Chronic Obstructive Pulmonary Disease: Clinical Integrative Physiology

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KEYWORDS

• Chronic obstructive pulmonary disease • Small airways • Lung mechanics • Dyspnea • Exercise • Cardiac output

KEY POINTS

- COPD is characterized by heterogeneous physiologic abnormalities that are not adequately represented by simple spirometry.
- Extensive peripheral airway dysfunction is often present in smokers with mild spirometric abnormalities and may have negative clinical consequences.
- Activity-related dyspnea and exercise intolerance in patients with mild airway obstruction are linked to increased ventilatory inefficiency and dynamic gas trapping during exercise.
- Progressive increases in dyspnea and activity restriction are explained, in many instances, by the consequences of progressive erosion of resting inspiratory capacity.
- Although restrictive mechanics and increasing neuromechanical uncoupling of the respiratory system contribute to exercise intolerance across the spectrum of COPD severity, coexistent cardiocirculatory impairment is also potentially important.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by inflammatory injury to the intrathoracic airways, lung parenchyma, and pulmonary vasculature in highly variable combinations. It follows that the measured physiologic abnormalities are equally heterogeneous and these, in turn, likely underscore the common clinical manifestations of this complex disease. Expiratory flow limitation (EFL) is a defining physiologic characteristic of COPD and represents the final expression of diverse derangements of respiratory mechanics. Spirometric measurement of reduced maximal expiratory flow rate is required for diagnosis of COPD and can be used to follow the course of the disease. However, such measurements as forced expiratory volume in 1 second (FEV_1) are not useful in predicting the cardinal symptoms of the disease, dyspnea and exercise intolerance. This article reviews the respiratory mechanical and cardiocirculatory abnormalities across the spectrum of mild to severe COPD, at rest and during the stress of exercise.

MILD COPD

Clinical Relevance

It is well established that those with mild-to-moderate disease severity represent most patients

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with COPD, yet this subpopulation is understudied.[1,2] For the purpose of this review, mild COPD refers to spirometrically defined mild airway obstruction (ie, FEV_1 80%–100 % predicted), which need not be synonymous with early COPD. There is evidence from several population studies that, compared with nonsmoking healthy populations, smokers with mild COPD show increased mortality (including cardiovascular mortality),[3,4] increased hospitalizations, decreased health-related quality of life,[5–10] increased activity-related dyspnea, and reduced daily physical activity levels.[11–15] The underlying pathophysiologic linkages between mild COPD, dyspnea, and activity restriction have only recently become the subject of systematic study.[16–18]

Resting Physiologic Abnormalities in Mild COPD

A recent cross-sectional study of patients with COPD attests to the vast physiologic heterogeneity that exists even in those with mild airflow obstruction (**Fig. 1**).[19] Thus, in patients with a largely preserved FEV_1 there is wide variability in airways resistance (and conductance); pulmonary gas trapping; resting lung hyperinflation; and the integrity of the alveolar-capillary gas exchanging interface. Quantitative computed tomography (CT) scans also confirm a broad range of structural abnormalities in mild COPD, which include emphysema, pulmonary gas trapping, airway wall thickening, and even vascular abnormalities.[20–22]

Small airways dysfunction

The small airways are believed to be the initial locus of inflammation in COPD, and refer to the membranous (<2 mm diameter) and respiratory bronchioles.[23] Previous studies have shown evidence of active inflammation and obliteration of peripheral airways in mild COPD.[23–25] McDonough and colleagues[25] have proposed that such loss of small airways precedes the development of centrilobular emphysema. Mucus hypersecretion as a result of chronic bronchitis can also result in extensive peripheral airway dysfunction.[24,25]

Hogg and colleagues[24] were the first to report that peripheral airway resistance, measured by retrograde catheters, was increased by up to four-fold in the excised lungs of smokers with mild emphysema compared with those of healthy control subjects. This increase occurred despite normal values of total airways resistance. With the progression of emphysema, the increasing

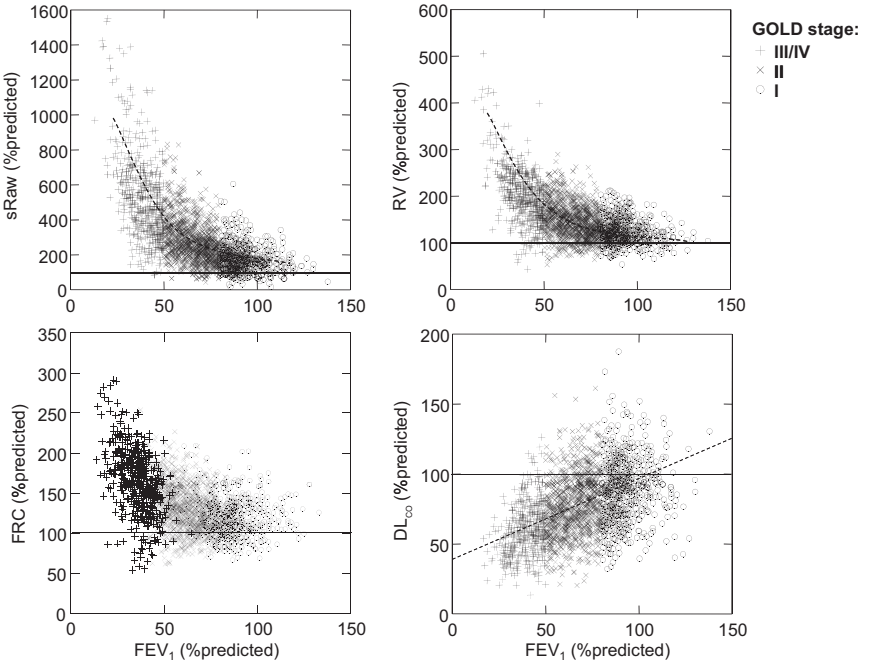

Fig. 1. Relationships between specific airway resistance (sRaw), residual volume (RV), functional residual capacity (FRC), and diffusing capacity of the lung (DL_{CO}) are shown against FEV_1 (all measurements expressed as % of predicted normal values). sRaw, RV, and FRC increased exponentially as FEV_1 decreased, and DL_{CO} decreased linearly as FEV_1 decreased. GOLD, Global Initiative on Obstructive Lung Disease. (*Modified from* Deesomchok A, Webb KA, Forkert L, et al. Lung hyperinflation and its reversibility in patients with airway obstruction of varying severity. COPD 2010;7(6):431; with permission.)

total airway resistance predominantly reflected the rise of peripheral airway resistance.[22] EFL, the hallmark of COPD, is present when the expired flows generated during spontaneous tidal breathing represent the maximal possible flow rates that can be achieved at that lung volume. EFL arises because of the combined effects of airway narrowing (caused by mucosal edema, mucus plugging, airway remodeling, and peribronchial fibrosis); reduced lung elastic recoil (reduced driving pressure for expiratory flow); and disrupted alveolar attachments, which predispose to dynamic airway collapse.[26–28] Corbin and colleagues[29] provided evidence that in smokers with mild airway obstruction, lung compliance increased in most subjects over a 4-year follow-up period: the increase in total lung capacity (TLC) correlated well with reduced static lung recoil pressure. Altered elastic properties of the lung potentially contribute to small airway dysfunction by reducing alveolar pressure gradients (particularly in panacinar emphysema) and by diminishing normal airway tethering.[28] The relative contribution of these factors to EFL in mild COPD varies from patient to patient and is difficult to quantify with any precision.[28]

The knowledge that extensive peripheral airways disease may exist in smokers with preserved spirometry and few respiratory symptoms has prompted the quest for sensitive tests of small airway function. These tests measure respiratory system resistance during tidal breathing or exploit the presence of nonuniform behavior of dynamic lung mechanics. The main physiologic manifestations of mild COPD as determined by such tests are summarized in **Box 1**. For instance, tidal esophageal pressure-derived measurements show increased frequency-dependence of dynamic lung compliance and resistance.[30] This behavior primarily reflects nonuniformity of mechanical time constants in the lung caused by regional changes in the compliance or resistance (or both) of alveolar units. Exaggerated frequency-dependence may also indicate the presence of delayed gas emptying in alveolar units that are slowly ventilated by collateral channels. Single-breath or multibreath nitrogen washout tests confirm maldistribution of ventilation and early airway closure.[31] Volume at isoflow during helium-oxygen and room air breathing indicates lack of a normal increase in flow during helium-oxygen in COPD and suggests that the major site of resistance is in the peripheral rather than central airways.[32,33] Forced and impulse oscillometry techniques measure respiratory system impedance. Typical abnormalities in mild COPD are increased respiratory system resistance; decreased reactance (increased elastance) at low oscillation frequencies; and increased resonant frequency.[34,35] Mid to low volume (effort-independent) maximal expiratory flow rates are often reduced below normal in smokers with a preserved FEV_1 and suggest small airway dysfunction.[36–38] Increased residual volume (RV) or RV/TLC ratio signifies increased pulmonary gas trapping caused by early airway closure, and provides indirect evidence of peripheral airways obstruction.[19,29]

Box 1
Pathophysiology of mild COPD

- Increased peripheral airway resistance
- Maldistribution of ventilation
- Disruption of pulmonary gas exchange
- Premature airway closure
- Increased pulmonary gas trapping
- Increased airway hyperresponsiveness

Nonspecific increased airway hyperresponsiveness is a well-documented finding in most patients with mild COPD and is believed to reflect inflammation and the combined morphometric changes in the peripheral airways. Increased airway hyperresponsiveness is more frequently found in women (reflecting their naturally smaller airway diameter) and in both genders predicts accelerated decline of FEV_1 with time and increased all-cause and specific mortality.[39–43] In an important study by Riess and colleagues,[43] in 77 patients with mild-to-moderate COPD, airway hyperresponsiveness was inversely related to airway wall thickness in resected lungs, after accounting for lung elastic recoil and FEV_1% predicted.

Ventilation-perfusion abnormalities

The diffusing capacity of the lung for carbon monoxide (DL_{CO}) is reduced in some patients with mild COPD, suggesting alteration of the surface area for gas exchange (see **Fig. 1**).[19,37] Patients with mild COPD and smokers with normal lung function have evidence of small-vessel disease affecting mainly the muscular pulmonary arteries.[22,44–49] Increased intimal thickness and narrow vessel lumen are the main manifestations of vascular injury in these patients.[44–46] Abnormal features include muscle cell proliferation and deposition of extracellular matrix proteins in the intima of pulmonary muscular arteries.[44–49] A recent noninvasive CT assessment of the cross-sectional area (CSA) of segmental and subsegmental small vessels revealed that the percentage of CSA of arteries less than 5 mm^2 was significantly lower in subjects with the emphysema phenotype than in

subjects with the bronchitis phenotype in all COPD Global Initiative on Obstructive Lung Disease (GOLD) stages.[22] In mild-to-moderate COPD, Barbera and colleagues[46,47] and Rodriguez-Roisin and colleagues[44] have demonstrated that significant alveolar ventilation (V_A)-to-perfusion (Q) mismatching and loss of protective hypoxic vasoconstriction can occur while breathing at rest. Thus, the resting alveolar-to-arterial oxygen tension gradient was abnormally widened (>15 mm Hg) in most of a small sample of patients with milder COPD who also had predominantly low regional V_A/Q ratios measured by multiple inert gas elimination techniques.[46,47]

Responses to Exercise in Mild COPD

High ventilatory requirements

In patients with mild COPD who report persistent activity-related dyspnea, peak oxygen uptake ($V'O_2$) measured during incremental exercise to tolerance has been shown to be diminished compared with healthy control subjects (**Fig. 2**).[15–18,50] One consistent abnormality has been the finding of higher than normal ventilation/carbon dioxide production slopes ($V'_E/V'CO_2$) during cycle and treadmill exercise.[15–18,50] Possible underlying causes of this increased ventilatory inefficiency include (1) increased physiologic dead space (DS) that fails to decline as normal during exercise, (2) altered set-point for $Paco_2$, and (3) a combination of the above. Future studies with measurement of $Paco_2$ are needed to determine if increased V_A/Q ratios are the main explanation. Significant arterial O_2 desaturation (>5%) has not been reported during incremental cycle exercise in symptomatic mild COPD.[15–18] Preservation of Pao_2 during exercise suggests that compensatory increases in ventilation (V'_E) in the setting of a normal increase in cardiac output ensure improved overall V_A/Q relations during exercise in mild-to-moderate COPD.[46–48] The lack of arterial O_2 desaturation during exercise also means that significant diffusion limitation of pulmonary O_2 transfer or intrapulmonary shunt are unlikely to be present to any significant degree. It remains plausible that in unfit patients, earlier lactate accumulation during physical exertion may provide an added stimulus to V'_E (by bicarbonate buffering and increased $V'CO_2$).[18] Finally, reduced oxidative capacity and reduced systemic O_2 delivery secondary to subclinical cardiocirculatory impairment, with an attendant early metabolic acidosis, may exist in some patients with mild COPD (see below).

Impairment of dynamic respiratory mechanics

We have proposed that the combination of increased ventilatory requirements, increased dynamic gas-trapping, and resultant restrictive mechanical constraints on tidal volume (V_T) expansion may contribute to reduced peak V'_E and peak $V'O_2$ in mild COPD.[15–18] The increased gas trapping during exercise reflects the combination of tachypnea and EFL: in alveolar units with slow mechanical time constants, expiratory time is insufficient to allow end-expiratory lung volume (EELV) to decline to its natural relaxation volume. To determine if mechanical factors represent the proximate limitation to exercise in mild COPD, Chin and colleagues[18] selectively stressed the respiratory system by adding DS to the breathing apparatus during exercise. Previous studies in younger healthy participants have shown that added DS (0.6 L) during exercise results in significant increases in peak V_T and V'_E and preservation of exercise capacity.[51–53] In mild COPD, the inability to further increase end-inspiratory lung volume (EILV), V_T, and V'_E at the peak of exercise in response to DS loading indicated that the respiratory system had reached its physiologic limits at end-exercise. This occurred in the presence of adequate cardiac reserve. Increased central chemostimulation during DS loading, in the face of such mechanical constraints on V_T expansion, caused an earlier onset of intolerable dyspnea in COPD but not in healthy control subjects.[18] Mechanical studies have also confirmed that dynamic lung compliance is decreased and pulmonary resistance, rest-to-peak changes in EELV, intrinsic positive end-expiratory pressures (PEEPi), and oxygen cost and work of breathing are all elevated in symptomatic mild COPD compared with healthy control subjects.[16,17]

Cardiocirculatory impairment

It is widely believed that the cardiovascular complications of COPD occur only in the advanced stage of the disease as a consequence of chronic hypoxemia (eg, pulmonary hypertension and cor pulmonale). More recently, however, several clinical and epidemiologic studies have shown cardiocirculatory abnormalities in patients in the early stages of COPD.[54–61] In fact, many patients with COPD have coexistent cardiovascular disease because smoking history is a common risk factor for both.[55,58,62,63] Notably, Lange and colleagues[4] recently showed that the presence of dyspnea in the setting of only mild airway obstruction was an independent predictor of cardiovascular mortality in a large Danish population. The Multiethnic Study of Atherosclerosis found that even in mild preclinical COPD, increases in airflow obstruction (as estimated by FEV_1/forced vital capacity ratio) and extent of emphysema (measured by CT) were linearly associated with reductions in

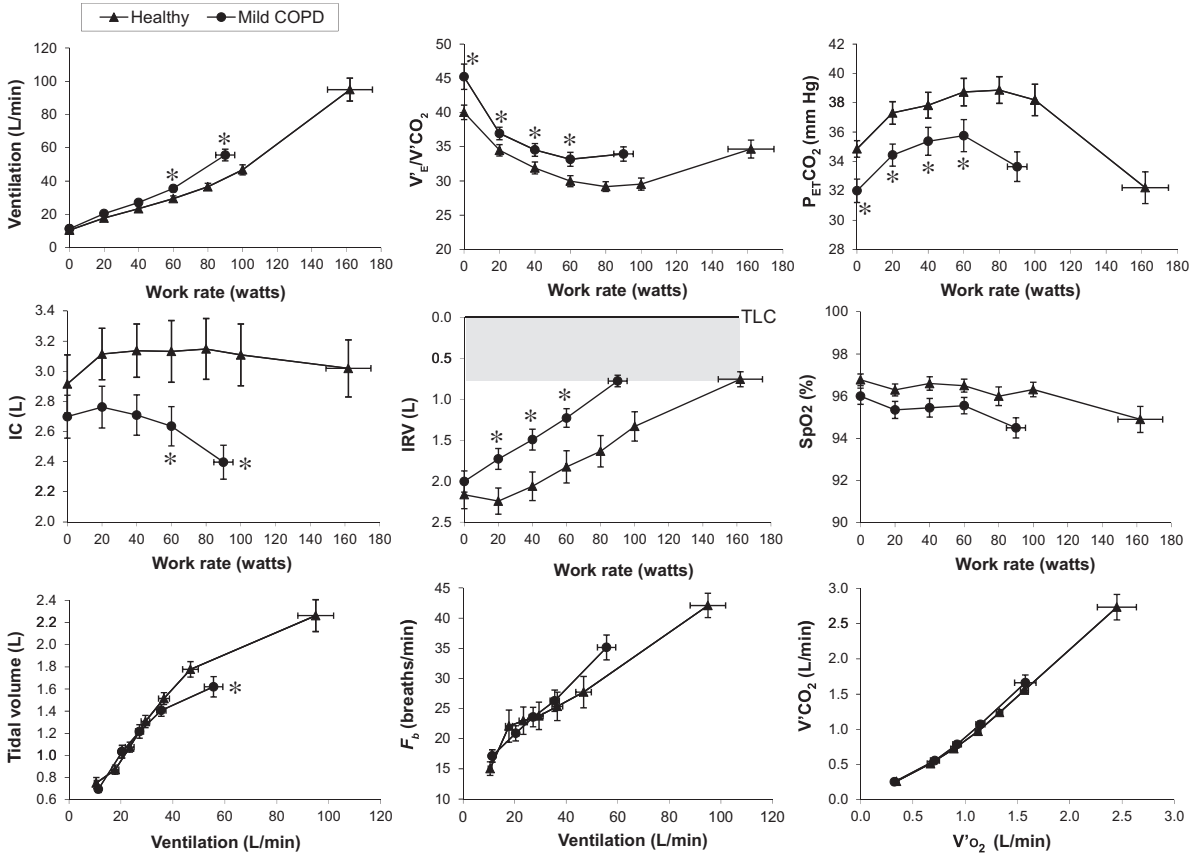

Fig. 2. Responses to incremental cycle exercise in mild COPD and in age- and gender-matched healthy normal subjects. *P<.05 COPD versus healthy group at standardized work rates or at peak exercise. Values are means ± SEM. F_b, breathing frequency; IC, inspiratory capacity; IRV, inspiratory reserve volume; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; SpO_2, oxygen saturation; $V'CO_2$, carbon dioxide production; $V'_E/V'CO_2$, ventilatory equivalent for carbon dioxide; $V'O_2$, oxygen consumption. (*Reprinted* with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Chin RC, Guenette JA, Cheng S, et al. Does the respiratory system limit exercise in mild COPD? Am J Respir Crit Care Med 2013;187(12):1319–20. Official Journal of the American Thoracic Society.)

left ventricular (LV) end-diastolic volume, stroke volume, and cardiac output measured by magnetic resonance imaging.[56,59] In the same study, pulmonary hyperinflation, as measured by RV or RV/TLC ratio, was associated with greater LV mass.[60] Malerba and colleagues[58] also found that minor emphysema determined by CT was related to impaired LV diastolic function and cardiac output.

The mechanisms underlying the cardiocirculatory abnormalities in mild COPD are unknown but they might include smoking-related pulmonary vascular damage,[22,49,61,64] impairments in nitric-oxide–induced vasodilatation,[65] simultaneous aging of the lungs and heart as indicated by "senile" emphysema and LV stiffness,[66] and negative central hemodynamic effects of exercise-related dynamic lung hyperinflation.[56,59,60] In fact, minor emphysema determined by CT imaging is associated with impaired LV diastolic function and cardiac output.[56] The pulmonary microvasculature, in particular, may become damaged early in the course of the disease because its endothelium is exquisitely sensitive to the deleterious effects of inflammation and hyperoxidative stress.[67,68] It is noteworthy that in the late 1950s, Liebow[69] suggested that alveolar destruction in emphysema is secondary to inflammation of the pulmonary microvasculature. Indirect support for this contention has been provided by Alford and colleagues[70] who found that smokers showing early signs of emphysema susceptibility had a greater heterogeneity in regional perfusion parameters by multidetector CT perfusion imaging than emphysema-free smokers and never-smokers. Thomashow and colleagues[61] found that markers of increased alveolar endothelial cell apoptosis were positively related to percent emphysema and inversely associated with pulmonary microvascular blood flow and diffusing capacity in patients with mild COPD. It is also remarkable that patients with early chronic heart failure[71] and mild COPD[72] have evidence of impaired cardiovascular autonomic regulation, decreased baroreceptor sensitivity, and heart rate variability suggesting common pathogenic pathways.

Skeletal muscle dysfunction

There is growing recognition that the peripheral skeletal muscles may show abnormalities in structure and function in mild COPD,[73–75] which might negatively impact on patients' exercise tolerance.[76] In fact, these patients report higher perceived leg effort ratings for a given metabolic demand compared with healthy control subjects.[15–18] Muscle biopsy studies also indicate that the general morphologic pattern of abnormalities form a continuum from mild-to-very severe COPD.[74,75] Unfitness and detraining are certainly important contributors, because regular daily physical activity decreases early in the course of the disease[77] and resistance exercise training can restore muscle function back to normal.[78] The relevance of sustained inactivity to muscle atrophy in mild COPD was emphasized by the findings of Shrikrishna and colleagues[79] who reported a close association between cross-sectional area of rectus femoris (measured by ultrasound) with physical activity levels in patients with GOLD stage I. Active smoking seems to play a significant role because it has several negative effects on muscle bioenergetics and protein synthesis.[75] The relevance of systemic inflammation in muscle dysfunction remains conjectural in mild COPD.[68]

MODERATE-TO-SEVERE COPD

Concepts of the natural history of COPD are strongly influenced by the seminal longitudinal population study of Fletcher and Peto[80] who have charted the decline in FEV_1 with time in susceptible smokers. Much less information is available on the temporal evolution of complex mechanical abnormalities and of pulmonary gas exchange abnormalities. Clearly, disease progression is characterized by worsening of the heterogeneous physiologic derangements already outlined in mild COPD. Recent short-term longitudinal studies have confirmed marked variability in change of FEV_1, which ranges from stability over time to accelerated decline.[81,82] Researchers are only beginning to understand the potentially important influences on the individual rate of physiologic decline of factors, such as obesity,[83] exacerbation history,[84,85] presence of comorbidities (eg, cardiocirculatory disease),[86] and the overlap with asthma. Clinical subtypes of COPD with dominant mucus hypersecretion (chronic bronchitis), structural emphysema, and a mixture of both have been identified for many years but the relative importance of these differing pathologic and physiologic features of COPD in contributing to dyspnea and activity restriction is still unclear.[87]

Resting Physiologic Abnormalities in Moderate-to-Severe COPD

Progression of resting lung hyperinflation

One of the major consequences of worsening EFL is lung hyperinflation (**Fig. 3**). The (reduced) resting inspiratory capacity (IC) and IC/TLC ratio have been shown to be independent risk factors for all-cause and respiratory mortality, and are linked to risk of exacerbation, activity-related dyspnea, and exercise limitation.[88–91] The presence of lung hyperinflation means that elastic properties of the

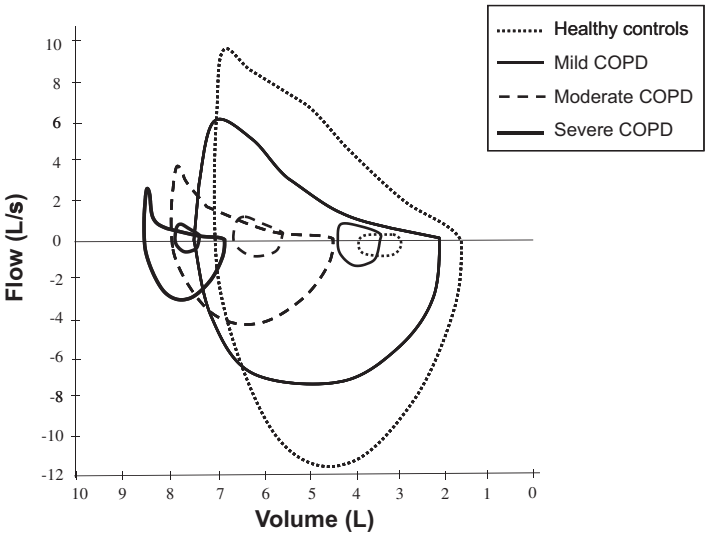

Fig. 3. Tidal flow-volume loops at rest are shown within their respective maximal loops. With worsening severity of disease, expiratory flow-limitation and static lung volumes increase. Resting inspiratory capacity progressively decreases with advancing disease so that tidal volume is closer to total lung capacity where elastic loading is increased.

lungs have changed (increased lung compliance) to such an extent that EELV fails to decline to the natural relaxation volume of the respiratory system. In flow-limited patients, resting EELV is also dynamically determined and varies with the prevailing breathing pattern and autonomic control of airway smooth muscle tone. This latter dynamic component of resting hyperinflation can be successfully manipulated by bronchodilator therapy.[92–98] Lung hyperinflation places the inspiratory muscles, especially the diaphragm, at a significant mechanical disadvantage by shortening its fibers, thereby compromising its force-generating capacity.[99] In patients with chronic lung hyperinflation, adaptive alterations in muscle fiber composition[100,101] and oxidative capacity[102] are believed to help preserve the functional strength and force-generating capacity of the diaphragm.[103]

Lung hyperinflation forces tidal breathing to take place nearer to the upper nonlinear extreme of the respiratory system's sigmoidal static pressure-volume relaxation curve where there is increased inspiratory threshold (auto-PEEP effect) and elastic loading of the inspiratory muscles.[104–107] High lung volumes in COPD attenuate increased airway resistance during resting breathing but this beneficial effect is negated if further "acute-on-chronic" dynamic hyperinflation (DH) occurs, for example, during physical activity[15,16,97,104,108–110] or during exacerbations.[84,111,112] In this latter circumstance, acute overloading and functional weakness of the inspiratory muscles may be linked to fatigue or even overt mechanical failure.[113]

Pulmonary gas exchange abnormalities

Among patients with COPD, those with predominant emphysema have high V_A/Q areas within the lungs, whereas those with predominant chronic bronchitis have low V_A/Q regions as a result of small airways distortion and mucus plugging.[44,45] The attendant abnormalities in arterial blood gases, if sustained, stimulate integrated compensatory adaptations over time. Thus, activation of neurohumoral, renal, and hemodynamic homeostatic mechanisms, together with modulation of the central respiratory controller, combine to preserve critical arterial oxygenation and acid-base status. Ultimately, in advanced COPD, the compensations may fail and reduced alveolar ventilation at a given $V'CO_2$ leads to CO_2 retention.[113] This occurs in the presence of abnormalities of the ventilatory control or as a result of critical respiratory muscle weakness (eg, nutritional and electrolytic deficiencies) and the negative mechanical effects of resting lung hyperinflation.

Responses to Exercise in Moderate-to-Severe COPD

Exercise limitation is multifactorial in COPD: peripheral muscle weakness and cardiocirculatory impairment undoubtedly contribute but increased central respiratory drive, dynamic mechanical impairment, and the associated dyspnea are major contributors, particularly in more advanced disease.[109,114–118]

Increased central respiratory drive

Ventilatory requirements progressively increase as COPD advances, primarily reflecting the consequences of worsening pulmonary gas exchange. Although the central drive to breathe during exercise steadily increases with worsening disease, VE/work rate slopes may not reflect this

because of the increasing mechanical constraints imposed on the respiratory system. At the limits of exercise tolerance in severe COPD, central neural drive has been shown to increase to near maximal values in response to the increased chemostimulation.[117–119] Recently, the potential for added ventilatory stimulation from metaboreceptors in the active locomotor muscles has been emphasized.[120] Critical arterial hypoxemia can also stimulate ventilation by peripheral chemoreceptor activation. This mainly reflects the effect of a fall in mixed venous O_2 on alveolar units with low V_A/Q ratios. Decreased mixed venous O_2 occurs because increase in cardiac output (or peripheral blood flow) is not commensurate with the increase in $V'O_2$ of the active locomotor muscles.

Dynamic respiratory mechanics across the continuum of COPD

The progression of COPD is associated with increasing erosion of the resting IC caused by increasing lung hyperinflation (**Fig. 4**). The resting IC dictates the limits of V_T expansion during exercise in flow-limited patients with COPD.[97,108–110,121–125] Thus, the lower the resting IC, the lower the peak V_T, and thus V'_E, achieved during exercise (see **Fig. 4**; **Fig. 5**).[97,108–110,121–125] Exercise DH further reduces the already diminished resting IC.[121,124] When V_T reaches approximately 70% of the prevailing IC (or EILV reaches ~90% of the TLC at a minimal inspiratory reserve volume), there is an inflection or plateau in the V_T/V'_E relation (see **Fig. 5**).[97,108,110,121] This critical volume restriction represents a mechanical limit where further sustainable increases in V'_E are impossible.[97,108,110,121] The inability to further expand V_T is associated with tachypnea, the only strategy available in response to the increasing central respiratory drive. Increased breathing frequency has added detrimental effects on inspiratory muscle function including further elastic loading caused by DH, increased velocity of shortening of the inspiratory muscles with associated functional weakness, and decreased dynamic lung compliance.[117–119] With worsening mechanical abnormalities, tidal esophageal pressure swings increase and, with it, the work and O_2 cost of breathing required to achieve a given increase (**Fig. 6**) in V'_E steadily increases. Theoretically, these collective derangements of respiratory mechanics can predispose to inspiratory muscle fatigue.[126,127] However, the evidence that measurable fatigue develops in COPD is inconclusive[100,102] even at the limits of exercise tolerance.[128] This may reflect temporal adaptations of the respiratory muscles or that exercise in many patients with COPD is terminated by intolerable respiratory discomfort before physiologic maxima are attained.

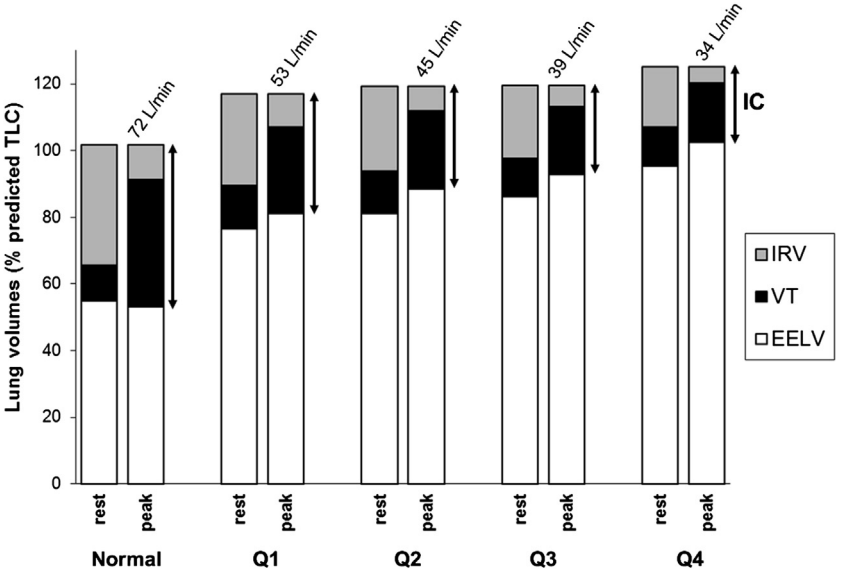

Fig. 4. Progressive hyperinflation, shown by increasing end-expiratory lung volume (EELV), is illustrated at rest and peak exercise as FEV_1 quartile worsens. Peak values of dynamic inspiratory capacity (IC), tidal volume (V_T), and ventilation (values shown above peak exercise bars) decreased with worsening severity, although similar peak ratings of dyspnea intensity were reached. Normative data are shown for comparison. IRV, inspiratory reserve volume; TLC, total lung capacity. (*From* O'Donnell DE, Guenette JA, Maltais F, et al. Decline of resting inspiratory capacity in COPD: the impact on breathing pattern, dyspnea, and ventilatory capacity during exercise. Chest 2012;141(3):758; with permission.)

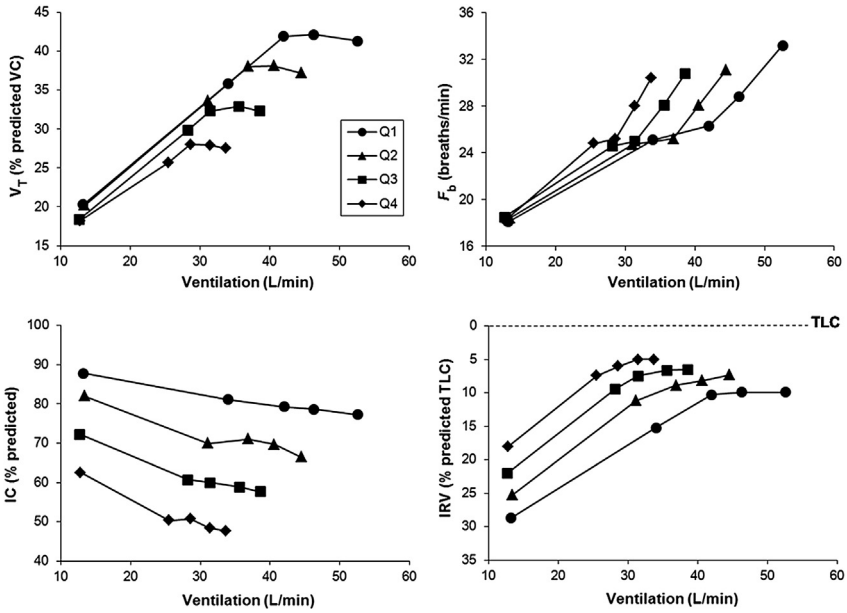

Fig. 5. Tidal volume (V_T), breathing frequency (F_b), dynamic inspiratory capacity (IC), and inspiratory reserve volume (IRV) are shown plotted against minute ventilation (V'_E) during constant work-rate exercise. Note the clear inflection (plateau) in the V_T/V'_E relationship, which coincides with a simultaneous inflection in the IRV. After this point, further increases in V'_E are accomplished by accelerating *F*. Data plotted are mean values at steady-state rest; isotime (ie, 2 minutes, 4 minutes); the V_T/V'_E inflection point; and peak exercise. TLC, total lung capacity; VC, vital capacity. (*From* O'Donnell DE, Guenette JA, Maltais F, et al. Decline of resting inspiratory capacity in COPD: the impact on breathing pattern, dyspnea, and ventilatory capacity during exercise. Chest 2012;141(3):759; with permission.)

Cardiocirculatory impairment

Acute-on-chronic hyperinflation may have deleterious effects on cardiac performance during exercise.[118,129–139] The resulting decreases in dynamic lung compliance with increasing levels of PEEPi require higher mean tidal intrathoracic pressure swings.[92,97] Increased intrathoracic pressure, in turn, decreases the gradient for venous return and leads to higher RV impedance. Of note, high right atrial pressures may contribute to decrease venous return but, conversely, can be beneficial in maintaining RV filling during expiration.[136] Juxta-alveolar capillary compression by high alveolar pressures also contributes to increased RV afterload.[136–139] Pulmonary vasoconstriction caused by hypoxemia and,

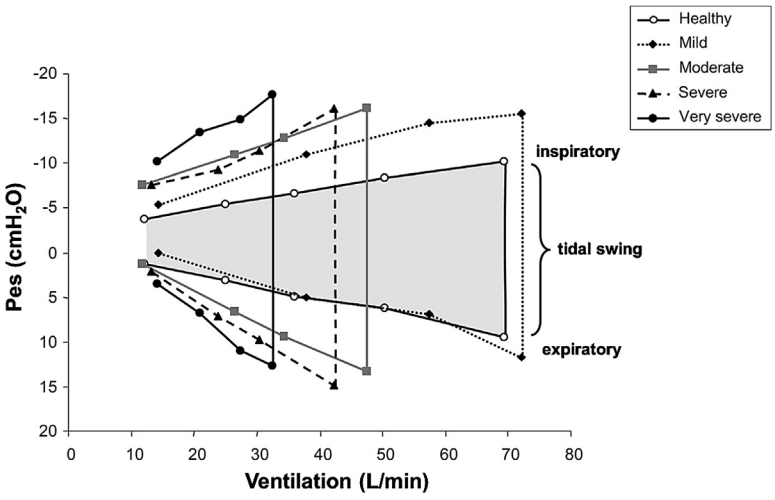

Fig. 6. Tidal esophageal pressure (Pes) swings are shown with varying severity of COPD and in age-matched healthy control subjects. As disease severity worsens, the amplitude of inspiratory and expiratory Pes increases for a given ventilation during exercise. The *shaded area* represents the tidal Pes swing in the healthy control subjects. (*Data from* Refs.[97,104,110] and unpublished data from the authors' laboratory, 2013.)

secondarily, hypercapnia and acid-base (acidosis) disturbances may further increase RV afterload. A recent prospective study with a large number of patients with COPD who underwent right heart catheterization during exercise found abnormal elevations in pulmonary artery pressures as a function of cardiac output, even in those without resting pulmonary hypertension.[140] In line with the concept that disturbed RV hemodynamics is relevant to cardiocirculatory impairment in COPD, exercise-related pulmonary hypertension has been closely related to impaired peripheral O_2 delivery in patients GOLD stages II to IV.[137] Combined effects of reduced RV preload and high afterload would then decrease stroke volume and cardiac output (**Fig. 7**).[54,56,140–144]

Impairment in LV diastolic filling is another consistent hemodynamic finding in advanced COPD,[56,142,143] even in patients without pulmonary hypertension.[145] Patients enrolled in the National Emphysema Treatment Trial, for instance, had elevated cardiac diastolic pressures and pulmonary capillary wedge pressures without systolic dysfunction,[146] which were improved with lung-volume reduction surgery.[146–148] Of note, LV filling rather than distensibility has been more closely associated with hyperinflation[56,59,143] suggesting that reduced preload might underlie LV diastolic dysfunction in COPD.[141,148,149] Tachycardia, a common finding in COPD, is likely to further reduce time for diastolic filling. The combination of increased RV dimensions and pressures with low end-diastolic LV volumes may heighten the transseptal pressure gradient. This would flatten or even displace the intraventricular septum toward the LV cavity thereby decreasing its compliance and filling.[150,151] Calcium-mediated abnormalities of myocardial relaxation induced by chronic hypoxemia may also contribute to impaired LV compliance.[152] The heart in the cardiac fossa can also be directly compressed by the overdistended lungs. Recent data confirm there is an inverse relationship between lung hyperinflation and cardiac size[60,143,148] more likely reflecting a combination of impaired LV filling and direct heart compression.

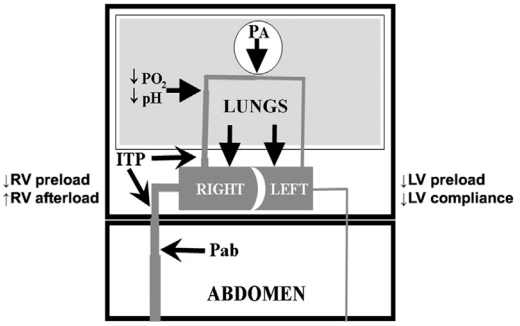

Fig. 7. Schematic illustration of dynamic cardiopulmonary interactions in patients with moderate-to-severe COPD presenting with expiratory flow limitation, intrinsic positive end-expiratory pressure, and lung hyperinflation. Hypercapnia-induced venous blood pooling, intra-abdominal compression of splanchnic vessels (particularly vena cava), and increased intrathoracic pressure (ITP) may have deleterious consequences on right ventricular (RV) preload. Increased ITP, pulmonary arteriolar vasoconstriction caused by alveolar hypoxia and respiratory acidosis, and juxtaalveolar capillary compression by supraphysiologic alveolar pressures (PA) might increase RV afterload. Hyperinflated lungs may also mechanically compress the heart, particularly the right chambers. Left ventricular (LV) stroke volume can be compromised by lower filling pressures, hypoxia-related myocardial stiffness, and decreased compliance caused by a leftward shift of the septum by the overdistended right ventricle. Large negative intrathoracic pressure with no change in lung volume at early inspiration can transitorily increase venous return and contribute to leftward shift of the septum. This chain of maladaptation is strongly modulated by fluid status, exercise, and comorbidities, especially chronic heart failure. Pab, abdominal pressure.

The functional impact of improving the negative cardiopulmonary interactions in COPD has been recently explored. In addition to lung-volume reduction surgery,[146–148,153] noninvasive positive pressure ventilation,[154,155] heliox,[130,156–158] and bronchodilators[129,159] have all been found to ameliorate the hemodynamic responses to exertion. Interestingly, some of these interventions had positive effects on peripheral muscle blood flow and $V'O_2$ kinetics.[130,156,157] These studies suggest that cardiocirculatory dysfunction might contribute to exercise impairment in advanced COPD. However, improvements secondary to those interventions occurred in parallel with decreases in work of breathing, DH, and dyspnea. It is difficult, therefore, to ascertain the relative contributions of increasing muscle blood flow to enhance patients' functional capacity.

Collectively, the bulk of evidence obtained in patients with advanced disease with a predominant emphysema phenotype indicates that LV function is impaired because of small LV end-diastolic dimensions secondary to increased RV afterload and dysfunctional ventricular interdependence. Although these abnormalities are particularly pronounced on exertion or during acute exacerbations, they might be present at rest in severely hyperinflated patients with end-stage disease. Concomitant intrinsic myocardial disease, a common feature in elderly patients with moderate-to-severe disease,[160] is expected

to further magnify exercise intolerance but clinical or experimental evidence to support this assertion is still lacking.

Skeletal muscle dysfunction

There is a long-standing interest in investigating the mechanisms and consequences of skeletal muscle dysfunction in COPD.[161] This is clinically relevant because loss of fat-free mass is a marker of disease severity and negative prognosis, particularly in patients with a predominantly emphysematous phenotype.[161] The same muscle morphologic and functional abnormalities observed in mild COPD are found in patients with advanced COPD albeit at a greater extent.[162–164] The putative relationships between proinflammatory/hyperoxidative stresses, nutritional abnormalities, neurohumoral disturbances, hypoxemia, and muscle loss were more convincingly demonstrated in patients with end-stage COPD.[165] Patients who develop peripheral muscle fatigue after exercise are more likely to benefit from exercise training,[166] although this is not a sine qua non.[161] The relative contribution of muscle dysfunction to exercise limitation in COPD is difficult to ascertain because multiple physiologic abnormalities are simultaneously present at different degrees in individual patients.

PHYSIOLOGIC MECHANISMS OF DYSPNEA IN COPD

Most patients with COPD experience dyspnea during daily activities.[117,124,167] As COPD progresses, dyspnea intensity ratings become progressively higher at any given V'_E, power output, or metabolic load (**Fig. 8**).[108] At the breakpoint of exercise healthy individuals report that their breathing requires more work or effort.[104] However, patients with COPD additionally report the sense of unsatisfied inspiration ("can't get enough air in").[97,104,110] These distinct qualitative dimensions of dyspnea likely have different neurophysiologic mechanisms. Increased sense of effort in COPD is related to the increased motor drive to respiratory muscles.[117,118,167–171] Contractile muscle effort is increased for any given V'_E in COPD because of the increased intrinsic mechanical (elastic/threshold) loading and functional muscle weakness, in part caused by resting and DH during exercise.[117,118,167–171] In this circumstance, greater neural drive or electrical activation of the muscle is required to generate a given force.[117,118,167–171] There is evidence that the amplitude of central motor command output to the respiratory muscles is sensed by neural interconnections (ie, central corollary discharge) between cortical motor and

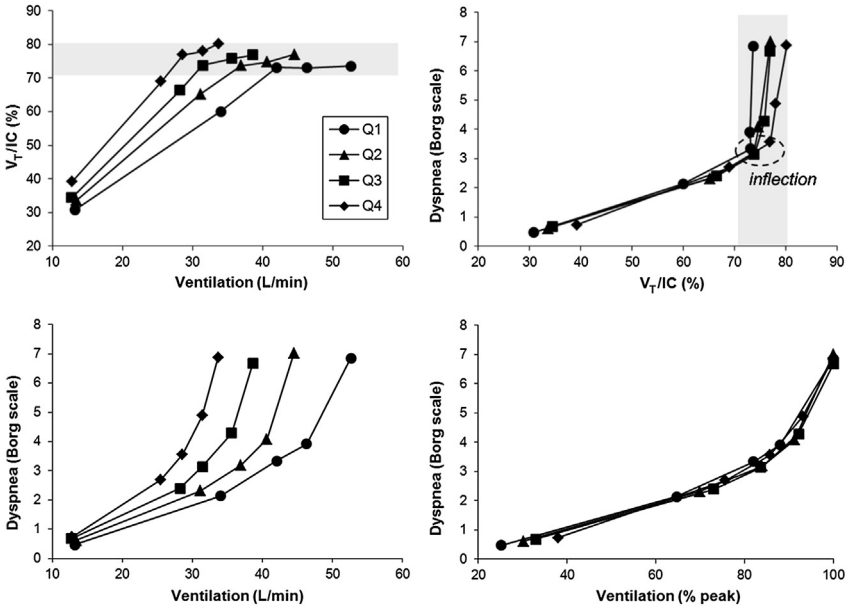

Fig. 8. Interrelationships are shown between exertional dyspnea intensity, the tidal volume/inspiratory capacity (V_T/IC) ratio, and ventilation. After the V_T/IC ratio plateaus (ie, the V_T inflection point), dyspnea rises steeply to intolerable levels. The progressive separation of dyspnea/minute ventilation (V'_E) plots with worsening quartile is abolished when ventilation is expressed as a percentage of the peak value. Data plotted are mean values at steady-state rest; isotime (ie, 2 minutes, 4 minutes); the V_T/V'_E inflection point; and peak exercise. (*From* O'Donnell DE, Guenette JA, Maltais F, et al. Decline of resting inspiratory capacity in COPD: the impact on breathing pattern, dyspnea, and ventilatory capacity during exercise. Chest 2012;141(3):760; with permission.)

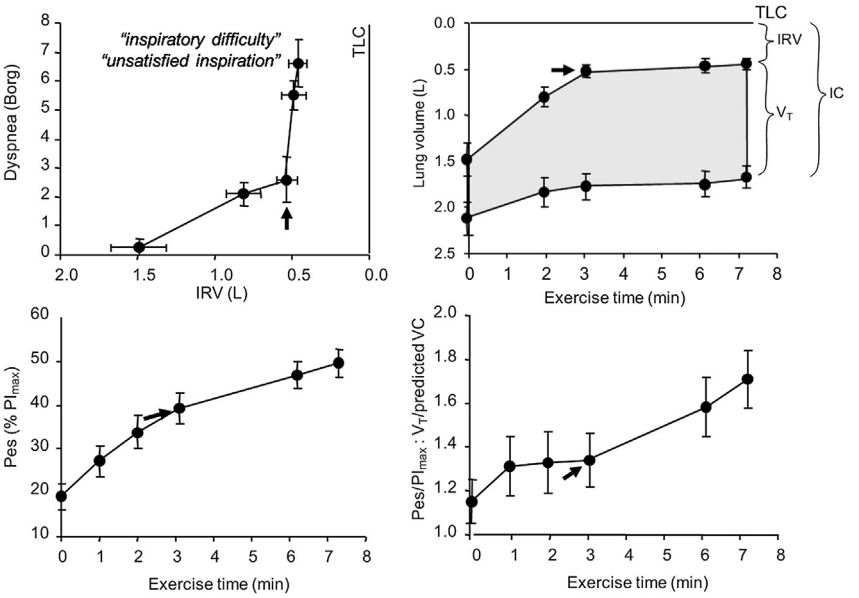

Fig. 9. The mechanical threshold of dyspnea is indicated by the abrupt rise in dyspnea after a critical "minimal" inspiratory reserve volume (IRV) is reached, which prevents further expansion of tidal volume (V_T) during exercise in COPD. Beyond this dyspnea/IRV inflection point during exercise, respiratory effort (tidal esophageal pressure swings as a fraction of the maximum inspiratory pressure [Pes/PI_{max}]) and the effort-displacement ratio continue to rise. *Arrows* indicate the dyspnea/IRV inflection point. Values are means ± SEM. IC, inspiratory capacity; TLC, total lung capacity; VC, vital capacity. (*Modified from* O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. J Appl Physiol 2006;101(4):1028; with permission.)

medullary centers in the brain and the somatosensory cortex.[117,118,167–171]

The neurophysiologic underpinnings of unsatisfied inspiration may be different.[117,118,167–171] The V_T/V'_E inflection point during exercise marks the point where dyspnea intensity sharply increases toward end-exercise and the dominant descriptor selected by patients changes from increased effort to unsatisfied inspiration.[110] The V_T inflection represents the onset of a widening disparity between increasing central neural drive and the mechanical/muscular response of the respiratory system (**Fig. 9**).[97,110] Dyspnea intensity seems to be more closely correlated with the change in EILV or inspiratory reserve volume during exercise than the change in EELV (ie, DH) per se (see **Fig. 9**).[97,108,110,121] Dyspnea intensity ratings also correlate well with indices of neuromechanical uncoupling, such as the ratio of V_T expansion to respired effort (relative to maximal possible effort). When vigorous inspiratory efforts become unrewarded, affective distress (anxiety, fear, panic) is evoked and is a major component of exertional dyspnea.[53,117,118,167–171]

SUMMARY

COPD is characterized by diverse physiologic derangements that are not adequately represented by simple spirometry. The human respiratory system has enormous reserve and develops effective compensatory strategies to fulfill its primary function of maintaining blood gas homeostasis even in the face of extensive injury to the small airways, lung parenchyma, and its microvasculature. These physiologic adaptations together with behavioral modification (eg, activity avoidance) can result in a prolonged preclinical phase (and late diagnosis) in susceptible smokers. In patients with spirometrically defined mild airway obstruction who report more persistent activity-related dyspnea, there is usually evidence of increased peripheral airways resistance and nonuniform behavior of dynamic respiratory mechanics. Increased dyspnea and exercise intolerance in this group is explained, at least in part, by increased ventilatory inefficiency and dynamic gas trapping during exercise. Additionally, there is new evidence that peripheral muscle dysfunction and cardiocirculatory impairment may variably contribute to exercise intolerance in patients with mild airway obstruction. As the disease progresses increasing dyspnea and activity restriction is explained by the combined effects of worsening respiratory mechanics and pulmonary gas exchange. Thus, the intensity and quality of dyspnea during physical activity is explained by the growing disparity between the increased

central neural drive to breathe (augmented by pulmonary gas exchange and metabolic abnormalities) and the reduced ability of the respiratory muscles to respond because of increased intrinsic mechanical loading and the effects of lung hyperinflation. The progressive erosion of the resting IC with time means progressively earlier mechanical limitation and ever-increasing neuromechanical uncoupling of the respiratory system, which together with the effects of impaired cardiocirculatory function lead to earlier onset of intolerable dyspnea during physical activity.

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