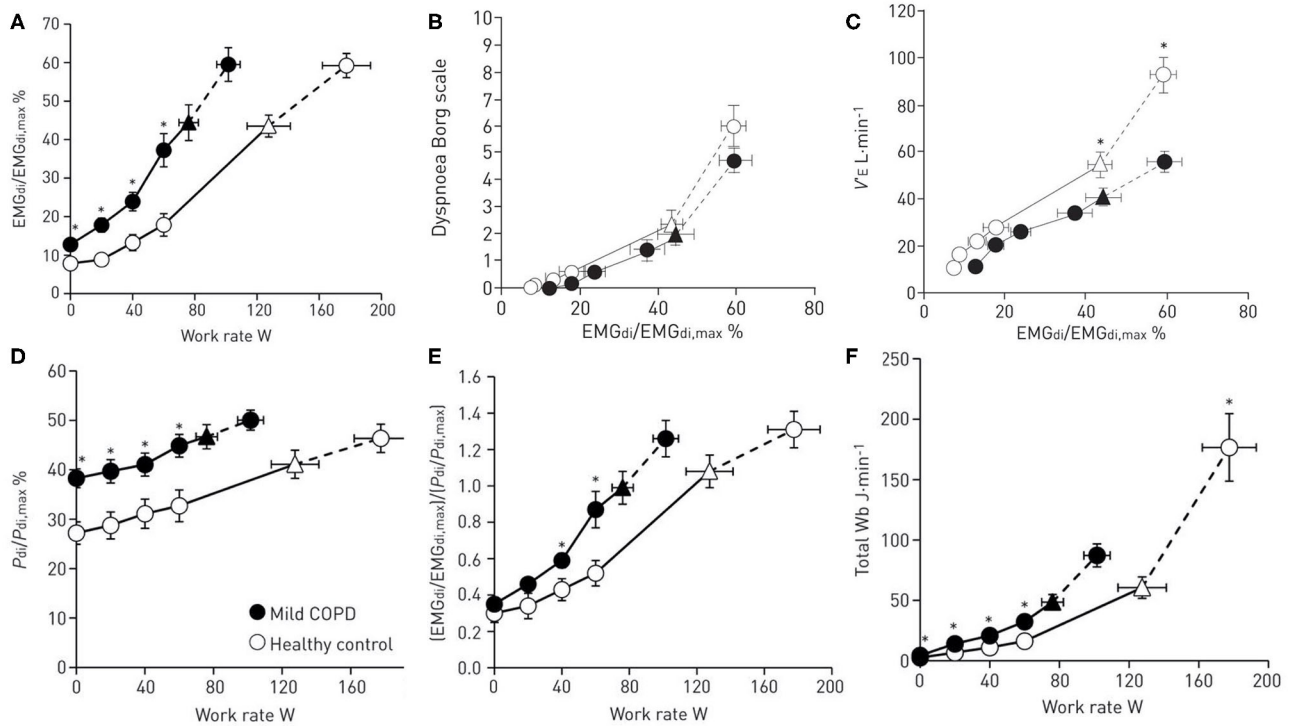

FIGURE 1 | Ventilatory drive and respiratory mechanical response to exercise in patients with mild chronic obstructive pulmonary disease (COPD) compared to healthy controls. **(A)** The ratio of diaphragmatic electromyography (EMGdi) to maximal EMGdi (EMGdi,max) relative to work rate, **(B)** dyspnea intensity (measured by modified 10-point Borg scale) relative to the ratio of EMGdi/EMGdi,max **(C)** ventilation (V_E) relative to the ratio of EMGdi/EMGdi,max **(D)** the ratio of transdiaphragmatic pressure (Pdi) relative to maximal Pdi (Pdi,max) relative to work rate **(E)** neuromechanical dissociation (represented as the ratio of EMGdi/EMGdi,max to Pdi/Pdi,max) relative to work rate **(F)** total work of breathing relative to work rate. Data are presented as Mean ± SEM. Triangles represent the tidal volume/minute ventilation inflection point. Reproduced with permission of the © ERS 2020: Guenette et al. (7).

may be present even in smokers with mild spirometric abnormalities (9, 23).

Moreover, new studies have shown that a low resting diffusing capacity for carbon monoxide (DLCO)—which provides a window into the microvasculature—is associated with ventilatory inefficiency (high V_E/VCO_2) and increased exertional dyspnea in smokers with and without airway obstruction (11, 24, 27). It has become clear that DLCO reliably evaluates the integrity of the alveolar-capillary interface in mild COPD where significant maldistribution of alveolar ventilation is absent, unlike more advanced disease (28). Elbehairy et al. demonstrated consistently higher ratings of dyspnea intensity and reduced exercise tolerance in COPD patients with a DLCO below the lower limit of normal (<LLN), when compared with patients with preserved DLCO [**Figure 2A**; (12)]. The higher dyspnea ratings and earlier exercise termination in the low DLCO groups were linked to significantly greater ventilatory inefficiency (i.e., high V_E/VCO_2) mainly reflecting higher physiological dead space [**Figure 2C**; (11, 12)]. Accordingly, compromised CO_2 elimination due to ventilation-perfusion inequalities and resultant increased chemo-stimulation gave rise to high ventilatory requirements (**Figure 2B**) that accelerates dynamic mechanical constraints (breathing pattern abnormalities and critical tidal volume constraints) at lower exercise intensities than patients with preserved DLCO (12).

Other chemical factors which are believed to contribute to increased IND during exercise in more advanced COPD are less likely to be important in mild COPD. These include: (1) increased chemosensitivity and a lower regulated level of arterial pCO_2 (21, 29–32); (2) increased chemoreceptor stimulation [due to critical arterial hypoxemia, low mixed venous O_2 returning to areas in the lung with low ventilation-perfusion (V/Q) ratios] (11, 33–36); (3) skeletal muscle deconditioning (manifesting as metabolic acidosis at relatively low VO_2) which result in increased afferent ergoreceptor activation (due to reduced O_2 delivery to the peripheral muscles) (37, 38); (4) reduced cardiac output as a result of reduced pulmonary vascular volume and low left ventricle filling (leading to increased V/Q mismatch and physiologic dead space) (39); (5) altered afferents from pulmonary vessels and right heart due to increased pulmonary vascular pressures (40); and (6) increased sympathetic nervous system activation which increases chemosensitivity (41, 42). At this point, there is insufficient evidence to implicate the above-listed chemical factors in contributing to increased IND in mild COPD with the notable exception of decreased ventilatory efficiency which is likely to be important.

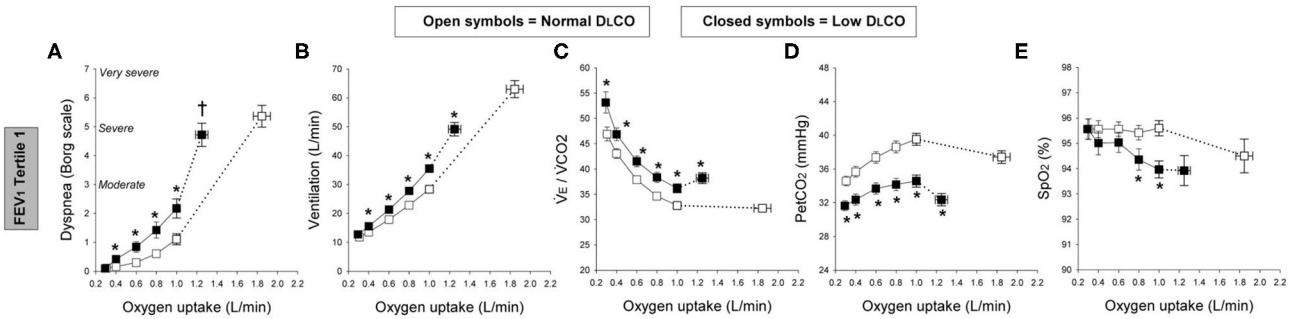

FIGURE 2 | Exertional dyspnea intensity (Borg scale; **A**), ventilation **(B)**, ventilatory equivalent for carbon-dioxide (V_E/VCO2; **C**), partial pressure of end-tidal CO2 ($P_{ET}CO_2$; **D**), and oxygen saturation by pulse oximetry (SpO_2; **E**); all for a given oxygen uptake during symptom-limited incremental cycle exercise in chronic obstructive pulmonary disease patients with normal single-breath diffusing capacity of the lung for carbon monoxide (DLCO; open symbols) and those with low DLCO (closed symbols) in the first tertile of forced expiratory volume in 1 s (FEV1). Tertile 1 (FEV1 > 73.5%predicted, square symbols). Data are means ± SE. $^*P < 0.05$, normal vs. low DLCO. $^\dagger P < 0.05$, difference in dyspnea/oxygen uptake slope between normal and low DLCO. Elbehairy et al. (12).

Dynamic Respiratory Mechanics

Small airway dysfunction and obliteration is regarded as the hallmark feature of mild COPD and has important clinical consequences. Indeed, one study in symptomatic smokers who did not meet spirometric criteria for COPD showed significantly increased IND during exercise compared with healthy controls, in proportion to increased airway resistance (EMGdi) (43). In mild GOLD Stage 1 COPD, in mild GOLD Stage 1 COPD, EFL is variably present at rest, and often quickly becomes evident during the hyperpnea of exercise where it is associated with dynamic lung hyperinflation (DH) and its important negative sensory consequences (44). In some individuals with mild COPD, defined by spirometric criteria, localized emphysematous destruction of the lung's connective tissue matrix can alter lung elasticity (increase in lung compliance), resetting the balance of forces between inward lung recoil pressure and outward chest wall recoil at end-expiration. This results in an increased relaxation volume of the respiratory system (end-expiratory lung volume, EELV) compared with healthy controls. In patients with mild COPD exhibiting EFL at rest, dynamic EELV is influenced by the prevailing breathing pattern. If F_B increases abruptly (and expiratory time decreases and/or V_T increases) in patients with mild COPD and significant EFL, EELV temporarily and variably increases above its resting value (i.e., increased DH) during exercise. DH reflects the effect of the slow mechanical time-constant for lung emptying: expiratory time with each breath during exercise is simply of insufficient duration to allow EELV to decline to the predicted relaxation volume (14, 45–47).

The resting inspiratory capacity (IC) and inspiratory reserve volume (IRV) in mild COPD are generally preserved and V_T is therefore positioned on the more linear, mid-portion of the relaxed respiratory system sigmoidal pressure-volume relationship (48). However, during exercise when DH occurs, V_T becomes positioned closer to TLC at relatively low work rate which means that the inspiratory muscle fibers are shortened and functionally weakened and must contend with increased elastic mechanical loading. The difference between end-inspiratory lung volume (EILV) and TLC (i.e., IRV) largely dictates the relationship between IND and the mechanical/muscular response of the respiratory system and the degree of perceived dyspnea (49). Thus, the rate of dynamic decrease in IRV in mild COPD provides indirect information about the extent of neuromechanical dissociation of the respiratory system and has strong correlation with dyspnea intensity (49). Thus, when V_T/IC ratio reaches ∼0.7 during exercise or IRV reaches <0.5–1.0 L), a widening disparity occurs between IND and the V_T response: IND continues to rise and V_T expansion becomes progressively constrained and eventually fixed, representing the onset of significant neuromechanical dissociation and escalation of dyspnea (50, 51).

Recent studies have clearly established that in mild COPD, reliance on traditional assessments of breathing reserve [estimated maximal ventilatory capacity (MVC) minus peak V_E] can underestimate true ventilatory limitation indicated by premature attainment of critical respiratory mechanical constraints and accompanying severe dyspnea at relatively low work rates (10).

The question arises whether bronchodilator treatment, which partially reverses the above described abnormal mechanics, provides subjective benefits in patients with mild COPD. A study of symptomatic mild COPD patients showed that short-acting bronchodilators improved FEV_1, reduced residual volume (RV) and resting airway resistance, DH, and work of breathing during exercise compared to placebo. However, there was no observed improvement in exercise endurance or exertional dyspnea, except at high V_E (52). A similar multi-center randomized double-blind study examining the effect of long-acting bronchodilator (tiotropium) in mild COPD patients showed a positive effect on resting and dynamic lung hyperinflation but with no improvement in exercise endurance or exertional dyspnea (53). The unimpressive effects of bronchodilators in mild COPD can be explained by the fact that resting IC is preserved in the majority of individuals. Thus, small improvements in dynamic respiratory mechanics at high ventilation levels near end-exercise are less likely to provide appreciable subjective benefit. Moreover, bronchodilators do not affect ventilatory inefficiency during

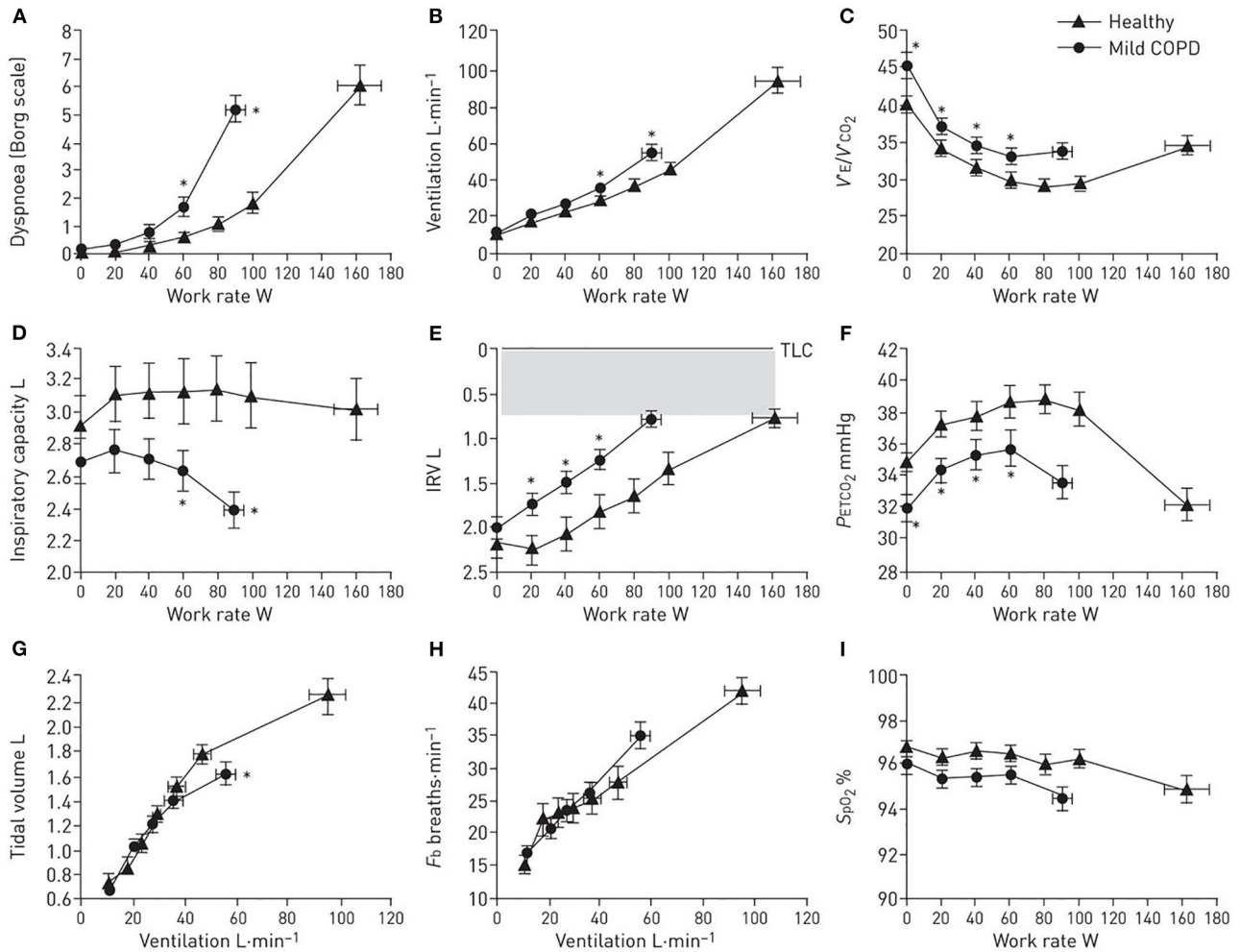

FIGURE 3 | (A–I) Proposed panel displays during interpretation of an incremental cardiopulmonary exercise test. Data showing selected perceptual, ventilatory control, dynamic respiratory mechanics, and breathing pattern response to incremental cycle exercise in patients with mild chronic obstructive pulmonary disease (COPD) and age-matched healthy controls. Data are presented as Mean ± SEM. V_E/VCO_2: ventilatory equivalent for carbon dioxide; IRV: inspiratory reserve volume; F_b: breathing frequency; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; SpO_2: arterial oxygen saturation measured by pulse oximetry; TLC: total lung capacity. *$p < 0.05$ mild COPD versus healthy controls at rest, at standardized work rates or at peak exercise. Adapted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved. Cite: Author(s)/Year/Title/Journal title/Volume/Pages. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at https://www.atsjournals.org/doi/full/10.1164/rccm.201211-1970OC The authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations.

exercise in mild COPD—a residual source of high IND and dyspnea (54).

THE ROLE OF CPET IN UNCOVERING THE CAUSE OF ACTIVITY-RELATED DYSPNOEA

Accurate clinical interpretation of CPET requires comprehensive pre-assessment in each individual. A number of validated questionnaires are available to evaluate the extent of exertional dyspnea and its impact on quality of life and the patient's ability to undertake everyday physical activities (55, 56). Those with habitually reduced physical activity may have significant skeletal muscle deconditioning (a known contributor to higher ventilatory demand and increased dyspnea) (57). Documentation of comorbidities such as asthma, obesity, cardiocirculatory disorders, and musculoskeletal problems is also important. All patients with dyspnea disproportionate to spirometry should undertake additional tests such as single breath DLCO and plethysmographic lung volumes and resting arterial O_2 saturation.

CPET Interpretation: Panel Displays

To evaluate the magnitude of dyspnea intensity and exercise intolerance (at peak work rate or VO_2) and identify potential contributing factors in mild COPD (**Figure 3**), the following responses are captured during incremental cycle CPET to tolerance: (1) *perceptual responses*: dyspnea (Borg) ratings as a function of work rate and/or V_E; (2) *ventilatory control:*

VO_2/work rate, V_E/work rate, (V_E/VCO_2)/work rate, O_2 saturation (SpO_2)/work rate, end-tidal CO_2 ($P_{ET}CO_2$)/work rate; (3) *dynamic respiratory mechanics*: change in IC, IRV, V_T, and breathing frequency (F_B), all as a function of increasing work rate or V_E; and (4) *cardiocirculatory responses:* heart rate relative to predicted peak heart rate and O_2 pulse.

From this simple format, we can evaluate the extent of dyspnea and exercise intolerance in the individual. We can determine if ventilation slopes are increased relative to controls (indicating higher ventilatory drive) and enumerate its potential underlying cause(s) [e.g., increased ventilatory inefficiency (V_E/VCO_2), critical hypoxemia, or early ventilatory threshold]. We can also evaluate the extent of mechanical respiratory constraints (operating lung volumes, breathing pattern) (see also *Evaluation of dynamic respiratory mechanical abnormalities during conventional CPET*).

The dominant abnormalities in patients with mild COPD include: (1) increased IND secondary to high V_D as indirectly assessed by V_E/VCO_2 (higher nadir and steeper slope, see also *Measurement and interpretation of exercise ventilatory efficiency*) compared to age- and sex-matched healthy controls (**Figure 3C**); and (2) increased pulmonary gas trapping due to the combined effects EFL and increased ventilatory demand. The result is earlier critical mechanical constraints (reduced IC and IRV due to increased EELV, **Figures 3D,E**), and consequently higher exertional dyspnea ratings earlier in exercise (**Figure 3A**), compared to age-matched healthy individuals. In mild COPD patients free from significant ventilatory constraints at lower exercise intensities, the measured V_E/VCO_2 (higher V_E/VCO_2 nadir and steeper V_E/VCO_2 slope compared to health) is a reliable surrogate for increased physiological dead space (58).

Influence of Co-morbidities in COPD CPET Interpretation

In smokers with persistent dyspnea but unremarkable spirometry there is justifiably a high index of suspicion for cardiovascular dysfunction which usually prompts a cascade of investigations to rule out active ischemic heart disease. The cardiocirculatory responses during CPET indicating concomitant left ventricular dysfunction include high V_E/VCO_2 nadir, uniformly low $P_{ET}CO_2$, relative tachycardia, reduced O_2 pulse (VO_2/HR), reduced VO_2/work rate slope, and early ventilatory threshold and complaints of dominant leg discomfort indicating impaired oxygen delivery to the peripheral muscles. It must be remembered that profound skeletal muscle deconditioning as a result of longstanding avoidance of physical activity can present with similar physiological responses to exercise as those encountered in patients with reduced cardiac output. Relevant clinical history and the incorporation of 12-lead ECG into CPET to detect undiagnosed ischemic heart disease in these patients can be informative. The findings of very high V_E/VCO_2 nadir (>35), arterial O_2 desaturation together with physiological features of LV dysfunction (listed above) raises the possibility of pulmonary arterial hypertension which should prompt further relevant investigations.

Obesity also influences exercise responses in COPD in a manner that is readily discernable (50, 59). There is an upward parallel shift in the VO_2/WR slope, explained by the increased metabolic requirement of lifting heavy limbs during cycling. Obese COPD patients have an increased resting IC (and thus lower EELV) which means that the patient can exercise to a higher ventilation before the V_T plateau or minimal IRV is reached (60). In severe obesity, IC becomes eroded due to mass loading effect and reduced respiratory system compliance, pulmonary gas exchange becomes compromised, PCO_2 may not decline or actually increase during exercise, and the load/capacity imbalance of the respiratory muscles reaches a critical level (59). These patients often attain physiological limits of the respiratory system and distressing dyspnea at relatively low exercise levels compared with those with normal weight COPD (59, 60).

Clinical and Therapeutic Implications

CPET uniquely exposes the nature and extent of physiological impairment that can exist in individual smokers with mild COPD who present to the clinician with troublesome symptoms of dyspnea and exercise intolerance. The new CPET-derived information alerts the clinician of the importance of careful follow-up to monitor disease progression and may persuade the patient to live a healthier lifestyle and avoid further lung injury from tobacco smoking. While CPET can provide a deeper understanding of the mechanisms of dyspnea in the individual, patients, management options are currently limited beyond smoking cessation, weight reduction (when appropriate) and encouragement of regular physical activity. In the setting of mechanical abnormalities such as dynamic lung hyperinflation during exercise, a trial of a short-or long-acting bronchodilator seems warranted even as we await definitive evidence from future clinical trials of bronchodilator efficacy in mild COPD populations. At present, no treatment options are available for a minority of symptomatic patients with mild COPD who manifest features of "a microvascular phenotype" (low DLCO; high V_E/VCO_2 nadir, with or without minor centrilobular emphysema on CT) (61). Future studies that elucidate the pathogenesis of vascular injury in smokers with mild COPD will hopefully lead to the development of new targeted therapies. Finally, CPET may help identify clinically important co-morbid conditions in patient with Mild COPD that require specific therapeutic interventions.

CONCLUSIONS

"Mild COPD" is in many respects a misnomer as it mainly signifies presence of mild airflow limitation, measured by simple spirometry. It is now well-established that such individuals often have persistent troublesome symptoms, and consistently report reduced physical activity and poor health status. We now know that spirometry, while useful for defining severity of airflow limitation, can obscure extensive and heterogeneous physiological impairment of the lungs that additional tests and modern imaging techniques can reliably uncover. CPET, which examines the respiratory system under stress, is uniquely positioned to expose, in an integrated manner, the nature and extent of physiological impairment, and its negative sensory consequences. The most consistent abnormalities in

mild COPD during exercise are high inspiratory neural drive, reduced ventilatory efficiency, and early dynamic mechanical constraints to increasing ventilation as metabolic demand increases. Patients with unremarkable spirometry (and normal arterial O_2 saturation during walking) who have DLCO <LLN and high V_E/VCO_2 nadir during CPET, are more likely to experience dyspnea and reduced exercise tolerance than those who do not exhibit these features. While CPET results do not currently influence therapeutic choices on an individual basis, the information obtained provides the clinician with valuable insights into the underlying causes of exertional dyspnea in mild COPD. Moreover, CPET is potentially important in helping to define discreet physiological phenotypes of COPD (e.g., dominant microvascular dysfunction, dominant small airway dysfunction, or mixed patterns) linked to clinical outcomes. This type of deep physiological phenotyping could allow more refined structure-function analysis to ascertain the clinical relevance of morphometric abnormalities revealed by novel imaging. Ultimately, such phenotypic characterization of individuals which incorporates CPET, has the potential to guide more precise interrogation of the pathobiology of COPD to hasten the discovery of new therapeutic targets for this complex disease.

AUTHOR CONTRIBUTIONS

All authors played a role in the content and writing of all sections of the review. In addition: DO'D provided the original idea for the review. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance–United States, 1971-2000. *MMWR Surveill Summ.* (2002) 51:1–16. Available online at: https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5106a1.htm
2. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet.* (2007) 370:741–50. doi: 10.1016/S0140-6736(07)61377-4
3. Tilert T, Dillon C, Paulose-Ram R, Hnizdo E, Doney B. Estimating the US prevalence of chronic obstructive pulmonary disease using pre- and post-bronchodilator spirometry: the National Health and Nutrition Examination Survey (NHANES) 2007-2010. *Respir Res.* (2013) 14:103. doi: 10.1186/1465-9921-14-103
4. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Int Med.* (2005) 142:233–9. doi: 10.7326/0003-4819-142-4-200502150-00005
5. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American thoracic society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med.* (2012) 185:435–52. doi: 10.1164/rccm.201111-2042ST
6. Ofir D, Laveneziana P, Webb KA, Lam Y-M, O'Donnell DE. Mechanisms of dyspnea during cycle exercise in symptomatic patients with gold stage I chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (2008) 177:622–9. doi: 10.1164/rccm.200707-1064OC
7. Guenette JA, Chin RC, Cheng S, Dominelli PB, Raghavan N, Webb KA, et al. Mechanisms of exercise intolerance in global initiative for chronic obstructive lung disease grade 1 COPD. *Eur Respir J.* (2014) 44:1177–87. doi: 10.1183/09031936.00034714
8. Estepar RS, Kinney GL, Black-Shinn JL, Bowler RP, Kindlmann GL, Ross JC, et al. Computed tomographic measures of pulmonary vascular morphology in smokers and their clinical implications. *Am J Respir Crit Care Med.* (2013) 188:231–9. doi: 10.1164/rccm.201301-0162OC
9. Kirby M, Owrangi A, Svenningsen S, Wheatley A, Coxson HO, Paterson NA, et al. On the role of abnormal DL(CO) in ex-smokers without airflow limitation: symptoms, exercise capacity and hyperpolarised helium-3 MRI. *Thorax.* (2013) 68:752–9. doi: 10.1136/thoraxjnl-2012-203108
10. Chin RC, Guenette JA, Cheng S, Raghavan N, Amornputtisathaporn N, Cortes-Telles A, et al. Does the respiratory system limit exercise in mild chronic obstructive pulmonary disease? *Am J Respir Crit Care Med.* (2013) 187:1315–23. doi: 10.1164/rccm.201211-1970OC
11. Elbehairy AF, Ciavaglia CE, Webb KA, Guenette JA, Jensen D, Mourad SM, et al. Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance. *Am J Respir Crit Care Med.* (2015) 191:1384–94. doi: 10.1164/rccm.201501-0157OC
12. Elbehairy AF, O'Donnell CD, Abd Elhameed A, Vincent SG, Milne KM, James MD, et al. Low Resting diffusion capacity, dyspnea and exercise intolerance in COPD. *J Appl Physiol.* (2019) 127:1107–16. doi: 10.1152/japplphysiol.00341.2019
13. Jones NL. *The Ins And Outs of Breathing: How We Learnt About the Body's Most Vital Function*. Bloomington, IN: iUniverse Publishing (2011).
14. Olafsson S, Hyatt RE. Ventilatory mechanics and expiratory flow limitation during exercise in normal subjects. *J Clin Invest.* (1969) 48:564–73. doi: 10.1172/JCI106015
15. Jolley CJ, Luo YM, Steier J, Reilly C, Seymour J, Lunt A, et al. Neural respiratory drive in healthy subjects and in COPD. *Eur Respir J.* (2009) 33:289–97. doi: 10.1183/09031936.00093408
16. Bradley TD, Chartrand DA, Fitting JW, Killian KJ, Grassino A. The relation of inspiratory effort sensation to fatiguing patterns of the diaphragm. *Am Rev Respir Dis.* (1986) 134:1119–24.
17. Means JH. Dyspnea. In *Medical Monograph*. 5th ed. Baltimore, MD: Williams & Wilkins (1924).
18. Jolley CJ, Luo YM, Steier J, Rafferty GF, Polkey MI, Moxham J. Neural respiratory drive and breathlessness in COPD. *Eur Respir J.* (2015) 45:355–64. doi: 10.1183/09031936.00063014
19. Faisal A, Alghamdi BJ, Ciavaglia CE, Elbehairy AF, Webb KA, Ora J, et al. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am J Respir Crit Care Med.* (2016) 193:299–309. doi: 10.1164/rccm.201504-0841OC
20. O'Donnell DE, Ora J, Webb KA, Laveneziana P, Jensen D. Mechanisms of activity-related dyspnea in pulmonary diseases. *Respir Physiol Neurobiol.* (2009) 167:116–32. doi: 10.1016/j.resp.2009.01.010
21. Rodriguez-Roisin R, Drakulovic M, Rodriguez DA, Roca J, Barbera JA, Wagner PD. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. *J Appl Physiol.* (2009) 106:1902–8. doi: 10.1152/japplphysiol.00085.2009
22. Blanco I, Gimeno E, Munoz PA, Pizarro S, Gistau C, Rodriguez-Roisin R, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am J Respir Crit Care Med.* (2010) 181:270–8. doi: 10.1164/rccm.200907-0988OC
23. Hueper K, Vogel-Claussen J, Parikh MA, Austin JH, Bluemke DA, Carr J, et al. Pulmonary microvascular blood flow in mild chronic obstructive pulmonary disease and emphysema. The MESA COPD study. *Am J Respir Crit Care Med.* (2015) 192:570–80. doi: 10.1164/rccm.201411-2120OC
24. Tedjasaputra V, van Diepen S, Phillips DB, Wong EYL, Bhutani M, Michaelchuk WW, et al. Pulmonary capillary blood volume response to exercise is diminished in mild chronic obstructive pulmonary disease. *Respir Med.* (2018) 145:57–65. doi: 10.1016/j.rmed.2018.10.015
25. Ross BA, Brotto AR, Fuhr DP, Phillips DB, van Diepen S, Bryan TL, et al. The supine position improves but does not normalize the blunted pulmonary

capillary blood volume response to exercise in mild COPD. *J Appl Physiol.* (2020) 128:925–33. doi: 10.1152/japplphysiol.00890.2019
26. Vogel-Claussen J, Schönfeld C-O, Kaireit TF, Voskrebenzev A, Czerner CP, Renne J, et al. Effect of indacaterol/glycopyrronium on pulmonary perfusion and ventilation in hyperinflated COPD patients (CLAIM): a double-blind, randomised, crossover trial. *Am J Respir Crit Care Med.* (2019) 199:1086–96. doi: 10.1164/rccm.201805-0995OC
27. Behnia M, Wheatley C, Avolio A, Johnson B. Influence of resting lung diffusion on exercise capacity in patients with COPD. *BMC Pulm Med.* (2017) 17:117. doi: 10.1186/s12890-017-0454-y
28. Neder JA, Berton DC, Muller PT, O'Donnell DE. Incorporating lung diffusing capacity for carbon monoxide in clinical decision making in chest medicine. *Clin Chest Med.* (2019) 40:285–305. doi: 10.1016/j.ccm.2019.02.005
29. Barberà JA, Riverola A, Roca J, Ramirez J, Wagner PD, Ros D, et al. Pulmonary vascular abnormalities and ventilation-perfusion relationships in mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (1994) 149:423–9. doi: 10.1164/ajrccm.149.2.8306040
30. Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. *Chest.* (2005) 128:2025–34. doi: 10.1378/chest.128.4.2025
31. Ward SA, Whipp BJ. Kinetics of the ventilatory and metabolic responses to moderate-intensity exercise in humans following prior exercise-induced metabolic acidaemia. *New Front Respir Control.* (2009) 669:323–6. doi: 10.1007/978-1-4419-5692-7_66
32. Rocha A, Arbex FF, Sperandio PA, Souza A, Biazzim L, Mancuso F, et al. Excess ventilation in chronic obstructive pulmonary disease-heart failure overlap. Implications for dyspnea and exercise intolerance. *Am J Respir Crit Care Med.* (2017) 196:1264. doi: 10.1164/rccm.201704-0675OC
33. Caviedes IR, Delgado I, Soto R. Ventilatory inefficiency as a limiting factor for exercise in patients with COPD. *Respir Care.* (2012) 57:583–9. doi: 10.4187/respcare.01342
34. Moreira MA, Medeiros GA, Boeno FP, Sanches PR, Silva Junior DP, Muller AF. Oxygen desaturation during the six-minute walk test in COPD patients. *J Bras Pneumol.* (2014) 40:222–8. doi: 10.1590/S1806-37132014000300004
35. Andrianopoulos V, Franssen FM, Peeters JP, Ubachs TJ, Bukari H, Groenen M, et al. Exercise-induced oxygen desaturation in COPD patients without resting hypoxemia. *Respir Physiol Neurobiol.* (2014) 190:40–6. doi: 10.1016/j.resp.2013.10.002
36. Neder JA, Arbex FF, Alencar MC, O'Donnell CD, Cory J, Webb KA, et al. Exercise ventilatory inefficiency in mild to end-stage COPD. *Eur Respir J.* (2015) 45:377–87. doi: 10.1183/09031936.00135514
37. Patessio A, Casaburi R, Carone M, Appendini L, Donner CF, Wasserman K. Comparison of gas exchange, lactate, and lactic acidosis thresholds in patients with chronic obstructive pulmonary disease. *Am RevRespir Dis.* (1993) 148:622–6. doi: 10.1164/ajrccm/148.3.622
38. Saey D, Debigare R, LeBlanc P, Mador MJ, Cote CH, Jobin J, et al. Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (2003) 168:425–30. doi: 10.1164/rccm.200208-856OC
39. Aaron CP, Hoffman EA, Lima JAC, Kawut SM, Bertoni AG, Vogel-Claussen J, et al. Pulmonary vascular volume, impaired left ventricular filling and dyspnea: the MESA lung study. *PLoS ONE.* (2017) 12:e0176180. doi: 10.1371/journal.pone.0176180
40. Haouzi P. Venous pressure and dyspnea on exertion in cardiac failure: was Tinsley Randolph Harrison right? *Respir Physiol Neurobiol.* (2009) 167:101–6. doi: 10.1016/j.resp.2008.09.001
41. Haarmann H, Folle J, Nguyen XP, Herrmann P, Heusser K, Hasenfuß G, et al. Sympathetic activation is associated with exercise limitation in COPD. *COPD J Chronic Obstruct Pulm Dis.* (2016) 13:589–94. doi: 10.3109/15412555.2015.1136272
42. Phillips DB, Steinback CD, Collins SE, Fuhr DP, Bryan TL, Wong EYL, et al. The carotid chemoreceptor contributes to the elevated arterial stiffness and vasoconstrictor outflow in chronic obstructive pulmonary disease. *J Physiol.* (2018) 596:3233–44. doi: 10.1113/JP275762
43. Elbehairy AF, Guenette JA, Faisal A, Ciavaglia CE, Webb KA, Jensen D, et al. Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J.* (2016) 48:694–705. doi: 10.1183/13993003.00077-2016
44. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* (2006) 3:180–4. doi: 10.1513/pats.200508-093DO
45. Stubbing DG, Pengelly LD, Morse JLC, Jones NL. Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. *J Appl Physiol.* (1980) 49:511–5. doi: 10.1152/jappl.1980.49.3.511
46. Dodd DS, Brancatisano T, Engel LA. Chest wall mechanics during exercise in patients with severe chronic air-flow obstruction. *Am Rev Respir Dis.* (1984) 129:33–8.
47. Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. *N Engl J Med.* (1991) 325:917–23. doi: 10.1056/NEJM199109263251304
48. O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. *J Appl Physiol.* (2006) 101:1025–35. doi: 10.1152/japplphysiol.01470.2005
49. Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE. Inspiratory capacity during exercise: measurement, analysis, and interpretation. *PulmMed.* (2013) 2013:956081. doi: 10.1155/2013/956081
50. O'Donnell DE, Guenette JA, Maltais F, Webb KA. Decline of resting inspiratory capacity in COPD: the impact on breathing pattern, dyspnea, and ventilatory capacity during exercise. *Chest.* (2012) 141:753–62. doi: 10.1378/chest.11-0787
51. Laveneziana P, Webb KA, Ora J, Wadell K, O'Donnell DE. Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *Am J Respir Crit Care Med.* (2011) 184:1367–73. doi: 10.1164/rccm.201106-1128OC
52. O'Donnell DE, Laveneziana P, Ora J, Webb KA, Lam YM, Ofir D. Evaluation of acute bronchodilator reversibility in patients with symptoms of GOLD stage I COPD. *Thorax.* (2009) 64:216–23. doi: 10.1136/thx.2008.103598
53. O'Donnell DE, Maltais F, Porszasz J, Webb KA, Albers FC, Deng Q, et al. The continuum of physiological impairment during treadmill walking in patients with mild-to-moderate COPD: patient characterization phase of a randomized clinical trial. *PLoS One.* (2014) 9:e96574. doi: 10.1371/journal.pone.0096574
54. Elbehairy AF, Webb KA, Laveneziana P, Domnik NJ, Neder JA, O'Donnell DE. Acute bronchodilator therapy does not reduce wasted ventilation during exercise in COPD. *Respir physiol Neurobiol.* (2018) 252–253:64–71. doi: 10.1016/j.resp.2018.03.012
55. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest.* (1984) 85:751–8. doi: 10.1378/chest.85.6.751
56. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest.* (1988) 93:580–6. doi: 10.1378/chest.93.3.580
57. Roig M, Eng JJ, MacIntyre DL, Road JD, Reid WD. Deficits in muscle strength, mass, quality, and mobility in people with chronic obstructive pulmonary disease. *J Cardio Pulm Rehabil Prev.* (2011) 31:120–4. doi: 10.1097/HCR.0b013e3181f68ae4
58. Neder JA, Berton DC, Muller PT, Elbehairy AF, Rocha A, Palange P, et al. Ventilatory inefficiency and exertional dyspnea in early chronic obstructive pulmonary disease. *Ann Am Thorac Soc.* (2017) 14:S22–9. doi: 10.1513/AnnalsATS.201612-1033FR
59. Ciavaglia CE, Guenette JA, Langer D, Webb KA, Alberto NJ, O'Donnell DE. Differences in respiratory muscle activity during cycling and walking do not influence dyspnea perception in obese patients with COPD. *J Appl Physiol.* (2014) 117:1292–301. doi: 10.1152/japplphysiol.00502.2014
60. Ora J, Laveneziana P, Wadell K, Preston M, Webb KA, O'Donnell DE. Effect of obesity on respiratory mechanics during rest and exercise in COPD. *J Appl Physiol.* (2011) 111:10–9. doi: 10.1152/japplphysiol.01131.2010

61. Neder JA, Milne KM, Berton DC, de-Torres JP, Jensen D, Tan WC, et al. Exercise tolerance according to the definition of airflow obstruction in smokers. *Am J Respir Crit Care Med.* doi: 10.1164/rccm.202002-0298LE. [Epub ahead of print].

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MINI REVIEW
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Evaluation of Dynamic Respiratory Mechanical Abnormalities During Conventional CPET

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Assessment of the ventilatory response to exercise is important in evaluating mechanisms of dyspnea and exercise intolerance in chronic cardiopulmonary diseases. The characteristic mechanical derangements that occur during exercise in chronic respiratory conditions have previously been determined in seminal studies using esophageal catheter pressure-derived measurements. In this brief review, we examine the emerging role and clinical utility of conventional assessment of dynamic respiratory mechanics during exercise testing. Thus, we provide a physiologic rationale for measuring operating lung volumes, breathing pattern, and flow–volume loops during exercise. We consider standardization of inspiratory capacity-derived measurements and their practical implementation in clinical laboratories. We examine the evidence that this iterative approach allows greater refinement in evaluation of ventilatory limitation during exercise than traditional assessments of breathing reserve. We appraise the available data on the reproducibility and responsiveness of this methodology. In particular, we review inspiratory capacity measurement and derived operating lung volumes during exercise. We demonstrate, using recent published data, how systematic evaluation of dynamic mechanical constraints, together with breathing pattern analysis, can provide valuable insights into the nature and extent of physiological impairment contributing to exercise intolerance in individuals with common chronic obstructive and restrictive respiratory disorders.

Keywords: respiratory physiology, dyspnea, respiratory mechanics, inspiratory capacity, cardiopulmonary exercise test

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INTRODUCTION

Assessment of the ventilatory response to exercise is important in evaluating mechanisms of dyspnea and exercise intolerance in cardiopulmonary diseases (1). The value of the information obtained during cardiopulmonary exercise tests (CPETs) is dependent on the degree to which physiological processes are accurately represented; the quality, reliability, and responsiveness of the measurements; and the interpretation of data to meaningfully impact clinical care. The insights provided by invasive respiratory mechanics using esophageal catheter techniques inform an understanding of respiratory system function during exercise. Although employed in research

settings for assessment of respiratory mechanics, during clinical CPETs, esophageal catheter insertion can be cumbersome and time-consuming. Simple, low-cost, non-invasive methods to assess respiratory mechanics in the clinical setting are therefore needed and are the focus of the current review.

Ventilatory limitation is traditionally measured as the ratio of ventilation (V_E) at peak exercise to measured or estimated maximal voluntary ventilation (V_E/MVV), with a ratio >85% used to identify ventilation as the cause of reduced exercise capacity (1). Measured MVV during hyperpnea at rest differs from peak exercise V_E in respiratory muscle recruitment, operating lung volumes, and breathing pattern (2). Additionally, a high V_E/MVV provides little information about the specific factors limiting the ventilatory response to exercise in the individual. Patients may perceive intolerable dyspnea during exercise before criteria defining ventilatory limitation are reached. In chronic obstructive pulmonary disease (COPD), 20–50% of patients experience exercise-limiting dyspnea in the setting of sufficient breathing reserve (3, 4). Relying solely on breathing reserve to assess ventilatory response may therefore underestimate physiologic impairment. Measurement of operating lung volumes including end-inspiratory lung volume (EILV), end-expiratory lung volume (EELV), and inspiratory reserve volume (IRV) can be derived from inspiratory capacity (IC) and tidal volume (V_T) measurement throughout exercise in combination with resting total lung capacity (TLC) (EILV = EELV + V_T, EELV = TLC – IC, and IRV = IC – V_T). Exercise flow–volume loops (FVLs) can provide complementary qualitative assessment of airflow limitation (5). Analysis of operating lung volumes, FVLs, and breathing pattern provides insight into mechanical constraints contributing to exercise limitation and dyspnea, avoiding sole reliance on breathing reserve to define ventilatory limitation (5).

Our objective is to provide a brief synopsis of characteristic respiratory mechanical responses to exercise, important assumptions, and limitations involved in measuring operating lung volumes using conventional IC maneuvers, and the rationale for these measurements as they apply to clinical CPET for the frontline clinician. We briefly review recommendations and resources for IC maneuver measurement and available evidence for reliability and reproducibility as well as present a rationale for interpreting operating lung volumes. Finally, we comment on the responsiveness of these dynamic measurements to therapeutic interventions. Other non-invasive methods of assessing respiratory mechanics (e.g., gas dilution techniques and optoelectronic plethysmography) are beyond the scope of this mini-review targeted for clinicians. We direct the interested reader to other recently published reviews on this topic (3, 4).

RESPIRATORY MECHANICS IN HEALTH AND DISEASE

Dynamic Respiratory Mechanics in Health

In health, V_E increases in response to the metabolic demands of exercise by increases in V_T and breathing frequency (f_B). V_T expansion reaches an inflection point at 50–60% of the resting vital capacity (VC), and subsequent rises in V_E are secondary to increased f_B (**Figures 1C,D**) (6). In young individuals (<35 years old), V_T expands with an increase in EILV and decrease in EELV (**Figure 2A**) (7). In contrast to passive expiration at rest, recruitment of expiratory muscles during exercise leads to a decrease in EELV. This permits V_T to expand within the linear compliant portion of the respiratory system pressure–volume curve (**Figure 2A**). This delays the point during exercise when IRV reaches its lowest value (i.e., EILV is 90–95% of TLC), and the inspiratory muscles must contend with increased elastic mechanical loading (**Figure 1B**) (8, 9).

FVLs collected during exercise provide a visual representation of V_T expansion relative to available capacity. Expiratory flow limitation (EFL) is dependent on the adopted breathing pattern, dynamic EILV and EELV, and maximum FVL (5). EFL can be qualitatively assessed as the percentage of V_T over which expiratory airflow is superimposed on or exceeds the maximal flow–volume envelope (**Figure 1E**) (5). With this approach, establishing an accurate maximal FVL is essential, and without accounting for the influence of thoracic gas compression during forced maneuvers and exercise induced changes in airway caliber overestimation of EFL may result (14). Assessment of maximal FVLs before and after exercise is therefore important. Concavity of the FVL expiratory limb has been associated with dynamic hyperinflation (DH) in severe COPD (15). EFL can be quantitatively assessed using negative expiratory pressure, where application of a standardized negative pressure during expiration and assessment of corresponding changes in expiratory flow are used to determine flow limitation (16–18).

Changes of the respiratory system in healthy aging (>70 years old) have previously been reviewed and include increased lung compliance, decreased chest wall compliance, increased EFL, and elevated ventilatory demand (19). During exercise, EFL occurs at lower V_E, and both EFL and increased EELV above resting values are more frequently observed at peak exercise in older individuals compared to young adults (20–23). The differences in exertional breathlessness observed in older adults are at least in part related to increased awareness of V_E and changes in respiratory mechanical responses during exercise (23–26).

Dynamic Respiratory Mechanics in Chronic Lung Disease

Defining Critical Respiratory Mechanical Constraints

In chronic lung disease, pathology of the lung parenchyma, chest wall, airways, and pulmonary vasculature alter respiratory system compliance, airway resistance, and pulmonary gas exchange, which in variable combination have a deleterious impact on exercise capacity (see reviews in this issue by Devin Phillips, "Measurement and interpretation of ventilatory efficiency during exercise," and by Denis O'Donnell, "An integrative approach to clinical CPET interpretation"). Increased exertional dyspnea intensity in chronic lung disease is closely related to increased magnitude of inspiratory neural drive (IND) (11) (see review in this issue by Matthew James, "Dyspnea and exercise limitation in COPD: the value of CPET"). Respiratory sensation becomes increasingly unpleasant as

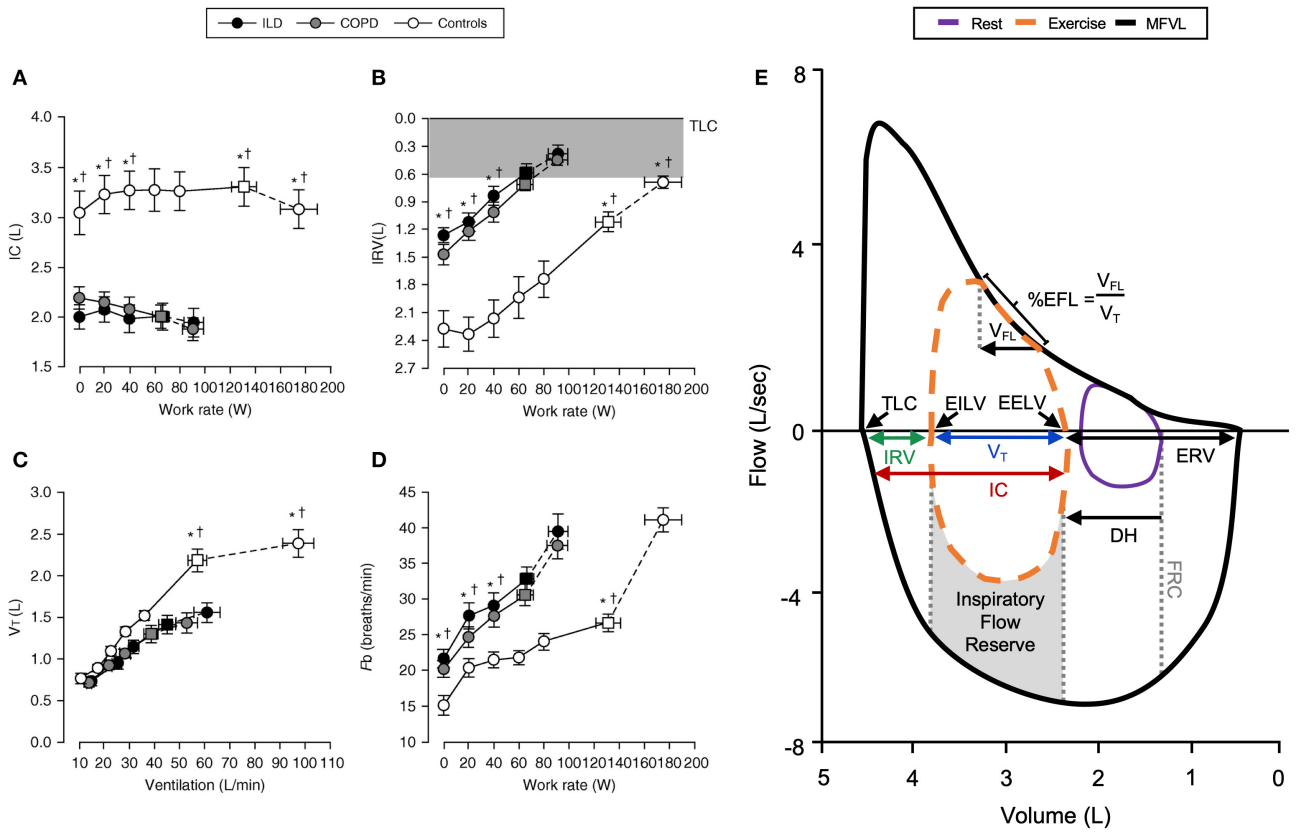

FIGURE 1 | Representative changes in **(A)** inspiratory capacity, **(B)** inspiratory reserve volume, **(C)** tidal volume, and **(D)** breathing frequency in COPD, ILD, and healthy controls during incremental exercise. Note the reduced IC and early critical reduction in IRV with corresponding V_T plateau in COPD and ILD subjects. Values are mean ± SEM. $^*p < 0.05$ for ILD vs. control, $^\dagger p < 0.05$ for COPD vs. control. Representative flow–volume loop observed in COPD **(E)** demonstrating operating lung volumes, dynamic hyperinflation, and expiratory flow limitation. COPD, chronic obstructive pulmonary disease; DH, dynamic hyperinflation; EELV, end-expiratory lung volume; EFL, expiratory flow limitation; EILV, end-inspiratory lung volume; ERV, expiratory reserve volume; Fb, breathing frequency; FRC, functional residual capacity; IC, inspiratory capacity; ILD, interstitial lung disease; IRV, inspiratory reserve volume; MFVL, resting maximal flow–volume loop; TLC, total lung capacity; V_{FL}, volume of tidal breath that is flow limited; V_T, tidal volume. Reprinted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved Faisal et al. (11). The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society (11). Adapted from Guenette et al. (10).

neuromechanical dissociation develops, marking the point where increased IND is met with reduced ability of the respiratory system to match increased demand (27). Development of critical respiratory mechanical constraint is defined by the point at which IRV is reduced (within 0.5–1 L of TLC and EILV/TLC > 90–95%), V_T expansion has reached an inflection or plateau (occurring at V_T/IC ∼ 70%, identified when V_T is plotted against V_E), and a pronounced increase in dyspnea severity and alteration in its quality (i.e., onset of "unsatisfied inspiration") occurs (6, 28–30). Importantly, in combination with measures of ventilatory inefficiency, critical mechanical constraints are a more robust predictor of exertional dyspnea and peak VO_2 compared with breathing reserve (31).

Dynamic Respiratory Mechanics in COPD

In COPD, increased lung compliance and EFL due to emphysematous parenchymal destruction and airway remodeling increase the heterogeneity of mechanical time constants for lung emptying. Under the stress of exercise, in the setting of EFL and increased V_E, there is insufficient time for complete lung emptying, and normal reduction of EELV is impaired (**Figures 1E,2B**) (32). Progressive increase in EELV during exercise (i.e., DH) undermines the optimal positioning of V_T on the pressure–volume curve of the respiratory system (**Figure 2B**), and dynamic lung compliance decreases while EELV increases in the setting of stable TLC (11, 32, 33). Progressive reduction of IC and IRV during exercise indirectly reflects increased intrinsic elastic mechanical loading of the inspiratory muscles. In flow-limited patients, the IC represents the operating limits for V_T expansion during exercise (30, 34, 35). Thus, as IC is reduced, compensatory tachypnea is the only means to increase V_E (**Figure 1D**). Identification of the V_T inflection or plateau plotted against V_E (**Figure 1C**) corresponds with the point where IRV reaches a critical minimal (**Figure 1B**) value in the face of increasing IND.

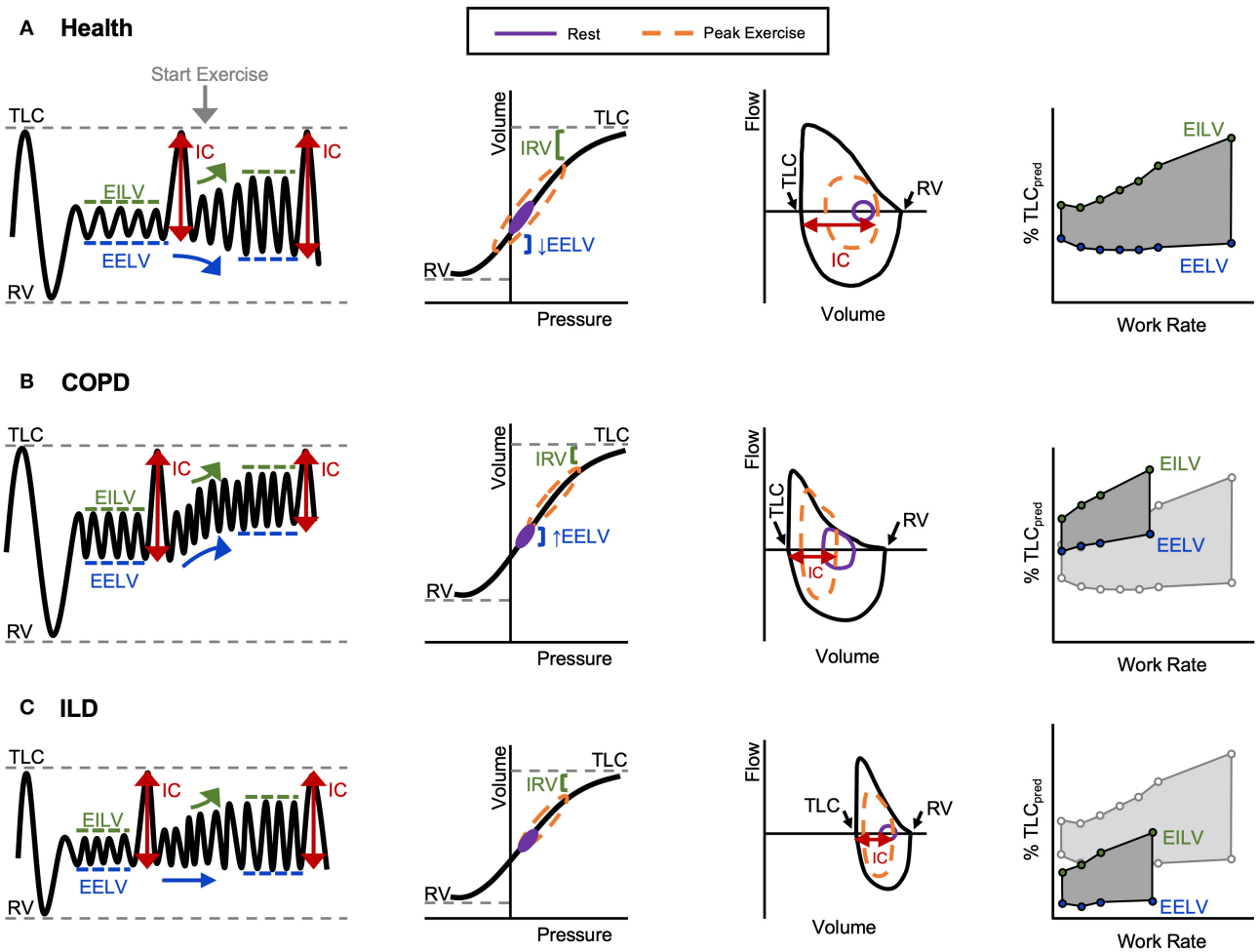

FIGURE 2 | Representative volume–time, pressure–volume, flow–volume, and operating lung volume relationships during exercise observed in **(A)** healthy controls, **(B)** COPD, and **(C)** ILD. COPD, chronic obstructive pulmonary disease; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; IC, inspiratory capacity; ILD, interstitial lung disease; IRV, inspiratory reserve volume; RV, residual volume; TLC, total lung capacity. Reprinted from O'Donnell et al. (12). Copyright (2019), with permission from Elsevier (12). Reprinted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved. O'Donnell et al. (13). Proceedings of the American Thoracic Society* is an official journal of the American Thoracic Society. *Now titled Annals of the American Thoracic Society (13).

Dynamic respiratory mechanical constraints not only strongly influence the adopted breathing pattern but are also key to the development of exertional dyspnea leading to reduced exercise capacity (30, 36–42).

Dynamic Respiratory Mechanics in ILD

In ILD, lung compliance, TLC, and IRV are all reduced, and V_T expansion is constrained during exercise reflecting a low IC (11, 43). As a result, critical reduction in IRV manifests early during exercise, and V_T is positioned close to the reduced TLC and upper extreme of the contracted pressure–volume curve (**Figure 2C**). In ILD patients with airway involvement, V_T expansion may additionally be restricted due to EFL and an increase in EELV (44, 45). Importantly, in these examples, the classically observed rapid shallow breathing pattern (**Figures 1C,D**) is a response to the reduced compliance of the respiratory system resulting from restriction of IC and IRV (**Figures 1A,B**). In both obstructive (COPD) and restrictive (ILD) diseases, "high-end" dynamic mechanics with increased elastic loading, restriction of V_T expansion, and relative tachypnea together contribute to functional respiratory muscle weakness, increased work of breathing, IND, and dyspnea (11).

Dynamic Respiratory Mechanics in Other Chronic Lung Diseases

Beyond the examples of COPD and ILD, changes in operating lung volumes during exercise have been observed in obesity (46), cystic fibrosis (47), and pulmonary arterial hypertension (PAH) (48). However, unlike healthy, COPD, and ILD populations, the assumptions underpinning IC-derived measurements outlined in the following section have not as yet been robustly investigated in these populations.

KEY ASSUMPTIONS AND LIMITATIONS OF IC-DERIVED OPERATING LUNG VOLUMES

Validity

IC-derived measurements have been shown to be a valid representation of respiratory mechanics during exercise when performed in conjunction with invasive evaluations using esophageal manometry (29, 49, 50). This has been most thoroughly assessed in COPD patients, and validation of IC-derived techniques in diverse patient populations is needed. IC is determined by the degree of lung hyperinflation and inspiratory muscle strength. Determination of changes in operating lung volumes assumes that changes in IC represent inverse changes in EELV during exercise. Thus, TLC and static inspiratory muscle strength at end-exercise must be similar to values generated at rest for reliable results (7, 33, 49). Stability of TLC during exercise has been demonstrated in healthy, COPD, and ILD populations (33, 45, 46). Furthermore, esophageal pressure (Pes) measured at peak inspired volume plateau (Pes at zero flow following IC) is stable during incremental CPET performed to symptom limitation in COPD (49). When expressed as a percentage of Pes during IC at rest, Pes at symptom limited peak exercise IC exceeds 90% of resting values (49). Additionally, preservation of inspiratory muscle strength assessed using maximal inspiratory pressure (MIP) and sniff Pes pre- and post-exercise demonstrates that respiratory muscle strength can be maintained during exercise (29, 37, 38, 40, 42, 50–53). Taken together, stability of TLC and preservation of Pes-derived assessment of respiratory muscle strength pre- and post-exercise as well as dynamically during exercise IC maneuvers provides evidence that changes in IC reflect changes in operating lung volumes.

Potential Limitations

Reliable IC-derived measurements additionally assume that maximal volitional effort results in maximal diaphragm activation. The diaphragm has been demonstrated to be maximally activated during voluntary effort in patients with COPD (54). Although maximal voluntary activation of the diaphragm is possible, reproducibility is challenging (55). A recently published study by Luo et al. demonstrated that in some severe COPD patients, IC measurements and associated diaphragm activation (assessed using diaphragmatic electromyography) were submaximal in comparison to supraphysiological experimental stimulation (inhaled 8% CO_2 gas mixture) (56). Assessing reproducible maximal volitional effort during IC maneuvers can be challenging in the clinical setting, and if patients are not able to perform reproducible IC maneuvers at rest, exercise measurements should not be performed.

Stability of TLC, preservation of maximal voluntary Pes during IC maneuvers, and the voluntary ability to maximally activate the diaphragm support the rationale for using IC maneuvers to measure operating lung volumes. Important clinical scenarios that limit the validity of IC-derived measurements to assess respiratory mechanics include respiratory muscle weakness (failure to successfully reach TLC during IC maneuver can lead to erroneous conclusion of DH), leak during IC maneuver (inability to maintain mouthpiece seal, e.g., bulbar muscle weakness), and inability of the patient to perform reproducible resting IC maneuvers. Additionally, IC-derived measurement of operating lung volumes cannot assess the contribution of chest wall mechanics directly during exercise, and added dead space of mouthpieces may influence breathing patterns. Clinicians should be alert to these situations and consider employing alternative tools for assessment of respiratory mechanics to avoid unreliable operating lung volume measurements.

PERFORMING HIGH-QUALITY REPRODUCIBLE IC MEASUREMENTS

Quality Assessment

To obtain reliable and reproducible measurements, IC maneuvers should be performed using a standardized approach. Factors that can interfere with the quality of IC measurements include insufficient instruction, inadequate number of pre-maneuver tidal breaths for assessment of EELV, unstable EELV due to anticipatory changes in breathing patterns, and inadequate effort (10). Quality control considerations, procedures for IC maneuvers, and strategies for ensuring a stable EELV prior to IC measurement are summarized in **Table 1** (10, 53). Interested readers are directed to a review by Guenette et al. that describes IC procedures and instructions in detail (10). International guidelines recommend that at least three acceptable resting IC maneuvers be performed and that the mean value of all acceptable resting IC maneuvers be reported (57, 58). IC measurement can be performed during constant work rate (CWR) (59–61) and incremental (62) CPET during both treadmill and cycle exercises (36, 63, 64). During incremental CPET, stepwise increases in work rate as opposed to ramp protocols are preferred so that V_E reaches relative stability during each incremental stage when an IC maneuver is performed (10).

Reproducibility

IC measurements at rest, submaximal, and peak exercise are highly reproducible over time (34, 53, 65, 66). Within-subject coefficient of variation for IC during exercise is 12–20% and has been reported to be higher at end-exercise (34, 65, 66). During CWR CPET performed in a multicenter clinical trial of patients with moderate to severe COPD, IC values at rest, iso-time, and end-exercise are highly repeatable between visits (intraclass correlation $R \geq 0.87$) (66, 67).

INTERPRETATION OF OPERATING LUNG VOLUMES

Operating lung volumes can be plotted vs. work rate, oxygen consumption (VO_2), or V_E during exercise (14, 30, 34). Concurrent displays of breathing pattern and FVLs add further refinement to the evaluation of dynamic mechanics. Operating lung volumes should preferably be shown with values derived from healthy age- and sex-matched controls from the same

TABLE 1 | Key steps in IC maneuver performance during CPET.

Prior to IC assessment	Technical considerations	• Use of bidirectional flow-sensing devices for integrated calculation of volume. Measurement of inspiratory and expiratory volumes is important for assessment of EELV and breathing pattern during IC maneuvers (10, 57, 65). • Breath-by-breath cardiopulmonary exercise metabolic system that accounts for thermodynamic drift (5, 65). • The technician conducting the exercise test should be able to view volume–time and/or flow–volume loop tracings preceding and during IC maneuvers.
	Clinical considerations	• Review presence of illness that may impact reliability of IC-derived operating lung volumes during exercise (e.g., respiratory muscle weakness and bulbar muscle weakness). • Consider need for alternative or invasive assessment of respiratory mechanics in patients in whom IC-derived measurements may not be reliable.
Resting IC assessment	Preparation and instructions	1. **General description of IC maneuver**: *"During the resting period and during each stage of exercise, you will be asked to take a deep breath in until your lungs are completely full. To do this, you will finish your normal breath out then fill up your lungs quickly until you are all the way full. When you can't get any more air in and are completely full, then you can go back to normal breathing"* (10). 2. **Demonstration of IC maneuver** by technician conducting the exercise test demonstrating normal stable breathing pattern followed by complete inhalation to TLC quickly and without hesitation during IC maneuver. 3. **Review instructions for initiation of IC maneuver** in order to obtain reproducible measurements at rest. Instructions may be tailored in response to anticipatory changes in breathing pattern by the patient as outlined below (66): • *"At the end of a normal breath out, take a deep breath all the way in until you are completely full"* (10, 53). This instruction may be given when anticipatory changes in breathing pattern are not observed prior to IC maneuvers. • *"At the end of this next breath out, take a deep breath all the way in until you are completely full"* (10, 53). This instruction may be helpful in patients who exhibit anticipatory changes prior to IC maneuvers. • *"Breath all the way in on this breath"* (10). This instruction may be given when anticipatory changes in breathing pattern are not successfully overcome with other sets of instructions, review of the technique, and demonstration. Timing of providing this instruction can be challenging, particularly at high exercise intensities. 4. **Repeat resting IC measurement** following a minimum of 60 s and only after breathing pattern has returned to pre-maneuver baseline. 5. **Verbal encouragement** during IC maneuvers to encourage patients to maximally inhale to TLC may be given; however, during research studies, it is particularly important for encouragement to be standardized.
	Quality assessment	• Acceptable IC measurement must not include cough, swallowing, evidence of an obstructed mouthpiece, or mouthpiece leak in the tidal breaths preceding or during the IC maneuver (57). • See *Dynamic IC assessment* below re: EELV. • Although current guidelines do not include reproducibility criteria for resting IC maneuvers (57), values within 10% of the largest acceptable value are frequently used as a threshold for reproducibility (66). • The mean of acceptable values should be reported (57).
Dynamic IC assessment	Preparation and instructions	• **Provide instructions for collection of peak exercise IC** prior to commencing exercise test: *"During this exercise test the goal is for you to exercise as long as you can until you feel you can't exercise any longer. When you feel you have 10–15 s left, give us a warning wave with your hand so that we can collect the final breathing maneuver"* (10).
	Quality assessment	• EELV assessment prior to IC maneuvers should include a minimum of four tidal breaths (10). • Breathing pattern (depth, frequency, and timing) and EELV should be stable prior to each IC maneuver (10, 65). Anticipatory changes in breathing pattern prior to IC maneuvers can frequently be overcome with adjustment of instructions during preparation at rest, see *Resting IC assessment* above. • EELV during expiration immediately prior to an IC maneuver may frequently overestimate or underestimate EELV, and in this case, the mean EELV for the breaths preceding the IC prompt should be used (65, 66). • Variability in EELV may reflect a mouthpiece leak, and patients should be reminded to maintain a seal on the mouthpiece. • IC measurements following unstable EELV should be discarded. Generally, during dynamic IC measurement, IC maneuvers are not repeated until the next planned interval. • Peak exercise IC during a CPET performed to symptom limitation should be obtained immediately prior to exercise cessation (10).

CPET, cardiopulmonary exercise test; EELV, end-expiratory lung volume; IC, inspiratory capacity; TLC, total lung capacity.

laboratory. When health and disease are compared, expressing values as a percentage of predicted TLC is appropriate, especially when disease alters TLC (10). When reporting individual data, expressing volumes in absolute values or as a percentage of measured TLC may be preferred (10). FVL analysis provides qualitative estimation of EFL and graphic displays of change in operating lung volumes when tidal FVLs are carefully placed on the absolute lung volume axis using serial IC maneuvers and resting TLC (5).

The methodology for describing operating lung volume behavior during exercise is most extensively described in COPD. Change in IC from rest to end-exercise is an accepted assessment of DH (34). An absolute volume threshold to define DH has been debated in the literature. The limitations of an absolute volume

definition potentially neglect the importance of interpreting any change in EELV as it relates to development of critical respiratory mechanical constraints, symptoms, and exercise intolerance. Change in IC during exercise should be interpreted in the context of the resting baseline value and critical reduction in IRV during exercise. The advantage of interpreting operating lung volumes and breathing pattern variables together during CPET is the ability to assess the integrated physiologic response to a standardized exercise task. Slopes of IC over time, VO_2, or V_E provide insight into submaximal changes in respiratory mechanics but may not follow a linear relationship (34). In studies comparing effects of bronchodilators with placebo, it is important to additionally assess whether the slope of IC throughout exercise was reduced (i.e., reduced rate of DH) or whether the slope is unchanged but is shifted downward in parallel to placebo, as often is the case. Both a reduced rate of DH and downward shift of EELV and EILV following bronchodilator therapy will delay onset of critical respiratory mechanical constraints, dyspnea, and allow for a longer exercise endurance time.

OPERATING LUNG VOLUME RESPONSIVENESS TO THERAPY

In COPD, a low resting IC usually reflects lung hyperinflation, and as a result, V_T expansion and increase in V_E are limited from the outset of exercise. Resting IC values are correlated with peak VO_2 (36). Furthermore, IC/TLC is related to mortality, acute exacerbation risk, and development of dyspnea in COPD (30, 68–71). DH is associated with increased mortality (72). Improvement in IC >0.14 L (or 4.5% predicted) exceeds 95% confidence intervals and is associated with significant clinically meaningful improvements in exercise endurance time (36).

Significant improvement in operating lung volumes are highly correlated with reduced exertional dyspnea in COPD following treatment with bronchodilators (34, 59, 60, 73–83). Hyperoxia in both ILD and COPD, by reducing IND and breathing frequency, delays the onset of critical mechanical constraints and extends exercise endurance time (36, 43, 84). In COPD, the effects of bronchodilators and oxygen are additive (85). Exercise training programs in COPD lead to a decrease in IND, V_E, and breathing frequency, thought to reflect a delay in metabolic acidosis in the subset of patients able to achieve physiologic training effects, in turn delaying onset of ventilatory constraints (86–90). Pulmonary rehabilitation improves exercise capacity in ILD patients, and the ongoing multicenter HOPE-IPF study examines the combined effect of exercise training and oxygen (91–95). During exercise while breathing heliox (21% O_2 and 79% He) in COPD, a lower gas density of helium leads to decreased airflow resistance, V_E, and DH (96–98). Bullectomy and lung volume reduction surgery improve static lung elastic recoil, DH, and respiratory muscle function in COPD (99–101). The impact of these interventions and the underlying mechanisms of improvement can be deduced by measuring dynamic respiratory mechanics.

CONCLUSIONS

Operating lung volumes measured throughout exercise provide an assessment of dynamic respiratory mechanics in the clinical setting. IC maneuvers during exercise are simple to perform and, provided sufficient attention is applied, are accurate and reproducible, providing important information about the cause of dyspnea and exercise limitation on an individual basis. Non-invasive measurement of operating lung volumes offers insight into the development of critical respiratory mechanical constraints during exercise, which have been shown to better predict VO_2 and dyspnea than traditional indices of breathing reserve.

Widespread adoption of conventional IC-derived non-invasive mechanics assessment in clinical CPET awaits development of normative population ranges for operating lung volumes throughout exercise and assessment of reliability in diverse patient populations. Standardized methods for data display and quality control using commercial metabolic carts will facilitate integrating these important physiologic measurements in clinical CPET so as to advance individualized clinical evaluation and management of symptomatic patients.

AUTHOR CONTRIBUTIONS

DO'D conceived the idea for the manuscript. KM wrote the first draft of the manuscript. KM, ND, DP, MJ, SV, JN, and DO'D provided critical review and revision of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article.

REFERENCES

1. American Thoracic Society and American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* (2003) 167:211–77. doi: 10.1164/rccm.167.2.211
2. Klas JV, Dempsey JA. Voluntary versus reflex regulation of maximal exercise flow: volume loops. *Am Rev Respir Dis.* (1989) 139:150–6. doi: 10.1164/ajrccm/139.1.150
3. Massaroni C, Carraro E, Vianello A, Miccinilli S, Morrone M, Levai IK, et al. Optoelectronic plethysmography in clinical practice and research: a review. *Respiration*. (2017) 93:339–54. doi: 10.1159/000462916
4. Houssein A, Ge D, Gastinger S, Dumond R, Prioux J. Estimation of respiratory variables from thoracoabdominal breathing distance: a review of different techniques and calibration methods. *Physiol Meas.* (2019) 40:03TR1. doi: 10.1088/1361-6579/ab0b63
5. Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest*. (1999) 116:488–503. doi: 10.1378/chest.116.2.488
6. Hey EN, Lloyd BB, Cunningham DJ, Jukes MG, Bolton DP. Effects of various respiratory stimuli on the depth and frequency of breathing in man. *Respir Physiol.* (1966) 1:193–205. doi: 10.1016/0034-5687(66)90016-8

7. Stubbing DG, Pengelly LD, Morse JL, Jones NL. Pulmonary mechanics during exercise in normal males. *J Appl Physiol Respir Environ Exerc Physiol.* (1980) 49:506–10. doi: 10.1152/jappl.1980.49.3.506
8. Henke KG, Sharratt M, Pegelow D, Dempsey JA. Regulation of end-expiratory lung volume during exercise. *J Appl Physiol.* (1985) 64:135–46. doi: 10.1152/jappl.1988.64.1.135
9. Younes M, Kivinen G. Respiratory mechanics and breathing pattern during and following maximal exercise. *J Appl Physiol Respir Environ Exerc Physiol.* (1984) 57:1773–82. doi: 10.1152/jappl.1984.57.6.1773
10. Guenette JA, Chin RC, Cory JM, Webb KA, O'Donnell DE. Inspiratory capacity during exercise: measurement, analysis, and interpretation. *Pulm Med*. (2013) 2013:956081. doi: 10.1155/2013/956081
11. Faisal A, Alghamdi BJ, Ciavaglia CE, Elbehairy AF, Webb KA, Ora J, et al. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am J Respir Crit Care Med.* (2016) 193:299–309. doi: 10.1164/rccm.201504-0841OC
12. O'Donnell DE, Milne KM, Vincent SG, Neder JA. Unraveling the causes of unexplained dyspnea: the value of exercise testing. *Clin Chest Med.* (2019) 40:471–99. doi: 10.1016/j.ccm.2019.02.014
13. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* (2006) 3:180–4. doi: 10.1513/pats.200508-093DO
14. Guenette JA, Dominelli PB, Reeve SS, Durkin CM, Eves ND, Sheel AW. Effect of thoracic gas compression and bronchodilation on the assessment of expiratory flow limitation during exercise in healthy humans. *Respir Physiol Neurobiol.* (2010) 170:279–86. doi: 10.1016/j.resp.2010.01.017
15. Varga J, Casaburi R, Ma S, Hecht A, Hsia D, Somfay A, et al. Relation of concavity in the expiratory flow-volume loop to dynamic hyperinflation during exercise in COPD. *Respir Physiol Neurobiol.* (2016) 234:79–84. doi: 10.1016/j.resp.2016.08.005
16. Valta P, Corbeil C, Lavoie A, Campodonico R, Koulouris N, Chasse M, et al. Detection of expiratory flow limitation during mechanical ventilation. *Am J Respir Crit Care Med.* (1994) 150(5 Pt 1):1311–7. doi: 10.1164/ajrccm.150.5.7952558
17. Koulouris NG, Valta P, Lavoie A, Corbeil C, Chasse M, Braidy J, et al. A simple method to detect expiratory flow limitation during spontaneous breathing. *Eur Respir J*. (1995) 8:306–13. doi: 10.1183/09031936.95.08020306
18. Koulouris NG, Dimopoulou I, Valta P, Finkelstein R, Cosio MG, Milic-Emili J. Detection of expiratory flow limitation during exercise in COPD patients. *J Appl Physiol.* (1985) 82:723–31. doi: 10.1152/jappl.1997.82.3.723
19. Jensen D, Ofir D, O'Donnell DE. Effects of pregnancy, obesity and aging on the intensity of perceived breathlessness during exercise in healthy humans. *Respir Physiol Neurobiol.* (2009) 167:87–100. doi: 10.1016/j.resp.2009.01.011
20. Frank NR, Mead J, Ferris BG Jr. The mechanical behavior of the lungs in healthy elderly persons. *J Clin Invest.* (1957) 36:1680–7. doi: 10.1172/JCI103569
21. Johnson BD, Reddan WG, Pegelow DF, Seow KC, Dempsey JA. Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. *Am Rev Respir Dis.* (1991) 143(5 Pt 1):960–7. doi: 10.1164/ajrccm/143.5_Pt_1.960
22. Johnson BD, Reddan WG, Seow KC, Dempsey JA. Mechanical constraints on exercise hyperpnea in a fit aging population. *Am Rev Respir Dis.* (1991) 143(5 Pt 1):968–77. doi: 10.1164/ajrccm/143.5_Pt_1.968
23. Molgat-Seon Y, Dominelli PB, Ramsook AH, Schaeffer MR, Molgat Sereacki S, Foster GE, et al. The effects of age and sex on mechanical ventilatory constraint and dyspnea during exercise in healthy humans. *J Appl Physiol.* (2018) 124:1092–106. doi: 10.1152/japplphysiol.00608.2017
24. DeLorey DS, Babb TG. Progressive mechanical ventilatory constraints with aging. *Am J Respir Crit Care Med.* (1999) 160:169–77. doi: 10.1164/ajrccm.160.1.9807045
25. Killian KJ, Summers E, Jones NL, Campbell EJ. Dyspnea and leg effort during incremental cycle ergometry. *Am Rev Respir Dis.* (1992) 145:1339–45. doi: 10.1164/ajrccm/145.6.1339
26. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Sex differences in the perceived intensity of breathlessness during exercise with advancing age. *J Appl Physiol.* (2008) 104:1583–93. doi: 10.1152/japplphysiol.00079.2008
27. O'Donnell DE, Ora J, Webb KA, Laveneziana P, Jensen D. Mechanisms of activity-related dyspnea in pulmonary diseases. *Respir Physiol Neurobiol.* (2009) 167:116–32. doi: 10.1016/j.resp.2009.01.010
28. Casaburi R, Rennard SI. Exercise limitation in chronic obstructive pulmonary disease. The O'Donnell threshold. *Am J Respir Crit Care Med.* (2015) 191:873–5. doi: 10.1164/rccm.201501-0084ED
29. Laveneziana P, Webb KA, Ora J, Wadell K, O'Donnell DE. Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *Am J Respir Crit Care Med.* (2011) 184:1367–73. doi: 10.1164/rccm.201106-1128OC
30. O'Donnell DE, Guenette JA, Maltais F, Webb KA. Decline of resting inspiratory capacity in COPD: the impact on breathing pattern, dyspnea, and ventilatory capacity during exercise. *Chest.* (2012) 141:753–62. doi: 10.1378/chest.11-0787
31. Neder JA, Berton DC, Marillier M, Bernard AC, O'Donnell DE, Canadian Respiratory Research Network. Inspiratory constraints and ventilatory inefficiency are superior to breathing reserve in the assessment of exertional dyspnea in COPD. *COPD*. (2019) 16:174–81. doi: 10.1080/15412555.2019.1631776
32. Potter WA, Olafsson S, Hyatt RE. Ventilatory mechanics and expiratory flow limitation during exercise in patients with obstructive lung disease. *J Clin Invest.* (1971) 50:910–9. doi: 10.1172/JCI106563
33. Stubbing DG, Pengelly LD, Morse JL, Jones NL. Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. *J Appl Physiol Respir Environ Exerc Physiol.* (1980) 49:511–5. doi: 10.1152/jappl.1980.49.3.511
34. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (1998) 158(5 Pt 1):1557–65. doi: 10.1164/ajrccm.158.5.9804004
35. O'Donnell DE, Elbehairy AF, Webb KA, Neder JA, Canadian Respiratory Research Network. The link between reduced inspiratory capacity and exercise intolerance in chronic obstructive pulmonary disease. *Ann Am Thorac Soc.* (2017) 14(Suppl 1):S30–9. doi: 10.1513/AnnalsATS.201610-834FR
36. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (2001) 164:770–7. doi: 10.1164/ajrccm.164.5.2012122
37. O'Donnell DE, Bertley JC, Chau LK, Webb KA. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med.* (1997) 155:109–15. doi: 10.1164/ajrccm.155.1.9001298
38. O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. *J Appl Physiol.* (1985). (2006) 101:1025–35. doi: 10.1152/japplphysiol.01470.2005
39. Elbehairy AF, Ciavaglia CE, Webb KA, Guenette JA, Jensen D, Mourad SM, et al. Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance. *Am J Respir Crit Care Med.* (2015) 191:1384–94. doi: 10.1164/rccm.201501-0157OC
40. Elbehairy AF, Guenette JA, Faisal A, Ciavaglia CE, Webb KA, Jensen D, et al. Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J.* (2016) 48:694–705. doi: 10.1183/13993003.00077-2016
41. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (2008) 177:622–9. doi: 10.1164/rccm.200707-1064OC
42. Guenette JA, Chin RC, Cheng S, Dominelli PB, Raghavan N, Webb KA, et al. Mechanisms of exercise intolerance in global initiative for chronic obstructive lung disease grade 1 COPD. *Eur Respir J.* (2014) 44:1177–87. doi: 10.1183/09031936.00034714
43. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, et al. Neurophysiological mechanisms of exertional dyspnoea in fibrotic interstitial lung disease. *Eur Respir J.* (2018) 51:1701726. doi: 10.1183/13993003.01726-2017
44. Dias OM, Baldi BG, Ferreira JG, Cardenas LZ, Pennati F, Salito C, et al. Mechanisms of exercise limitation in patients with chronic

hypersensitivity pneumonitis. *ERJ Open Res.* (2018) 4:00043–2018. doi: 10.1183/23120541.00043-2018
45. Marciniuk DD, Sridhar G, Clemens RE, Zintel TA, Gallagher CG. Lung volumes and expiratory flow limitation during exercise in interstitial lung disease. *J Appl Physiol.* (1994) 77:963–73. doi: 10.1152/jappl.1994.77.2.963
46. Ofir D, Laveneziana P, Webb KA, O'Donnell DE. Ventilatory and perceptual responses to cycle exercise in obese women. *J Appl Physiol.* (2007) 102:2217–26. doi: 10.1152/japplphysiol.00898.2006
47. Quon BS, Wilkie SS, Ramsook AH, Schaeffer MR, Puyat JH, Wilcox PG, et al. Qualitative dimensions of exertional dyspnea in adults with cystic fibrosis. *J Appl Physiol.* (2016) 121:449–56. doi: 10.1152/japplphysiol.00391.2016
48. Laveneziana P, Garcia G, Joureau B, Nicolas-Jilwan F, Brahimi T, Laviolette L, et al. Dynamic respiratory mechanics and exertional dyspnoea in pulmonary arterial hypertension. *Eur Respir J.* (2013) 41:578–87. doi: 10.1183/09031936.00223611
49. Yan S, Kaminski D, Sliwinski P. Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (1997) 156:55–9. doi: 10.1164/ajrccm.156.1.9608113
50. Laveneziana P, Webb KA, Wadell K, Neder JA, O'Donnell DE. Does expiratory muscle activity influence dynamic hyperinflation and exertional dyspnea in COPD? *Respir Physiol Neurobiol.* (2014) 199:24–33. doi: 10.1016/j.resp.2014.04.005
51. Kyroussis D, Polkey MI, Keilty SE, Mills GH, Hamnegard CH, Moxham J, et al. Exhaustive exercise slows inspiratory muscle relaxation rate in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (1996) 153:787–93. doi: 10.1164/ajrccm.153.2.8564133
52. O'Donnell DE, Elbehairy AF, Faisal A, Neder JA, Webb KA, Canadian Respiratory Research Network. Sensory-mechanical effects of a dual bronchodilator and its anticholinergic component in COPD. *Respir Physiol Neurobiol.* (2018) 247:116–25. doi: 10.1016/j.resp.2017.10.001
53. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. *Am Rev Respir Dis.* (1993) 148:1351–7. doi: 10.1164/ajrccm/148.5.1351
54. Newell SZ, McKenzie DK, Gandevia SC. Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with chronic airflow limitation. *Thorax.* (1989) 44:903–12. doi: 10.1136/thx.44.11.903
55. Gandevia SC, McKenzie DK. Activation of the human diaphragm during maximal static efforts. *J Physiol.* (1985) 367:45–56. doi: 10.1113/jphysiol.1985.sp015813
56. Luo YM, Qiu ZH, Wang Y, He BT, Qin H, Xiao SC, et al. Absence of dynamic hyperinflation during exhaustive exercise in severe COPD reflects submaximal IC maneuvers rather than a nonhyperinflator phenotype. *J Appl Physiol.* (2020) 128:586–95. doi: 10.1152/japplphysiol.00695.2018
57. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med.* (2019) 200:e70–88. doi: 10.1164/rccm.201908-1590ST
58. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J.* (2005) 26:319–38. doi: 10.1183/09031936.05.00034805
59. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J.* (2004) 23:832–40. doi: 10.1183/09031936.04.00116004
60. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (1999) 160:542–9. doi: 10.1164/ajrccm.160.2.9901038
61. Berton DC, Reis M, Siqueira AC, Barroco AC, Takara LS, Bravo DM, et al. Effects of tiotropium and formoterol on dynamic hyperinflation and exercise endurance in COPD. *Respir Med.* (2010) 104:1288–96. doi: 10.1016/j.rmed.2010.05.017
62. Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (1996) 153:967–75. doi: 10.1164/ajrccm.153.3.8630581
63. Hsia D, Casaburi R, Pradhan A, Torres E, Porszasz J. Physiological responses to linear treadmill and cycle ergometer exercise in COPD. *Eur Respir J.* (2009) 34:605–15. doi: 10.1183/09031936.00069408
64. Puente-Maestu L. Physiological rationale of commonly used clinical exercise tests. *Pulmonology.* (2020) 26:159–65. doi: 10.1016/j.pulmoe.2019.10.004
65. Dolmage TE, Goldstein RS. Repeatability of inspiratory capacity during incremental exercise in patients with severe COPD. *Chest.* (2002) 121:708–14. doi: 10.1378/chest.121.3.708
66. O'Donnell DE, Travers J, Webb KA, He Z, Lam YM, Hamilton A, et al. Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. *Eur Respir J.* (2009) 34:866–74. doi: 10.1183/09031936.00168708
67. Puente-Maestu L, Palange P, Casaburi R, Laveneziana P, Maltais F, Neder JA, et al. Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *Eur Respir J.* (2016) 47:429–60. doi: 10.1183/13993003.00745-2015
68. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (2005) 171:591–7. doi: 10.1164/rccm.200407-867OC
69. Marin JM, Carrizo SJ, Gascon M, Sanchez A, Gallego B, Celli BR. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during the 6-minute-walk test in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (2001) 163:1395–9. doi: 10.1164/ajrccm.163.6.2003172
70. Tantucci C, Donati P, Nicosia F, Bertella E, Redolfi S, De Vecchi M, et al. Inspiratory capacity predicts mortality in patients with chronic obstructive pulmonary disease. *Respir Med.* (2008) 102:613–9. doi: 10.1016/j.rmed.2007.11.004
71. Zaman M, Mahmood S, Altayeh A. Low inspiratory capacity to total lung capacity ratio is a risk factor for chronic obstructive pulmonary disease exacerbation. *Am J Med Sci.* (2010) 339:411–4. doi: 10.1097/MAJ.0b013e3181d6578c
72. Ozgur ES, Nayci SA, Ozge C, Tasdelen B. An integrated index combined by dynamic hyperinflation and exercise capacity in the prediction of morbidity and mortality in COPD. *Respir Care.* (2012) 57:1452–9. doi: 10.4187/respcare.01440
73. Beeh KM, Korn S, Beier J, Jadayel D, Henley M, D'Andrea P, et al. Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: the BRIGHT study. *Respir Med.* (2014) 108:584–92. doi: 10.1016/j.rmed.2014.01.006
74. Beeh KM, Wagner F, Khindri S, Drollmann AF. Effect of indacaterol on dynamic lung hyperinflation and breathlessness in hyperinflated patients with COPD. *COPD.* (2011) 8:340–5. doi: 10.3109/15412555.2011.594464
75. Maltais F, Hamilton A, Marciniuk D, Hernandez P, Sciurba FC, Richter K, et al. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest.* (2005) 128:1168–78. doi: 10.1378/chest.128.3.1168
76. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J.* (2004) 24:86–94. doi: 10.1183/09031936.04.00072703
77. Maltais F, Celli B, Casaburi R, Porszasz J, Jarreta D, Seoane B, et al. Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. *Respir Med.* (2011) 105:580–7. doi: 10.1016/j.rmed.2010.11.019
78. Man WD, Mustfa N, Nikoletou D, Kaul S, Hart N, Rafferty GF, et al. Effect of salmeterol on respiratory muscle activity during exercise in poorly reversible COPD. *Thorax.* (2004) 59:471–6. doi: 10.1136/thx.2003.019620
79. Neder JA, Fuld JP, Overend T, Thirlwell J, Carter R, Stevenson R, et al. Effects of formoterol on exercise tolerance in severely disabled patients with COPD. *Respir Med.* (2007) 101:2056–64. doi: 10.1016/j.rmed.2007.06.006
80. O'Donnell DE, Sciurba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, et al. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest.* (2006) 130:647–56. doi: 10.1378/chest.130.3.647

81. Worth H, Forster K, Eriksson G, Nihlen U, Peterson S, Magnussen H. Budesonide added to formoterol contributes to improved exercise tolerance in patients with COPD. *Respir Med.* (2010) 104:1450–9. doi: 10.1016/j.rmed.2010.07.006
82. Beeh KM, Singh D, Di Scala L, Drollmann A. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial. *Int J Chron Obstruct Pulmon Dis*. (2012) 7:503–13. doi: 10.2147/COPD.S32451
83. O'Donnell DE, Casaburi R, Vincken W, Puente-Maestu L, Swales J, Lawrence D, et al. Effect of indacaterol on exercise endurance and lung hyperinflation in COPD. *Respir Med.* (2011) 105:1030–6. doi: 10.1016/j.rmed.2011.03.014
84. Somfay A, Porszasz J, Lee SM, Casaburi R. Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients. *Eur Respir J*. (2001) 18:77–84. doi: 10.1183/09031936.01.00082201
85. Peters MM, Webb KA, O'Donnell DE. Combined physiological effects of bronchodilators and hyperoxia on exertional dyspnoea in normoxic COPD. *Thorax*. (2006) 61:559–67. doi: 10.1136/thx.2005.053470
86. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis.* (1991) 143:9–18. doi: 10.1164/ajrccm/143.1.9
87. Maltais F, LeBlanc P, Jobin J, Berube C, Bruneau J, Carrier L, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (1997) 155:555–61. doi: 10.1164/ajrccm.155.2.9032194
88. O'Donnell DE, McGuire M, Samis L, Webb KA. General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. *Am J Respir Crit Care Med.* (1998) 157(5 Pt 1):1489–97. doi: 10.1164/ajrccm.157.5.9708010
89. Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. *Chest*. (2005) 128:2025–34. doi: 10.1378/chest.128.4.2025
90. Puente-Maestu L, Abad YM, Pedraza F, Sanchez G, Stringer WW. A controlled trial of the effects of leg training on breathing pattern and dynamic hyperinflation in severe COPD. *Lung*. (2006) 184:159–67. doi: 10.1007/s00408-005-2576-x
91. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev*. (2014) 2014:CD006322. doi: 10.1002/14651858.CD006322.pub3
92. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. *Thorax*. (2008) 63:549–54. doi: 10.1136/thx.2007.088070
93. Huppmann P, Sczepanski B, Boensch M, Winterkamp S, Schonheit-Kenn U, Neurohr C, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. *Eur Respir J.* (2013) 42:444–53. doi: 10.1183/09031936.00081512
94. Ryerson CJ, Camp PG, Eves ND, Schaeffer M, Syed N, Dhillon S, et al. High oxygen delivery to preserve exercise capacity in patients with idiopathic pulmonary fibrosis treated with nintedanib. Methodology of the HOPE-IPF study. *Ann Am Thorac Soc.* (2016) 13:1640–7. doi: 10.1513/AnnalsATS.201604-267OC
95. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respir Med.* (2014) 108:203–10. doi: 10.1016/j.rmed.2013.11.016
96. Eves ND, Petersen SR, Haykowsky MJ, Wong EY, Jones RL. Helium-hyperoxia, exercise, and respiratory mechanics in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (2006) 174:763–71. doi: 10.1164/rccm.200509-1533OC
97. Laveneziana P, Valli G, Onorati P, Paoletti P, Ferrazza AM, Palange P. Effect of heliox on heart rate kinetics and dynamic hyperinflation during high-intensity exercise in COPD. *Eur J Appl Physiol.* (2011) 111:225–34. doi: 10.1007/s00421-010-1643-z
98. Palange P, Valli G, Onorati P, Antonucci R, Paoletti P, Rosato A, et al. Effect of heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients. *J Appl Physiol*. (2004) 97:1637–42. doi: 10.1152/japplphysiol.01207.2003
99. Lammi MR, Ciccolella D, Marchetti N, Kohler M, Criner GJ. Increased oxygen pulse after lung volume reduction surgery is associated with reduced dynamic hyperinflation. *Eur Respir J.* (2012) 40:837–43. doi: 10.1183/09031936.00169311
100. Martinez FJ, de Oca MM, Whyte RI, Stetz J, Gay SE, Celli BR. Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. *Am J Respir Crit Care Med.* (1997) 155:1984–90. doi: 10.1164/ajrccm.155.6.9196106
101. O'Donnell DE, Webb KA, Bertley JC, Chau LK, Conlan AA. Mechanisms of relief of exertional breathlessness following unilateral bullectomy and lung volume reduction surgery in emphysema. *Chest*. (1996) 110:18–27. doi: 10.1378/chest.110.1.18

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MINI REVIEW
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Clinical Utility of Measuring Inspiratory Neural Drive During Cardiopulmonary Exercise Testing (CPET)

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Cardiopulmonary exercise testing (CPET) has traditionally included ventilatory and metabolic measurements alongside electrocardiographic characterization; however, research increasingly acknowledges the utility of also measuring inspiratory neural drive (IND) through its surrogate measure of diaphragmatic electromyography (EMGdi). While true IND also encompasses the activation of non-diaphragmatic respiratory muscles, the current review focuses on diaphragmatic measurements, providing information about additional inspiratory muscle groups for context where appropriate. Evaluation of IND provides mechanistic insight into the origins of dyspnea and exercise limitation across pathologies; yields valuable information reflecting the integration of diverse mechanical, chemical, locomotor, and metabolic afferent signals; and can help assess the efficacy of therapeutic interventions. Further, IND measurement during the physiologic stress of exercise is uniquely poised to reveal the underpinnings of physiologic limitations masked during resting and unloaded breathing, with important information provided not only at peak exercise, but throughout exercise protocols. As our understanding of IND presentation across varying conditions continues to grow and methods for its measurement become more accessible, the translation of these principles into clinical settings is a logical next step in facilitating appropriate and nuanced management tailored to each individual's unique physiology. This review provides an overview of the current state of understanding of IND measurement during CPET: its origins, known patterns of behavior and links with dyspnea in health and major respiratory diseases, and the possibility of expanding this approach to applications beyond exercise.

Keywords: inspiratory neural drive, CPET cardiopulmonary exercise testing, diaphragmatic electromyogram EMGdi, respiratory muscles, respiratory disease (RD), chronic obstructive pulmonary disease, diaphragm

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INTRODUCTION

Measuring diaphragmatic electromyography (EMGdi) as a surrogate of inspiratory neural drive (IND) has a tradition extending over 100 years. Its ability to reveal the mechanistic underpinnings of exercise limitation and dyspnea during cardiopulmonary exercise testing (CPET) has popularized its use in research; however, IND is rarely measured in non-research clinical settings. With aims of familiarizing a broad audience with the fundamental principles of IND

measurement and its presentation in health and respiratory disease, this review outlines the valuable insights provided by IND measurement during the physiologic stressor of exercise, what these reveal beyond standard testing approaches, and emerging areas of interest in applying IND in diverse research settings. It also reflects on current barriers to the clinical adoption of IND assessment and how these might be overcome.

FUNDAMENTALS OF IND MEASUREMENT

Muscles of Inspiration

The inspiratory muscles fall into two categories: primary (i.e., diaphragm, external intercostal, scalene, and parasternal internal intercostal muscles) and accessory (e.g., sternocleidomastoid, pectoralis minor, etc.) (1, 2). The diaphragm is the foremost driver of inspiration at rest and during exercise, accounting for ∼2/3 of lung volume change (3, 4). The scalene and external intercostal muscles show lesser activation during healthy quiet breathing but play an increasingly important role in loaded, high-volume, or distressed breathing patterns (5, 6), while the parasternal internal intercostal muscles are active during resting eupneic breathing, assisting with upper thoracic expansion as well as stabilizing the thorax to the effects of diaphragmatic movement (7, 8). The accessory muscles contribute to inspiration in conditions with higher ventilatory requirements or where breathing pattern is altered (e.g., more rapid) as a result of impaired respiratory mechanics (1). Diaphragmatic IND is the focus of this review. While not discussed herein, the expiratory muscles (i.e., abdominal muscles and internal intercostals) also play an active role in forced exhalations and in supporting the increased ventilation of exercise (9, 10). This is especially critical in conditions of gas trapping, where expiratory recruitment supports subsequent inspiration through elevation of the diaphragm at end-expiration (11, 12).

It is worth noting that rather than being a singular entity, as implied by the nomenclature, the diaphragm consists of two distinct regions: the costal diaphragm, apposing the ribs, and the crural diaphragm, the electrically active region of which is located medially and forms the esophageal hiatus (13, 14). Whereas, the costal diaphragm is involved in the displacement of both abdominal contents and the ribcage, the crural diaphragm displaces abdominal contents only in its caudal, inspiratory descent (13). Thus, the crural diaphragm has a lesser role in thoracic expansion and force generation than the costal diaphragm.

History of Neural Drive Measurement

EMG measurement via intramuscular needle electrodes has been used to investigate ventilatory mechanisms since the early 20th century (15–19). These earliest observations in dogs and rabbits demonstrated the direct link between phrenic nerve activity and diaphragmatic activation: namely, that action potentials of the phrenic nerve result in electrical activation of the diaphragm (20). Later work ultimately determined the origin of this phrenic activity to be ventilatory drive from the respiratory medulla (21–23). However, the invasive nature and contamination of intramuscular EMGdi with adjacent intercostal muscle activation and breathing movement artifact limited the uptake of this approach in human populations (24). This spurred the development of less invasive techniques using either surface electrodes to measure costal or parasternal EMGdi (25–28) or nasally inserted esophageal catheters to measure crural EMGdi (29–33). Although appealingly non-invasive and relatively easy to use, surface measurements can underestimate EMG activity (vs. esophageal recordings), be contaminated by the electrical activity of neighboring accessory muscles (34–36), or be vulnerable to position and limb muscle mobilization (37, 38). By contrast, esophageal measurements of crural EMGdi are relatively robust, but more technically demanding and potentially uncomfortable for patients. However, the authors' own experiences using this technology, as well as the documented experiences of others, support esophageal catheters being well-tolerated by most patients when skillfully utilized (39).

Contemporary catheter designs build off of earlier designs that utilized a single electrode pair (40, 41). These were prone to artifactual changes in EMG activity due to the relative movement of the diaphragm during breathing as compared with the fixed catheter electrode. Current designs employ multiple electrode arrays arranged as overlapping pairs, which help with positioning the electrodes across the electrically active region (EAR) of the crural diaphragm via cross-correlation analysis as well as compensate for movement of the EAR relative to the electrode during breathing (42–44). [For a more detailed review of esophageal EMGdi measurement, please refer to Luo et al. (45)].

Recent findings suggest that while crural and costal diaphragmatic activation is similar at rest, costal activation (measured by intramuscular recording) increases disproportionately to crural activation when ventilation increases either voluntarily or involuntarily (46–48). This differs from earlier studies that measured costal activity via surface EMG and found parallel increases in costal and crural activity during increase ventilation; however, this difference in findings may be attributable to the greater contamination of surface costal EMGdi with intercostal and abdominal muscle activity (14–16). Thus, while there is significant methodological appeal in the robustness of relatively non-invasive esophageal measurements, it is worth considering that crural recordings may not fully represent IND to the diaphragm, especially during increased ventilatory demand. Parasternal intercostal surface EMG has also gained recent attention as a potential alternative to esophageal crural measurements of IND (49, 50), with emerging data showing strong congruence in baseline activation and profiles of increasing activation in response to increasing IND between surface parasternal intercostal and esophageal crural measurements (28, 50–53).

Contemporary Approaches to Measuring Neural Drive

Modern IND assessment increasingly combines multipair esophageal EMGdi with invasive (esophageal/gastric manometry) or non-invasive (please see accompanying

review by (54): "Non-invasive evaluation of dynamic respiratory mechanics") measurement of respiratory mechanics (45, 55). EMGdi now routinely replaces traditional IND estimates during CPET, such as minute ventilation (V_E), esophageal (Pes), transdiaphragmatic (Pdi), or mouth occlusion pressures (37). While these are influenced by obesity (56) or disease-altered respiratory mechanics (57–61), measuring the initiating contractile signal rather than resulting mechanical response provides a more direct assessment of IND. Measuring centrally originating IND with the resulting mechanical (e.g., Pdi) or ventilatory [V_E, tidal volume/vital capacity (V_T/VC), or V_T/VC_{pred}] response of the system additionally enables direct investigation of neuromechanical and neuroventilatory coupling or dissociation, respectively (55, 62). Whereas coupling is used to refer to the efficiency with which the electrical signal is converted into a mechanical or ventilatory response, dissociation refers to EMGdi not translating into a mechanical or ventilatory response as efficiently as in health. While there is some variation in how EMGdi is reported alongside mechanical or ventilatory outcomes between authors, in the present work, these are represented by the commonly employed EMGdi:Pdi and EMGdi:V_T/VC_{pred}, respectively, unless stated otherwise.

Although modern esophageal EMGdi is relatively robust to movement artifact or neighboring muscle activity, two technical notes are warranted. (1) While crural EMGdi necessarily contains electrocardiographic artifact, its regularity and distinct profile allows for ready isolation (visual or computational) from the surrounding respiratory signal (45, 63). (2) Between-individual (or within-individual, when measured during different sessions) differences in electrode: muscle fiber orientation, impedance, muscle blood flow, and distance (or amount of tissue) between electrode and muscle surface necessitate signal standardization (64). As per the values reported in this review, this is typically achieved by presenting EMGdi as a percentage of maximum voluntary activation ($EMGdi_{\%max}$) obtained during inspiratory capacity (IC) or sniff maneuvers (65, 66). Such maximum maneuvers show strong between-visit reliability (67); however, it is worth mentioning evidence that $EMGdi_{\%max}$ may most appropriately be used to normalize for between-group differences, while normalization to ECG R-wave amplitude or to resting tidal EMGdi may be more reliable when investigating intra-individual, inter-visit differences (68).

NEURAL DRIVE IN THE EVALUATION OF THE BREATHLESS PATIENT

The Spectrum of Normal

In healthy adults, resting tidal EMGdi represents only 7–10% of maximum voluntary activation (39, 69). However, this range belies variations. Resting EMGdi can double to $22\%_{max}$ in obesity, for example, due to increased ventilatory load and effort (Pes) (70). Healthy aging's impact on baseline IND is also an important consideration, especially when assessing individuals with chronic respiratory diseases. This is particularly relevant considering the strong relationship between IND and dyspnea (71, 72), i.e., the "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (73). Unlike the V_E:dyspnea relationship, which is limited when respiratory mechanics are impaired, $EMGdi_{\%max}$ robustly correlates with dyspnea in health and across disease severity (50, 74). Dyspnea is thought to reflect awareness of the mismatch that results when increased IND does not or cannot result in an adequate mechanical or ventilatory response (75). While not present during resting tidal breathing in health, the stressor of exercise or pathophysiologic processes of disease typically provoke sensations of dyspnea (76).

Aging induces emphysema-like changes in the lung (increased pulmonary compliance) while decreasing chest wall compliance (77, 78). Aging additionally reduces inspiratory muscle strength, decreases diffusing capacity, decreases the proportion of Type II muscle fibers in the diaphragm, and decreases the number of phrenic motoneurons (79–81). Investigation into whether these changes translate into altered IND found that resting crural EMGdi was 40% greater in individuals $>$ 51 years than those $<$ 50 years (39); however, these findings standardized EMGdi to maximum voluntary activation, which may be reduced (e.g., inability to achieve—or motivation to perform—truly maximal maneuvers) (82, 83). Recent work specifically investigating motor unit discharge rate (monopolar needle recording of costal diaphragm) found no changes across age groups at rest, despite neurogenic changes in motor unit potential area and discharge time that may become more relevant at higher ventilation (84). Interestingly, despite known sex differences in pulmonary structure [smaller lungs, narrower airways (85)] and function [increased resistive work of breathing and greater propensity for expiratory flow limitation and exercise-induced hypoxemia (86)], resting EMGdi does not vary between age-matched healthy males and females (87, 88).

Healthy Responses to Exercise

Two common exercise protocols that are used to study IND are constant work rate (i.e., constant load; CWR), where a constant submaximal output is maintained, and incremental (ICR), where work rate increases in stepwise fashion at predetermined time intervals. The ability of ICR protocols to interrogate the IND profile to the boundaries of maximal exercise capacity offers unique advantages over CWR protocols, including continually increasing IND in concert with continually increasing dyspnea from rest to symptom limitation. This is in contrast with CWR protocols, where IND initially increases before maintaining a submaximal plateau until end exercise (**Figure 1A**). EMGdi activation during exercise typically plateaus at submaximal values $<80\%_{max}$, with some variability reported between studies and populations (55, 69, 89, 90). This begs the question: is this submaximal activation appropriate for the required output or reflective of central inhibition (69, 91, 92)**?** The maintenance of maximal voluntary IND as achieved through IC maneuver throughout various exercise protocols suggest that the former interpretation of task-appropriate IND is true, rather than neural inhibition (69).

Ventilation and dyspnea parallel EMGdi during exercise: all three increase with exercise time and intensity [**Figures 1C,D**; **2A–C**; (57, 69)]. Neuroventilatory and neuromechanical

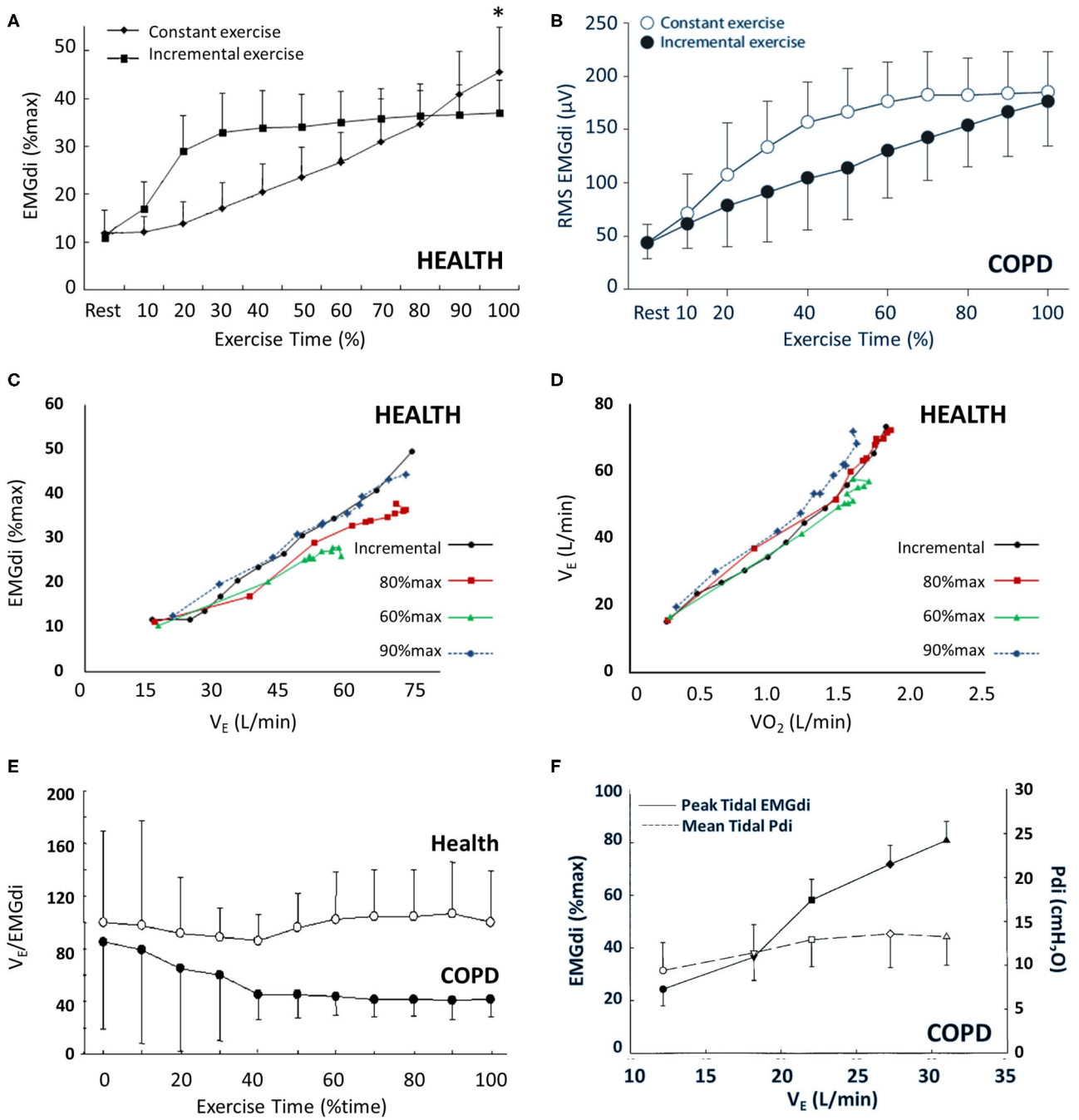

FIGURE 1 | EMGdi behavior during incremental (ICR) and constant work rate (CWR) exercise in health and COPD. Panel **(A)** shows the gradual increase in EMGdi (%max) associated with ICR and the rapid increase in EMGdi (%max) and subsequent plateau associated with CWR exercise in health (*$p < 0.05$). A similar pattern of behavior is seen in COPD **(B)**. The relationship between EMGdi and V_E **(C)** and between V_E and VO_2 **(D)** is maintained regardless of exercise type (ICR vs. CWR) or intensity (CWR at 60, 80, or 90% of maximum work rate). While V_E/EMGdi is maintained in health during CWR **(E)**, and Pdi/EMGdi is maintained in COPD **(F)**, there is uncoupling of V_E and EMGdi in COPD during exercise **(E,F)**. Panels **(A)**, **(C)**, and **(D)** were adapted from (69); panel **(B)** was adapted from (57); panel **(E)** was adapted from (89); and panel **(F)** was adapted from (90). Panels **(A)**, **(C)**, and **(D)** are reprinted from *Resp Physiol Neurobiol*, 189(1), Zhang D, Gong H, Lu G, Guo H, Li R, Zhong N, et al. Respiratory motor output during an inspiratory capacity maneuver is preserved despite submaximal exercise, 87–92, Copyright 2013, with permission from Elsevier. Panel **(B)** is reprinted from *Respiration* 81(4), Luo YM, Li RF, Jolley C, Wu HD, Steier J, Moxham J, et al., Neural respiratory drive in patients with COPD during exercise tests. 294–301, Copyright 2011, with permission from S. Karger AG, Basel. Panel **(E)** is reprinted from *Chest*, 138(6), Qin YY, Steier J, Jolley C, Moxham J, Zhong NS, Luo YM. Efficiency of neural drive during exercise in patients with COPD and healthy subjects, 1309–1315, Copyright 2010, with permission from Elsevier. Panel **(F)** is adapted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved. Cite: Sinderby C, Spahija J, Beck J, Kaminski D, Yan S, Comtois N, et al. (2001) Diaphragm activation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 163(7):1637–41. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at https://doi.org/10.1164/ajrccm.163.7.2007033. The authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations.

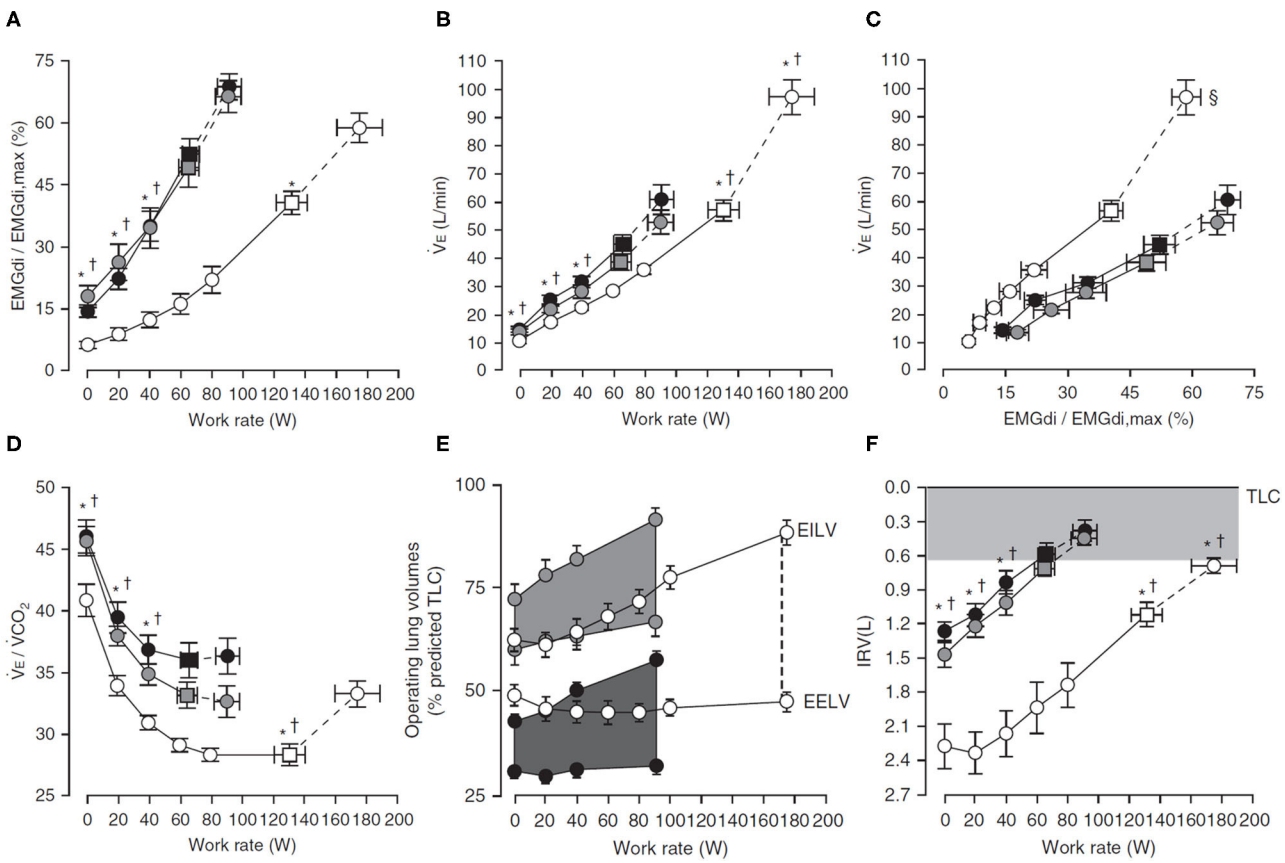

FIGURE 2 | Response to incremental cycle exercise in health (Controls), COPD, and ILD. Values are mean ± SEM, and squares represent V_T-V_E inflection points. *$p < 0.05$ (ILD vs. Control); †$p < 0.05$ (COPD vs. Control); ‡$p < 0.05$ (COPD vs. ILD); §$p < 0.05$ for for differences in VE/(EMGdi/EMGdi,max) slopes between patient groups and control participants. Panel **(A)** shows IND as EMGdi (%max) increasing throughout ICR, panel **(B)** shows the associated ventilatory response (V_E), and panel **(C)** shows the coupling of EMGdi with V_E. Respiratory efficiency is decreased **(D)** (i.e., V_E/VCO_2 increased) in respiratory disease relative to Control, in part due to significant ventilatory constraints occurring alongside dynamic hyperinflation [**(E)**, V_T expansion during exercise and earlier attainment of inspiratory reserve volume threshold, **(F)**]. Figure adapted from (55). Figure is adapted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved. Faisal A, Alghamdi BJ, Ciavaglia CE, Elbehairy AF, Webb KA, Ora J, et al. (2016) Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders. *Am J Respir Crit Care Med*, 193(3):299–309. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at https://doi.org/10.1164/rccm.201504-0841OC. The authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations.

relationships (EMGdi relative to V_E or Pdi) are maintained throughout exercise in health (69, 89, 90). This is especially relevant in the context of healthy aging, which is accompanied by decreased ventilatory efficiency (i.e., increased V_E/VCO_2) and increased ventilatory demand (80). These changes are thought to occur as a result of increased physiologic dead space, i.e., ventilation–perfusion (V/Q) inequalities (93, 94), decreased $PaCO_2$ setpoint (95–97), increased anatomic dead space (95), and greater likelihood of terminal airway closure at higher closing volumes (98). Exertional dyspnea also increases alongside loss of static muscle strength in aging, and older females report greater dyspnea than older males for a given absolute V_E (99). While you will recall the lack of sex differences in healthy resting EMGdi, exercise protocol type seems to influence the occurrence of sex-specific exercise responses in young adults. Specifically, while EMGdi does not vary between healthy young males and females during CWR protocols performed at the same relative intensity (87), females have higher $EMGdi_{\%max}$ and dyspnea for given absolute workloads during ICR exercise (88). This likely reflects the higher ventilation (as a fraction of maximum ventilatory capacity) required to sustain a given absolute work rate in females vs. males (85, 88, 100, 101).

Neural Drive and Dyspnea Are Elevated in Respiratory Disease

Many respiratory conditions with diverse underlying pathological mechanisms result in elevated resting tidal IND and dyspnea. In chronic obstructive pulmonary disease

(COPD), resting IND is increased 2-fold ($EMGdi_{\%max}$ >20%) vs. age-matched health (39, 90). Similar magnitudes of increase are seen in interstitial lung disease (ILD) (55, 102) and cystic fibrosis (49). This is linked to pathophysiologic alterations in mechanical and chemical factors (103) and can already appear in very early disease, as detailed in the accompanying review by (104): "Dyspnea and Exercise Limitation in COPD: the value of CPET."

In obstructive disease, mechanically characterized by increased compliance, gas trapping, hyperinflation, and reduced IC, IND correlates with the severity of airflow limitation (decreased forced expired volume in 1 s; FEV_1) and degree of hyperinflation (39, 49), due to reduced pressure-generating ability of the diaphragm (105). Mechanical impairment causing increased IND is experimentally supported by acutely increased EMGdi alongside loss of FEV_1 post-histamine bronchoprovocation challenge in asthmatic children (106). IND is also increased in restrictive diseases like ILD, where decreased compliance and low lung volumes decrease IC. Thus, in both obstructive and restrictive conditions, IND typically increases alongside increasing mechanical impairment (39). Such situations of increased diaphragmatic loading or impairment also increase recruitment of non-diaphragmatic inspiratory muscles (5, 6).

Increased IND can reflect underlying mechanical impairment, but how chemical impairment (e.g., gas exchange abnormalities) might also be reflected is of increasing interest. For example, it has been demonstrated that increased physiologic dead space (i.e., V/Q mismatch), necessitating increased V_E, reducing ventilatory efficiency, and ultimately resulting in earlier attainment of mechanical constraints, contributes to the increased IND observed in disease (107, 108). This is experimentally supported by increased IND during dead space loading (109) or acute increases in $PaCO_2$ in health, with the EMGdi-PCO_2 relationship suggested as an index of chemosensitivity (68). Data suggest that IND also increases linearly with increasing CO_2 during rebreathing in COPD (110); however, the impact of chronic hypercapnia on IND and CO_2 responsiveness in respiratory disease is equivocal. While some groups report blunted CO_2 responsiveness in hypercapnic COPD (111), others report increased IND in hypercapnic COPD with equivalent mechanical impairment to normocapnic COPD (112). These differences may arise from methodological or group differences (acute CO_2 exposure vs. chronic hypercapnia; degree of mechanical impairment; analysis of the EMG signal through integration, moving average, or peak) and highlight the need for further studies to clarify the role of chronic hypercapnia, increased physiologic dead space, and diffusion impairment on IND. Increased IND secondary to hypercapnia is likely attributable to a combination of chemosensory inputs, resultant ventilatory changes and the mechanical limitations they precipitate, and afferent signals from mechanically overloaded inspiratory muscles (113). Finally, patients with hypercapnic COPD tend to also experience chronic hypoxia, which may further contribute to IND via chemo-afferent pathways (114, 115) and through diaphragmatic fatigue (116).

Diaphragmatic Responses to Exercise in Respiratory Disease

Despite different pathophysiologic underpinnings, there is interesting similarity in the diaphragmatic and ventilatory responses to exercise seen in obstructive and restrictive diseases, both of which are exaggerated compared with health [**Figures 2A–C**; see also (117)]. As in health, baseline IND increases with increasing exercise and metabolic CO_2 output in respiratory disease (57, 89, 90), either to a plateau in CWR protocols or until end exercise is achieved in ICR protocols [**Figure 1B**; (57, 89)], but the relative IND is elevated for an absolute work rate vs. health. Further, whereas EMGdi is maintained relative to V_E throughout CWR exercise in health, both V_E and Pdi gradually decline relative to EMGdi throughout exercise in COPD [**Figures 1E,F**; (89, 90)], indicative of a declining efficiency of IND during exertion in this population. A similar pattern is seen in the neuromechanical and neuroventilatory dissociation of EMGdi/Pdi and $EMGdi_{\%max}$:V_T/VC_{pred} during ICR, with persistently increasing IND in the face of earlier constraints in increasing Pdi or V_T.

The higher ventilatory requirements of exercise stress the physiologic tolerances of the respiratory system, exposing underlying impairments. For example, in COPD, baseline CO_2 retention occurring due to ventilation–perfusion mismatch at rest is further exaggerated during exercise by the inability of the mechanically disadvantaged system to meet the increased metabolic demands of exercise (**Figures 2C,D**) (118). This, in turn, further increases IND and ventilation. When paired with a rapid, shallow breathing pattern increasing dead space, and underlying expiratory flow limitation leading to dynamic hyperinflation and encroachment of tidal volume on critical inspiratory reserve (**Figure 2E**) (119, 120), early cessation of exercise and a higher symptom burden for a given work rate ensue (75). In ILD, low diffusing capacity and low pulmonary compliance result in increased ventilatory drive and a rapid, shallow breathing pattern due to limited V_T expansion, ultimately also leading to premature termination of exercise and exaggerated dyspnea (55).

The exercise limitations observed in obstructive and restrictive disease are due to an inadequate mechanical response to the higher IND, with the lower IC of both populations limiting V_T expansion and causing earlier attainment of the lowest critical inspiratory reserve volume, IRV, and a reliance on increases in breathing frequency to increase V_E [**Figures 2E,F**; (90, 119–121)]. Whether resulting from the hyperinflation-disadvantaged length–tension relationships of the diaphragm (122, 123) and impaired ability to generate inspiratory pressure in situations of increased inspiratory flow (41, 124, 125) in COPD or due to low compliance and low operating lung volumes in ILD, mechanical impairments prevent the efficient translation of drive into ventilatory response. Thus, in both obstructive and restrictive disease, the slope of the relationship between $EMGdi_{\%max}$ and work rate is increased relative to health, as is the slope of the dyspnea: work rate relationship (55).

Using Exercise to Reveal Impairments Hidden at Rest

The utility of CPET as an adjunct to resting pulmonary function testing is further highlighted by respiratory conditions with normal or relatively preserved resting IND, such as exercise-induced laryngeal obstruction (EILO), which presents primarily in young individuals during high-intensity exercise (126). Here, normal resting IND becomes progressively augmented relative to health at increasing work rates, reflecting increasing inspiratory resistive work of breathing, with a significantly elevated IND approaching end exercise (127). Thus, in contrast to the possible beneficial effects of exercise-associated laryngeal closure associated with obstructive pulmonary conditions (128), the laryngeal closure observed in EILO causes both mechanical impairment and increased IND (127). Interestingly, individuals with EILO and those with obstructive pulmonary disease report "unsatisfied inspiration" at high work rates, a convergence of symptoms despite markedly different underlying pathophysiological mechanism contributing to each group's increased IND (117, 127).

IND measurement and CPET are particularly valuable in smokers at risk of COPD and individuals with mild COPD. Despite relatively preserved resting spirometry, subtle decreases in diffusive capacity, increases in dead space, and changes in pulmonary mechanics translate into increased IND at rest, helping to explain the symptoms experienced by these individuals despite relatively preserved lung function (108, 129). These resting differences are exaggerated throughout exercise, with decreased exercise endurance, increased IND, and increased dyspnea in smokers-at-risk and mild COPD vs. health (108, 129). This increased dyspnea has recently been linked to ventilatory inefficiency causing premature mechanical constraint, with individuals with DLCO lower than the lower limit of normal (LLN) experiencing a higher ventilatory requirement and thus greater dyspnea and exercise intolerance than patients with DLCO > LLN despite equivalent spirometry (130). This topic is covered in greater detail in the accompanying review by (104). "Dyspnea and Exercise Limitation in Mild COPD: the value of CPET."

NEW FRONTIERS FOR NEURAL DRIVE MEASUREMENT

Evaluating Responses to Interventions

In addition to providing insight into the mechanisms of exercise intolerance, IND measurement enables a more detailed mechanistic assessment of pharmacotherapeutic and other interventions. For example, bronchodilator-based improvements in neuromechanical coupling mirroring improvements in dyspnea during exercise challenges are documented in COPD (131, 132), while respiratory system unloading (i.e., helium unloading) independent of airway tone is similarly associated with improved indices of neuromuscular output (133, 134). Other interventions, such as supplemental O_2 therapy or opiates, are specifically targeted at decreasing IND rather than altering respiratory mechanics (135, 136). Thus, the measurement of EMGdi in research settings can provide valuable information about IND, ultimately helping to better inform clinical approaches targeted at improving exercise performance and/or dyspnea. A possible application would include the measurement of EMGdi alongside respiratory mechanics (e.g., as outlined in the accompanying review by (54) "Non-invasive evaluation of dynamic respiratory mechanics") to help evaluate pulmonary rehabilitation interventions targeting sarcopenia or the deconditioning of aging or chronic respiratory disease.

One application where this approach has been increasingly applied is in the evaluation of improvements in dyspnea and reductions in IND following inspiratory muscle training (IMT), proposed to occur due to improved neuromechanical coupling (137). As different IMT protocols have been assessed in diverse populations, these studies have yielded equivocal results. This includes no improvements in IND despite improvements in dyspnea and maximum inspiratory pressure when used by healthy young adults (138) or improved (decreased) IND despite maintained V_E and breathing pattern in COPD with baseline inspiratory muscle weakness (137). Differences in IMT study outcomes may also in part be due to the preferential recruitment of accessory muscles of inspiration during different IMT approaches and resulting breathing patterns (51, 138). Use of EMGdi measurement during IMT performed with inspiratory threshold training has shown this approach to generate better diaphragmatic recruitment and activation than IMT performed using inspiratory resistive devices in severe COPD with inspiratory muscle weakness (74, 139), while focused instruction outlining diaphragmatic breathing strategies similarly improves diaphragmatic activation during IMT in health (140). Pursed-lip breathing, a commonly employed intervention linked with improved symptoms of dyspnea and resulting in deeper and slower breathing patterns, has also been associated with reduced diaphragmatic recruitment and increased engagement of accessory muscles in advanced COPD (141). These types of targeted investigations may help optimize future rehabilitation approaches (142), and further investigation is needed to clarify those results attributable to training protocol vs. those linked directly to between-population differences.

Applying IND Measurement in Non-CPET Settings

Emerging interest lies in the measurement of IND within novel areas of research. Two with promise are sleep and acute exacerbations of COPD. IND measurement can successfully differentiate periods of central vs. obstructive sleep apnea (143), while continuous monitoring of overnight EMGdi shows greater decreases in IND in the transition from wakefulness to non-rapid eye movement (NREM) and REM sleep in COPD vs. health, possibly holding clues to the nocturnal hypoventilation commonly observed in COPD (144). More recent work has shown the benefits of nocturnal bronchodilator therapy in improving overnight IND and respiratory mechanics (145). IND monitoring has also generated interest as a possible means of predicting recovery from acute exacerbations, with failure of acutely increased parasternal EMGdi to return to baseline

conditions after hospitalization for exacerbation strongly correlated with failure to experience subjective improvements in dyspnea (Borg), lack of clinical improvement, and likelihood of readmission (146).

Overcoming Barriers to Clinical Adoption

The integration of IND measurement into clinical settings has historically been limited by the cost of one-time use electrodes, the relative invasiveness and complexity of crural measurement approaches, challenges in standardizing measurements between visits or between individuals, and the significant technical complexities and time requirements associated with existing manual analysis approaches (39, 70). Advances in surface assessment of parasternal EMG hold significant promise for overcoming the technical barriers and patient burden associated with esophageal catheter use. This has already been successfully employed in diverse and vulnerable populations, including pediatric asthma (147), and may form the foundation of more routine adoption of IND assessment in clinical practice. The reporting of normalized values, regardless of approach, also helps to account for possible differences in signal detection between testing sessions (64).

Addressing concerns surrounding complex and time-consuming analysis approaches, significant computational advances now enable semi-automated analyses of crural EMGdi (63) as well as novel approaches to IND assessment via diaphragmatic signal entropy (148, 149), significantly improving analysis speed and consistency. Further, there is promise in the fully automated, real-time integration of IND information to inform mechanical ventilation approaches through EMGdi-based or non-invasive Neurally Adjusted Ventilatory Assist (150–152). The ongoing refinement of these approaches provides fertile ground for a more seamless integration of IND measurement into standard care. A final requirement for the translation of IND from research to clinical laboratories is the establishment of normative resting and exercise values of EMGdi in both sexes across age groups. Until such values are available, the use of age- and sex-matched comparator populations is essential in the investigation of disease.

CONCLUSIONS

As far back as 1929, the *Lancet* submitted a "plea for a careful clinical study of the diaphragm in chest disease" (153). In the century that has followed, significant progress has been made in elucidating not only the structure, but increasingly the function, of our primary pump muscle. The foundation that has been laid surrounding the utility of EMGdi as a marker of IND and its associated sequelae of dyspnea and exercise limitation is now well-positioned for translation into clinical practice. The ability of IND to reflect alterations in ventilatory load and capacity holds significant promise for its possible use as a global marker of disease severity and ventilatory dysfunction, as well as a useful target for monitoring the success of therapeutic interventions.

AUTHOR CONTRIBUTIONS

ND contributed to planning and drafting of the submission. ND, EW, and DL all contributed to editing of the article and approved the submitted version.

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REFERENCES

1. Roussos C, Macklem PT. The respiratory muscles. *N Engl J Med.* (1982) 307:786–97. doi: 10.1056/NEJM198209233071304
2. Campbell EJ. The role of the scalene and sternomastoid muscles in breathing in normal subjects; an electromyographic study. *J Anat.* (1955) 89:378–86.
3. Mead J, Loring SH. Analysis of volume displacement and length changes of the diaphragm during breathing. *J Appl Physiol.* (1982) 53:750–5. doi: 10.1152/jappl.1982.53.3.750
4. Wade OL. Movements of the thoracic cage and diaphragm in respiration. *J Physiol.* (1954) 124:193–212. doi: 10.1113/jphysiol.1954.sp005099
5. Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* (2003) 168:10–48. doi: 10.1164/rccm.2206020
6. Tobin MJ. Why physiology is critical to the practice of medicine: a 40-year personal perspective. *Clin Chest Med.* (2019) 40:243–57. doi: 10.1016/j.ccm.2019.02.012
7. De Troyer A, Sampson MG. Activation of the parasternal intercostals during breathing efforts in human subjects. *J Appl Physiol.* (1982) 52:524–9. doi: 10.1152/jappl.1982.52.1.286-s
8. Han JN, Gayan-Ramirez G, Dekhuijzen R, Decramer M. Respiratory function of the rib cage muscles. *Eur Respir J.* (1993) 6:722–8.
9. Henke KG, Sharratt M, Pegelow D, Dempsey JA. Regulation of end-expiratory lung volume during exercise. *J ApplPhysiol.* (1988) 64:135–46. doi: 10.1152/jappl.1988.64.1.135
10. Loring SH, Mead J. Abdominal muscle use during quiet breathing and hyperpnea in uninformed subjects. *J Appl Physiol.* (1982) 52:700–4. doi: 10.1152/jappl.1982.52.3.700
11. Wolfson DA, Strohl KP, Dimarco AF, Altose MD. Effects of an increase in end-expiratory volume on the pattern of thoracoabdominal movement. *Respir Physiol.* (1983) 53:273–83. doi: 10.1016/0034-5687(83)90119-6
12. Martin JG, De Troyer A. The behaviour of the abdominal muscles during inspiratory mechanical loading. *Respir Physiol.* (1982) 50:63–73. doi: 10.1016/0034-5687(82)90007-X
13. De Troyer A, Sampson M, Sigrist S, Macklem PT. The diaphragm: two muscles. *Science.* (1981) 213:237–8. doi: 10.1126/science.7244632
14. Sharshar T, Hopkinson NS, Ross ET, Jonville S, Dayer MJ, Nickol AH, et al. Motor control of the costal and crural diaphragm–insights from transcranial magnetic stimulation in man. *Respir Physiol Neurobiol.* (2005) 146:5–19. doi: 10.1016/j.resp.2004.10.010
15. Tokizane T, Kawamata K, Tokizane H. Electromyographic studies on the human respiratory muscles; studies on the activity pattern of neuromuscular units. *Jpn J Physiol.* (1952) 2:232–47. doi: 10.2170/jjphysiol.2.232
16. Rossier PH, Nieporent HJ, Pipberger H, Kalin R. [Electromyographical studies of respiratory muscle function in normal test persons]. *Z Gesamte Exp Med.* (1956) 127:39–52. doi: 10.1007/BF02053581
17. Adrian ED, Bronk DW. The discharge of impulses in motor nerve fibres. *J Physiol.* (1929) 67:9–151. doi: 10.1113/jphysiol.1929.sp002557

18. Dittler R. Über die Innervation des zwerchfelles als beispiel einer tonischen innervation. *Arch Ges Physiol Menschen Tiere.* (1909) 130:400–43. doi: 10.1007/BF01686342
19. Dittler R. Über die Aktionsströme des Nervus phrenicus bei natürlicher Innervation. *Arch Ges Physiol Menschen Tiere.* (1910) 131:581–8. doi: 10.1007/BF01679856
20. Dittler R, Garten S. Die zeitliche folge der aktionsströme in phrenicus und zwerchfell bei der natürlichen innervation. *Zeitsch Biol.* (1912) 58:420–50.
21. Duffin J. A model of respiratory rhythm generation. *Neuroreport.* (1991) 2:623–6. doi: 10.1097/00001756-199110000-00018
22. Richter DW, Ballanyi K, Schwarzacher S. Mechanisms of respiratory rhythm generation. *Curr Opin Neurobiol.* (1992) 2:788–93. doi: 10.1016/0959-4388(92)90135-8
23. Berger AJ, Dick TE, Jodkowski JS, Viana F. Phrenic motoneurons: decscending inputs, electrical properties and recruitment. In: Lahiri S, Forster RE, Davies RO, Pack AI, editors. *Chemoreceptors and Reflexes in Breathing: Cellular and Molecular Aspects*. Oxford: Oxford University Press (1989). p. 343–50.
24. Hodges PW, Gandevia SC. Pitfalls of intramuscular electromyographic recordings from the human costal diaphragm. *Clin Neurophysiol.* (2000) 111:1420–4. doi: 10.1016/S1388-2457(00)00341-2
25. Tusiewicz K, Moldofsky H, Bryan AC, Bryan MH. Mechanics of the rib cage and diaphragm during sleep. *J Appl Physiol.* (1977) 43:600–2. doi: 10.1152/jappl.1977.43.4.600
26. Prechtl HF, van Eykern LA, O'Brien MJ. Respiratory muscle EMG in newborns: a non-intrusive method. *Early Hum Dev.* (1977) 1:265–83. doi: 10.1016/0378-3782(77)90040-8
27. Lansing R, Savelle J. Chest surface recording of diaphragm potentials in man. *Electroencephalogr Clin Neurophysiol.* (1989) 72:59–68. doi: 10.1016/0013-4694(89)90031-X
28. Lin L, Guan L, Wu W, Chen R. Correlation of surface respiratory electromyography with esophageal diaphragm electromyography. *Respir Physiol Neurobiol.* (2019) 259:45–52. doi: 10.1016/j.resp.2018.07.004
29. Petit JM, Milic-Emili G, Delhez L. [Examination of the electrical activity of the diaphragm by the esophageal approach in the normal man]. *J Physiol.* (1960) 52:190–1.
30. Hixon TJ, Siebens AA, Minifie FD. An EMG electrode for the diaphragm. *J Acoust Soc Am.* (1969) 46:1588–90. doi: 10.1121/1.1911912
31. Gandevia SC, McKenzie DK. Human diaphragmatic EMG: changes with lung volume and posture during supramaximal phrenic stimulation. *J Appl Physiol.* (1986) 60:1420–8. doi: 10.1152/jappl.1986.60.4.1420
32. Luo YM, Polkey MI, Johnson LC, Lyall RA, Harris ML, Green M, et al. Diaphragm EMG measured by cervical magnetic and electrical phrenic nerve stimulation. *J Appl Physiol.* (1998) 85:2089–99. doi: 10.1152/jappl.1998.85.6.2089
33. Macklem PT, Roussos C, Gross D, Ladd H, Riley E, Grassino A, et al. Diaphragmatic fatigue [proceedings]. *Am Rev Respir Dis.* (1979) 119(2 Pt 2):93.
34. Repko KD, Greene JG, Enderle JD. A comparison of esophageal and chest electrodes in studying the diaphragmatic EMG. *Biomed Sci Instrum.* (1989) 25:89–91.
35. Sharp JT, Hammond MD, Aranda AU, Rocha RD. Comparison of diaphragm EMG centroid frequencies: esophageal versus chest surface leads. *Am Rev Respir Dis.* (1993) 147:764–7. doi: 10.1164/ajrccm/147.3.764
36. Sinderby C, Friberg S, Comtois N, Grassino A. Chest wall muscle cross talk in canine costal diaphragm electromyogram. *J Appl Physiol.* (1996) 81:2312–27. doi: 10.1152/jappl.1996.81.5.2312
37. Ramsook AH, Mitchell RA, Bell T, Calli S, Kennedy C, Lehmann J, et al. Is parasternal intercostal EMG an accurate surrogate of respiratory neural drive and biomarker of dyspnea during cycle exercise testing? *Respir Physiol Neurobiol.* (2017) 242:40–4. doi: 10.1016/j.resp.2017.03.003
38. Hudson AL, Butler JE. Assessment of 'neural respiratory drive' from the parasternal intercostal muscles. *Respir Physiol Neurobiol.* (2018) 252–253:16–7. doi: 10.1016/j.resp.2017.11.003
39. Jolley CJ, Luo YM, Steier J, Reilly C, Seymour J, Lunt A, et al. Neural respiratory drive in healthy subjects and in COPD. *Eur Respir J.* (2009) 33:289–97. doi: 10.1183/09031936.00093408
40. Petit JM, Milic-Emili G, Delhez L. Role of the diaphragm in breathing in conscious normal man: an electromyographic study. *J Appl Physiol.* (1960) 15:1101–6. doi: 10.1152/jappl.1960.15.6.1101
41. Agostoni E, Sant'Ambrogio G, Del Portillo Carrasco H. Electromyography of the diaphragm in man and transdiaphragmatic pressure. *J Appl Physiol.* (1960) 15:1093–7. doi: 10.1152/jappl.1960.15.6.1093
42. Beck J, Sinderby C, Weinberg J, Grassino A. Effects of muscle-to-electrode distance on the human diaphragm electromyogram. *J Appl Physiol.* (1995) 79:975–85. doi: 10.1152/jappl.1995.79.3.975
43. Beck J, Sinderby C, Lindstrom L, Grassino A. Influence of bipolar esophageal electrode positioning on measurements of human crural diaphragm electromyogram. *J Appl Physiol.* (1996) 81:1434–49. doi: 10.1152/jappl.1996.81.3.1434
44. Luo YM, Lyall RA, Harris ML, Hawkins P, Hart N, Polkey MI, et al. Effect of lung volume on the oesophageal diaphragm EMG assessed by magnetic phrenic nerve stimulation. *Eur Respir J.* (2000) 15:1033–8. doi: 10.1034/j.1399-3003.2000.01510.x
45. Luo YM, Moxham J, Polkey MI. Diaphragm electromyography using an oesophageal catheter: current concepts. *Clin Sci.* (2008) 115:233–44. doi: 10.1042/CS20070348
46. Tagliabue G, Ji M, Suneby Jagers JV, Zuege DJ, Kortbeek JB, Easton PA. Distinct neural-mechanical efficiency of costal and crural diaphragm during hypercapnia. *Respir Physiol Neurobiol.* (2019) 268:103247. doi: 10.1016/j.resp.2019.06.004
47. Ikegami T, Ji M, Fujimura N, Suneby Jagers JV, Kieser TM, Easton PA. Costal and crural diaphragm function during sustained hypoxia in awake canines. *J Appl Physiol.* (2019) 126:1117–28. doi: 10.1152/japplphysiol.00242.2018
48. Nguyen DAT, Amirjani N, McCaughey EJ, Gandevia SC, Butler JE, Hudson AL. Differential activation of the human costal and crural diaphragm during voluntary and involuntary breaths. *J Appl Physiol.* (2020) 128:1262–70. doi: 10.1152/japplphysiol.00790.2019
49. Reilly CC, Ward K, Jolley CJ, Lunt AC, Steier J, Elston C, et al. Neural respiratory drive, pulmonary mechanics and breathlessness in patients with cystic fibrosis. *Thorax.* (2011) 66:240–6. doi: 10.1136/thx.2010.142646
50. Wu W, Guan L, Li X, Lin L, Guo B, Yang Y, et al. Correlation and compatibility between surface respiratory electromyography and transesophageal diaphragmatic electromyography measurements during treadmill exercise in stable patients with COPD. *Int J Chron Obstruct Pulmon Dis.* (2017) 12:3273–80. doi: 10.2147/COPD.S148980
51. Rodrigues A, Louvaris Z, Dacha S, Janssens W, Pitta F, Vogiatizis I, et al. Differences in respiratory muscle responses to hyperpnea or loaded breathing in COPD. *Med Sci Sports Exerc.* (2019) 52:1126–34. doi: 10.1249/MSS.0000000000002222
52. Nguyen DAT, Amirjani N, McCaughey EJ, Gandevia SC, Butler JE, Hudson AL. Electromyographic activity in the human costal and crural diaphragm during voluntary and involuntary breaths. In:*16th International Conference of Sleep and Breathing*. Tampere (2019).
53. Amirjani N, Hudson AL, Butler JE, Gandevia SC. Comparison of EMG in teh costal and crural diaphragm with increments in tidal volume. In: *American Thoracic Society*. Denver (2011). doi: 10.1164/ajrccm-conference.2011.183.1_MeetingAbstracts.A5287
54. Milne KM, Domnik NJ, Phillips DB, James MD, Vincent SG, Neder JA. Evaluation of dynamic respiratory mechanical abnormalities during conventional CPET. *Front Med.* (2020). doi: 10.3760/cma.j.issn.0366-6999.2012.20.006
55. Faisal A, Alghamdi BJ, Ciavaglia CE, Elbehairy AF, Webb KA, Ora J, et al. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am J Respir Crit Care Med.* (2016) 193:299–309. doi: 10.1164/rccm.201504-0841OC
56. Ora J, Laveneziana P, Wadell K, Preston M, Webb KA, O'Donnell DE. Effect of obesity on respiratory mechanics during rest and exercise in COPD. *J Appl Physiol.* (2011) 111:10–9. doi: 10.1152/japplphysiol.01131.2010
57. Luo YM, Li RF, Jolley C, Wu HD, Steier J, Moxham J, et al. Neural respiratory drive in patients with COPD during exercise tests. *Respiration.* (2011) 81:294–301. doi: 10.1159/000317136
58. Hamnegard CH, Polkey MI, Kyroussis D, Mills GH, Green M, Bake B, et al. Maximum rate of change in oesophageal pressure assessed from unoccluded

breaths: an option where mouth occlusion pressure is impractical. *Eur Respir J.* (1998) 12:693–7. doi: 10.1183/09031936.98.12030693
59. Polkey MI, Hamnegard CH, Hughes PD, Rafferty GF, Green M, Moxham J. Influence of acute lung volume change on contractile properties of human diaphragm. *J Appl Physiol.* (1998) 85:1322–8. doi: 10.1152/jappl.1998.85.4.1322
60. Ninane V, Rypens F, Yernault JC, De Troyer A. Abdominal muscle use during breathing in patients with chronic airflow obstruction. *Am Rev Respir Dis.* (1992) 146:16–21. doi: 10.1164/ajrccm/146.1.16
61. Xiao SC, Lu YR, Guo HX, Qiu ZH, Luo YM. Effect of expiratory load on neural inspiratory drive. *Chin Med J.* (2012) 125:3629–34.
62. Jolley CJ, Luo YM, Steier J, Rafferty GF, Polkey MI, Moxham J. Neural respiratory drive and breathlessness in COPD. *Eur Respir J.* (2015) 45:355–64. doi: 10.1183/09031936.00063014
63. Dacha S, Janssens L, Rodrigues A, Louvaris Z, Janssens L, Gosselink R, et al. Comparison between manual and (semi-)automated analyses of esophageal diaphragm electromyography during endurance cycling in patients with COPD. *Front Physiol.* (2019) 10:885. doi: 10.3389/fphys.2019.00885
64. Halaki M, Ginn K. Normalization of EMG signals: to normalize or not to normalize and what to normalize to? In: Naik GR, editor. *Computational Intelligence in Electromyography Analysis: A Perspective on Current Applications and Future Challenges*. London: IntechOpen Ltd. (2012). doi: 10.5772/49957
65. Sinderby C, Beck J, Spahija J, Weinberg J, Grassino A. Voluntary activation of the human diaphragm in health and disease. *J Appl Physiol.* (1998) 85:2146–58. doi: 10.1152/jappl.1998.85.6.2146
66. Ramsook AH, Schaeffer MR, Syed N, Wilkie SS, Guenette JA. Which respiratory maneuvers generate the greatest electromyography activity of the inspiratory muscles? *Am J Respir Crit Care Med.* (2015) 191:A2682.
67. Mendonca CT, Schaeffer MR, Riley P, Jensen D. Physiological mechanisms of dyspnea during exercise with external thoracic restriction: role of increased neural respiratory drive. *J Appl Physiol.* (2014) 116:570–81. doi: 10.1152/japplphysiol.00950.2013
68. Singh B, Panizza JA, Finucane KE. Diaphragm electromyogram root mean square response to hypercapnia and its intersubject and day-to-day variation. *J Appl Physiol.* (2005) 98:274–81. doi: 10.1152/japplphysiol.01380.2003
69. Zhang D, Gong H, Lu G, Guo H, Li R, Zhong N, et al. Respiratory motor output during an inspiratory capacity maneuver is preserved despite submaximal exercise. *Respir Physiol Neurobiol.* (2013) 189:87–92. doi: 10.1016/j.resp.2013.07.008
70. Steier J, Jolley CJ, Seymour J, Roughton M, Polkey MI, Moxham J. Neural respiratory drive in obesity. *Thorax.* (2009) 64:719–25. doi: 10.1136/thx.2008.109728
71. O'Donnell DE, Milne KM, Vincent SG, Neder JA. Unraveling the causes of unexplained dyspnea: the value of exercise testing. *Clin Chest Med.* (2019) 40:471–99. doi: 10.1016/j.ccm.2019.02.014
72. Sinderby C, Spahija J, Beck J. Changes in respiratory effort sensation over time are linked to the frequency content of diaphragm electrical activity. *Am J Respir Crit Care Med.* (2001) 163:905–10. doi: 10.1164/ajrccm.163.4.2005121
73. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med.* (2012) 185:435–52. doi: 10.1164/rccm.201111-2042ST
74. Wu W, Guan L, Zhang X, Li X, Yang Y, Guo B, et al. Effects of two types of equal-intensity inspiratory muscle training in stable patients with chronic obstructive pulmonary disease: a randomised controlled trial. *Respir Med.* (2017) 132:84–91. doi: 10.1016/j.rmed.2017.10.001
75. O'Donnell DE, Milne KM, James MD, de Torres JP, Neder JA. Dyspnea in COPD: new mechanistic insights and management implications. *Adv Ther.* (2019) 37:41–60. doi: 10.1007/s12325-019-01128-9
76. Jensen D, Ofir D, O'Donnell DE. Effects of pregnancy, obesity and aging on the intensity of perceived breathlessness during exercise in healthy humans. *Respir Physiol Neurobiol.* (2009) 167:87–100. doi: 10.1016/j.resp.2009.01.011
77. Veldhuizen RAW, McCaig LA, Pape C, Gill SE. The effects of aging and exercise on lung mechanics, surfactant and alveolar macrophages. *Exp Lung Res.* (2019) 45:113–22. doi: 10.1080/01902148.2019.1605633
78. Estenne M, Yernault JC, De Troyer A. Rib cage and diaphragm-abdomen compliance in humans: effects of age and posture. *J Appl Physiol.* (1985) 59:1842–8. doi: 10.1152/jappl.1985.59.6.1842
79. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis.* (1969) 99:696–702.
80. Faisal A, Webb KA, Guenette JA, Jensen D, Neder JA, O'Donnell DE. Effect of age-related ventilatory inefficiency on respiratory sensation during exercise. *Respir Physiol Neurobiol.* (2015) 205:129–39. doi: 10.1016/j.resp.2014.10.017
81. Fogarty MJ, Omar TS, Zhan WZ, Mantilla CB, Sieck GC. Phrenic motor neuron loss in aged rats. *J Neurophysiol.* (2018) 119:1852–62. doi: 10.1152/jn.00868.2017
82. Newell SZ, McKenzie DK, Gandevia SC. Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with chronic airflow limitation. *Thorax.* (1989) 44:903–12. doi: 10.1136/thx.44.11.903
83. Allen GM, McKenzie DK, Gandevia SC, Bass S. Reduced voluntary drive to breathe in asthmatic subjects. *Respir Physiol.* (1993) 93:29–40. doi: 10.1016/0034-5687(93)90065-I
84. Nguyen DAT, Lewis RHC, Gandevia SC, Butler JE, Hudson AL. Discharge properties of human diaphragm motor units with ageing. *J Physiol.* (2019) 597:5079–92. doi: 10.1113/JP278498
85. Harms CA, Rosenkranz S. Sex differences in pulmonary function during exercise. *Med Sci Sports Exerc.* (2008) 40:664–8. doi: 10.1249/MSS.0b013e3181621325
86. Guenette JA, Sheel AW. Exercise-induced arterial hypoxaemia in active young women. *Appl Physiol Nutr Metab.* (2007) 32:1263–73. doi: 10.1139/H07-122
87. Mitchell RA, Schaeffer MR, Ramsook AH, Wilkie SS, Guenette JA. Sex differences in respiratory muscle activation patterns during high-intensity exercise in healthy humans. *Respir Physiol Neurobiol.* (2018) 247:57–60. doi: 10.1016/j.resp.2017.09.002
88. Schaeffer MR, Mendonca CT, Levangie MC, Andersen RE, Taivassalo T, Jensen D. Physiological mechanisms of sex differences in exertional dyspnoea: role of neural respiratory motor drive. *Exp Physiol.* (2014) 99:427–41. doi: 10.1113/expphysiol.2013.074880
89. Qin YY, Steier J, Jolley C, Moxham J, Zhong NS, Luo YM. Efficiency of neural drive during exercise in patients with COPD and healthy subjects. *Chest.* (2010) 138:1309–15. doi: 10.1378/chest.09-2824
90. Sinderby C, Spahija J, Beck J, Kaminski D, Yan S, Comtois N, et al. Diaphragm activation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (2001) 163:1637–41. doi: 10.1164/ajrccm.163.7.2007033
91. Ferguson GT. Effects of oxygenation and hypercapnia on diaphragmatic function and central drive during respiratory failure. *J Appl Physiol.* (1995) 78:1764–71. doi: 10.1152/jappl.1995.78.5.1764
92. Ferguson GT. Respiratory failure due to altered central drive during inspiratory loading in rabbits. *Respir Physiol.* (1995) 99:75–87. doi: 10.1016/0034-5687(94)00073-9
93. Wagner PD, Laravuso RB, Uhl RR, West JB. Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100 per cent O2. *J Clin Invest.* (1974) 54:54–68. doi: 10.1172/JCI107750
94. Mummery HJ, Stolp BW, de LDG, Doar PO, Natoli MJ, Boso AE, et al. Effects of age and exercise on physiological dead space during simulated dives at 2.8 ATA. *J Appl Physiol.* (2003) 94:507–17. doi: 10.1152/japplphysiol.003i67.2002
95. Habedank D, Reindl I, Vietzke G, Bauer U, Sperfeld A, Glaser S, et al. Ventilatory efficiency and exercise tolerance in 101 healthy volunteers. *Eur J Appl Physiol Occup Physiol.* (1998) 77:421–6. doi: 10.1007/s004210050354
96. Neder JA, Nery LE, Peres C, Whipp BJ. Reference values for dynamic responses to incremental cycle ergometry in males and females aged 20 to 80. *Am J Respir Crit Care Med.* (2001) 164(8 Pt 1):1481–6. doi: 10.1164/ajrccm.164.8.2103007
97. Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med.* (2002) 166:1443–8. doi: 10.1164/rccm.2202033
98. Leblanc P, Ruff F, Milic-Emili J. Effects of age and body position on "airway closure" in man. *J Appl Physiol.* (1970) 28:448–51. doi: 10.1152/jappl.1970.28.4.448

99. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Sex differences in the perceived intensity of breathlessness during exercise with advancing age. *J Appl Physiol.* (2008) 104:1583–93. doi: 10.1152/japplphysiol.00079.2008
100. Harms CA. Does gender affect pulmonary function and exercise capacity? *Respir Physiol Neurobiol.* (2006) 151:124–31. doi: 10.1016/j.resp.2005.10.010
101. Kilbride E, McLoughlin P, Gallagher CG, Harty HR. Do gender differences exist in the ventilatory response to progressive exercise in males and females of average fitness? *Eur J Appl Physiol.* (2003) 89:595–602. doi: 10.1007/s00421-003-0853-z
102. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, et al. Neurophysiological mechanisms of exertional dyspnoea in fibrotic interstitial lung disease. *Eur Respir J.* (2018) 51:1701726. doi: 10.1183/13993003.01726-2017
103. Reilly CC, Jolley CJ, Ward K, MacBean V, Moxham J, Rafferty GF. Neural respiratory drive measured during inspiratory threshold loading and acute hypercapnia in healthy individuals. *Exp Physiol.* (2013) 98:1190–8. doi: 10.1113/expphysiol.2012.071415
104. James MD, Milne KM, Phillips DB, Neder JA, O'Donnell DE. Dyspnea and Exercise Limitation in Mild COPD: The Value of CPET. *Front Med.* (2020). doi: 10.3389/fmed.2020.00442
105. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Green M, Moxham J. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (1996) 154:1310–7. doi: 10.1164/ajrccm.154.5.8912741
106. Sprikkelman AB, Van Eykern LA, Lourens MS, Heymans HS, Van Aalderen WM. Respiratory muscle activity in the assessment of bronchial responsiveness in asthmatic children. *J Appl Physiol.* (1998) 84:897–901. doi: 10.1152/jappl.1998.84.3.897
107. Wagner PD, Dantzker DR, Dueck R, Clausen JL, West JB. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J Clin Invest.* (1977) 59:203–16. doi: 10.1172/JCI108630
108. Elbehairy AF, Ciavaglia CE, Webb KA, Guenette JA, Jensen D, Mourad SM, et al. Pulmonary gas exchange abnormalities in mild chronic obstructive pulmonary disease. Implications for dyspnea and exercise intolerance. *Am J Respir Crit Care Med.* (2015) 191:1384–94. doi: 10.1164/rccm.201501-0157OC
109. Jensen D, O'Donnell DE, Li R, Luo YM. Effects of dead space loading on neuro-muscular and neuro-ventilatory coupling of the respiratory system during exercise in healthy adults: implications for dyspnea and exercise tolerance. *RespirPhysiol Neurobiol.* (2011) 179:219–26. doi: 10.1016/j.resp.2011.08.009
110. Luo YM, Moxham J. Measurement of neural respiratory drive in patients with COPD. *Respir Physiol Neurobiol.* (2005) 146:165–74. doi: 10.1016/j.resp.2004.12.014
111. Lourenco RV, Miranda JM. Drive and performance of the ventilatory apparatus in chronic obstructive lung disease. *N Engl J Med.* (1968) 279:53–9. doi: 10.1056/NEJM196807112790201
112. Gorini M, Spinelli A, Ginanni R, Duranti R, Gigliotti F, Scano G. Neural respiratory drive and neuromuscular coupling in patients with chronic obstructive pulmonary disease (COPD). *Chest.* (1990) 98:1179–86. doi: 10.1378/chest.98.5.1179
113. Roussos C, Moxham J. Respiratory muscle fatigue. In: Roussos C, Macklem PT, editors. *The Thorax (Part B).* New York, NY: Marcel Dekker (1985). p. 829–70.
114. Sorli J, Grassino A, Lorange G, Milic-Emili J. Control of breathing in patients with chronic obstructive lung disease. *Clin Sci Mol Med.* (1978) 54:295–304. doi: 10.1042/cs0540295
115. Lee KD, Bishop JM. The reflex hypoxic respiratory drive in patients with chronic bronchitis. *Clin Sci Mol Med.* (1974) 46:347–56. doi: 10.1042/cs0460347
116. Babcock MA, Johnson BD, Pegelow DF, Suman OE, Griffin D, Dempsey JA. Hypoxic effects on exercise-induced diaphragmatic fatigue in normal healthy humans. *J Appl Physiol.* (1995) 78:82–92. doi: 10.1152/jappl.1995.78.1.82
117. O'Donnell DE, Ora J, Webb KA, Laveneziana P, Jensen D. Mechanisms of activity-related dyspnea in pulmonary diseases. *Respir Physiol Neurobiol.* (2009) 167:116–32. doi: 10.1016/j.resp.2009.01.010
118. O'Donnell DE, D'Arsigny C, Fitzpatrick M, Webb KA. Exercise hypercapnia in advanced chronic obstructive pulmonary disease: the role of lung hyperinflation. *Am J Respir Crit Care Med.* (2002) 166:663–8. doi: 10.1164/rccm.2201003
119. Casaburi R, Rennard SI. Exercise limitation in chronic obstructive pulmonary disease. The O'Donnell threshold. *Am J Respir Crit Care Med.* (2015) 191:873–5. doi: 10.1164/rccm.201501-0084ED
120. Chin RC, Guenette JA, Cheng S, Raghavan N, Amornputtisathaporn N, Cortes-Telles A, et al. Does the respiratory system limit exercise in mild chronic obstructive pulmonary disease? *Am J Respir Crit Care Med.* (2013) 187:1315–23. doi: 10.1164/rccm.201211-1970OC
121. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation. *Am Rev Respir Dis.* (1993) 148:1351–7. doi: 10.1164/ajrccm/148.5.1351
122. Cassart M, Pettiaux N, Gevenois PA, Paiva M, Estenne M. Effect of chronic hyperinflation on diaphragm length and surface area. *Am J Respir Crit Care Med.* (1997) 156(2 Pt 1):504–8. doi: 10.1164/ajrccm.156.2.9612089
123. Gauthier AP, Verbanck S, Estenne M, Segebarth C, Macklem PT, Paiva M. Three-dimensional reconstruction of the *in vivo* human diaphragm shape at different lung volumes. *J Appl Physiol.* (1994) 76:495–506. doi: 10.1152/jappl.1994.76.2.495
124. Agostoni E, Fenn WO. Velocity of muscle shortening as a limiting factor in respiratory air flow. *J Appl Physiol.* (1960) 15:349–53. doi: 10.1152/jappl.1960.15.3.349
125. Hyatt RE, Flath RE. Relationship of air flow to pressure during maximal respiratory effort in man. *J Appl Physiol.* (1966) 21:477–82. doi: 10.1152/jappl.1966.21.2.477
126. Olin JT, Clary MS, Fan EM, Johnston KL, State CM, Strand M, et al. Continuous laryngoscopy quantitates laryngeal behaviour in exercise and recovery. *Eur Respir J.* (2016) 48:1192–200. doi: 10.1183/13993003.00160-2016
127. Walsted ES, Faisal A, Jolley CJ, Swanton LL, Pavitt MJ, Luo YM, et al. Increased respiratory neural drive and work of breathing in exercise-induced laryngeal obstruction. *J Appl Physiol.* (2018) 124:356–63. doi: 10.1152/japplphysiol.00691.2017
128. Baz M, Haji GS, Menzies-Gow A, Tanner RJ, Hopkinson NS, Polkey MI, et al. Dynamic laryngeal narrowing during exercise: a mechanism for generating intrinsic PEEP in COPD? *Thorax.* (2015) 70:251–7. doi: 10.1136/thoraxjnl-2014-205940
129. Elbehairy AF, Guenette JA, Faisal A, Ciavaglia CE, Webb KA, Jensen D, et al. Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J.* (2016) 48:694–705. doi: 10.1183/13993003.00077-2016
130. Elbehairy AF, O'Donnell CD, Abd Elhameed A, Vincent SG, Milne KM, James MD, et al. Low resting diffusion capacity, dyspnea and exercise intolerance in COPD. *J Appl Physiol.* (2019) 127:1107–16. doi: 10.1152/japplphysiol.00341.2019
131. Qin YY, Li RF, Wu GF, Zhu Z, Liu J, Zhou CZ, et al. Effect of tiotropium on neural respiratory drive during exercise in severe COPD. *Pulm Pharmacol Ther.* (2015) 30:51–6. doi: 10.1016/j.pupt.2014.11.003
132. O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. *J Appl Physiol.* (2006) 101:1025–35. doi: 10.1152/japplphysiol.01470.2005
133. DeWeese EL, Sullivan TY, Yu PL. Ventilatory and occlusion pressure responses to helium breathing. *J Appl Physiol.* (1983) 54:1525–31. doi: 10.1152/jappl.1983.54.6.1525
134. Hussain SN, Pardy RL, Dempsey JA. Mechanical impedance as determinant of inspiratory neural drive during exercise in humans. *J Appl Physiol.* (1985) 59:365–75. doi: 10.1152/jappl.1985.59.2.365
135. Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, et al. Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. *Eur Respir J.* (2017) 49:1602494. doi: 10.1183/13993003.02494-2016
136. Abdallah SJ, Wilkinson-Maitland C, Saad N, Li PZ, Smith BM, Bourbeau J, et al. Effect of morphine on breathlessness and exercise endurance in advanced COPD: a randomised crossover study. *Eur Respir J.* (2017) 50:1701235. doi: 10.1183/13993003.01235-2017
137. Langer D, Ciavaglia CE, Faisal A, Webb KA, Neder JA, Gosselink R, et al. Inspiratory muscle training reduces diaphragm activation and dyspnea during exercise in COPD. *J Appl Physiol.* (2018) 125:381–92. doi: 10.1152/japplphysiol.01078.2017

138. Ramsook AH, Molgat-Seon Y, Schaeffer MR, Wilkie SS, Camp PG, Reid WD, et al. Effects of inspiratory muscle training on respiratory muscle electromyography and dyspnea during exercise in healthy men. *J Appl Physiol.* (2017) 122:1267–75. doi: 10.1152/japplphysiol.00046.2017
139. Wu W, Zhang X, Lin L, Ou Y, Li X, Guan L, et al. Transdiaphragmatic pressure and neural respiratory drive measured during inspiratory muscle training in stable patients with chronic obstructive pulmonary disease. *Int J Chron Obst Pulm Dis.* (2017) 12:773–81. doi: 10.2147/COPD.S126354
140. Ramsook AH, Koo R, Molgat-Seon Y, Dominelli PB, Syed N, Ryerson CJ, et al. Diaphragm recruitment increases during a bout of targeted inspiratory muscle training. *Med Sci Sports Exerc.* (2016) 48:1179–86. doi: 10.1249/MSS.0000000000000881
141. Breslin EH. The pattern of respiratory muscle recruitment during pursed-lip breathing. *Chest.* (1992) 101:75–8. doi: 10.1378/chest.101.1.75
142. Langer D, Ciavaglia CE, Neder JA, Webb KA, O'Donnell DE. Lung hyperinflation in chronic obstructive pulmonary disease: mechanisms, clinical implications and treatment. *Exp Rev Respir Med.* (2014) 8:731–49. doi: 10.1586/17476348.2014.949676
143. Luo YM, Tang J, Jolley C, Steier J, Zhong NS, Moxham J, et al. Distinguishing obstructive from central sleep apnea events: diaphragm electromyogram and esophageal pressure compared. *Chest.* (2009) 135:1133–41. doi: 10.1378/chest.08-1695
144. Luo YM, He BT, Wu YX, Yuan H, Xu J, Moxham J, et al. Neural respiratory drive and ventilation in patients with chronic obstructive pulmonary disease during sleep. *Am J Respir Crit Care Med.* (2014) 190:227–9. doi: 10.1164/rccm.201402-0302LE
145. Domnik NJ, James MD, Scheeren RE, Ayoo GA, Taylor SM, Di Luch AT, et al. Deterioration of nighttime respiratory mechanics in chronic obstructive pulmonary disease: impact of bronchodilator therapy. *Chest.* (2020). doi: 10.1016/j.chest.2020.06.033
146. Murphy PB, Kumar A, Reilly C, Jolley C, Walterspacher S, Fedele F, et al. Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. *Thorax.* (2011) 66:602–8. doi: 10.1136/thx.2010.151332
147. Maarsingh EJ, van Eykern LA, Sprikkelman AB, Hoekstra MO, van Aalderen WM. Respiratory muscle activity measured with a noninvasive EMG technique: technical aspects and reproducibility. *J Appl Physiol.* (2000) 88:1955–61. doi: 10.1152/jappl.2000.88.6.1955
148. Lozano-Garcia M, Sarlabous L, Moxham J, Rafferty GF, Torres A, Jolley CJ, et al. Assessment of inspiratory muscle activation using surface diaphragm mechanomyography and crural diaphragm electromyography. *Conf Proc IEEE Eng Med Biol Soc.* (2018) 2018:3342–5. doi: 10.1109/EMBC.2018.8513046
149. Estrada L, Torres A, Sarlabous L, Jane R. Improvement in neural respiratory drive estimation from diaphragm electromyographic signals using fixed sample entropy. *IEEE J Biomed Health Inform.* (2016) 20:476–85. doi: 10.1109/JBHI.2015.2398934
150. Karagiannidis C, Strassmann S, Schwarz S, Merten M, Fan E, Beck J, et al. Control of respiratory drive by extracorporeal CO2 removal in acute exacerbation of COPD breathing on non-invasive NAVA. *Crit Care.* (2019) 23:135. doi: 10.1186/s13054-019-2404-y
151. Beck J, Emeriaud G, Liu Y, Sinderby C. Neurally-adjusted ventilatory assist (NAVA) in children: a systematic review. *Minerva Anestesiol.* (2016) 82:874–83. doi: 10.1007/978-3-319-21653-9_15
152. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation in respiratory failure. *Nat Med.* (1999) 5:1433–6. doi: 10.1038/71012i
153. The Diaphragm in health and disease. *Lancet.* (1929) 214:79. doi: 10.1016/S0140-6736(01)04061-2

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REVIEW
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Cardiopulmonary Exercise Testing in the Assessment of Dysfunctional Breathing

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Dysfunctional breathing (DB) is a disabling condition which affects the biomechanical breathing pattern and is challenging to diagnose. It affects individuals in many circumstances, including those without underlying disease who may even be athletic in nature. DB can also aggravate the symptoms of those with established heart or lung conditions. However, it is treatable and individuals have much to gain if it is recognized appropriately. Here we consider the role of cardiopulmonary exercise testing (CPET) in the identification and management of DB. Specifically, we have described the diagnostic criteria and presenting symptoms. We explored the physiology and pathophysiology of DB and physiological consequences in the context of exercise. We have provided examples of its interplay with co-morbidity in other chronic diseases such as asthma, pulmonary hypertension and left heart disease. We have discussed the problems with the current methods of diagnosis and proposed how CPET could improve this. We have provided guidance on how CPET can be used for diagnosis, including consideration of pattern recognition and use of specific data panels. We have considered categorization, e.g., predominant breathing pattern disorder or acute or chronic hyperventilation. We have explored the distinction from gas exchange or ventilation/perfusion abnormalities and described other potential pitfalls, such as false positives and periodic breathing. We have also illustrated an example of a clinical pathway utilizing CPET in the diagnosis and treatment of individuals with suspected DB.

Keywords: dysfunctional breathing, breathing pattern disorder, hyperventilation syndrome, CpEt, cardiopulmonary exercise testing

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BACKGROUND

Dysfunctional breathing (DB) is a collective term used to describe a collection of conditions where the normal biomechanical pattern of breathing is disrupted, resulting in dyspnea and associated non-respiratory symptoms that cannot be fully explained by disease pathophysiology (Barker and Everard, 2015). DB has an overall prevalence of around 9% in the general population but is more prevalent in patients with an underlying respiratory disease, such as asthma or COPD; in asthmatic populations, prevalence has been reported to be as high as 29% (Thomas et al., 2005). There is currently no gold standard diagnosis or classification system and thus the condition is still poorly understood by many clinicians.

When DB was initially described in the literature, a group of symptoms were noted to be associated with inappropriate hyperventilation and over-breathing (Lum, 1975). This was termed hyperventilation syndrome and continues to be a heavily discussed form of DB. However, we now understand this as being just one type of DB as not all patients with DB show hyperventilation responses. More recent literature has looked at the wider picture of DB, with several attempts to classify the different patterns into subtypes (Barker and Everard, 2015; Boulding et al., 2016).

The most important identifying criterion is the presence of breathlessness after organic disease pathology has been ruled out or optimized by pharmacological treatment. This is often described as "disproportionate breathlessness" (Prys-Picard et al., 2006; Barker and Everard, 2015); in other words, the breathlessness is greater than can be ascribed to any potential organic disease. However, as no gold-standard diagnostic method exists, diagnosis is often made using questionnaire-based techniques or following assessment by expert physiotherapists and clinicians.

A major problem with this practice, in our clinical experience, is that symptoms of DB can often be missed or attributed to more severe respiratory disease than there is in reality, resulting in inappropriately high doses of medication that are not beneficial. Identification of DB, on the other hand, would allow patients to benefit from breathing retraining programs delivered by physiotherapists. This will decrease their symptom burden and reduce the need for medication, an overall improvement in their clinical management.

Having said that, we advocate that cardiopulmonary exercise testing (CPET) can be an attractive method to objectively diagnose DB. In that sense, CPET, can identify DB patterns while ruling out other cardiac, respiratory, metabolic and muscular abnormalities (Neder et al., 2018). During CPET, DB often presents with an inappropriately high breathing frequency and erratic patterning of both breathing frequency and tidal volume in response to exercise. Additionally, the patient may report symptoms of DB during the test itself: breathlessness at a low workload, chest tightness, dizziness or tingling sensations in their lips and/or fingers.

This review focusses on the pathophysiology and proposed tests to diagnose DB, followed by a brief discussion on how such tests might aid in planning personalized patient care. It is important to note that, despite the growing interest in DB in recent years, published research evidence that supports our understanding of the condition is limited. Thus, some of the information provided and discussed here comes from expert opinion and clinical experiences, as well as research published only in abstract form.

PATHOPHYSIOLOGY OF DYSFUNCTIONAL BREATHING

Dysfunctional breathing encompasses any change in the normal biomechanical pattern of breathing; within this, there have been attempts to classify DB into subtypes. Barker and Everard suggested a classification system which splits DB into thoracic (alterations in the respiratory muscle activity) or extra-thoracic (with upper airway involvement too). The thoracic and extra-thoracic types were then each further split into structural and functional subtypes (Barker and Everard, 2015; Depiazzi and Everard, 2016). Within thoracic DB, Boulding and colleagues proposed a classification system largely based on the pathophysiological pattern of disruption to the respiratory muscle activation, identifying five key types of DB: hyperventilation syndrome, periodic deep sighing, thoracic dominant breathing, forced abdominal expiration and thoraco-abdominal asynchrony (Boulding et al., 2016).

Thoracic and extra-thoracic DB are diagnosed and managed differently in clinical practice. For the purposes of this manuscript, we have focused on the thoracic types of DB, as CPET is useful for their identification. However, it is important to be aware of the subclassifications which exist within DB.

Regarding the pathophysiology of thoracic DB, it is often physiological or psychological stress which provokes symptoms (Depiazzi and Everard, 2016). These stressful events can include excessive aerobic training, bereavement or a health-related illness (Courtney, 2009). Respiratory diseases (such as asthma or COPD) as well as musculoskeletal dysfunction, pain or an altered chest wall shape can also cause DB, by triggering the diaphragm into an abnormal pattern of breathing (Barker and Everard, 2015; Berton et al., 2020).

Fluoroscopic studies have demonstrated that when an individual is exposed to emotional stress the diaphragm becomes flattened, hypertonic and relatively immobile, causing intercostal and accessory muscles to contribute more to ventilation (Courtney, 2009). This is associated with mild hyperinflation, an irregular rate and volume of respiration and frequent sighing. DB can therefore be seen as an unconsciously learned habitual change in the normal pattern of breathing which may become apparent at rest or only when stressed (Barker and Everard, 2015). In some patients, there is a sufficient increase in minute ventilation to cause hypocapnia. This occurs for varying lengths of time, depending on the cause. However, only a small proportion of patients with thoracic DB exhibit hyperventilation as defined by the presence of hypocapnia.

A certain level of hyperventilation may be associated with increased sympathetic activity when stressed, which has the potential beneficial effect of increasing neuronal activity. However excessive sympathetic activity with further hyperventilation and hypocapnia results in the depression of neuronal activity. Overall it has been shown that exercise has a greater effect on respiratory volumes in comparison to anxiety, which is associated more with irregular breathing (Barker and Everard, 2015).

Extra-thoracic subtypes of DB have a different pathophysiology, characterized by upper airway changes (Barker and Everard, 2015; Depiazzi and Everard, 2016). The most common of these extra-thoracic changes are inducible laryngeal obstruction (ILO) and laryngomalacia. ILO is the intermittent, abnormal, paradoxical adduction of the vocal folds with respiration, causing variable upper airway obstruction (Krey and Best, 2014; Matrka, 2014; Halvorsen et al., 2017).

In laryngomalacia there is intermittent airway obstruction due to collapse of the supraglottic tissues during inspiration when an individual is exercising vigorously and generating large negative intrathoracic pressures (Shembel et al., 2017). It is also possible that the changes to the diaphragm seen on fluoroscopic studies also occur in the glottis leading to paradoxical vocal fold dysfunction.

DIAGNOSIS METHODS

There are a wide range of diagnostic methods in use in clinics today. However, there is no gold-standard, validated method being consistently applied. Centers utilize different strategies which unfortunately do not show complete overlap in the diagnoses picked up by the different methods (Todd et al., 2018).

Questionnaire-based approaches, such as the Nijmegen questionnaire (NQ) and the self-evaluation of breathing questionnaire (SEBQ), are common methods used to identify DB. The NQ is the most widespread method, despite only being designed to identify hyperventilation syndrome. It utilizes a series of questions to identify how frequently a patient experiences certain symptoms, assigns each response a score of 0–4 and a total NQ score is calculated. If this NQ score is above the threshold of 23, a DB diagnosis can be considered likely.

The NQ was found to have a sensitivity of 91% and specificity of 95% in detecting hyperventilation (van Dixhoorn and Duivenvoorden, 1985); the submaximal sensitivity was proposed to be due the questionnaire using an incomplete list of symptoms and thus missing some patients with unusual sets of symptoms. Alternatively, patients may not necessarily notice or report their own symptoms as abnormal, which would also result in the questionnaire failing to detect the hyperventilation. In the context of subjects with other conditions, such as poorly managed asthma, COPD, panic disorder and anxiety, the specificity of the NQ is lower due to an inability to distinguishing DB from underlying co-morbidities (Stanton et al., 2008; van Dixhoorn and Folgering, 2015). Thus, it has been proposed that the NQ represents a subjective score of "functional respiratory complaints" that may point to but not be unique to DB or hyperventilation (van Dixhoorn and Folgering, 2015).

Other diagnostic methods utilize direct observation and examination by expert physiotherapists. Physiotherapists can use a tool such as the Breathing pattern assessment tool (BPAT) (Todd et al., 2018) or the manual assessment of respiratory motion (MARM) method (Courtney et al., 2008). The benefit of these methods is that the assessment of the breathing pattern is made by an observer, rather than relying on patient-reported symptoms. Moreover, an expert physiotherapist specializing in this field can rapidly make an assessment of the breathing mechanics; they are able to pick up on visual and physical clues and utilize pattern recognition to help to make the diagnosis. A potential difficulty is that it requires expert chest physiotherapists familiar with DB and the observational and analytic skills require frequent exposure to DB to build up. Thus, it may not be possible to put this into practice in all centers.

A less frequently used method which can be used in the diagnosis of DB is plethysmography, either optoelectronic or inductive. These methods rely on measuring the changes in volume of the chest wall, ribcage and abdomen in order to analyze the underlying breathing mechanics. This has the potential to be a sensitive technique to study thoracic-dominant DB or thoracic-abdominal asynchrony. Despite its current limited clinical use, literature has supported that plethysmography may be a useful tool to characterize breathing patterns (Levai et al., 2016).

Finally, ramp-incremental CPET can be very helpful for the investigation of dyspnea of unknown etiology. It allows identification of any pathophysiological cause of breathlessness on exertion which could not be demonstrated by tests performed at rest. In that sense, aerobic, ventilatory, cardiac, gas exchange and muscle response to exercise can be determined and compared to normal predicted responses (Wasserman, 1997). Thus, it is an attractive method by which to identify DB clinically (Toma et al., 2010; Griffiths and Anindo, 2014; Costa et al., 2016; Jayadev et al., 2017; Roberts et al., 2017; Brat et al., 2019).

The CPET begins with a resting phase analysis of the patient's spirometry, ECG, blood pressure and oxygen saturation. For some patients, DB may be apparent at rest. The patient is asked to quantify their feeling of breathlessness and muscle fatigue at the start of the test, measures which will be revisited at the end of the test. Additionally, an evaluation is made of the subject's functional status and baseline level of fitness, enabling the physiologist to estimate a predicted workload ramp rate to use during the test. Subsequently, the exercise test proceeds to the exercise phase of the test, typically carried out on a stationary bike. This begins with unloaded cycling, followed by incrementally increased load until the patient is stopped by symptoms or the physiologist stops the test due to safety concerns. Ideally this maximal exertion should be reached after about 8–12 min of loaded exercise. The patient's physiological response to exercise is monitored throughout the exercise and subsequent recovery, until the patient returns back to their baseline. At peak exercise, the patient is asked to quantify their feeling of breathlessness and muscle fatigue. In patients with DB, the factor leading to cessation of exercise will often be sensations of breathlessness or air hunger due to the inefficient breathing pattern. A standard CPET protocol has been described in detail in the European Respiratory Society's statement on standardization of CPET testing in chronic lung diseases (Radtke et al., 2019).

The literature in the CPET field is heavily weighted toward stationary cycle ergometers as the exercise modality of choice. In practice, it would be possible to apply an incrementally increasing workload using other modalities, such as treadmills or indoor rowing machines. For instance, treadmills are the exercise method utilized in the Bruce protocol, which is typically used for exercise stress tests in the context of cardiology (Bruce et al., 2004). Alternative exercise modalities could be particularly useful for athletic individuals, providing a method to analyze their physiological response to exercise in a scenario that is closer to their typical training regime. This suggestion has been made in the literature for cardiology stress tests (Sarma and Levine, 2016). Use of the Bruce protocol or alternative exercise modality has not

been described in the literature for the purposes of DB, but it is possible that a similar approach could be utilized.

A major benefit of CPET is that, unlike the questionnaires and observation-based approaches, it gives objective measurements and plots data which can be directly analyzed. The nine-panel plot provides an excellent visual method to analyze these data. Erratic or abnormal responses in the respiratory panels can point to a diagnosis of DB. This will be discussed in further depth in the next section. Moreover, CPET can help to rule out other causes of exercise limitation. The cardiac panels, ECG and metabolic analysis can exclude other pathologies or drivers to DB. As discussed, this is a vital step in making a diagnosis of DB. CPET can provide reassurance that there is no underlying disease pathology, helping to confirm whether DB is the main cause of a patient's symptoms (Toma et al., 2010; Costa et al., 2016).

The use of CPET to aid in the diagnosis of patients with unexplained dyspnea has been supported in recent literature. A proportion of these patients were found to have DB upon analysis of CPET data (Thing et al., 2011). This, however, is likely to be an underestimate, as we would argue that DB is still underdiagnosed by most clinicians. This underdiagnosis probably stems from the lack of a consistent definition and classification system. Hyperventilation syndrome remains the most widely discussed type of DB, but it should not be taken to be synonymous with DB. Unfortunately, many clinicians are not familiar enough with the different types of DB to identify the rarer types that do not present with hyperventilation.

CPET DATA INTERPRETATION

Using maximal ramp-incremental CPET to rule out other causes of breathlessness is important when investigating DB, as DB is sometimes a diagnosis of exclusion. It may also be very reassuring to patients to know that there is no obvious underlying disease process.

The first step in interpreting the results of a CPET is pattern recognition using techniques such as the 9-panel plot. The nine-panel plot gives a useful overview of the aerobic, ventilatory, cardiac, gas exchange, and muscle response to exercise, which can be used to suggest the presence, severity and relevance of any pathophysiology. If there is no disease pathophysiology detected, or the degree of symptoms exceed what would be expected from the pathophysiology, this may suggest an element of DB.

There are different approaches when analysing CPET results. We recommend standardizing the reading according to the following steps: (Barker and Everard, 2015) check that the test fulfils criteria for maximum effort; (Thomas et al., 2005) analyze the physiologic responses to exercise, moving sequentially from metabolic responses, to cardiovascular responses and finally to ventilatory and gas exchange responses; (Lum, 1975) assess causes for stopping exercise (dyspnea and/or leg discomfort) and other potential accompanying symptoms such as light headedness, chest pain or perioral numbness. Here we describe what physicians should expect to encounter at each of these steps when exercise intolerance is due to DB. It should be stressed that some of the information provided below is derived from expert opinion and clinical experience, but appropriate research papers are referenced when the evidence is available.

1. Checking criteria for maximum effort

   Patients with DB may not fulfill the usual criteria for maximum effort. It is not uncommon for them to stop exercising at heart rates which fall below 85% of the predicted maximal, usually at low work rates (**Figure 1A**) and showing additional evidences of submaximal test. The respiratory exchange ratio (RER) at peak exercise, on the other hand, can be lower or higher than 1 depending on the breathing pattern the patient assumes during exercise. Patients who develop significant hyperventilation may start and finish exercise with RER values persistently above 1 (Neder et al., 2018). Conversely, development of an erratic ventilatory pattern may result in tremendous unpredictable variations of its value over time, so that RER at peak exercise may fall randomly below 1 (**Figures 1B,C**).

2. Analysis of physiologic responses to exercise

a. Metabolic responses

   Patients with DB might present with normal or reduced VO_2 at peak exercise (MartinezI, 1994; Chenivesse et al., 2014; Brat et al., 2019). In the latter case, it is not uncommon for the test not to fulfill criteria of maximum effort. The anaerobic threshold (AT) might be difficult or even impossible to determine in cases were erratic ventilation develops, as the ventilatory equivalents become too variable and unpredictable over time (**Figure 1F**). Also, the AT may not be reached if patients stop exercising prematurely. However, when AT is present and identifiable, the VO_2 is expected to be within the normal range (MartinezI, 1994). The VO_2/W slope is usually (although not always - **Figure 1A**) possible to estimate and is expected to be within the normal range as well.

b. Cardiovascular responses

   Patients with exercise intolerance due to DB are expected to have normal cardiovascular responses to exercise. In that sense, HR, arterial pressure and oxygen pulse should increase appropriately with progressively higher exercise intensities. For most patients, peak HR is higher than 85% of the predicted maximal (MartinezI, 1994; Brat et al., 2019), but lower peak HR can be seen in the context of submaximal effort. Having said that, it is important to analyze submaximal variables such as HR/VO_2 slope, as they are expected to remain in the normal range even if exercise is stopped prematurely (**Figure 1D**).

   Oxygen pulse (VO_2/HR) is yet another important variable to assess, as it is considered a surrogate for stroke volume and is generally reduced in cardiovascular and pulmonary vascular disease (Degani-Costa et al., 2019). In patients

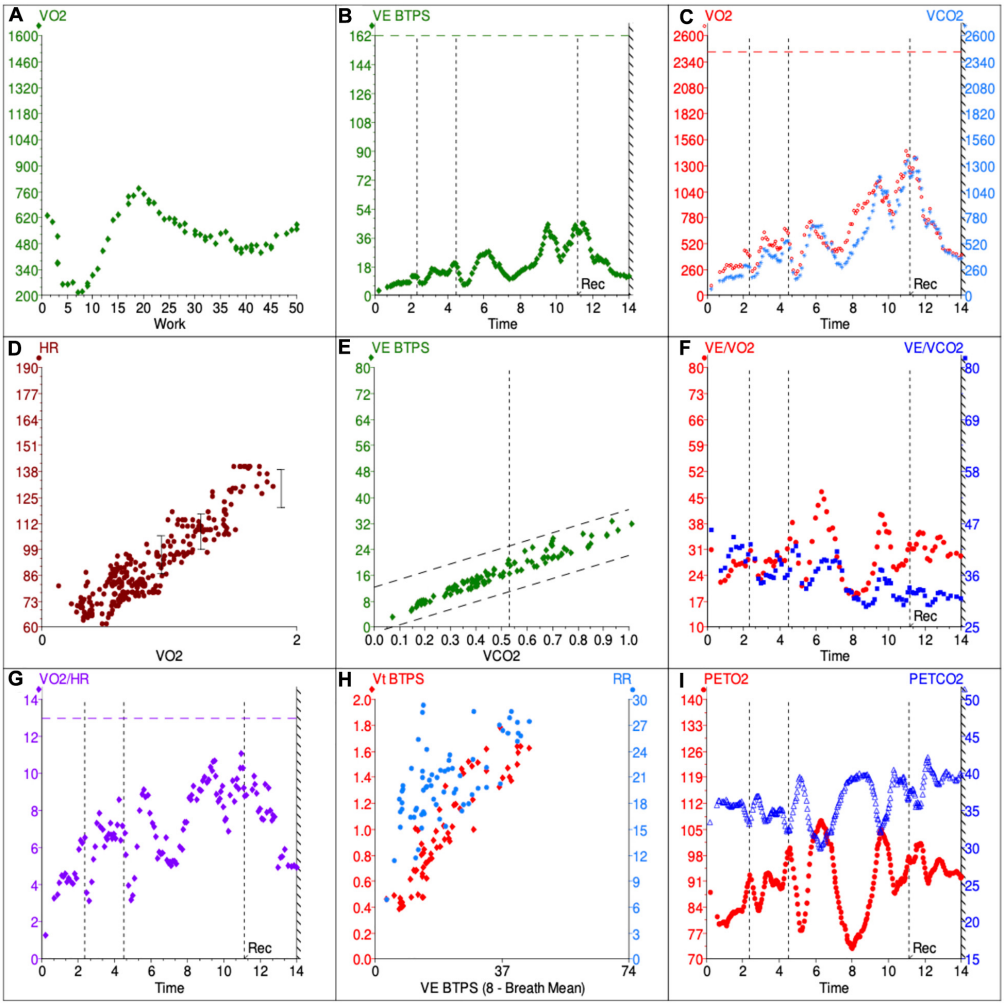

FIGURE 1 | Example 9-panel plot showing patterns consistent with DB. The panels give an overview of metabolic **(A,C)**, cardiovascular **(D,G)**, ventilatory **(B,E,F,H)** and gas exchange **(I)** responses during the CPET. VO2, volume of O_2 used per minute; VCO2, volume of CO2 produced per minute; VE, minute ventilation; BTPS, body temperature and standard pressure; HR, heart rate, VE/VCO2, ventilatory equivalent for CO_2; VE/VO2, ventilatory equivalent for O_2. PETCO2, end-tidal CO_2; PETO2, end-tidal O_2.

with DB, O_2 pulse at peak exercise is expected to be normal (MartinezI, 1994), but development of erratic breathing might make it difficult to analyze its submaximal trajectory or even determine its peak value accurately. The more erratic the ventilation, the more scattered averaged VO_2/HR values become, even if the data is adequately smoothed (**Figure 1G**).

c. Ventilatory and gas exchange responses

The ventilatory and gas exchange variables are the ones that can be most informative to distinguish DB from other causes of exercise intolerance. In healthy individuals, increments in ventilation (V_E) during the early phases of exercise are primarily due to an increase in V_t, with minimal increases in B_f (**Figures 2A,B**). As the subject faces progressively higher workloads, V_t plateaus and further increments in ventilation become strongly dependent on the rise of B_f. This physiological response minimizes dead space (V_D/V_T) and allows V_E to increase linearly (and predictably) with carbon dioxide production (V_{CO2}) throughout the greater part of loaded exercise, until the V_E/V_{CO2} slope demonstrates an inflection as the respiratory compensation point is reached (Wasserman, 1997; Neder et al., 2003).

On the other hand, patients with DB usually present with high B_f at rest which increases inappropriately quickly in early exercise, while V_t may remain essentially unchanged. This can increase dead space ventilation and alter the kinetics of many CPET variables (Neder et al., 2016), typically increasing V_E/V_{CO2} slope (**Figure 1E**). Also, this rapid shallow breathing pattern, characteristic of hyperventilation syndrome, may result in increased

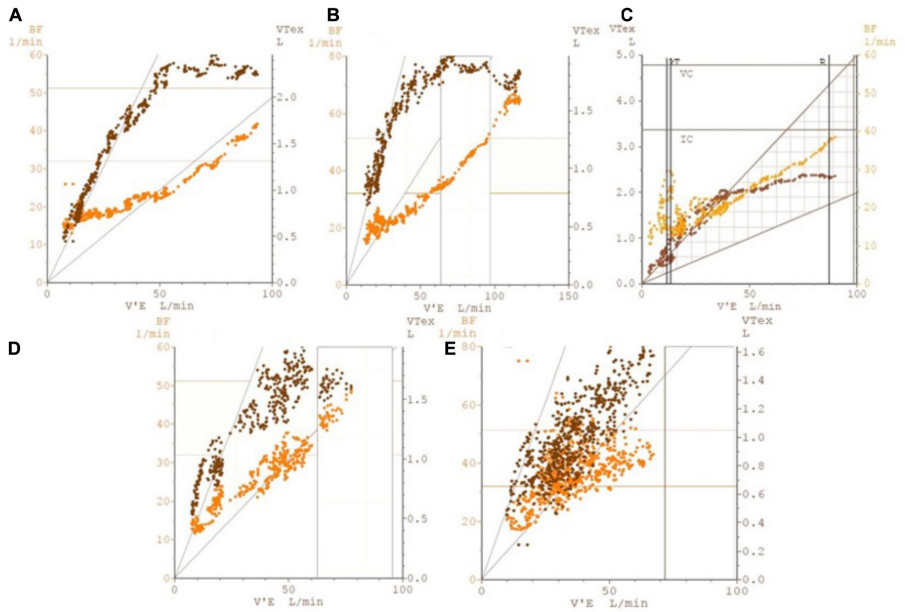

FIGURE 2 | Illustrative plots of breathing frequency (labeled as BF on left *y*-axis) and tidal volume (labeled as VTex on right *y*-axis) against minute ventilation (labeled as V'E on *x*-axis), showing breathing pattern responses to ramp-incremental CPET in five possible scenarios. Such plots allow for greater insight into the breathing pattern over the course of the CPET, looking at both V_t and B_f changes with ventilation. The five scenarios illustrated are: **(A)** normal individual **(B)** athletic individual **(C)** early DB that resolves on exercise **(D)** DB manifesting upon commencement of exercise **(E)** DB throughout. Particular attention should be paid to the predictable pattern of breathing frequency and tidal volume increases in plots **(A,B)**, allowing for an efficient mechanism for minute ventilation to increase; this can be contrasted to the erratic patterns that can be observed in plots **(C–E)**, which are indicative of DB. BF, breathing frequency; V'E, minute ventilation; VTex, tidal volume.

end-inspiratory and end-expiratory lung volumes, therefore reducing inspiratory capacity and possibly contributing to the unpleasant dyspnea sensation irrespective of the occurrence of true hypocapnia (Boulding et al., 2016).

In many cases, however, frequent sighing also occurs in the middle of this rapid shallow breathing, generating a chaotic and irregular breathing pattern (Boulding et al., 2016), with highly variable V_t and B_f for a given V_E. When this occurs, the impact of the breathing pattern on operating lung volumes is poorly understood, as it is virtually impossible to perform inspiratory capacity maneuvers correctly without ensuring regular and stable V_t.

Such DB patterns (hyperventilation, erratic ventilation and/or periodic sighing) may disappear later in exercise as the subject becomes more focused on the task (**Figure 2C**) or, on occasions, only begin only after the patient starts pedaling (**Figure 2D**). In some cases, though, they persist throughout the whole test (**Figures 1H**, **2E**). Since CPET collects both resting and exercise data, all of these patterns of DB can be identified. DB that only becomes obvious on exertion can be missed by other clinical assessment methods.

While identification of erratic ventilation may seem rather straightforward at first, in practice many cases can pose a significant challenge. Given the irregular and unpredictable nature of this ventilatory pattern (which clearly distinguishes it from periodic breathing), to date no objective, measurable and standardized criteria have been developed to define it. As such, the diagnosis of erratic ventilation requires the utilization of pattern recognition skills of the clinician interpreting the CPET data. In our experience, looking at a few specific plots can be helpful: (1) V_E/V_{O2} and V_E/V_{CO2} against time; (2) $P_{ET}CO_2$ and $P_{ET}O_2$ against time; (3) B_f and V_t against time; (4) B_f and V_t against V_E. On these plots, the respiratory equivalents, $P_{ET}CO_2$ and $P_{ET}O_2$ show irregular and erratic kinetics (**Figures 1F,I**) and B_f and V_t data points appear scattered rather than linear (**Figures 1H**, **2E**). Of course, this analysis depends on adequate smoothing of the data, and either moving average of eight breaths or running average of five of seven breaths can be used. Still, identifying erratic ventilation can be rather subjective in some cases.

Previous authors have attempted to propose strategies for pattern recognition and cut-offs for gas exchange variables which could reliably identify DB on CPET. More specifically, Boulding and colleagues proposed classifying DB patterns taking into account not only incremental CPET data, but also the behavior of B_f, V_t, and respiratory muscle mechanics before and after exercise (Boulding et al., 2016). By that approach, in addition to hyperventilation syndrome and erratic ventilation,

other abnormal breathing patterns might be identified: thoracic dominant breathing, forced expiratory pattern and thoraco-abdominal asynchrony. Thoracic dominant breathing pattern was characterized by a lack of costal expansion and a high reliance on upper thoracic muscles during inspiration. As with hyperventilation, thoracic dominant pattern was associated with high operating lung volumes and reduced inspiratory capacity. The forced-expiratory pattern, on the other hand, results in the patient breathing on very low lung volumes, therefore reducing functional residual capacity.

However, the inherent caveats of CPET data interpretation make it usually impossible to rely solely on breathing patterns to establish a diagnosis of DB. For instance, thoracic-dominant and forced expiratory breathing patterns may develop in patients with COPD in response to pulmonary hyperinflation, in which case they should not be regarded as dysfunctional, but rather as a physiological adaptation. Similarly, thoracic-dominant patterns may be seen in morbidly obese patients in response to their low abdominal compliance. Finally, significant hyperventilation may occur in patients with increased dead space ventilation, such as those with heart failure or pulmonary hypertension.

Therefore, in patients undergoing CPET for unexplained dyspnea who present with abnormal breathing patterns, additional physiological information (summarized in **Table 1**) must be analyzed before establishing any diagnosis, as certain cardiac or respiratory pathologies can present similarly to DB on CPET. First of all, patients with purely DB generally stop exercising with a high breathing reserve, although ventilation is clearly dissociated from the metabolic demand (Neder et al., 2018). Second, patients are not expected to desaturate during exercise, unlike patients with lung parenchyma and pulmonary vascular disease. Importantly, arterial or capillary blood gases at rest and peak exercise can also help discriminate DB from cardiopulmonary conditions. In that sense, patients with DB usually present with resting hypocapnia and normal PaO_2, $P(A\text{-}a)O_2$ gradient, V_D/V_T and $P(a\text{-}ET)CO_2$ gradient at end-exercise, which can help differentiate from other conditions in which chronic hyperventilation occurs, such as heart failure or PAH.

Conversely, while resting $P_{ET}CO_2$ below 30 mmHg, unchanging $P_{ET}CO_2$ and $VeqCO_2$ or an inverse trend of $P_{ET}CO_2$ and $VeqCO_2$ kinetics during loaded exercise (i.e., early decrease in $P_{ET}CO_2$ and increase in $VeqCO_2$ rather than the opposite) have been suggested as highly specific of primary hyperventilation syndrome, a similar pattern can also be seen in patients with pulmonary arterial hypertension (Brat et al., 2019).

It should be noted that the presence of erratic ventilation does not automatically exclude alternative clinical diagnoses. DB frequently coexists with asthma and is recognized as a cause of severe and difficult-to-treat asthma (Boulding et al., 2016). Also, patients with a history of stridor or those who develop stridor during the test should be investigated for vocal cord dysfunction. On the other hand, there is no specific recommendation to treat DB when erratic ventilation is an incidental finding and the patient is asymptomatic. Of course, since CPET is usually performed as a diagnostic test to identify a cause of dyspnea in patients who are symptomatic, identification of DB in these patients is likely to be of clinical significance.

Finally, it is important to consider particular differentials of erratic ventilation, such as pulmonary arterial hypertension or periodic breathing associated with heart failure. These conditions may also present with an "erratic-looking" B_f and V_t plots, but as described above it is possible to use further CPET plots and variables to distinguish between these two entities (**Figure 3**). Similarly, periodic breathing can be readily distinguished from DB by carefully analysing nine-panel plots, particularly the one portraying V_E over time. Periodic breathing is a recognized marker of disease severity in patients with heart failure due to left ventricular systolic dysfunction and may develop at rest or during exercise. As happens in DB, periodic breathing may last throughout the whole phase of incremental workload or disappear toward the end of exercise. However, the characteristic periodicity of waxing and waning of V_t (and consequently of V_E) seen in periodic breathing (Agostoni et al., 2017) is in clear contrast to the unpredictable and irregular breathing pattern of DB (**Figures 3A,B,D,E**). Given its predictable behaviour, standardized criteria have been adopted to define periodic breathing, the most widely accepted one requiring the amplitude of a single V_E oscillation to be greater or equal to 15% of the resting average V_E and the phenomenon to last at least 60% of the exercise phase (Agostoni et al., 2017).

d. Reasons for stopping exercise and accompanying symptoms

Enquiring after the reasons for stopping the test and accompanying symptoms can also aid in differentiating between DB and other clinical conditions. For example, the development of perioral numbness, tingling and peripheral paraesthesia is highly suggestive of DB and a dissociation between dyspnea intensity and the workload level can also be seen (Neder et al., 2016).

CPET AS A GUIDE TO TREATMENT

Dysfunctional breathing is usually very responsive to breathing retraining by specialized physiotherapists (Thomas et al., 2003). In our clinic, we provide follow-ups after the initial assessment visit, where patient progress can be tracked. If the patient can consciously control their breathing pattern at follow-up, the next

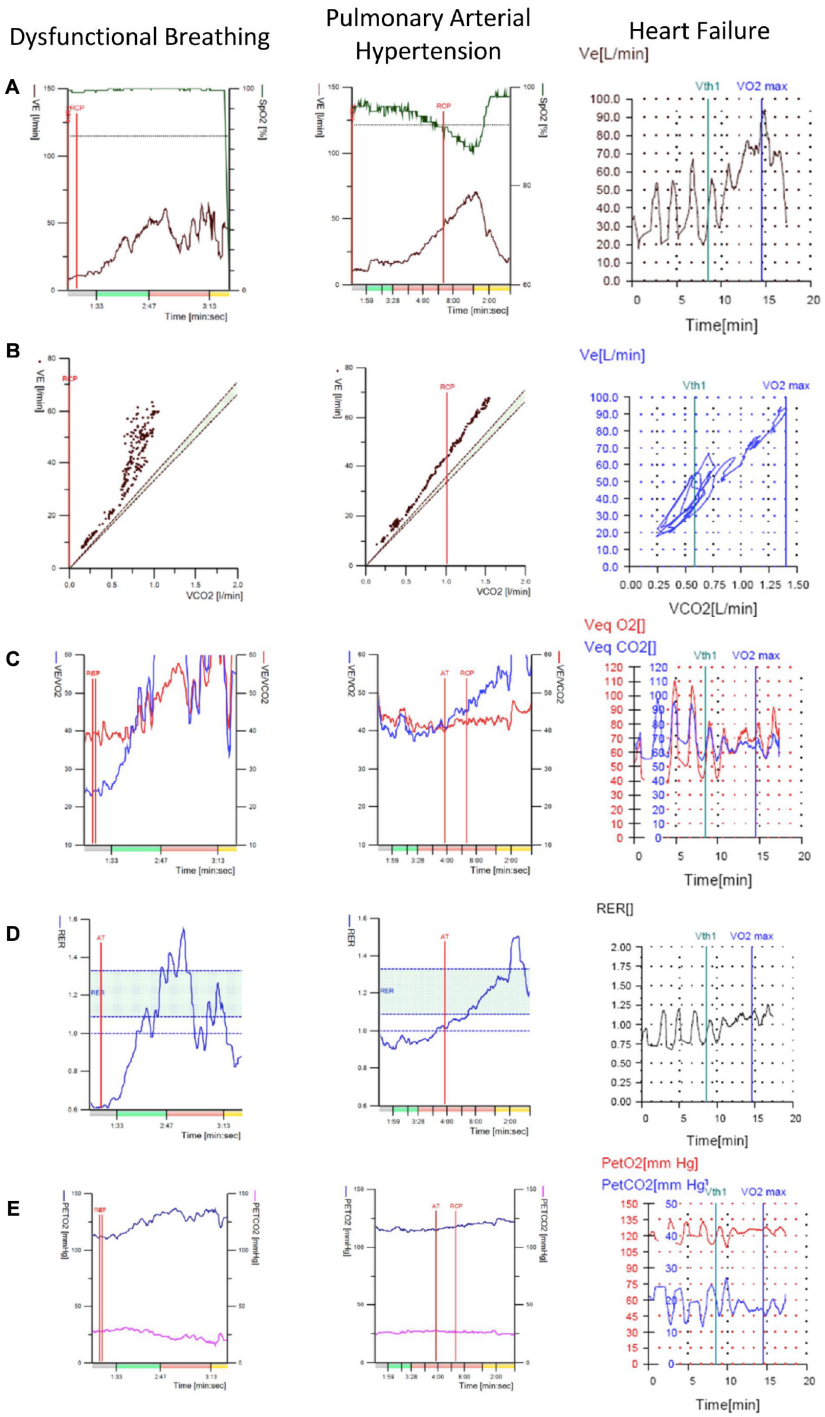

FIGURE 3 | Representative CPET plots that can be used to help distinguish between DB, pulmonary arterial hypertension and heart failure with periodic breathing. These conditions may be differentials in patients undergoing CPET for unexplained dyspnea suspected to be DB All three may present with seemingly erratic patterns of V_t and B_f responses to exercise. Therefore these plots can be used to narrow down the diagnosis when interpreting a CPET. Note that in columns 1 and 2 the colors on the *x*-axis indicate the phase of exercise; gray is rest, green is unloaded cycling red is linearly increasing workload and yellow is recovery. In the third column, unloaded cycling began at 2 min and loaded cycling at 5 min. **(A)** Plot of minute ventilation and oxygen saturation against time. **(B)** Plot of minute ventilation against volume of CO_2 exhaled per minute. **(C)** Plot of ventilatory equivalents for CO_2 and O_2 against time. **(D)** Plot of respiratory exchange ratio against time. **(E)** Plot of end-tidal CO_2 and O_2 against time. Particular points to take from this figure are the similarity in appearance of DB and pulmonary arterial hypertension plots. Major differences include the desaturation in pulmonary arterial hypertension and the fall in respiratory exchange ratio in later exercise in DB. Additionally, note the clear periodicity across the plots in the case of heart failure with periodic breathing; this is not the case for DB. V_E, minute ventilation; SpO_2, oxygen saturation; V_E/V_{CO2} or $VeqCO_2$, ventilatory equivalent for CO_2; V_E/V_{O2} or $VeqO_2$, ventilatory equivalent for O_2; $P_{ET}CO_2$, end-tidal CO_2; $P_{ET}O_2$, end-tidal O_2; RER, respiratory exchange ratio; RCP, respiratory compensation point; Vth1, first ventilatory threshold; VO_2max, point of maximal O_2 consumption; AT, anaerobic threshold.

TABLE 1 | Summary of typical blood gas and CPET findings in DB compared to other diseases.

	Dysfunctional breathing (DB)	Left heart disease (without PAH)	Pulmonary arterial hypertension (PAH)	Interstitial lung disease (ILD)	COPD
$PaCO_2$ at rest	Normal or low	Normal to low	Low	Normal	Normal or high
PaO_2 at end-exercise	High or normal	Normal	Low	Low	Normal
$P(A\text{-}a)O_2$ gradient	Normal	Normal	High	High	Normal
$P_{ET}CO_2$ at AT or end exercise	Typically low	Normal to low	Very low	Normal to low	Normal to high
V_E/V_{CO2} slope	Typically high	Normal to high	Very high	High	GOLD I-II: High GOLD III-IV: normal to low
$P(a\text{-}ET)CO_2$ gradient	Normal but can be high	Normal	High	High	High
V_D/V_t	Normal but can be high	Normal	High	High	High

The conditions below have been highlighted as clinical scenarios that may present similarly on CPET, but can be distinguished from DB by using the parameters detailed in the table. $PaCO_2$, arterial partial pressure of CO; PaO_2, arterial partial pressure of O_2; $P(A\text{-}a)O_2$ gradient, alveolar-arterial gradient of O_2; $P_{ET}CO_2$, end-tidal partial pressure of CO_2; AT, anaerobic threshold; V_E, minute ventilation; V_{CO2}, volume of CO_2 exhaled per minute; P(a-ET)CO2, arterial – end-tidal CO_2 gradient; V_D, dead volume; V_t, tidal volume.

step is to try to perform the same breathing pattern in a more challenging scenario, for instance when walking along a corridor, going up and down stairs, or having a conversation. This will help them train the new way of breathing to become subconscious. There is no published data describing the role of CPET in guiding individual therapy.

Educating patients about DB is a key component and first step in the breathing retraining program. In this context, CPET can help patients and clinicians by reassuring them that dyspnea is not the result of an underlying organic pathology, Furthermore, the modified Vt and Bf plot guides the clinician to understand the variance in the breathing pattern and adds a degree of objectiveness to their assessment of the breathing pattern. Showing the patient this plot can also provide visual feedback to the patient about the changes in their breathing pattern, which then allows the clinician to promote awareness of the effective breathing pattern and improve patient engagement with breathing retraining.

Over the course of the therapy, progress from the initial assessment to subsequent visits is often tracked using NQ, SEBQ, or BPAT scores. As discussed before, these are quite subjective methods to assess symptoms and breathing pattern. Moreover, when used as a method to monitor progress, they can also risk being biased. If the questionnaire is being filled out by a patient, they know they are undergoing therapy, and may try to, either consciously or subconsciously, answer the questions as they think the practitioner wants them to, decreasing the scores given to describe the frequency of their symptoms to show the treatment working. Importantly, the physiotherapist or other assessing practitioner may themselves show a certain degree of bias in the follow-up assessments, since they know that the patient has had therapy and so will be looking to see that this therapy has worked.

In reality, it has been observed that patient symptoms and quality of life improve even if the NQ/SEBQ/BPAT scores do not show a significant change from the baseline. Thus, perhaps we have been going about trying to quantify the degree of breathing pattern change incorrectly. Indeed, Thomas and colleagues identified that the change in the AQLQ score (a questionnaire aimed to quantify asthma-related quality of life) showed a more significant response to breathing retraining in asthmatics with DB compared to the NQ score (Thomas et al., 2003).

Cardiopulmonary exercise testing may be useful as an objective assessment tool, to guide the process of breathing retraining and monitor the progress over the course of therapy. Comparing a patient's CPET data before and after therapy could provide objective support that the breathing retraining therapy is having a beneficial effect. Problems may arise in terms of CPET availability, limiting the extent to which this modality could be used to monitor patients' progress.

KEY MESSAGES

Dysfunctional breathing is a condition which is variably classified and lacks a standardized investigation and management approach. This paper highlights the many disparate methods used to diagnose DB, consequent on the lack of consensus on how best to diagnose the condition (van Dixhoorn and Folgering, 2015; Todd et al., 2018). In order to alleviate this confusion, it is important that there is a single clear definition of DB with one classification system. There also needs to be a single objective test which can analyze and define erratic ventilation in order to diagnose DB. Creating these standards will make it easier to identify and manage the condition.

Cardiopulmonary exercise testing represents a particular opportunity to objectively assess different aspects of individuals' physiology, particularly the presence of underlying organic disease and/or evidence of erratic ventilation (Costa et al., 2016). Thus, CPET is an ideal candidate to be the standard objective diagnostic method for DB.

A key component of identifying DB using CPET is recognizing the abnormal erratic breathing pattern response to exercise. This is not a parameter that can be easily quantified, and as such, there is no absolute diagnostic threshold. However, clinicians' use of pattern recognition when analysing the Bf and V_t plot is of high importance. This can be supplemented by using the further CPET variables highlighted. A low $P_{ET}CO_2$ at rest or during work (Brat et al., 2019) and a high $VeqCO_2$ during work (Kinnula and Sovijarvi, 1993; Brat et al., 2019) in the absence of desaturation are particularly suggestive of DB. Suggested cut-off values for these parameters have been proposed in the literature: a $P_{ET}CO_2$ below 30 mmHg at rest

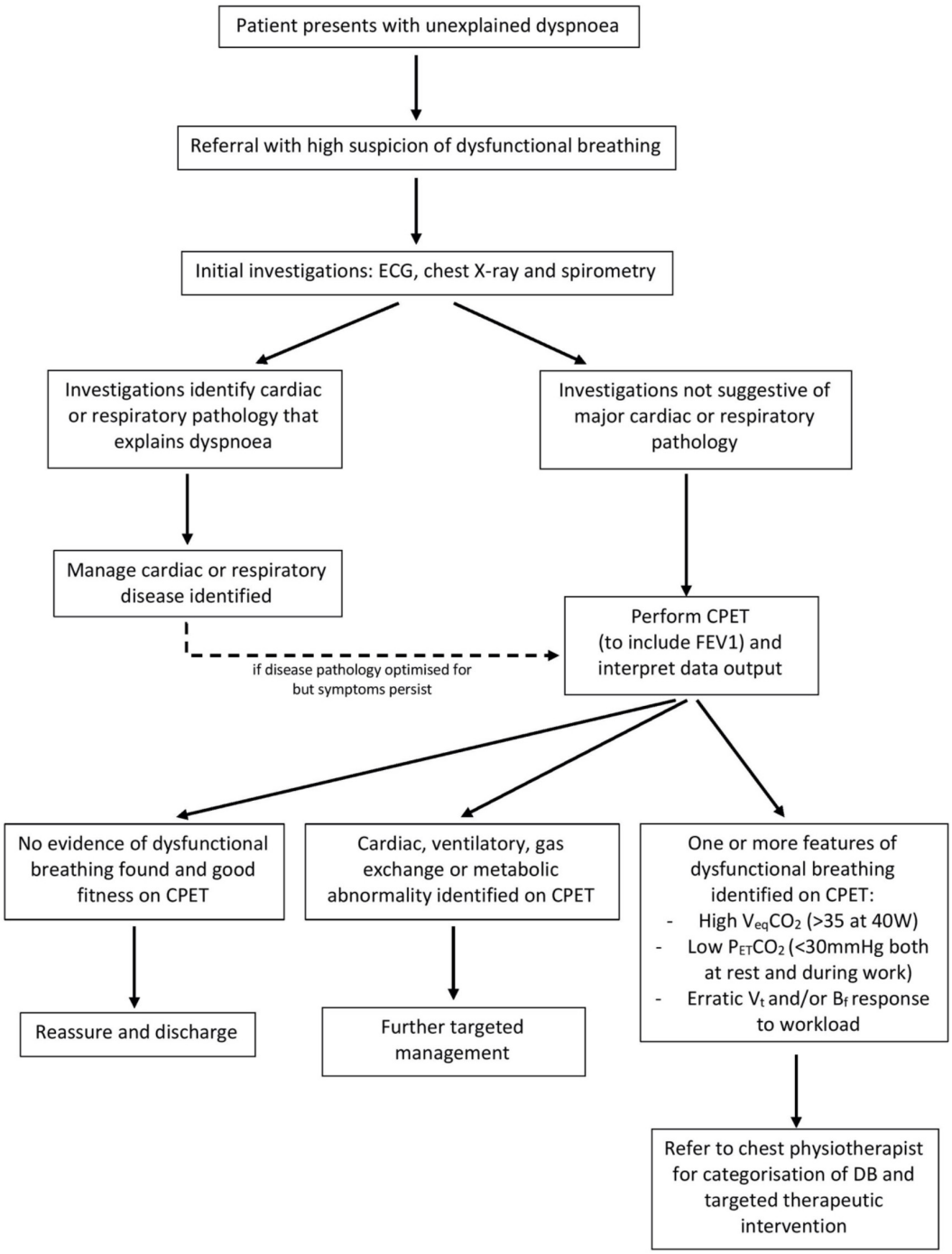

FIGURE 4 | Flowchart to illustrate a proposed clinical pathway for DB identification and therapy, based on current practice at Cambridge University Hospitals NHS trust. Suggested cut-off values are based on studies cited in this paper (Kinnula and Sovijarvi, 1993; Brat et al., 2019). FEV1, forced expiratory volume in 1 s; VeqCO2, ventilatory equivalent for CO2; $P_{ET}CO2$, end-tidal CO2; V_t, tidal volume; B_f, breathing frequency.

or during work (Brat et al., 2019) and a $VeqCO_2$ above 35 at a workload of 40–50 W (Kinnula and Sovijarvi, 1993) may help to make the diagnosis of DB. However, it is not as straightforward as having diagnostic thresholds beyond which a diagnosis can be definitively made. These CPET data should be interpreted in the context of other investigations, such as blood gas readings, to provide the entire clinical picture for the diagnosis of DB.

Nevertheless, CPET is not a perfect tool. Since it is just a snapshot into the subject's physiology for 20–40 min, a

major problem is that patients may not always manifest DB during the test. Patients with a constant DB pattern or whose DB is strongly linked to exertion are easily picked up by CPET, but patients who only occasionally exhibit DB may be missed, resulting in false negatives. Similarly, upper airway abnormalities, such as laryngeal disorders, commonly present with exertional breathlessness and require specific investigations such as laryngoscopy during exercise for their identification (Hull et al., 2016).

Moreover, many gaps remain in our knowledge that warrant further research. Despite the fact that erratic breathing patterns can be identified on CPET as discussed, CPET alone may not be able to sub-classify DB patients into the different sub-types. Further in-depth analysis of CPET data from patients with DB may help to elucidate patterns that define the different sub-types and thus improve our ability to classify DB. It may be that a combination approach using the patient's history, assessment by a physiotherapist and CPET is required to classify DB.

In addition, CPET cannot currently directly quantify the degree of irregularity of the erratic breathing pattern. One small study has used calculation of approximate entropy to quantify ventilatory irregularity and was able to differentiate controls from patients with DB (Bansal et al., 2018). Though this technique requires further validation, it may prove useful not only for diagnostic purposes, but also as a way to quantify the severity of DB.

FUTURE DIRECTIONS

Looking to the future, the implementation of CPET into standard clinical practice would greatly improve the diagnosis and management of DB. In the flowchart below, we provide an example as to where CPET can be incorporated into clinical practice to support the diagnosis of DB and subsequent therapeutic intervention (**Figure 4**). For dyspneic symptoms which remain despite obvious disease pathology being ruled out or optimized for, there should be a high suspicion of DB. CPET can then provide a useful method to investigate and confirm the presence of any abnormal breathing patterns, thus confirming the presence of DB.

The next steps may well be to improve CPET as a tool by targeting the limitations explained above. CPET, whilst being an attractive diagnostic method, currently cannot quantify the severity of DB, nor classify it into sub-types. Further study into potential ways to quantify and classify the DB using the CPET data should enhance the usefulness of the technique.

Additionally, since it remains difficult to provide specific diagnostic cut-off values for DB, there may be a role for artificial intelligence to aid CPET interpretation in the future. Pattern recognition performed by an artificial intelligence system could identify erratic breathing, characteristic of DB, thereby simplifying the process of making a diagnosis. This may be an interesting avenue to consider as we look to refine CPET as a tool for the identification of DB.

Dysfunctional breathing is a condition driving significant symptom burden, which is difficult to characterize and yet has treatment options (Thomas et al., 2003). We have highlighted that the prevalence of DB is disproportionately high in patients with chronic disease such as asthma or COPD (Thomas et al., 2005) and that traditional diagnostic questionnaires may struggle to diagnose these cases of DB (Stanton et al., 2008). We encourage clinicians to consider the possibility of DB in those living with such conditions to avoid unnecessary and potentially harmful escalation of treatment.

Cardiopulmonary exercise testing represents the optimal modality of diagnosis of DB. In particular its ability to identify individuals' functional capacity, as well as presence of concurrent disease, strengthens its clinical utility.

AUTHOR CONTRIBUTIONS

MI was primary author and was responsible for planning and putting together the first draft of the manuscript. MI, SM-B, LD-C, and CP contributed sections of the manuscript. JF, KS, MJ, and MI contributed figures. MJ contributed the table. All authors were involved in editing and finalizing the manuscript. JF oversaw and co-ordinated the process.

REFERENCES

Agostoni, P., Corrà, U., and Emdin, M. (2017). Periodic Breathing during Incremental Exercise. *Ann. Am. Thorac. Soc.* 14(Suppl._1), S116–S122. doi: 10.1513/AnnalsATS.201701-003FR

Bansal, T., Haji, G. S., Rossiter, H. B., Polkey, M. I., and Hull, J. H. (2018). Exercise ventilatory irregularity can be quantified by approximate entropy to detect breathing pattern disorder. *Respir. Physiol. Neurobiol.* 255, 1–6. doi: 10.1016/j.resp.2018.05.002

Barker, N., and Everard, M. L. (2015). Getting to grips with 'dysfunctional breathing. *Paediatr. Respir. Rev.* 16, 53–61. doi: 10.1016/j.prrv.2014.10.001

Berton, D. C., Gass, R., Feldmann, B., Plachi, F., Hutten, D., Mendes, N. B. S., et al. (2020). Responses to progressive exercise in subjects with chronic dyspnea and inspiratory muscle weakness. *Clin. Respir. J.* Preprint. doi: 10.1111/crj.13265

Boulding, R., Stacey, R., Niven, R., and Fowler, S. J. (2016). Dysfunctional breathing: a review of the literature and proposal for classification. *Eur. Respir. Rev.* 25, 287–294. doi: 10.1183/16000617.0088-2015

Brat, K., Stastna, N., Merta, Z., Olson, L. J., Johnson, B. D., and Cundrle, I. Jr. (2019). Cardiopulmonary exercise testing for identification of patients with hyperventilation syndrome. *PLoS One* 14:e0215997. doi: 10.1371/journal.pone.0215997

Bruce, R. A., Blackmon, J. R., Jones, J. W., and Strait, G. (2004). Exercising Testing in Adult Normal Subjects and Cardiac Patients. *Ann. Noninvasive Electrocardiol.* 9, 291–303. doi: 10.1111/j.1542-474X.2004.93003.x

Chenivesse, C., Similowski, T., Bautin, N., Fournier, C., Robin, S., Wallaert, B., et al. (2014). Severely impaired health-related quality of life in chronic hyperventilation patients: Exploratory data. *Respir. Med.* 108, 517–523. doi: 10.1016/j.rmed.2013.10.024

Costa, L. H. D., Rodrigues, M. T., Fonseca, A. X. C., Ferreira, E. V. M., Ota-Arakaki, J., Ramos, R. P., et al. (2016). The role of cardiopulmonary exercise testing in the diagnosis of psychogenic dyspnoea. *Eur. Respir. J. Confer.* 48(Suppl. 60):OA2016.

Courtney, R. (2009). The functions of breathing and its dysfunctions and their relationship to breathing therapy. *Int. J. Osteopathic Med.* 12, 78–85. doi: 10.1016/j.ijosm.2009.04.002

Courtney, R., van Dixhoorn, J., and Cohen, M. (2008). Evaluation of breathing pattern: comparison of a Manual Assessment of Respiratory Motion (MARM) and respiratory induction plethysmography. *Appl. Psychophysiol. Biofeedback* 33, 91–100. doi: 10.1007/s10484-008-9052-3

Degani-Costa, L. H., Nery, L. E., Rodrigues, M. T., Gimenes, A. C., Ferreira, E. V., Ota-Arakaki, J. S., et al. (2019). Does oxygen pulse trajectory during incremental exercise discriminate impaired oxygen delivery from poor muscle oxygen utilisation? *ERJ Open Res.* 5:2018. doi: 10.1183/23120541.00108-2018

Depiazzi, J., and Everard, M. L. (2016). Dysfunctional breathing and reaching one's physiological limit as causes of exercise-induced dyspnoea. *Breathe* 12, 120–129. doi: 10.1183/20734735.007216

Griffiths, O., and Anindo, B. (2014). Cardiopulmonary exercise testing (CPET) in patients with unexplained dyspnoea. *Eur. Respir. J. Confer.* 44(Suppl. 58):4886.

Halvorsen, T., Walsted, E. S., Bucca, C., Bush, A., Cantarella, G., Friedrich, G., et al. (2017). Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. *Eur. Respir. J.*50:1602221. doi: 10.1183/13993003.02221-2016

Hull, J. H., Backer, V., Gibson, P. G., and Fowler, S. J. (2016). Laryngeal Dysfunction: Assessment and Management for the Clinician. *Am. J. Respir. Crit. Care Med.* 194, 1062–1072. doi: 10.1164/rccm.201606-1249CI

Jayadev, A., Devani, N., Geddes, L., Kyriacou, C., Jeetley, P., Canal, V., et al. (2017). The role of cardiopulmonary exercise testing in the investigation of complex unexplained breathlessness. *Eur. Respir. J. Confer.* 50(Suppl. 61): A4538.

Kinnula, V. L., and Sovijarvi, A. R. (1993). Elevated ventilatory equivalents during exercise in patients with hyperventilation syndrome. *Respiration* 60, 273–278. doi: 10.1159/000196215

Krey, D., and Best, T. (2014). Dyspneic athlete. *Curr. Rev. Musculoskelet Med.* 7, 373–380. doi: 10.1007/s12178-014-9236-9

Levai, I. K., Massaroni, C., Hull, J. H., Whyte, G., Silvestri, S., Winters, S., et al. (2016). Optoelectronic plethysmography (OEP) in the assessment of dysfunctional breathing (DB) in athletes. *Eur. Respir. J. Confer.* 48(Suppl. 60):A2248.

Lum, L. C. (1975). Hyperventilation: the tip and the iceberg. *J. Psychosom. Res.* 19, 375–383. doi: 10.1016/0022-3999(75)90017-3

Martinez, F. J. I (1994). Stanopoulos, R. Acero, F. S. Becker, R. Pickering and J. F. Beamis: Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. *Chest* 105, 168–174. doi: 10.1378/chest.105.1.168

Matrka, L. (2014). Paradoxic Vocal Fold Movement Disorder. *Otolaryngol. Clin. North Am.* 47, 135–146. doi: 10.1016/j.otc.2013.08.014

Neder, J. A., Berton, D. C., Rocha, A., Arbex, F. F., Alencar, M. C. N., Degani-Costa, L. H., et al. (2018). "Abnormal patterns of response to incremental CPET," in *Clinical Exercise Testing*, eds P. Palange, P. Laveneziana, J. A. Neder, and S. A. Ward (Lausanne: European Respiratory Society), doi: 10.1183/2312508X.erm8018

Neder, J. A., Dal Corso, S., Malaguti, C., Reis, S., De Fuccio, M. B., Schmidt, H., et al. (2003). The pattern and timing of breathing during incremental exercise: a normative study. *Eur. Respir. J.* 21, 530-8.

Neder, J. A., Hirai, D. M., Jones, J. H., Zelt, J. T., Berton, D. C., and O'Donnell, D. E. (2016). A 56-Year-Old, Otherwise Healthy Woman Presenting With Light-headedness and Progressive Shortness of Breath. *Chest* 150, e23–e27. doi: 10.1016/j.chest.2016.02.672

Prys-Picard, C. O., Kellett, F., and Niven, R. M. (2006). Disproportionate breathlessness associated with deep sighing breathing in a patient presenting with difficult-to-treat asthma. *Chest* 130, 1723–1725. doi: 10.1378/chest.130.6.1723

Radtke, T., Crook, S., Kaltsakas, G., Louvaris, Z., Berton, D., Urquhart, D. S., et al. (2019). Vogiatzis and H. Hebestreit: ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur. Respir. Rev.* 28:180101. doi: 10.1183/16000617.0101-2018

Roberts, S., Macdonald, W., Townson, M., and Sutherland, T. (2017). Cardiopulmonary excercise testing in the diagnosis of chronic unexplained dyspnoea. *Eur. Respir. J. Confer.* 50(Suppl. 61):A4537.

Sarma, S., and Levine, B. D. (2016). Beyond the Bruce Protocol: Advanced Exercise Testing for the Sports Cardiologist. *Cardiol. Clin.* 34, 603–608. doi: 10.1016/j.ccl.2016.06.009

Shembel, A. C., Sandage, M. J., and Verdolini Abbott, K. (2017). Episodic Laryngeal Breathing Disorders: Literature Review and Proposal of Preliminary Theoretical Framework. *J. Voice* 31, e7–.e125. doi: 10.1016/j.jvoice.2015.11.027

Stanton, A. E., Vaughn, P., Carter, R., and Bucknall, C. E. (2008). An observational investigation of dysfunctional breathing and breathing control therapy in a problem asthma clinic. *J. Asthma* 45, 758–765. doi: 10.1080/02770900802252093

Thing, J. E. R., Mukherjee, B., Murphy, K., Tighe, H., and Howard, L. (2011). Evaluation of the role of cardio-pulmonary exercise testing in the diagnosis of unexplained breathlessness. *Thorax* 66, A144–A145.

Thomas, M., McKinley, R. K., Freeman, E., Foy, C., and Price, D. (2005). The prevalence of dysfunctional breathing in adults in the community with and without asthma. *Prim. Care Respir. J.* 14, 78–82. doi: 10.1016/j.pcrj.2004.10.007

Thomas, M., McKinley, R. K., Freeman, E., Foy, C., Prodger, P., and Price, D. (2003). Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. *Thorax* 58, 110–115. doi: 10.1136/thorax.58.2.110

Todd, S., Walsted, E. S., Grillo, L., Livingston, R., Menzies-Gow, A., and Hull, J. H. (2018). Novel assessment tool to detect breathing pattern disorder in patients with refractory asthma. *Respirology* 23, 284–290. doi: 10.1111/resp.13173

Toma, N., Bicescu, G., Enache, R., Dragoi, R., and Cinteza, M. (2010). Cardiopulmonary exercise testing in differential diagnosis of dyspnea. *Maedica* 5, 214–218.

van Dixhoorn, J., and Duivenvoorden, H. J. (1985). Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. *J. Psychosom. Res.* 29, 199–206. doi: 10.1016/0022-3999(85)90042-x

van Dixhoorn, J., and Folgering, H. (2015). The Nijmegen Questionnaire and dysfunctional breathing. *ERJ Open Res.* 1:2015. doi: 10.1183/23120541.00001-2015

Wasserman, K. (1997). Diagnosing cardiovascular and lung pathophysiology from exercise gas exchange. *Chest* 112, 1091–1101. doi: 10.1378/chest.112.4.1091

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PERSPECTIVE
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Clinical Interpretation of Cardiopulmonary Exercise Testing: Current Pitfalls and Limitations

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Several shortcomings on cardiopulmonary exercise testing (CPET) interpretation have shed a negative light on the test as a clinically useful tool. For instance, the reader should recognize patterns of dysfunction based on clusters of variables rather than relying on rigid interpretative algorithms. Correct display of key graphical data is of foremost relevance: prolixity and redundancy should be avoided. Submaximal dyspnea ratings should be plotted as a function of work rate (WR) and ventilatory demand. Increased work of breathing and/or obesity may normalize peak oxygen uptake ($\dot{V}O_2$) despite a low peak WR. Among the determinants of $\dot{V}O_2$, only heart rate is measured during non-invasive CPET. It follows that in the absence of findings suggestive of severe impairment in O_2 delivery, the boundaries between inactivity and early cardiovascular disease are blurred in individual subjects. A preserved breathing reserve should not be viewed as evidence that "the lungs" are not limiting the subject. In this context, measurements of dynamic inspiratory capacity are key to uncover abnormalities germane to exertional dyspnea. A low end-tidal partial pressure for carbon dioxide may indicate either increased "wasted" ventilation or alveolar hyperventilation; thus, direct measurements of arterial (or arterialized) PO_2 might be warranted. Differentiating a chaotic breathing pattern from the normal breath-by-breath noise might be complex if the plotted data are not adequately smoothed. A sober recognition of these limitations, associated with an interpretation report free from technicalities and convoluted terminology, is crucial to enhance the credibility of CPET in the eyes of the practicing physician.

Keywords: exercise, dyspnea, lung function, cardiopulmonal capacity, exercise test interpretation

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INTRODUCTION

Cardiopulmonary exercise testing (CPET) might be helpful in uncovering the causes of exercise intolerance in patients with (or at risk of) cardiorespiratory diseases (Marciniuk et al., 2013). In the pulmonology practice, CPET is usually requested as part of the work-up for unexplained or "out-of-proportion" dyspnea (Neder et al., 2019a). The test, however, rarely pinpoints to a specific diagnosis; thus, it should be better considered as part of the initial assessment to guide further investigative efforts (if required). Unfortunately, however, CPET remains poorly

understood and, therefore, largely underused in clinical practice. Apart from operational issues (e.g., high costs, limited availability, and poor reimbursement relative to time spent on the test), there are several shortcomings on testing interpretation which have not helped to improve this state of affairs (Neder et al., 2018b). In this concise *Perspective*, some of these pitfalls and challenges are outlined: owing to the absence of large randomized trials exploring CPET limitations, they were selected based on our long-standing experience with CPET reading and teaching. Moreover, we focused on the limitations more likely to impact on clinical-decision making (**Table 1**). Of note, we specifically assume that the reader is already familiar with clinical CPET interpretation; thus, a thorough discussion of interpretative strategies is beyond the scope of this viewpoint article. When feasible, we provide a brief account of the available strategies to avoid key interpretative mistakes (**Table 1**). If the limitations are deemed insurmountable at this point in time, we caution the reader that the best (and more honest) approach is to refrain from testing over-interpretation. Finally, representative examples are not provided due to space constraints.

TABLE 1 | Selected pitfalls and limitations on cardiopulmonary exercise testing (CPET) interpretation which are more likely to negatively impact on clinical-decision making in respiratory medicine.

Pitfall/limitation	Potential consequence	Recommended approach
Over-Reliance on Rigid Interpretative Algorithms	Misdiagnosis of the mechanisms leading to exercise intolerance	Identify cluster of findings indicative of syndromic patterns of dysfunction
Incorrect Display of Graphical Data	Distraction and redundancy	Focus on the dynamic relationships more likely to expose the patterns of dysfunction
Considering Dyspnea a Secondary Outcome	Poor diagnostic yield in patients under investigation for indetermined dyspnea	Obtain submaximal dyspnea scores which should be expressed as a function of both work rate and ventilation
Misinterpretation of a "Preserved" Peak $\dot{V}O_2$ as Evidence of Normality	False negative for exercise intolerance	Carefully review all available data, even in the presence of a "preserved" peak $\dot{V}O_2$
Ignoring the Effects of Obesity on the $\Delta\dot{V}O_2/\Delta$ Work Rate Relationship	As above	As above; value potential decrements in peak work rate
Failure to Recognize the Poor Diagnostic Performance of CPET in Indicating Cardiac Disease	Misdiagnosis of potential cardiovascular abnormalities	A cautious, non-committal approach when ruling in or out a cardiac disease when the pre-test likelihood of disease is unclear
Misdiagnosis of Mechanical-Ventilatory Limitation	Failure to recognize an etiologic role for "the lungs" in limiting the subject	Routine measurement of dynamic IC (operating lung volumes)
Under-Recognition of the Limitations of Non-invasive Assessment of Pulmonary Gas Exchange	Over- or under-calling of gas exchange inefficiency for O_2 or CO_2	Recognize that measurements of arterial (or arterialized) blood gases might be warranted
Over- or Under Recognition of Chaotic Breathing Pattern/Dysfunctional Breathing	Misdiagnosis of behavioral/psychogenic abnormalities	Adequate data smoothing; apply a gestalt approach to breathing pattern analysis

$\dot{V}O_2$, oxygen uptake; IC, inspiratory capacity.

DISCUSSION

Over-Reliance on Rigid Interpretative Algorithms

There is a pervasive sense that, in similarity with pulmonary function tests, CPET can be meaningfully interpreted considering some dichotomous decision nodes in a hierarchic evaluation tree. In fact, if any, the clinical interpretation of CPET is full of *chance nodes*: from these nodes, one can only infer the meaning of a certain result given a set of pre-existing conditions. In other words, no variable holds discriminative properties when seen in isolation, i.e., without a proper estimation of the pre-test likelihood of abnormality (Bayes theorem). More realistically, cluster of findings may indicate the presence of certain patterns: (a) a normal maximal or sub-maximal test, (b) obesity, (c) O_2 delivery/utilization impairment, (d) mechanical-ventilatory impairment, (e) pulmonary gas exchange impairment, and (f) dysfunctional breathing-hyperventilation disorder (Neder et al., 2018a). The referring physician should be specifically aware that individual features overlap across diseases. It is the referring physician's responsibility to amalgamate the described pattern(s) of abnormalities on his/her diagnostic plan or prognostic assessment. Although these recommendations seem rather obvious, they are not easily implemented in practice either because: (a) the requester over-estimates the test sensitivity/specificity and/or (b) the reader fails to recognize its important limitations. A detailed account of testing interpretation in light of these precautionary considerations is provided by Neder et al. (2018a).

Incorrect Display of Graphical Data

The great majority of CPETs performed by respiratory patients are symptom-limited. Thus, appreciation of the sensory responses to exercise is an integral part of testing interpretation (O'Donnell et al., 2019). The fundamental task of the reader is to select the more appropriated dependent variables in response to their physiological determinants (or, at least, their closest correlates) taken into consideration the principles of biological plausibility and simplicity (Occam's razor principle). In order to maximize the yield of information and minimize distraction, redundancy must be avoided. Although rapidly-incremental tests (frequently following a ramp forcing regimen; Laveneziana et al., 2017) are almost universally used nowadays, in practice, there is an ample variability in the rates of work increment and stages duration across laboratories. Thus, work rate (WR) and time

might not always be the best independent variables to judge the response normalcy in individual subjects. The test is based on the fundamental physiological principle that the heart and the lungs ultimately support the uptake of O_2 and release of CO_2 – which vary markedly for a given work rate or testing time elapsed. Thus, it could be argued that metabolic-cardiovascular responses, minute ventilation ($\dot{V}E$), and lung mechanics/breathing pattern in the *y*-axis are better expressed relative to their closest determinants in the *x*-axis, i.e., oxygen uptake ($\dot{V}O_2$; Whipp and Ward, 1982), carbon dioxide output ($\dot{V}CO_2$; Whipp, 1977), and $\dot{V}E$ (O'Donnell et al., 2017), respectively.

The Wasserman et al. (1987) nine-panels remain the most popular display. It has, however, important limitations which are frequently overlooked (Dumitrescu and Rosenkranz, 2017):

- the panels are heavily biased to depict metabolic/cardiovascular responses: not less than five graphs are basically devoted to the identification of gas exchange and ventilatory thresholds (Wasserman et al., 1973; Beaver et al., 1986);
- $\dot{V}O_2$ and work rate are both expressed as a function of time. Thus, the fundamental relationship of clinical interest [$\dot{V}O_2$ (*y*) vs. work rate (*x*); Whipp and Ward, 1982] is not shown. Even if $\dot{V}O_2$-to-work rate ratio is correctly scaled to 10:1, significant departures from linearity in $\dot{V}O_2$ (i.e., lack of parallel increase in $\dot{V}O_2$ as related to work rate) might not be readily apparent in patients with poor exercise tolerance;
- tidal volume (VT) is plotted as a function of $\dot{V}E$. VT is also compared to vital capacity (VC) and resting inspiratory capacity (IC), whereas maximal voluntary ventilation (MVV) is shown as the upper limit for $\dot{V}E$. Resting IC, however, is not the correct benchmark to contrast against the VT trajectory as IC usually increases with exercise in healthy subjects or decreases in patients showing expiratory flow limitation (Guenette et al., 2013). VC is substantially greater than IC and the former does not allow a clear recognition of the limits for VT expansion, i.e., exercise IC (O'Donnell et al., 2019). MVV is not a consistent ceiling for a $\dot{V}E$ increase and severe dyspnea might arise in patients with still-preserved breathing reserve (Neder et al., 2019a,b; see also Misdiagnosis of Mechanical-Ventilatory Limitation section; **Figure 1**); and
- the operating lung volumes and dyspnea readings are ignored (see also Considering Dyspnea a Secondary Outcome section).

Alternative displays which avoid these errors and omissions are provided elsewhere (O'Donnell et al., 2017, 2019).

Considering Dyspnea a Secondary Outcome

The burden to provide a resolution to complex cases of persistent shortness of breath is frequently directed to the pulmonologist (Mahler and O'Donnell, 2015). CPET is a non-invasive procedure which was meant to uncover the causes of exertional breathlessness (Wasserman and Whipp, 1975; Wasserman et al., 1987; Jones, 1988; Weisman and Zeballos, 1996). Indeed, the test measures a multitude of physiological responses important for the genesis of the symptom; thus, at least theoretically, CPET is well-suited to the task (Arena and Sietsema, 2011). In this context, it is rather axiomatic that a special attention should be given to the measurement and interpretation of dyspnea scores. Unfortunately, this is more an exception than a rule in most clinical laboratories nowadays.

In order to fully recognize the advantages of incorporating dyspnea readings on CPET interpretation, it is instructive to consider some basic neurobiological concepts. At a close inspection, exertional dyspnea boils down to a heightened sense of inspiratory load (Campbell and Howell, 1963; Killian and Campbell, 1983). More specifically, the respiratory controller (i.e., pontine-medullary centers and their cortical-limbic connections) continuously appraise "how much ventilation" is performed at a given point in the time. Such quantitative perspective of the load is influenced by chemo-stimulation of central and peripheral receptors (Plataki et al., 2013) and the efferent motor output to the inspiratory muscles (Killian and Campbell, 1983). In the absence of critical mechanical constraints, increased reflex chemostimulation (Plataki et al., 2013) translates into excessive ventilatory response relative to metabolic demand (Neder et al., 2015; Rocha et al., 2017). Consequently, when the increased drive to breathe can be freely converted into the act of breathing, patients tend to report higher dyspnea for a given work rate *but* similar dyspnea for a given $\dot{V}E$ compared to normal subjects (Kearon et al., 1991; Killian et al., 1992). Conversely, when VT becomes positioned close to the upper reaches of the S-shaped pressure-volume relation of the relaxed respiratory system, compliance decreases, the inspiratory muscles are functionally weakened, and intolerable dyspnea quickly ensues. As a corollary, dynamic mechanical constraints lead to higher dyspnea ratings as a function of *both* work rate and $\dot{V}E$ (O'Donnell et al., 2019; Plachi et al., 2020). Thus, dyspnea should be carefully measured and plotted as a function of exercise intensity as reflected by increases in power output and ventilatory demand. Normative values have been recently published (Neder et al., 2020).

Misinterpretation of a "Preserved" Peak $\dot{V}O_2$ as Evidence of Normality

Peak $\dot{V}O_2$ is highly dependent on the averaging method used to decrease the variability of breath-by-breath data. As expected, the shorter the averaging interval (and the lower the number of breaths considered for averaging), the higher the peak $\dot{V}O_2$. Unfortunately, there are no consistent recommendations among existing guidelines on the averaging method. In practice, the most common settings range from 10- to 60-s periods: rolling averages of 15–20 s usually provide reproducible estimates of peak $\dot{V}O_2$ in respiratory patients. Peak $\dot{V}O_2$ is usually interpreted without the help of previous values for a meaningful longitudinal comparison. Thus, substantial loss of aerobic capacity might be missed if an impaired subject had, at an unknown baseline, a supra-normal peak $\dot{V}O_2$ (Neder et al., 1998). A peak $\dot{V}O_2$ within expected limits may coexist with extensive sub-maximal abnormalities; in fact, some of them (e.g., increased work of breathing) may increase "whole-body" $\dot{V}O_2$, bringing the peak value up to the limits of reference (Neder et al., 2018a).

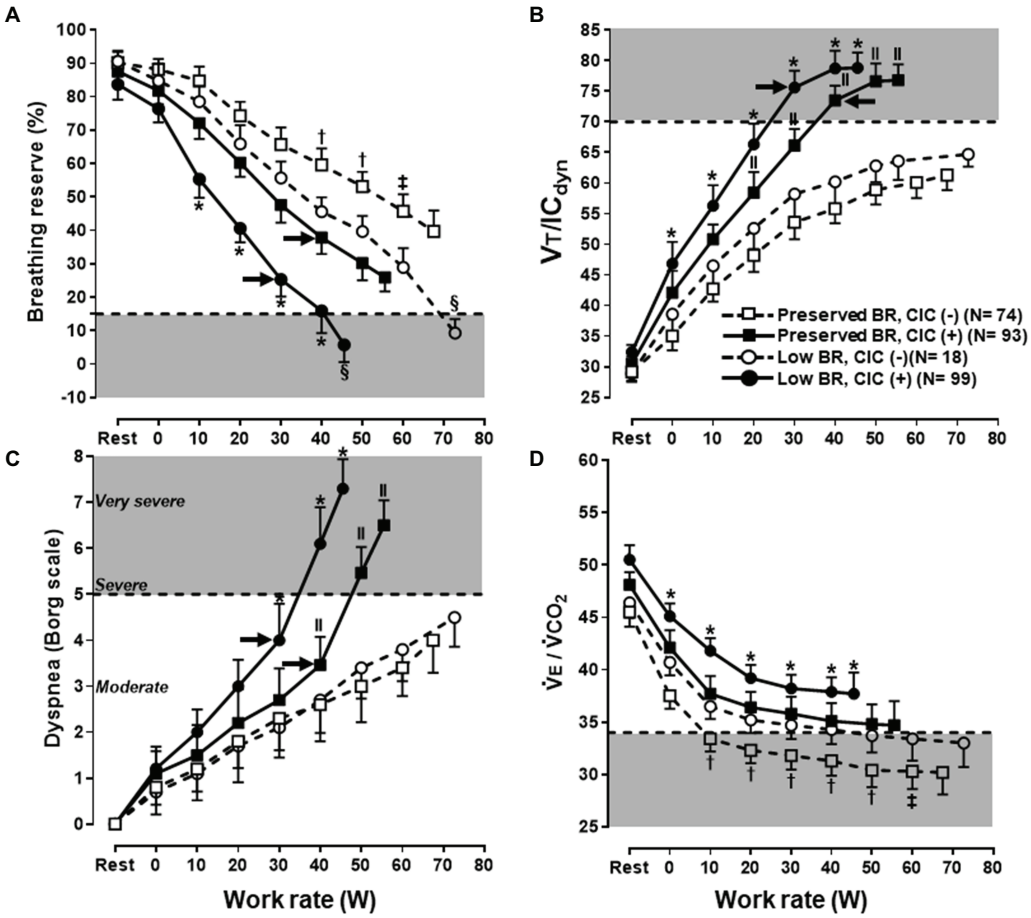

FIGURE 1 | Selected ventilatory and sensory responses to symptom limited incremental CPET in subjects under investigation for exertional dyspnea. Subjects were separated according to the combination of preserved or low peak breathing reserve (BR) vs. absence (–) or presence (+) of critical inspiratory constraints (CIC). Note that a low BR **(A)** was found in subjects who either low or high levels of dyspnea **(C)**; conversely, a sizeable fraction of subjects with preserved BR reported severe dyspnea. Regardless of the BR, subjects who develop CIC **(B)** and/or presented with poor ventilatory efficiency [high ventilation ($\dot{V}_E$)/carbon dioxide output ($\dot{V}O_2$) in **D**] were consistently more dyspneic. Note the additive effects of these physiological abnormalities. Shaded areas represent the limits for a low BR, CIC, high dyspnea burden, and poor ventilatory efficiency, respectively. The arrows in **(A–C)** indicate the exercise intensities associated with an upward inflection in dyspnea ratings in CIC(+) subjects. See the text for further elaboration. Data are mean ± SEM. *$p < 0.05$ vs. all groups; † vs. low BR, CIC(–) and preserved BR, CIC(+); ‡ vs. low BR, CIC(–); § vs. preserved BR, CIC(–) and preserved BR, CIC(+); ‖ vs. low BR, CIC(–) and preserved BR, CIC(–). V_T, tidal volume; IC, inspiratory capacity. Reproduced, with the permission of the publisher, from Neder (2019a).

Ignoring the Effects of Obesity on the $\Delta\dot{V}O_2/\Delta$ Work Rate Relationship

Obese subjects expend more O_2 to perform a given amount of external work as they need to displace a larger mass against gravity (Whipp and Davis, 1984). High $\dot{V}O_2$/work rate ratio in an obese subject may result in normal or even increased peak $\dot{V}O_2$ (L/min) despite a low peak work rate. This is not easily fixed by attempts to "correct" $\dot{V}O_2$ for the mass displaced, i.e., total body and leg mass on treadmill and cycle ergometer, respectively (Neder et al., 2000). Expressing $\dot{V}O_2$ as a function of total body mass (ml/min/kg) is a more reasonable approach in treadmill-based tests. Conversely, it tends to penalize the obese exercising on a stationary bike (Neder et al., 1998). A valid alternative is to use reference values for peak $\dot{V}O_2$ based on height or ideal body weight and analyze results in percentage predicted (Hansen et al., 1984). In an obese subject showing low peak work rate but preserved peak $\dot{V}O_2$, the former is likely to better reveal subject's functional capacity. This is particularly true if peak work rate is predicted from studies which included a large number of obese subjects (e.g., Koch et al., 2009; Myers et al., 2017).

Failure to Recognize the Poor Diagnostic Performance of CPET in Indicating Cardiac Disease

The accuracy at which the syndrome of impaired O_2 delivery/utilization reflects cardiocirculatory disease is based on the assumptions that: (a) the "downstream" (to the heart) consequences of these diseases are always present and (b) isolated or concurrent abnormalities at the muscle level can

be differentiated from those occurring "upstream." Unfortunately, these premises are not consistently met in practice. It should also be recognized that non-invasive CPET only measures one of the three variables that are known to determine $\dot{V}O_2$: heart rate (HR), stroke volume, and O_2 extraction. Deficits in stroke volume can be compensated by increases in HR and/or O_2 extraction; moreover, HR can be impaired in the absence of structural cardiac disease (see also below). Thus, in the absence of findings suggestive of severe ("out-of-proportion" to physical deconditioning) impairment in O_2 delivery, the boundaries between inactivity and early cardiovascular disease are blurred in individual subjects. Thus, whereas a CPET deemed highly-suggestive of cardio-circulatory dysfunction deserves further investigation, a normal test in a subject with high pre-test likelihood of disease should be better seen as "not consistent with current moderate-to-severe dysfunction" (Neder et al., 2018a,b).

It should be explicitly recognized that a sizeable fraction of patients referred to clinical CPET have their resting and exertional HR under pharmacological or external control, e.g., β-blockers and pacemakers, respectively. Moreover, the prevalence of chronotropic incompetence has increased markedly in tandem with inactivity, obesity, and metabolic disorders (Brubaker and Kitzman, 2011). Thus, CPET variables based on HR, including the double-product (HR times systolic blood pressure), should be viewed with caution in these patients. Specifically, shallow $\Delta HR/\Delta\dot{V}O_2$ and/or high O_2 pulse should not be erroneously assumed as indicative of normality. Quite the opposite: a severely blunted $\Delta HR/\Delta\dot{V}O_2$ in a CPET interrupted with objective and subjective evidences of maximal effort should be clinically valued as a potential source of exercise intolerance (Brubaker and Kitzman, 2011).

Misdiagnosis of Mechanical-Ventilatory Limitation

Maximal voluntary ventilation is a poor index of maximum breathing capacity during exercise (Babb and Rodarte, 1993). Regardless of the clinical scenario, relying on single cut-off of $\dot{V}E/MVV$ ratio to rule out ventilatory limitation might be misleading. The ratio correlates poorly to exertional dyspnea in individual patients with both obstructive and restrictive disorders (O'Donnell et al., 2014; Faisal et al., 2016): as discussed above, it might serve as a metric of the quantitative ("*how much* $\dot{V}E$") mechanisms of dyspnea, but it is insensitive to its qualitative foundations ("*how appropriate* $\dot{V}E$ *is performed*"). Some dyspnoeic patients with chronic obstructive pulmonary disease (COPD), particularly those with mild-moderate airflow limitation (O'Donnell et al., 2016), stop exercising with preserved $\dot{V}E/MVV$ but with clear evidences of constrained mechanics (**Figure 1**; O'Donnell et al., 2017; Neder et al., 2019b) Moreover, a still-preserved end-exercise $\dot{V}E/MVV$ might be relevant for dyspnea and exercise intolerance if reached at a low peak work rate Thus, a high $\dot{V}E/MVV$ might be valued to indicate low ventilatory reserves but a low $\dot{V}E/MVV$ should never be considered as the definitive proof that mechanical-ventilatory abnormalities are not relevant to patient's dyspnoea (Neder et al., 2019a).

The assessment of the operating lung volumes is based on the basic premise that a full inspiratory effort has been performed (Guenette et al., 2013). For instance, progressively lower IC due to inspiratory muscle weakness may be misinterpreted as indicative of dynamic hyperinflation. A common mistake is the belief that lack of IC decrement from rest signal for a normal response. Due to pronounced gas trapping at rest, however, patients with advanced COPD may not be able to further decrease IC during exercise (O'Donnell et al., 2017). A plateau in VT at higher operating lung volumes should raise the suspicion of the attainment of critical inspiratory constraints (Casaburi and Rennard, 2015); nevertheless, VT also tends to plateau after the respiratory compensation point (Neder and Stein, 2006). Thus, it is advisable to double-check whether such a plateau coincides or not with near-maximum end-inspiratory volumes, e.g., VT/exercise IC $\geq$ 0.8 and/or end-inspiratory lung volume/TLC $\geq$ 0.9 (Guenette et al., 2013). The maximum flow-volume loop provides a poor frame of reference of the flow reserves at a given lung volume on effort, particularly in the presence of moderate to severe airflow limitation (Johnson et al., 1999). In practice, it is commonly valuable to assess changes on tidal expiratory limb's morphology (from convex to rectified or concave; Varga et al., 2016) and eventual leftward shifts in the tidal flow-volume loop as exercise progresses, i.e., dynamic hyperinflation.

Under-Recognition of the Limitations of Non-invasive Assessment of Pulmonary Gas Exchange

Due to the sigmoid shape of the O_2 dissociation curve and the high noise-to-signal ratio of pulse oximeters on exertion, mild-moderate decrements in the arterial partial pressure for O_2 (PaO_2) might be missed by measurements of the arterial O_2 saturation by this method (SpO_2). A pattern of impaired O_2 delivery/utilization might be seen in "respiratory" patients with severe exertional hypoxemia. The end-tidal partial pressure for CO_2 ($PETCO_2$) is a particularly poor indicator of $PaCO_2$ in patients with respiratory diseases (ERS Task Force et al., 2007). Thus, low $PETCO_2$ values may indicate high ventilation/perfusion or alveolar hyperventilation, i.e., dissimilar phenomena with opposite clinical implications. Conversely, a high $PETCO_2$ might either reflect the late emptying of poorly-ventilated units with higher alveolar PCO_2 or alveolar hypoventilation (Hansen et al., 2007). In addition, a superficial and fast breathing pattern may decrease $PETCO_2$ since less alveolar air is sampled and the expiratory time becomes too short, i.e., there is not enough time for PCO_2 to raise up to its highest value (Whipp and Ward, 1982). This explains why "automatic," non-invasive dead space/VT ratio (using $PETCO_2$) underestimates the true dead space/VT in patients with ventilation-perfusion inequalities (Lewis et al., 1994), i.e., a "preserved" non-invasive dead space/VT is not useful to rule out poor gas exchange efficiency. Minimally-invasive or non-invasive alternatives to $PaCO_2$ include capillary (arterialized) PCO_2 (McLoughlin et al., 1992) or transcutaneous PCO_2 (Hoffmann et al., 1990). If these techniques are used, serial measurements

(at least three) are particularly useful to track the trajectory during incremental exercise (Rocha et al., 2017).

Over- or Under Recognition of Chaotic Breathing Pattern/Dysfunctional Breathing

There is a large heterogeneity on the presence and extension of dysfunctional breathing and hyperventilation across individuals, including the timing as related to rest and/or exercise. Detailed normative values for the timing and pattern of breathing at a given $\dot{V}_E$ have long been published (Neder et al., 2003); unfortunately, they are not commonly available in commercial software. As expected, differentiating a chaotic breathing pattern from the normal breath-by-breath noise might be complex if the plotted data is not adequately smoothed. Unless potential underlying abnormalities have been carefully excluded (e.g., neuromuscular disease, respiratory muscle weakness, asthma, and paradoxical vocal cord motion; Boulding et al., 2016), it is prudent to avoid labeling the phenomenon as "primary" or "merely psychogenic." Specific care should be taken to rule out a cyclic pattern of $\dot{V}_E$ oscillation which represents an important sign of cardiovascular disease and/or breathing control instability (periodic breathing; Leite et al., 2003) Relative to the later phenomenon, care should be taken to depict plot the $\dot{V}_E$ axis (here, as an exception, vs. work rate or time) with sufficient resolution to appreciate the cycling changes. Owing to the fact that the ventilatoty and metabolic data oscillate in phase (Neder et al., 2003), period breathing is usually missed if only $\dot{V}_E$ vs. $\dot{V}CO_2$ is examined.

CONCLUSION

There remains a long way for CPET to be widely recognized as a clinically-useful tool for the investigation of the mechanisms of dyspnea and exercise intolerance in patients with chronic cardiorespiratory disease. As discussed in this *Perspective*, we have advanced substantially in the identification of common pitfalls for testing interpretation. We are also more aware of CPET limitations, particularly in this era of advanced imaging and invasive diagnostic procedures. A sober recognition of these limitations, associated with a final report free from technicalities and convoluted terminology, is crucial to enhance the credibility of CPET in the eyes of the practicing physician.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JAN wrote the first draft. All authors were involved in the manuscript preparation, contributed to the article, and approved the submitted version.

REFERENCES

Arena, R., and Sietsema, K. E. (2011). Cardiopulmonary exercise testing in the clinical evaluation of patients with heart and lung disease. *Circulation* 123, 668–680. doi: 10.1161/CIRCULATIONAHA.109.914788

Babb, T. G., and Rodarte, J. R. (1993). Estimation of ventilatory capacity during submaximal exercise. *J. Appl. Physiol.* 74, 2016–2022. doi: 10.1152/jappl.1993.74.4.2016

Beaver, W. L., Wasserman, K., and Whipp, B. J. (1986). A new method for detecting anaerobic threshold by gas exchange. *J. Appl. Physiol.* 60, 2020–2027. doi: 10.1152/jappl.1986.60.6.2020

Boulding, R., Stacey, R., Niven, R., and Fowler, S. J. (2016). Dysfunctional breathing: a review of the literature and proposal for classification. *Eur. Respir. Rev.* 25, 287–294. doi: 10.1183/16000617.0088-2015

Brubaker, P. H., and Kitzman, D. W. (2011). Chronotropic incompetence: causes, consequences, and management. *Circulation* 123, 1010–1020. doi: 10.1161/CIRCULATIONAHA.110.940577

Campbell, E. J., and Howell, J. B. (1963). The sensation of breathlessness. *Br. Med. Bull.* 19, 36–40. doi: 10.1093/oxfordjournals.bmb.a070002

Casaburi, R., and Rennard, S. I. (2015). Exercise limitation in chronic obstructive pulmonary disease. The O'Donnell threshold. *Am. J. Respir. Crit. Care Med.* 191, 873–875. doi: 10.1164/rccm.201501-0084ED

Dumitrescu, D., and Rosenkranz, S. (2017). Graphical data display for clinical cardiopulmonary exercise testing. *Ann. Am. Thorac. Soc.* 14, S12–S21. doi: 10.1513/AnnalsATS.201612-955FR

ERS Task Force, Palange, P., Ward, S. A., Carlsen, K. -H., Casaburi, R., Gallagher, C. G., et al. (2007). Recommendations on the use of exercise testing in clinical practice. *Eur. Respir. J.* 29, 185–209. doi: 10.1183/09031936.00046906

Faisal, A., Alghamdi, B. J., Ciavaglia, C. E., Elbehairy, A. F., Webb, K. A., Ora, J., et al. (2016). Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am. J. Respir. Crit. Care Med.* 193, 299–309. doi: 10.1164/rccm.201504-0841OC

Guenette, J. A., Chin, R. C., Cory, J. M., Webb, K. A., and O'Donnell, D. E. (2013). Inspiratory capacity during exercise: measurement, analysis, and interpretation. *Pulm. Med.* 2013:956081. doi: 10.1155/2013/956081

Hansen, J. E., Sue, D. Y., and Wasserman, K. (1984). Predicted values for clinical exercise testing. *Am. Rev. Respir. Dis.* 129, S49–S55. doi: 10.1164/arrd.1984.129.2P2.S49

Hansen, J. E., Ulubay, G., Chow, B. F., Sun, X. -G., and Wasserman, K. (2007). Mixed-expired and end-tidal CO_2 distinguish between ventilation and perfusion defects during exercise testing in patients with lung and heart diseases. *Chest* 132, 977–983. doi: 10.1378/chest.07-0619

Hoffmann, U., Essfeld, D., and Stegemann, J. (1990). Comparison of arterial, end-tidal and transcutaneous PCO_2 during moderate exercise and external CO_2 loading in humans. *Eur. J. Appl. Physiol.* 61, 1–4. doi: 10.1007/BF00236685

Johnson, B. D., Weisman, I. M., Zeballos, R. J., and Beck, K. C. (1999). Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest* 116, 488–503. doi: 10.1378/chest.116.2.488

Jones, N. (1988). *Clinical exercise testing. 3rd Edn*. Philadelphia, PA: W.B Saunders Company.

Kearon, M. C., Summers, E., Jones, N. L., Campbell, E. J., and Killian, K. J. (1991). Effort and dyspnoea during work of varying intensity and duration. *Eur. Respir. J.* 4, 917–925.

Killian, K. J., and Campbell, E. J. (1983). Dyspnea and exercise. *Annu. Rev. Physiol.* 45, 465–479. doi: 10.1146/annurev.ph.45.030183.002341

Killian, K. J., Summers, E., Jones, N. L., and Campbell, E. J. (1992). Dyspnea and leg effort during incremental cycle ergometry. *Am. Rev. Respir. Dis.* 145, 1339–1345. doi: 10.1164/ajrccm/145.6.1339

Koch, B., Schäper, C., Ittermann, T., Spielhagen, T., Dörr, M., Völzke, H., et al. (2009). Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP study. *Eur. Respir. J.* 33, 389–397. doi: 10.1183/09031936.00074208

Laveneziana, P., Ward, S., Neder, J. A., and Poberezhets, V. (2017). Clinical exercise testing: basic principles and practice. *Breathe* 13, 163–164. doi: 10.1183/20734735.009717

Leite, J. J., Mansur, A. J., de Freitas, H. F. G., Chizola, P. R., Bocchi, E. A., Terra-Filho, M., et al. (2003). Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J. Am. Coll. Cardiol.* 41, 2175–2181. doi: 10.1016/s0735-1097(03)00460-1

Lewis, D. A., Sietsema, K. E., Casaburi, R., and Sue, D. Y. (1994). Inaccuracy of noninvasive estimates of VD/VT in clinical exercise testing. *Chest* 106, 1476–1480. doi: 10.1378/chest.106.5.1476

Mahler, D. A., and O'Donnell, D. E. (2015). Recent advances in dyspnea. *Chest* 147, 232–241. doi: 10.1378/chest.14-0800

Marciniuk, D. D., Johnson, B. D., Neder, J. A., and O'Donnell, D. E. (2013). Cardiopulmonary exercise testing. *Pulm. Med.* 2013:686104. doi: 10.1155/2013/686104

McLoughlin, P., Popham, P., Linton, R. A., Bruce, R. C., and Band, D. M. (1992). Use of arterialized venous blood sampling during incremental exercise tests. *J. Appl. Physiol.* 73, 937–940. doi: 10.1152/jappl.1992.73.3.937

Myers, J., Kaminsky, L. A., Lima, R., Christle, J. W., Ashley, E., and Arena, R. (2017). A reference equation for normal standards for VO_2 max: analysis from the fitness registry and the importance of exercise national database (FRIEND registry). *Prog. Cardiovasc. Dis.* 60, 21–29. doi: 10.1016/j.pcad.2017.03.002

Neder, J. A., Arbex, F. F., Alencar, M. C. N., O'Donnell, C. D. J., Cory, J., Webb, K. A., et al. (2015). Exercise ventilatory inefficiency in mild to end-stage COPD. *Eur. Respir. J.* 45, 377–387. doi: 10.1183/09031936.00135514

Neder, J. A., Berton, D. C., Marillier, M., Bernard, A. -C., O'Donnell, D. E., and Canadian Respiratory Research Network (2019a). The role of evaluating inspiratory constraints and ventilatory inefficiency in the investigation of dyspnea of unclear etiology. *Respir. Med.* 158, 6–13. doi: 10.1016/j.rmed.2019.09.007

Neder, J. A., Berton, D. C., Marillier, M., Bernard, A. -C., O'Donnell, D. E., and Canadian Respiratory Research Network (2019b). Inspiratory constraints and ventilatory inefficiency are superior to breathing reserve in the assessment of exertional dyspnea in COPD. *COPD* 16, 174–181. doi: 10.1080/15412555.2019.1631776

Neder, J. A., Berton, D. C., Nery, L. E., Tan, W. C., Bourbeau, J., O'Donnell, D. E., et al. (2020). A frame of reference for assessing the intensity of exertional dyspnoea during incremental cycle ergometry. *Eur. Respir. J.* 56:2000191. doi: 10.1183/13993003.00191-2020

Neder, J. A., Berton, D. C., Rocha, A., Arbex, F., Alencar, M. C., Degani-Costa, L. H., et al. (2018a). "Abnormal patterns of response to incremental CPET" in *2018 clinical exercise testing European respiratory monograph*. eds. P. Palange, P. Laveneziana, J. A. Neder and S. A. Ward (Sheffield, UK: European Respiratory Society), 34–58.

Neder, J. A., Dal Corso, S., Malaguti, C., Reis, S., De Fuccio, M. B., Schmidt, H., et al. (2003). The pattern and timing of breathing during incremental exercise: a normative study. *Eur. Respir. J.* 21, 530–538. doi: 10.1183/09031936.03.00045402

Neder, J. A., Laveneziana, P., Ward, S. A., and Palange, P. (2018b). "CPET in clinical practice. Recent advances, current challenges and future directions" in *2018 clinical exercise testing european respiratory monograph*. eds. P. Palange, P. Laveneziana, J. A. Neder and S. A. Ward (Sheffield, UK: European Respiratory Society), x–xxv.

Neder, J. A., Nery, L. E., Andreoni, S., Sachs, A., and Whipp, B. J. (2000). Oxygen cost for cycling as related to leg mass in males and females, aged 20 to 80. *Int. J. Sports Med.* 21, 263–269. doi: 10.1055/s-2000-8885

Neder, J. A., Nery, L. E., Bagatin, E., Lucas, S. R., Anção, M. S., and Sue, D. Y. (1998). Differences between remaining ability and loss of capacity in maximum aerobic impairment. *Braz. J. Med. Biol. Res.* 31, 639–646. doi: 10.1590/S0100-879X1998000500006

Neder, J. A., and Stein, R. (2006). A simplified strategy for the estimation of the exercise ventilatory thresholds. *Med. Sci. Sports Exerc.* 38, 1007–1013. doi: 10.1249/01.mss.0000218141.90442.6c

O'Donnell, D. E., Elbehairy, A. F., Berton, D. C., Domnik, N. J., and Neder, J. A. (2017). Advances in the evaluation of respiratory pathophysiology during exercise in chronic lung diseases. *Front. Physiol.* 8:82. doi: 10.3389/fphys.2017.00082

O'Donnell, D. E., Laveneziana, P., Webb, K., and Neder, J. A. (2014). Chronic obstructive pulmonary disease: clinical integrative physiology. *Clin. Chest Med.* 35, 51–69. doi: 10.1016/j.ccm.2013.09.008

O'Donnell, D. E., Milne, K. M., Vincent, S. G., and Neder, J. A. (2019). Unraveling the causes of unexplained dyspnea: the value of exercise testing. *Clin. Chest Med.* 40, 471–499. doi: 10.1016/j.ccm.2019.02.014

O'Donnell, D. E., Neder, J. A., and Elbehairy, A. F. (2016). Physiological impairment in mild COPD. *Respirology* 21, 211–223. doi: 10.1111/resp.12619

Plachi, F., Balzan, F. M., Fröhlich, L. F., Gass, R., Mendes, N. B., Schroeder, E., et al. (2020). Exertional dyspnoea-ventilation relationship to discriminate respiratory from cardiac impairment. *Eur. Respir. J.* 55:1901518. doi: 10.1183/13993003.01518-2019

Plataki, M., Sands, S. A., and Malhotra, A. (2013). Clinical consequences of altered chemoreflex control. *Respir. Physiol. Neurobiol.* 189, 354–363. doi: 10.1016/j.resp.2013.04.020

Rocha, A., Arbex, F. F., Sperandio, P. A., Souza, A., Biazzim, L., Mancuso, F., et al. (2017). Excess ventilation in COPD-heart failure overlap: implications for dyspnea and exercise intolerance. *Am. J. Respir. Crit. Care Med.* 196, 1264–1274. doi: 10.1164/rccm.201704-0675OC

Varga, J., Casaburi, R., Ma, S., Hecht, A., Hsia, D., Somfay, A., et al. (2016). Relation of concavity in the expiratory flow-volume loop to dynamic hyperinflation during exercise in COPD. *Respir. Physiol. Neurobiol.* 234, 79–84. doi: 10.1016/j.resp.2016.08.005

Wasserman, K., Hansen, J., Sue, D., and Whipp, B. (1987). *Principles of exercise testing and interpretation*. Philadelphia, PA: Lea & Ferbiger.

Wasserman, K., and Whipp, B. J. (1975). Exercise physiology in health and disease. *Am. Rev. Respir. Dis.* 112, 219–249. doi: 10.1164/arrd.1975.112.2.219

Wasserman, K., Whipp, B. J., Koyl, S. N., and Beaver, W. L. (1973). Anaerobic threshold and respiratory gas exchange during exercise. *J. Appl. Physiol.* 35, 236–243. doi: 10.1152/jappl.1973.35.2.236

Weisman, I. M., and Zeballos, R. J. (1996). Clinical evaluation of unexplained dyspnea. *Cardiologia* 41, 621–634.

Whipp, B. J. (1977). The hyperpnea of dynamic muscular exercise. *Exerc. Sport Sci. Rev.* 5, 295–311. doi: 10.1249/00003677-197700050-00010

Whipp, B. J., and Davis, J. A. (1984). The ventilatory stress of exercise in obesity. *Am. Rev. Respir. Dis.* 129, S90–S92. doi: 10.1164/arrd.1984.129.2P2.S90

Whipp, B. J., and Ward, S. A. (1982). Cardiopulmonary coupling during exercise. *J. Exp. Biol.* 100, 175–193.

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