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Lung Hyperinflation as Treatable Trait in Chronic Obstructive Pulmonary Disease: A Narrative Review

Maud Koopman[1–3], Rein Posthuma[1–3], Lowie EGW Vanfleteren[4], Sami O Simons[2,3], Frits ME Franssen[1–3]

[1]Research and Development, Ciro+, Horn, the Netherlands; [2]NUTRIM, Institute of Nutrition and Translational Research in Metabolism, University Maastricht, Maastricht, the Netherlands; [3]Department of Respiratory Medicine, Maastricht University Medical Center (MUMC+), Maastricht, the Netherlands; [4]COPD Center, Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden

Correspondence: Frits ME Franssen, CIRO+, Hornerheide 1, Horn, 6085, NM, the Netherlands, Email fritsfranssen@ciro-horn.nl

Abstract: Lung hyperinflation (LH) is a common clinical feature in patients with chronic obstructive pulmonary disease (COPD). It results from a combination of reduced elastic lung recoil as a consequence of irreversible destruction of lung parenchyma and expiratory airflow limitation. LH is an important determinant of morbidity and mortality in COPD, partially independent of the degree of airflow limitation. Therefore, reducing LH has become a major target in the treatment of COPD over the last decades. Advances were made in the diagnostics of LH and several effective interventions became available. Moreover, there is increasing evidence suggesting that LH is not only an isolated feature in COPD but rather part of a distinct clinical phenotype that may require a more integrated management. This narrative review focuses on the pathophysiology and adverse consequences of LH, the assessment of LH with lung function measurements and imaging techniques and highlights LH as a treatable trait in COPD. Finally, several suggestions regarding future studies in this field are made.

Keywords: COPD, hyperinflation, treatable trait, emphysema, phenotype

Introduction

Chronic obstructive pulmonary disease (COPD) has in recent decades been recognized as a complex condition consisting of more than airflow limitation alone. Both additional pulmonary as well as extra-pulmonary features contribute to the burden of the disease.[1–3] The concept of identifying treatable traits in individual patients was a step forward in addressing the complexity and heterogeneity of COPD.[4] Lung hyperinflation (LH) is considered a pulmonary trait for which diagnostic criteria and specific interventions are available.[4] Indeed, LH, resulting from destruction of lung parenchyma and loss of lung elastic recoil, is one of the hallmarks of the disease.[5] Its partial independence from the degree of airflow limitation[1,6] and its strong link with morbidity[7] and mortality,[8] combined with the availability of targeted treatments, justify its status as a treatable trait. However, rather than an isolated trait, LH may be part of a broader phenotype of the disease, with typical pulmonary features, symptoms, disease trajectory, extra-pulmonary features and comorbidities.[9]

This narrative review focusses on the pathophysiology and adverse consequences of LH, its assessment and position as a treatable trait in COPD. Identified knowledge gaps are summarized as suggestions for future studies.

Definition, Mechanisms and Pathophysiology

Hyperinflation is defined by an increase in the amount of gas in the lungs and airways at the end of a spontaneous expiration, amounting to a functional residual capacity (FRC) above the upper 95th percentile of the predicted values.[10,11] LH can most accurately be defined as an increase in total lung capacity (TLC) above the upper limit of normal, with an FRC/TLC or residual volume (RV)/TLC above the upper limit of normal.[12] An increase in TLC >120%

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of the predicted value or an increase in RV above the upper limit of normal are also often used as definitions of LH in literature.[13]

Static Hyperinflation

Static LH, defined by increased resting lung volumes, is determined by a modification of the elastic properties of the respiratory system due to a decrease of the inward elastic recoil of the lungs without changes of the natural outward elastic properties of the chest wall.[14] Pulmonary emphysema, characterized by destruction of lung parenchyma and loss of elastic fibers in the lungs, is the most important cause of LH.[15] This results in a displacement of the volume–pressure curve of the lungs leftward and upward (Figure 1).[13,16] At the end of a spontaneous expiration, the lung compensates for a reduced recoil pressure by acquiring a larger volume than normal to balance the outward recoil of the chest wall in patients with COPD. The static/elastic equilibrium point of the total respiratory system is moved towards a higher-than-normal lung volume, and the respiratory system's relaxation volume or FRC is permanently increased.

RV in turn is increased in COPD, not only due to reduced elastic recoil but also due to premature closure of the small airways and expiratory airflow limitation at low lung volume, also known as gas trapping.[10] This is already observed in COPD patients with mild airflow limitations.[17,18] Moreover, a reduced duration for expiration due to the development of unendurable respiratory discomfort contributes to the increase in RV.[13] TLC also increases due to loss of lung recoil. With increasing severity of the disease, the rise in RV becomes greater than the increase in TLC, because TLC is limited by the thoracic cage. This, together with a fall in vital capacity (VC) due to premature airway closure, will lead to a higher RV/TLC ratio, which also impacts on a further reduction in forced expiratory volume in the first second (FEV_1). In these severe cases, spirometry in COPD can show not only an obstructive but also a restrictive pattern.[19]

While the degree of airflow limitation and static hyperinflation are directly correlated in most patients,[1,19] some patients have distinct hyperinflation without severe airflow limitation,[1] as is also shown in Figure 2. The figure shows a self-organizing map of 467 patients with stable COPD that participated in the Chance Study: an observational,

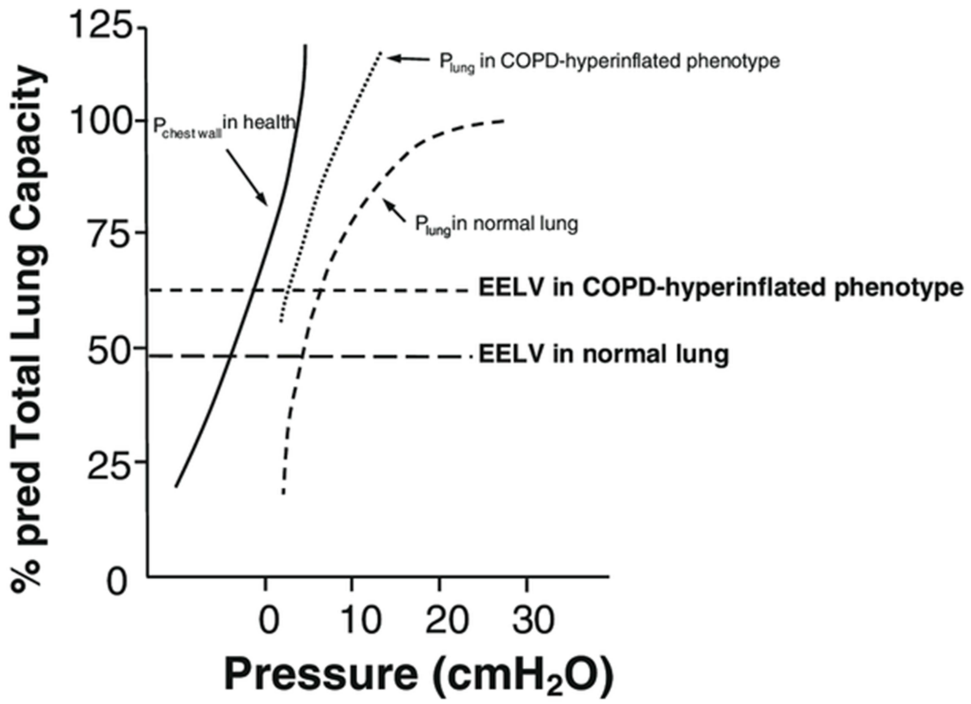

Figure 1 Change in end-expiratory lung volume (EELV) with COPD. EELV is set at the point at which the elastic recoil pressures of the lung and chest wall are equal and opposite in direction. In COPD patients with hyperinflation, emphysema decreases lung elastic recoil pressure and causes a reset of functional residual capacity, or EELV, at a higher absolute lung volume. The difference between expected (long-dashed horizontal lines) and observed EELV (short-dashed horizontal lines) represent static hyperinflation. Reprinted from Dubé B, Guerder, (**A**), Morelot-Panzini, (**C**) et al. The clinical relevance of the emphysema-hyperinflated phenotype in COPD. COPD Research and Practice. 2015;2(1). This source is Open Access, the figure was copied under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).[16]

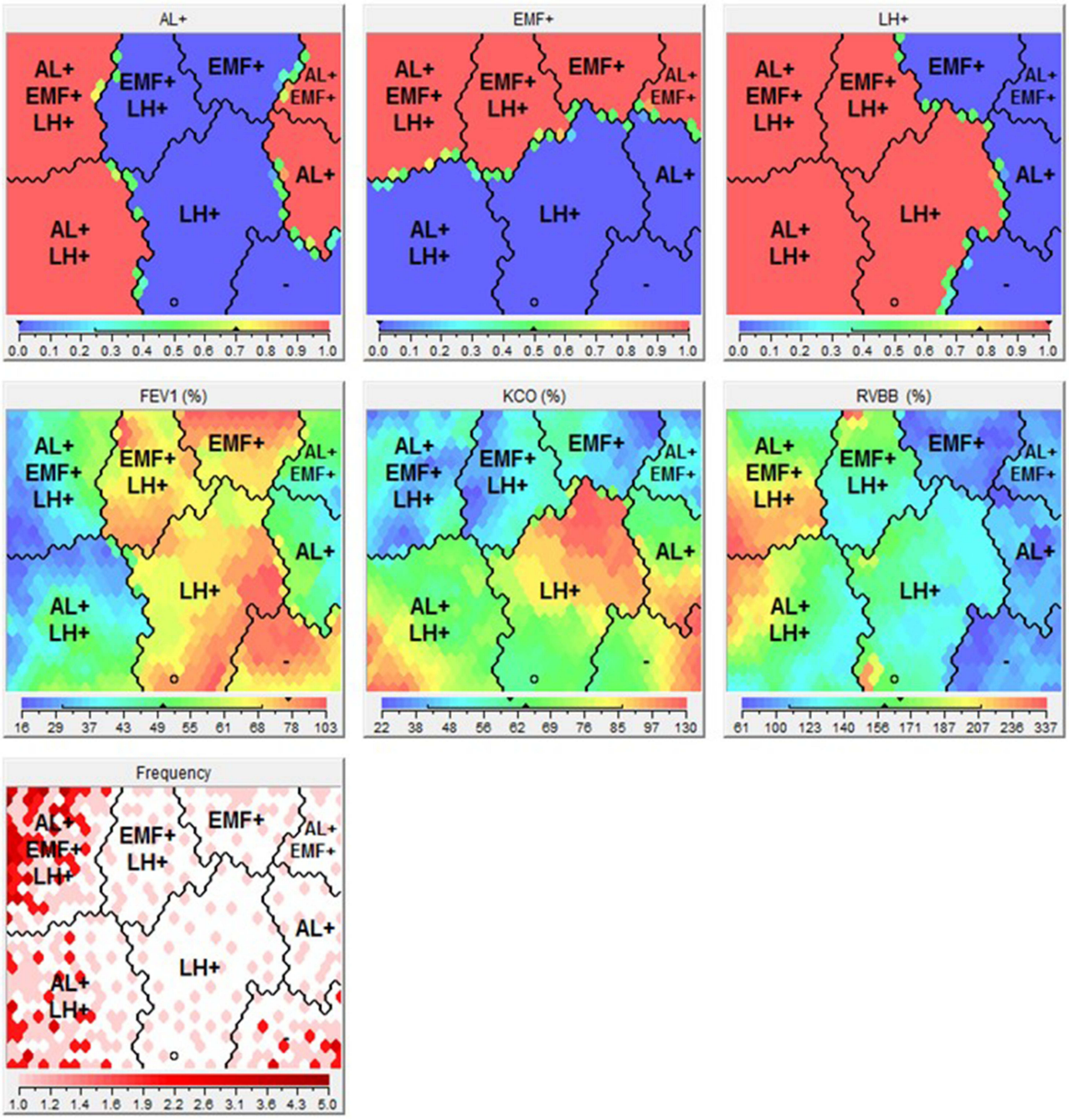

Figure 2 Heterogeneity of lung function impairment in patients with COPD.

Notes: The panels were generated using Viscovery (Viscovery Software GmbH, Vienna, Austria). The Viscovery program placed all patients in a specific position on the map based on their profile of a comprehensive lung function assessment. When looking at the different lung function attributes, patients appear red on the chart when the attribute is relatively high within this sample, appear green if the attribute is moderate and appear blue when the attribute is relatively low within this sample. The more patients show resemblance in terms of their overall lung function, the closer they are on the map. By drawing lines on the map, the Viscovery program could identify eight different clusters of patients with COPD with significantly different lung function profile. AL+: airflow limitation (FEV1 <60% predicted); EMF+: emphysema (KCO < 60% predicted); LH+: lung hyperinflation (RV >120% predicted); -: not fulfilling any of these criteria for severity of lung function impairment (neither airflow limitation, emphysema or lung hyperinflation).

prospective, single-center study about COPD, health status and cardiovascular co-morbidities (METC 11-3-070).[20] Patients were ordered based on the absence or presence of airflow limitation (AL): (FEV_1 < 60% predicted); emphysema (EMF): carbon monoxide transfer coefficient (KCO) <60% predicted; and lung hyperinflation (LH): RV > 120% predicted. Eight clusters could be identified with a significantly different lung function profile. In this cohort, 14% of

the patients had LH without significant expiratory airflow limitation. Moreover, 8% of the patients had emphysema without significant lung hyperinflation. Hence, although most COPD patients have a combination of AL, LH and EMF, these data implicated that the presence of LH does not always mean coexistence of airflow limitation or emphysema in patients with COPD.

Dynamic Hyperinflation

Dynamic hyperinflation (DH) is defined as a temporary increase of end expiratory volume (EELV) above its resting value when ventilation increases in patients with expiratory airflow limitation.[13] It results from a discrepancy between the time required for the lungs to empty during exhalation and the time available between two consecutive inspiratory efforts. Reduced expiratory airflow limits the exhaled volume over time, while increased breathing frequency shortens the time available to expire. Several factors can further worsen DH: high inspired volume combined with insufficient expiration, ie during exercise; high frequency of breathing, eg during spontaneous breathing, exercise, anxiety or panic attacks; decreased driving pressure for expiration; increased airflow resistance, during exacerbation; expiratory airflow limitation, when small airways become excessively compressed due to destruction of supporting alveolar attachments.[21]

Although most COPD patients have DH during exercise, Guenette et al confirmed that approximately 15–20% of patients with moderate-to-severe COPD do not, even with only slightly less resting hyperinflation.[22] It was suggested they counteract DH by contracting the expiratory muscles, although DH can occur during exercise despite increased expiratory muscle activity.[23]

Airway Remodeling

It has been well established that small conducting airways less than 2 mm in diameter, which account for less than 10% of the total airflow resistance in normal lungs,[24] become the major site of airflow obstruction in COPD.[25] The terminal bronchioles are also known to disappear in patients with very severe COPD, and it is suggested that this destruction might precede emphysematous tissue destruction in COPD.[26] Koo et al performed micro-CT's and histological assessments of the matching lung tissue and showed that the lungs of patients with mild and moderate COPD have significantly fewer conducting terminal bronchioles and respiratory transitional bronchioles compared with age-matched smokers with normal lung function, and that this loss is also present in apparently non-emphysematous lungs.[27] However, since Koo et al performed cross-sectional analyses it is unclear if this is due to abnormal development of the lungs or due to destruction of airways. Imaging studies using parametric response mapping to assess gas trapping resulting from small airways disease showed that this is also the dominant cause of hyperinflation in mild to moderate COPD.[28] Other studies demonstrate that loss of elastic recoil due to emphysematous destruction potentially causes further airway obstruction,[29] which in turn can lead to LH. Acknowledgement of these findings is important in light of the development of effective treatments and interpreting outcomes of clinical trials in COPD. By inclusion of advanced COPD populations, most previous trials studied the effects of treatments on lungs with substantially fewer terminal and transitional bronchioles. To develop disease-modifying treatments for COPD, an understanding of disease pathogenesis within these small airways and in patients without clinically apparent (or with very early disease) is essential.

Diagnosing Static and Dynamic Hyperinflation

The most commonly used methods for lung volume measurements are body plethysmography, gas dilution techniques (helium dilution method and nitrogen washout method) and imaging (computed tomography).[30] Magnetic resonance imaging (MRI) can also be used but appears to be more suitable for functional imaging.[31]

Measuring Static Hyperinflation by Lung Function Techniques

Body plethysmography is the reference method for the measurement of lung volume and measures intrathoracic gas volume (ITGV), FRC, and allows calculation of RV and TLC.[32,33] FRC measured by plethysmography can overestimate the true FRC in the presence of abdominal gas or by significant pressure losses between alveoli and airway opening in the presence of severely obstructed airways.[34] Moreover, in plethysmography mouth pressure and alveolar pressure are assumed to be equal, which is not the case in severe COPD. This can lead to overestimation of lung volumes.[12] Both RV/

TLC ratio and RV have recently been demonstrated to be relevant indicators of hyperinflation and patient-related outcomes in patients with severe emphysema.[35]

The gas dilution techniques can be used as an alternative in patients who cannot perform body plethysmography, including patients with claustrophobia or severe obesity.[36] However, typically in patients with severe emphysema, FRC can be largely underestimated as the measured volume corresponds with the well-ventilated areas only.[34]

Spirometrically assessed inspiratory capacity (IC) can indirectly indicate the presence of LH. The IC is the maximal volume of air that can be inhaled after a spontaneous expiration to FRC and is the difference between TLC and FRC. Pharmacological studies in COPD have established that IC as a measure of hyperinflation correlates stronger with dyspnea and exercise performance than FEV_1.[37,38] However, the use of IC for measuring LH ignores an isolated increase in RV and assumes that TLC does not change during the course of the disease as a result of an exacerbation or bronchodilation therapy.[21] A recent study showed that gas trapping or LH in terms of RV/TLC ratio could be estimated using only FEV_1 and FVC.[39] Das et al showed that severe hyperinflation in COPD patients can potentially be indicated by measuring the area under the forced expiratory flow-volume loop.[40] However, as the authors emphasized, a reference value for this method does not yet exist, and the study focused only on severe static hyperinflation.

Measuring Static Hyperinflation by Imaging Techniques

Conventional chest radiographs can show signs of increased lung volume but are not a standardized method for measuring LH. The most supportive radiographic signs of LH are a flattened diaphragm,[41] an increase in the retrosternal air space of more than 2.5 cm and an increase in lung height.[21]

A more important method for assessment of LH is computer tomography (CT). Lung volumes measured by CT are less prone to inaccuracies related to chest wall or image distortion compared to chest x-rays. Usually, TLC measured by plethysmography and CT have a very high correlation ($r > 0.9$).[42] The difference between TLC through plethysmography and CT is greatest among patients with $FEV_1 < 30\%$ of predicted.[43] A limitation of measurement of LH with CT is the difficulty with maximum inspiratory maneuvers and breath-holding techniques during scanning. Also, because CT measures TLC in supine position and plethysmographic techniques are performed in the sitting position, TLC is greater in plethysmography.[21] This discrepancy can be even larger in obese patients.

CT imaging has made an important contribution to the diagnosis and management of COPD for many years,[44] especially, it allows the identification of emphysema.[45] The extent of emphysema on CT has been shown to correlate significantly with hyperinflation determined by lung function testing.[46] Moreover, by combining LH and emphysema additional information that is useful for predicting the course of disease can be obtained.[47] Volumetric acquired high-resolution CT (HRCT) is excellent for measuring the presence, pattern, distribution, and extent of emphysema.[48] The NETT study demonstrated that the regional distribution and heterogeneity of emphysema on HRCT are clinically important features to help select patients who better respond to lung volume reduction surgery.[49] Also, the extent of emphysema on CT predicts (absence of) response to pharmacotherapies in COPD.[50] Additionally, CT has widespread availability and rapid image acquisition and may aid in the early detection of COPD, as the comparison between inspiratory and expiratory images can show air trapping and help to distinguish COPD phenotypes.[51] However, the presence of emphysema does not always imply the presence of hyperinflation (Figure 2).

Quantitative CT (QCT) uses software to quantify, either at lobar or whole lung level, the extent of emphysema, based on voxel-by-voxel attenuation; the degree of bronchial wall thickening, based on the ratio of average lumen diameter to wall area in the small airways and the extent of gas trapping, based on differences between inspiratory and expiratory phase images.[28,52,53] Parametric response mapping, a voxel-based image analysis technique, enables differentiation between gas trapping from emphysema or small airways disease.[28] QCT indices correlate independently with clinical outcomes including disease progression, mortality and symptoms.[28,53] Currently, QCT is mainly used in emphysematous patients with severe LH to select candidates for bronchoscopic lung volume reduction.[54]

Imaging emphysema with magnetic resonance imaging (MRI) is a major challenge due to the loss of lung tissue and reduced blood volume, resulting in a marked reduction of lung parenchymal signal.[55] MRI might be used in COPD for assessment of functional parameters like perfusion and respiratory dynamics.[56] There is no literature describing imaging of LH with MRI.

Measuring Dynamic Hyperinflation

DH can be measured by performing IC maneuvers during a cycle ergometer test or 6WMT, with a decline in IC during exercise being indicative of the presence of DH. A decrease in IC from baseline >150 mL during exercise indicates DH.[57] Several studies consider a decline of 10% as clinically relevant.[58,59] IC maneuvers during exercise provide valuable information on ventilatory constraints during exercise,[60,61] but require logistics and repetitive IC maneuvers that can be difficult to perform for patients,[62] especially for those with advanced stages of COPD. Metronome-paced tachypnea (MPT) is considered to be a feasible alternative to measure DH.[62] By applying mandatory tachypnea for a short period while sitting at rest, and performing an IC maneuver before and after, it mimics the dynamic respiratory pattern that occurs during exertion.[63] It is suggested that a minimal decrease in IC of 11.1% is the optimal cut-off for MPT-induced DH.[58] It must be noted that the sensitivity of this method is 85%, but with limited specificity, which can lead to overdiagnosis of DH.[64]

Esophageal pressure is a well-known surrogate of the pleural pressure and is considered the golden standard to measure dynamic hyperinflation during exercise.[65] A balloon catheter is placed nasally at approximately the lower third of the esophagus to minimize cardiogenic oscillations.[66] The use of esophageal catheters to measure hyperinflation is customary in research settings, while it requires a high technical effort and the insertion can be cumbersome and time-consuming in daily clinical practice.

Optoelectronic plethysmography is another established technique to visualize dynamic hyperinflation, by measuring tidal changes in the volume of the chest wall and its compartments.[67] A number of reflective markers are placed on selected anatomical reference sites of the thoraco-abdominal surface of the subject. A set of cameras placed nearby the subject and a system for human motion analysis measures the three-dimensional coordinates and motion of these markers.[68] Also this technique is mostly suited for laboratory research settings.

Hyperinflation as Part of the Systemic Disease COPD

Although hyperinflation may be approached as an isolated pulmonary trait in COPD that only partially correlates with other lung function measurements[1] (Figure 1), it may alternatively be seen as one of the distinct features of a specific disease phenotype.[9] The emphysematous phenotype was traditionally described as the "pink puffer", known for its characteristic barrel chest deformity as a consequence of emphysema and low body weight,[10] which can also be found in patients with hyperinflation (Figure 3). In the past decades, additional features of the emphysematous phenotype but also the hyperinflated patient and its therapeutic implications have been studied extensively and these will be discussed here.

Dyspnea, Exercise Limitation, Exacerbations, Gas Exchange

LH importantly contributes to the degree of (exertional) dyspnea and exercise limitation,[38] impacting daily life activities.[69] DH also exists in mild COPD with no or only mild static hyperinflation.[70]

The presence of a higher RV/TLC ratio or IC/TLC ratio, as a marker of hyperinflation, is independently associated with frequent exacerbations, hospitalizations and all-cause mortality.[71–74] Zeng et al even showed that smoking subjects with a higher RV/TLC ratio but with preserved spirometry were more likely to have higher all-cause mortality.[75]

It has been shown that in patients with stable COPD, severe hypoxemia is independently associated with higher RV, RV/TLC, FRC and TLC.[76,77] Also, hypercapnic COPD patients have greater degrees of hyperinflation.[78] Hyperinflation places the diaphragm and other inspiratory muscles at severe mechanical disadvantage, producing alveolar hypoventilation and hypercapnia.[79] In the presence of DH, there is an increase in ventilation-perfusion mismatching, which in turn leads to hypoxemia.[80] Also, DH can lead to hypercapnia, due to increased fatigue of the inspiratory muscles, leading to rapid shallow breathing and diminished CO_2 removal.[21]

Cardiac Impairment and Cardiovascular Disease

The link between LH and cardiac dysfunction in COPD patients is increasingly recognized.[81] Lung hyperinflation and the corresponding increased intrathoracic pressure directly affect the cardiovascular system. This, along with larger swings in intrapleural pressure, can cause diminished venous return and increase left ventricle afterload by compressing the large

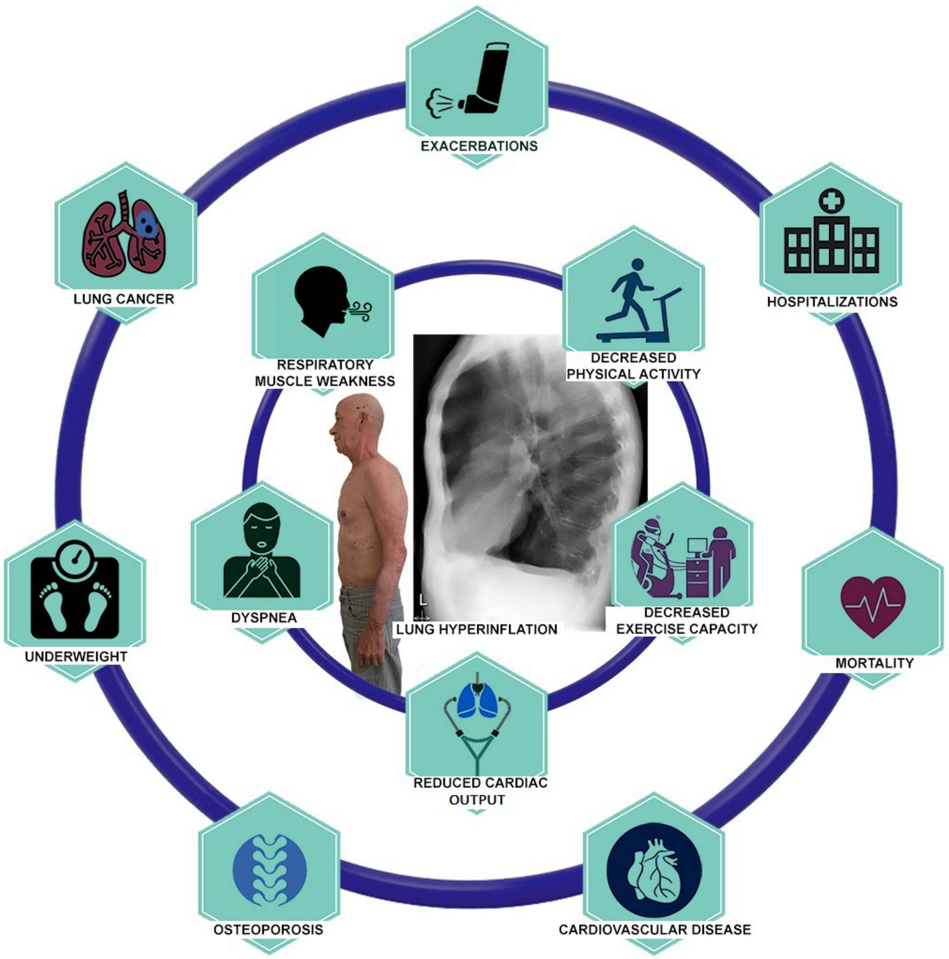

Figure 3 Clinical and radiologic presentation of lung hyperinflation.

and small pulmonary arterial vessels and the heart chambers.[82,83] Due to left ventricular failure and alveolar hypoxia, in association with high pulmonary capillary pressures, this effect increases the right ventricle afterload.[83] In patients with severe COPD and normal cardiac function at rest, the rise in EELV during tachypnea was associated with an increase in right atrial pressure, mean pulmonary artery pressure and wedge pressure.[84] Hyperinflated lungs in severe emphysematous patients have been shown to be associated with intrathoracic hypovolemia, decreased biventricular preload and reduced cardiac performance.[85] Next to systolic dysfunction, it has been established that airway obstruction and LH are associated with impaired left heart diastolic filling that can be detected by echocardiography.[86] Conversely, lung deflation by long-acting bronchodilators improves diastolic function and stroke volume in COPD. Reduction of hyperinflation using bronchoscopic lung volume reduction with endobronchial valves can improve cardiac preload and output.[87–89]

Recently, coronary artery disease was found to be strongly associated with lung hyperinflation in current and former smokers.[90]

Pulmonary hypertension can develop in COPD patients as a result of loss of alveolar capillary bed or as a consequence of chronic alveolar hypoxia with secondary vasoconstriction.[91] LH was associated with raised pulmonary artery pressure during exercise and larger pulmonary artery pressure at rest.[92,93] However, evidence regarding LH as the cause of pulmonary hypertension is lacking.

Muscle Dysfunction

Muscle dysfunction is a well-established systemic manifestation of COPD, affecting both respiratory and peripheral muscles in all COPD stages.[30,94] LH increases the work of breathing as it flattens and shortens the diaphragm, which

results in a non-optimal strength-length position of the diaphragm. It also shifts the tidal volume towards a less favorable part of the compliance curve. This higher work of breathing might lead to progressively higher nutrient and oxygen demands of respiratory muscles.[95]

A direct link between LH and peripheral muscle dysfunction has not been fully established. Peripheral muscle dysfunction is common in COPD, probably mainly driven by muscle deconditioning by disuse of the locomotor muscles.[94,96] Disuse results from exertional dyspnea, DH and redistribution of blood flow during exercise from locomotor muscles to respiratory muscles.[97] However, other intrinsic and systemic factors are also involved. This is indicated by the only partial reversal of functional and structural limb muscle changes with exercise training.[95] Therefore, hyperinflation might also be indirectly related to peripheral muscle dysfunction.[98]

Body Composition, Sarcopenia and Bone Density

Emphysema is often associated with low body mass index (BMI) and low fat-free mass index (FFMI).[99] COPD patients with advanced emphysema constitute a specific phenotype characterized by an enhanced loss of tissue mass over time in multiple organs.[100] This is likely to be in relation to abnormal tissue loss/repair capacity. Patients with severe emphysema not only showed lower BMI and FFMI at baseline but also accelerated loss of BMI and FFMI over time. Moreover, these patients had more exacerbations, hospitalizations, and higher mortality during three-year follow-up,[100] indicating that proper identification of patients with severe emphysema and excessive loss of tissue is clinically relevant. However, data describing BMI and FFMI in relation to LH are scarce. One study researched the impact of increasing BMI on static lung volumes and showed a reduction of RV, FRC and TLC with increasing BMI.[6]

Patients with severe emphysema and LH undergoing lung volume reduction surgery can show an increase in FFMI after six months, implying that the systemic effects of the disease on body composition can, at least partly, be reversed.[101] Weight gain and skeletal muscle remodeling following bronchoscopic lung volume reduction have also been observed and were associated with functional improvements.[102]

Osteopenia and osteoporosis are especially associated with the presence and severity of emphysema.[103] Studies evaluating the pathophysiologic mechanisms underlying this relationship are limited, although systemic inflammation[104,105] and abnormal tissue loss/repair capacity[100] are commonly suggested as underlying mechanisms for multi-organ tissue loss. Again, these were studies describing relationships between emphysema and bone density, but not LH. One small retrospective study showed improvements in bone mineral density after lung volume reduction surgery; however, these results have not been confirmed in a randomized trial.[106]

Lung Cancer

Several studies have reported an association between emphysema and lung cancer.[107,108] Recently, LH has been shown to be an independent risk factor for the development of lung cancer in COPD patients.[109] However, emphysema as a confounding factor was not ruled out.

Pharmacologic Treatment

Bronchodilators

Long-acting brochodilators (LABDs) are the cornerstone of pharmacological treatment of patients with COPD.[110] In general, they increase FEV_1, improve dyspnea and exercise performance and reduce exacerbation frequency. Bronchodilators improve airway conductance,[111] relax airway smooth muscle, improve small airway patency and enhance lung deflation, which is reflected by a reduction in static and dynamic LH.[112] Breathing at lower operating lung volumes decreases work of breathing while placing the respiratory muscles in a more efficient arrangement for pressure generation,[113] delaying time to respiratory muscle fatigue.[114] Bronchodilators seem to be even more effective in patients with relatively limited airway obstruction but marked hyperinflation compared to patients without hyperinflation,[115] and LH might serve as an objective marker for aggressive pharmacological intervention.[116] Clinical trials demonstrated that a combination of two long-acting LABDs is superior to a single bronchodilator[117,118] and to long-acting beta2-agonist (LABA) and inhaled corticosteroids (ICS) in improving spirometry measures of hyperinflation.[119]

Administration of bronchodilators in LH also reduces exacerbation frequency, probably by improving lung mechanics, reducing the work of breathing and degree of dyspnea and a potential reduction of mechanical stress in the lungs.[120] In addition, it was shown that LABDs improve diastolic function in COPD, in accordance with the finding that lung deflation can improve cardiac filling.[88] Moreover, lung deflation by tiotropium has been demonstrated to increase oxygen pulse as a non-invasive surrogate of stroke volume.[89] Thus, it can be speculated that LABDs antagonize the decreased left atrium size in COPD resulting from LH, improve early left ventricular filling and increase left heart preload and filling, and improve stroke volume.

Anti-Inflammatory Agents

Few studies investigated the add-on effects of ICS on bronchodilators with regard to LH in COPD. Significant improvements in inspiratory capacity, as a marker of LH, and exercise endurance time during ICS/LABA treatment were reported compared with LABA and with placebo.[121,122] Another study, however, did not confirm benefits with ICS over LABA monotherapy.[121,122] Thus, LH is not a specific indication for ICS therapy in current international guidelines. Roflumilast, an oral phosphodiesterase-4 (PDE4) inhibitor, is indicated to prevent exacerbations in COPD patients with severe airflow obstruction, chronic bronchitis, and frequent exacerbations. It was also shown to improve IC, but without effect on resting hyperinflation.[123]

Opioids

Opioids can be useful in patients with COPD and symptoms of severe dyspnea and impaired exercise capacity, to relieve breathlessness,[124] improve exercise endurance,[125] and health status,[126] and that these effects might occur without actually decreasing DH.[127]

Non-Pharmacologic Treatment

Management of Dyspnea

Pursed-Lips Breathing

Pursed-lips breathing (PLB) is a strategy frequently adopted spontaneously by patients with COPD to reduce dyspnea by prolonging expiration[128] and counterbalancing intrinsic positive end-expiratory pressure (PEEP). PLB is frequently taught during respiratory physical therapy and pulmonary rehabilitation programs to reduce dyspnea and improve exercise tolerance.[129] By breathing out through partly closed lips, expiratory airway pressure is increased, expiratory airway collapse is reduced and thus expiratory airflow rate is improved. A recent meta-analysis showed that PLB during exercise is effective in reducing minute ventilation and respiratory rate, however, it does not significantly improve walking distance or dyspnea.[130] Probably, lack of methodological quality and the restricted number of patients included in the trials contributed to this result.

Inspiratory Muscle Training

Inspiratory muscle training (IMT) is effective in increasing inspiratory muscle function and exercise performance in COPD when used as a stand-alone intervention,[131] and has been recommended in patients with inspiratory muscle weakness.[132] It is postulated that IMT decreases inspiratory time during loaded breathing tasks. This is likely the result of increased velocity of diaphragmatic contraction due to increase in the number of fast-twitch type 2 muscle fibers.[133] Consequently, expiratory time is prolonged, thereby decreasing DH and reducing dyspnea.[134] However, its additional benefit as an adjunct to whole body exercise training is questionable.[135]

Exercise Training

Exercise training decreases ventilatory requirements, resulting in lower respiratory rate at a given level of exercise. The longer available time for expiration results in less DH and therefore less dyspnea.[136] There is a lot of evidence regarding leg training decreasing breathing frequency during exercise and increasing IC.[21] Even in patients with (very) severe LH and accompanying low exercise capacity, pulmonary rehabilitation has been shown to be effective.[137]

Oxygen Therapy

Oxygen supplementation during exercise can improve exercise endurance by reducing the respiratory rate and thereby DH and dyspnea in normoxemic COPD patients,[138] and those with resting hypoxemia or exercise-induced desaturation.[139] However, a recently published randomized controlled trial investigating the effect of oxygen supplementation during an 8-week supervised exercise training program in normoxemic COPD patients with exercise induced desaturation, who also had LH, showed no greater improvements in exercise capacity with oxygen supplementation than with medical air.[140] The current evidence does not support the routine use of oxygen supplementation during exercise in COPD patients with DH, except in patients who already receive long-term oxygen therapy.[132]

Heliox (mixture of helium/oxygen 80:20) can improve exercise endurance, peak ventilation time and IC, reducing DH and dyspnea at isotime in COPD.[141] The mixture decreases turbulent airflow in large airways.[141] However, the results are variable and their application during exercise training remains to be established.[132]

Relieving Inspiratory Threshold Load

PLB can relieve inspiratory threshold load, as described above. Another method to accomplish this is applying external PEEP.

Intrinsic PEEP can account for about 1/3 of the total work of breathing in patients with dynamic airway collapse, and small amounts of external PEEP or continuous positive airway pressure (CPAP) can be beneficial during exercise.[142] It unloads inspiratory muscles from the inspiratory threshold load induced by intrinsic PEEP. The application of PEEP and inspiratory pressure support or proportional assisted ventilation can decrease the inspiratory workload in mechanically ventilated patients.[143,144] Inspiratory pressure support applied during exercise can improve endurance time and reduce dyspnea.[145] Proportional assisted ventilation unloads respiratory muscles, and thereby reduces dyspnea and prevents exercise-induced diaphragmatic fatigue.[146] Expiratory positive airway pressure (EPAP) aims to increase resistance in the expiratory phase, which is thought to reduce physiological dead space and increase tidal volume. However, a recent systematic review showed that the use of EPAP in COPD patients did not modify DH and reduced exercise time.[147] Bilevel positive airway pressure (BiPAP) decreases inspiratory workload and FRC through a modification of the breathing pattern.[148] BiPAP can reduce or delay DH during exercise[98] or during an acute exacerbation of COPD[149] and can reduce the load of overburdened inspiratory muscles and the work of breathing.[145] However, patients without hypercapnia currently do not have an indication for non-invasive ventilation (NIV) during exercise or during an acute exacerbation of COPD.[150]

Freitas et al showed a reduction in RV in 72 patients with hypercapnia after two years of treatment with long-term NIV.[151] However, a two-year RCT in 122 stable COPD patients with chronic hypercapnia showed no difference in lung function after introducing long-term NIV.[152] However, non-hypercapnic patients with hyperinflation currently do not have an indication for long-term NIV.[150,153]

Lung Volume Reduction

Static hyperinflation can also be reduced by improving elastic recoil. There are several therapies that aim to eliminate the most emphysematous or hyperinflated portions of the lung, allowing the remaining pulmonary parenchyma and the respiratory muscles to function more effectively. A classic invasive technique to eliminate emphysematous lung tissue is lung-volume-reduction surgery (LVRS). The NETT was a large clinical trial that confirmed that patients with COPD with upper-lobe emphysema and low exercise capacity had improved survival when treated with LVRS compared to standard medical treatment.[49] Also, LVRS can restore body weight and body composition, improve right ventricular function, stroke volume and bone mineral density.[106,154] However, patients with high post-pulmonary rehabilitation exercise capacity had no difference in survival after LVRS.[49] Moreover, LVRS results in higher mortality in patients with severe emphysema with an FEV_1 less than or equal to 20% predicted, and either homogeneous emphysema or diffusing capacity of the lung for carbon monoxide of less than or equal to 20% predicted.[155]

As a less-invasive and safe alternative for surgical lung volume reduction,[49] endobronchial valve placement can improve lung volumes, reduce FRC, improve exercise endurance and quality of life in a highly selected group of COPD patients with severe emphysema and severe LH.[156] Recently, it has been shown that reduction of LH by endobronchial

valve placement can improve cardiac preload and output.[87] Moreover, the therapy might prevent further loss or even increase muscle mass.[102] Long-term efficacy, such as impact on exacerbations, hospitalizations and survival remains to be established,[157] although preliminary data are promising in terms of exacerbation reduction and survival benefit.[158] Endobronchial coil placement is a different technique for patients without intact lobar fissures, inducing regional parenchymal volume reduction and restoring lung recoil with comparable effects.[159]

Currently, health insurance companies worldwide require mandatory pulmonary rehabilitation prior to LVRS and endobronchial valve placement, and clinical trials evaluating LVRS and endobronchial valves required pulmonary rehabilitation prior to randomization.[160] The NETT trial showed that pulmonary rehabilitation prior to LVRS resulted in improvements in exercise capacity and quality of life.[161] A post-hoc analysis of the VENT trial showed modest improvements in exercise capacity and dyspnea.[160] The SOLVE trial was designed to study the impact of optimal timing of pulmonary rehabilitation on exercise capacity and patient reported outcomes in patients found eligible for endobronchial valve placement. They found that the combination of pulmonary rehabilitation with endobronchial valve placement did not result in increased exercise capacity, improved patient-reported outcomes or increased daily step count compared to endobronchial valve placement alone.[162] However, their study also included participants who had undergone rehabilitation in the past. Subsequent rehabilitation has been demonstrated to be less impactful than the initial treatment.[161]

Both the use of biological sealant agents and thermal vapor ablation induce atelectasis due to airway occlusion and subsequent remodeling. The remodeling will cause contraction of lung parenchyma and loss of hyperinflated areas.[163,164] Thermal vapor ablation has been acknowledged as a possible lung volume reduction treatment; however, the availability for clinical practice is limited to a small number of centers.[165] Biological sealant agents have been found to lead to relatively high incidence of adverse events.[166,167]

How to Approach the COPD Patient with Hyperinflation

Although LH is common in patients with COPD and plays a central role in the burden and outcomes of the disease, its presence and severity cannot reliably be derived from the degree of airflow limitation (Figure 2) and thus requires specific assessment. As patients with mild or no airflow limitation can develop LH and/or DH, there is a rationale for assessment of LH in all patients with dyspnea during their daily life activities. Spirometrically assessed IC can indirectly indicate the presence of LH. Subsequently, body plethysmography is used to indicate the presence and severity of hyperinflation. When DH is suspected, with or without the presence of severe airflow limitation and/or LH, IC maneuvers during exercise testing can be used.

Bronchodilators can reduce static and dynamic LH, improve dyspnea, exercise performance and reduce exacerbation frequency. There is no specific indication for ICS therapy in current guidelines for LH, but additional therapy might improve exercise endurance.

PLB can be easily taught during physical therapy to reduce dyspnea and improve exercise tolerance. Exercise training in patients with LH decreases respiratory rate at a given level of exercise. Also, pulmonary rehabilitation has been shown to be effective in patients with very severe LH. Current evidence does not support the routine use of oxygen supplementation in normoxemic patients with DH. Moreover, patients without hypercapnia currently do not have an indication for NIV during exercise or long-term nocturnal NIV.

In patients with severe hyperinflation, assessment of regional distribution and heterogeneity of emphysema by (quantitative) CT can be performed in consideration of bronchoscopic or surgical lung volume reduction. This can improve exercise endurance, body weight and composition and cardiac function. Efficacy on exacerbations, hospitalizations and survival remains to be established, although preliminary data are promising in terms of exacerbation reduction and survival benefit.

Cardiac impairment and muscle dysfunction might be present in patients with LH and can contribute to dyspnea and exercise limitation. The presence of low BMI, osteopenia and osteoporosis can be considered, although the presence of these treatable traits is mainly reported in patients with emphysema. Lastly, it should be noted that LH has been shown to be a risk factor for the development of lung cancer.

Box 1 Unanswered Questions Regarding Hyperinflation in COPD

- What are the trajectories of hyperinflation in COPD?
- Do patients with hyperinflation benefit to the same extent from exercise training as patients without hyperinflation?
- What is the optimal exercise modality in patients with hyperinflation?
- Is hyperinflation variable throughout the day?
- Which patients do or do not benefit from LABDs, are there actually non-responders?
- How do patients with hyperinflation respond to a combination of interventions?
- Is treatment of hyperinflation useful and effective in patients with hyperinflation but without obstruction?
- What is the association between reduction of hyperinflation and improvements in patient-related outcomes in individual patients?
- Does reduction of hyperinflation lower cardiovascular risk?
- Does reduction of hyperinflation improve mortality in COPD patients?

The interplay of factors contributing to the clinical presentation of LH in an individual patient is complex and may alter over time. Thus, an integrated approach is warranted to provide personalized management. Although LH is recognized as a treatable trait of COPD, breaking down the disease into a list of traits for which specific treatments are available may deny its true complexity and multi-level relationships between disease characteristics. Also, underlying pathophysiologic mechanisms will remain unrevealed and clinical phenotypes might not be recognized. At the same time, it should be acknowledged that COPD phenotypes are not mutually exclusive, emphasizing the need for comprehensive assessment and personalized treatments in COPD. In Box 1, a few potentially interesting future research questions regarding LH in COPD are listed.

Conclusion

Lung hyperinflation represents a treatable feature of patients with COPD that requires specific lung function and/or radiological assessment. Effective pharmacological and non-pharmacological treatments are available for this trait but must be applied in the broader context of the health condition of the individual patient.

Acknowledgments

The person in Figure 3 provided written informed consent for publication of his image. This manuscript has not been submitted to another journal and has not been published in whole or in part elsewhere previously.

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