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The clinical relevance of the emphysema-hyperinflated phenotype in COPD

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Abstract

The classification of chronic pulmonary obstructive disease (COPD) into clinical and pathophysiological subsets is not new, but increasing data is available on the relation of these different phenotypes to clinically meaningful outcomes. This review focuses on the "emphysema-hyperinflation" (EH) phenotype, which is characterised by a prominent loss of lung elastic recoil and hyperinflation burden that translates into marked exercise intolerance and a heightened sense of dyspnoea.

Although no single genetic profile has been associated with the EH phenotype, recent data have shown that certain single nucleotide polymorphisms, such as DNAH5, appear to have an effect on the preferential development of hyperinflation in smokers. Static and dynamic hyperinflation are hallmarks of the EH phenotype, and abnormal increases in resting lung function indices such as total lung capacity (TLC), functional residual capacity (FRC) and inspiratory to TLC ratio (IC/TLC) seem more associated with the clinical EH phenotype than others markers of gas trapping.

An increased level of dyspnoea on exertion and exercise intolerance are also characteristic of the EH presentation and are likely related in part to critical mechanical constraints imposed on tidal volume expansion in situations where ventilatory demands are increased, but also possibly on cardiac and hemodynamic anomalies related to emphysema and hyperinflation. Importantly, the clinical relevance of the EH phenotype is underlined by the finding that indices of hyperinflation such as IC/TLC and residual volume (RV) can be used as independent predictors of mortality in patients with COPD.

Treatment of patients with the EH phenotype should primarily focus on smoking cessation and maximal bronchodilator therapy. New long-acting combined bronchodilators options provide clinicians with safe and effective ways to address the hyperinflation issue in this population. Pulmonary rehabilitation also has a positive impact on exercise tolerance, quality of life and hyperinflation, and should be routinely considered in patients with EH presentation that remain symptomatic despite optimal treatment, whereas as lung volume reduction techniques should be reserved for highly selected patients.

Keywords: Static hyperinflation, Dynamic hyperinflation, Phenotype, Dyspnoea, COPD, Emphysema

Introduction

The emergence of COPD phenotypes

Chronic obstructive pulmonary disease (COPD) is a significant public health concern that has worldwide repercussions as an important source of mortality and morbidity [1–3]. Although scientific progress regarding COPD may have been hindered by its perception as a self-inflicted and irreversible disease [4], the last decades have witnessed an increasing interest in research regarding the epidemiological and pathophysiological aspects of COPD, as well as the development of new therapeutic agents. Since the first Global Initiative for Obstructive Lung Disease (GOLD) statement was published in 2001, there has been growing understanding of the clinical relevance of the heterogeneous and complex nature of the disease. Although the last update of the GOLD statement still suggests a definition of COPD based on lung function indices, it also clearly

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acknowledges the importance of other disease components, such as dyspnoea, exacerbations and disability/health status [5]. This allows clinicians to modulate their assessment of the disease's severity beyond the classical FEV_1 criterion, which alone is known to be an imperfect reflection of disease burden [6] and prognosis [7, 8]. Chronic activity-related dyspnea, for example, is recognised as a better predictor of mortality [9] than FEV_1 alone.

The recognition that COPD is a multifaceted entity is far from novel [10–12], but it is only recently that its different clinical presentations were identified and integrated as relevant potential markers of symptomatology, response to treatment and prognosis: the so-called COPD phenotypes [13–18].

A group of expert defined these COPD phenotypes as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)" [19]. Many such phenotypes have been tentatively described: emphysema-hyperinflation, chronic bronchitis, and asthma-COPD overlap syndrome, the first two being further possibly associated with the frequent or infrequent exacerbator profile [13, 17, 20]. Of note, the term "phenotype" usually refers to the actual observable characteristics and properties of an organism, which stem from the interaction between its genetic background and its environment. Although considerable progress has been made regarding the genetic determinants of COPD since the sequencing of the human genome, there is still insufficient data to clearly delineate a unique causative genetic component for each of these proposed subgroups. It is therefore important to emphasize the clinical nature of these phenotypes.

This review will focus on the emphysema-hyperinflation (EH) phenotype. Although no clear and generalized definition of this phenotype has been described, we will, for the purpose of this review, define it as a subgroup of patients that present with predominant dyspnea, a significant emphysema burden (assessed using either computed tomography scanner or pulmonary function testing) and/or lung hyperinflation (assessed using pulmonary function testing), while not presenting characteristics associated with other recognized phenotypes such as chronic bronchitis or asthma-COPD overlap syndrome.

Review

Identification of the emphysema-hyperinflation phenotype

Genetic determinants

The observations that only a minority of smokers will develop COPD and that there are instances of familial clustering of COPD among relatives of patients with the disease support the fact that genetic factors play a role in the pathogenesis of COPD. A complete overview of the potential genetic determinants of COPD is beyond the scope of this text, but we briefly review some of the evidence regarding emphysema and hyperinflation.

Single nucleotide polymorphisms (SNPs) linked to the development of emphysema have been identified in several candidate genes in recent years, especially following the National Emphysema Treatment Trial (NETT) [21]. These SNPs usually involve genes related to xenobiotic metabolism, preservation of the extracellular matrix, host defense, control of inflammation and telomere regulation. Polymorphisms in glutathione S-transferase P1 (GSTP1) and microsomal epoxide hydrolase (EPHX1) are associated with apical emphysema and rapid lung function decline [22–25]. SNPs in EPHX1 are also related to exercise capacity, D_LCO and dyspnoea [26].

Recently, the first genome-wide association study of hyperinflation was performed in patients of the COPDGene [27], Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) [28] and GenKOLS [29] studies. A SNP in dynein, axonemal, heavy chain 5 (DNAH5) was associated with increased computed tomography (CT) derived total lung capacity (TLC). DNAH5 encodes a dynein found in the respiratory cilia and whose mutation can cause primary ciliary dyskinesia type 3 or Kartagener syndrome. In this study, no data relative to exercise tolerance, symptoms or other markers of hyperinflation were available [30].

Characteristics of the EH phenotype: Hyperinflation

Static hyperinflation Central to the concept of the EH phenotype is static hyperinflation, which refers to the reset of the resting relaxation volume of the respiratory system to an abnormally high volume, and mainly results from changes in the elastic proprieties of the lung and chest wall [31, 32]. It is important to recognise that the term "static" refers to the determination of lung volumes using the static pressure-volume relaxation curve of the respiratory system [33, 34] (see Fig. 1).

While the criteria used to diagnose airway obstruction (using FEV1/FVC ratio) and assess its severity (using FEV1) are uniformly recognized [5, 35], the presence and severity of gas trapping and static hyperinflation can be described using a plurality of indices, the most common being residual volume (RV), functional residual capacity (FRC), total lung capacity (TLC), RV/TLC ratio and FRC/TLC ratio. Although no precise cut-off value for these indices has been defined, it is generally accepted that lung hyperinflation is present when they exceed either the upper limit of normality (ULN, as defined as the upper 95 % confidence limit of a reference population) or an arbitrary 120 % of the predicted value. Thus, an elevated value of RV and/or RV/TLC implies pulmonary gas trapping, while an abnormally high FRC, TLC and/or FRC/

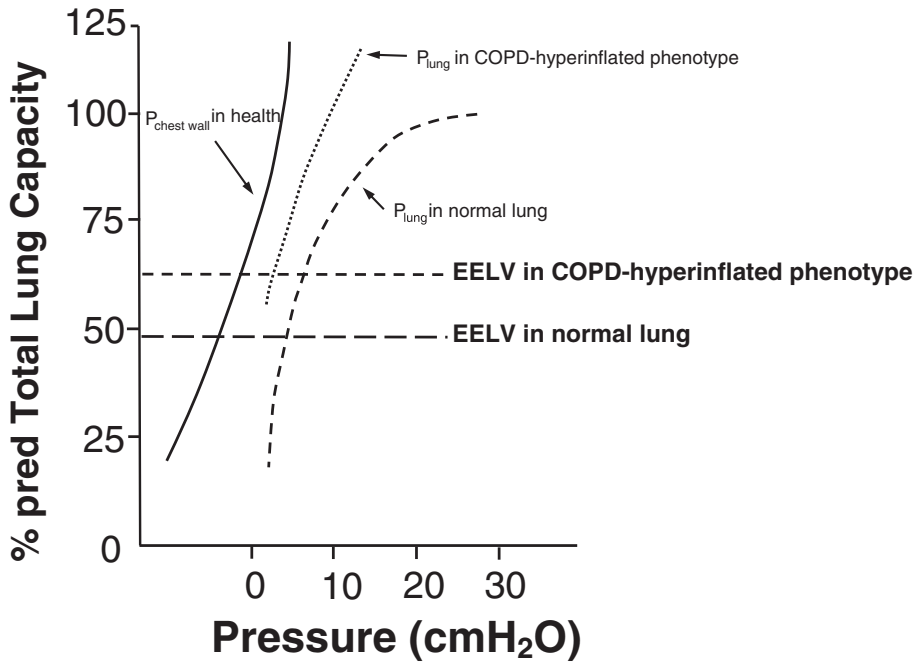

Fig. 1 Change in end-expiratory lung volume (EELV) with COPD. EELV is set at the point at which the elastic recoil pressures of the lung and chest wall are equal and opposite in direction. In COPD patients with hyperinflation, emphysema decreases lung elastic recoil pressure and causes a reset of functional residual capacity, or EELV, at a higher absolute lung volume. The difference between expected (long-dashed lines) and observed EELV (short-dashed lines) represent static hyperinflation

TLC ratio signify lung hyperinflation. Of note, while the use of resting inspiratory capacity (IC) or IC/TLC ratio to assess hyperinflation is frequent, it must be emphasized that in some patients with significant lung hyperinflation, end-expiratory lung volume (EELV) and TLC may increase in a parallel and proportional way, leading to a preserved IC. In the same manner, if hyperinflation is concomitant to other conditions influencing EELV (such as respiratory muscle weakness) or TLC (such as interstitial lung disease), IC becomes an unreliable marker of hyperinflation.

Recent data suggest that among these indices, a larger FRC, TLC and decreased IC/TLC are preferentially associated with percent emphysema on CT scan, greater dyspnoea and lower body mass index (BMI) – all characteristics of the EH phenotype [36].

The natural evolution of hyperinflation in patients with COPD is unclear, but data suggest that it can present even in patients with mild COPD, and increases exponentially as disease severity worsens [37]. On a related note, there is increasing evidence supporting the correlation of CT-derived emphysema assessment with physiological markers of hyperinflation (most commonly RV, RV/TLC and resting IC and FRC) [38–42].

Of interest is the observation that significant lung hyperinflation may alter the measurement of forced expiratory flows. During a forced expiratory manoeuvre, thoracic gas is compressed by the increase in intrathoracic pressures, causing a decrease in lung volume and elastic recoil that will in turn decrease driving airflow pressure and FEV1 [43]. Measurement of compression-free FEV1 using body plethysmography confirms that it is underestimated in patients with significant hyperinflation, to the extent of affecting the grading of disease severity [44]. This finding supports the increasingly prevalent notion that FEV_1 alone can be misleading or unreliable when trying to grade COPD severity.

Dynamic hyperinflation In contrast to static hyperinflation (which, as mentioned, refers to an increase of FRC above the 95th percentile of the predicted value when the elastic recoil pressure of the respiratory system is zero [33]), dynamic hyperinflation (DH) refers to an "increase of the FRC above the relaxation volume in situations where the duration of expiration is insufficient for deflating the lung to its relaxation volume prior to the next inspiratory effort and where, as a result, the elastic recoil pressure of the respiratory system becomes positive". [33, 45, 46]. As a result, operating lung volumes progressively shift closer to TLC, tidal volume expansion becomes limited by high intrathoracic pressures and work of breathing is increased [47] (see Fig. 2). The discrepancy between tidal volume expansion limitation and increasing neural respiratory drive (neuromechanical uncoupling) sharply

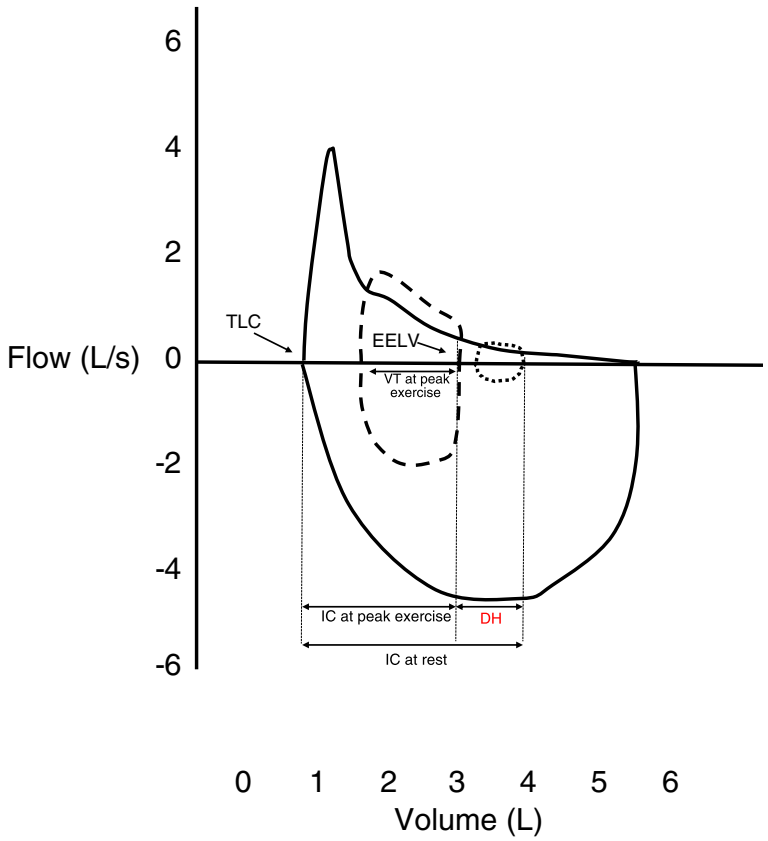

Fig. 2 Dynamic hyperinflation. This is a real-life example of a 51 years-old woman with severe COPD (FEV_1/FVC ratio 0.50, FEV_1 1.31 L, 47 % predicted) who performed inspiratory capacity maneuvers during incremental cardiopulmonary exercise testing of cycle ergometer. Forced expiratory flow is shown in full black line, and resting tidal volume in short-dashed line. At peak exercise, VT expansion is produced at the expense of inspiratory reserve volume (long-dashed line), EELV increases and inspiratory capacity decreases. The difference in EELV between resting and exercise represents dynamic hyperinflation (DH). TLC = total lung capacity. EELV = end-expiratory lung volume. FEV_1 = forced expiratory volume in 1 s. FVC = forced vital capacity. VT = tidal volume. IC = inspiratory capacity. DH = dynamic hyperinflation

increases shortness of breath [48–50], and a mechanical dyspnoea threshold is reached when inspiratory reserve volume (IRV) decreases to approximately 0.6-0.4 L [51]. Further increase in minute ventilation will preferentially be accomplished by increased respiratory rate, with consequently deceased expiratory time, which aggravates DH to a greater extent.

The presence of DH is correlated to resting hyperinflation [45, 52], disease severity [48], exercise tolerance, dyspnoea and mortality, [45, 48, 53, 54] and as such is a hallmark of the EH phenotype.

However, the direct role of DH as a limiting factor during exercise in COPD has been challenged by a study that found no difference in exercise capacity or dyspnoea rating during constant work-rate cycle exercise in hyperinflated COPD patients at rest presenting with and without DH [55]. In this study, although both groups of patients showed significant resting hyperinflation, patients who did not hyperinflate during exercise had a slightly higher FEV1/FVC ratio and less resting lung hyperinflation (FRC%pred and TLC%pred were less than the hyperinflators group), suggesting less airway dysfunction than the group who hyperinflated. Given that ventilatory demand and the volume and timing components of breathing during exercise were similar in both groups, we can assume that differences in IC behaviour during exercise primarily reflected unmeasured differences in mechanical time constants for lung emptying. Nonetheless, the attainment of a critical mechanical tidal volume/IRV constraint on exertion (which was similar in both groups) appeared to be a more pivotal contributor to exercise-induced dyspnoea than absolute DH.

Characteristics of the EH phenotype: Emphysema

Emphysema is pathologically defined as lung tissue destruction and dilatation beyond the terminal bronchioles [56]. The EH phenotype, when contrasted with chronic bronchitis, is characterised by a larger emphysema burden, and DLCO can be used to approximate pathological and radiological emphysema [41, 57–60].

FEV1 in itself is more poorly related to radiological emphysema in some [40, 61, 62], but not all [39, 41, 42, 63] studies. These findings suggest that CT scanning may play a role in the punctual or longitudinal assessment of the severity of COPD, especially when emphysema is the predominant pattern [64].

Clinical relevance of the emphysema-hyperinflation phenotype

Respiratory symptoms and exercise tolerance

Hyperinflation and emphysema are related to respiratory symptoms and quality of life [45, 62]. Compared with patients with COPD and normal lung volumes, those with resting hyperinflation have higher baseline dyspnoea [36, 65, 66] and significant intolerance to exercise [45]. Albuquerque et al. studied a cohort of patients with COPD and described how resting IC/TLC was the best predictor of a low peak oxygen uptake (VO2) during incremental cardiopulmonary testing, with a cut-off value of 0.28 having a sensitivity and specificity of 80.0 % and 89.6 % in identifying patients with a peakVO2 of less than 60 % predicted [67]. Similarly, Diaz et al. showed that, in a similar cohort, IC was strongly correlated to peakVO2 and that, in patients with resting expiratory flow limitation, it was the sole predictor of aerobic capacity [53]. O'Donnell et al. reported that, in 105 patients with COPD undergoing incremental exercise testing, peakVO2 correlated best with peak tidal volume reached, which itself was closely related to DH. Moreover, when compared with COPD patients with a preserved DLCO, patients with a reduced DLCO (and, presumably, a larger emphysema burden compatible with the EH phenotype) had lower peak VO2, larger resting hyperinflation and more frequently had dyspnoea as exercise stopping reason, despite no difference in FEV1 between the groups [45].

The almost universal exercise intolerance of patients with EH phenotype has repercussions in their everyday lives, and hyperinflation again emerges as an important predictive factor in this context. A study of 56 COPD evaluated the relation between lung function indices (including a measure of DH during an activity of daily living (ADL) task performed at the patient's home) and average daily physical activity. The authors found that both resting IC/TLC ratio and ADL-induced change in IC were the two main determinants of daily activity levels, with no significant contribution of FEV1 [68].

Garcia-Rio et al. similarly reported that, in patients with COPD, the presence of DH, the absolute change in IC during exercise and the 6-minute walking distance explained 89 % of the variance in mean daily physical activity [69], while FEV1 correlated with activity only in univariate analyses. Finally, in a study evaluating the magnitude of DH during self-paced ADL across COPD severity groups, Hannink et al. showed that DH occurs irrespective of disease severity, but that there was a trend for a lesser magnitude of change in EELV in the most severe patients. This could either be explained by the fact that GOLD IV patients have more resting hyperinflation and cannot generate as much "new" hyperinflation as the others, or by the fact that these patients seemed to have performed ADL with lesser metabolic cost (lower VO2 and minute-ventilation). Although the study was not specifically designed to assess this, IRV during ADL was correlated to FEV1 and decreased to 0.51 liters in GOLD IV patients, who also described a significantly higher level of dyspnoea [52]. This seems consistent with the notion that a critical mechanical constraint of IRV, rather than absolute DH, relates to exercise-induced dyspnoea.

Body mass index, muscle wasting and osteoporosis

Echoing Frank Netter's classic representation of the cachectic pink puffer patient, some studies have reported a relationship between the EH phenotype and a low BMI and/or peripheral muscle strength [36, 62, 65, 70, 71]. The pathophysiology behind the changes in body composition seen in some patients with COPD remains unclear, but evidence suggests it may be related to an increased secretion of inflammatory cytokines [72–77]. Resistive breathing, which mimics the increased work of breathing experienced by patients with hyperinflation, has been shown to directly induce a systemic inflammatory response [78].

In addition, serum and bronchoalveolar lavage levels of adiponectin are higher in patients with COPD than in healthy subjects [79], and adiponectin-deficient mice seem protected against the development of emphysema and inflammation in response to cigarette smoke [80]. In humans, CT-assessed emphysema and low BMI are closely related to serum adiponectin levels [81]. Although it is still unclear whether adiponectin has a causative role in the pathophysiology of emphysema or is secreted in reaction to increased systemic inflammation, this cytokine shows promise as a potential marker of COPD, and of the EH phenotype. Finally, there is increasing data supporting the association of COPD and osteoporosis. The causative mechanisms underlying this association are still being investigated, but are likely modulated by gender, clinical phenotype (with a significant relationship to the severity of emphysema) and genetic predisposition [82–85].

Cardiovascular disease

Both hyperinflation (by increasing intrathoracic pressures) and emphysema (by destroying distal pulmonary vessels) have negative consequences on cardiac and circulatory function by decreasing ventricular preload, size and

function. Barr et al. showed that, in a population-derived sample, CT emphysema and FEV1/FVC ratio were significantly correlated to left ventricular end-diastolic volume, stroke volume, cardiac output, but not to left ventricular ejection fraction [86]. Similarly, Jorgensen et al. compared patients with significant baseline hyperinflation (mean RV 272 % predicted and mean FRC 219 % predicted) to matched controls and found lower intrathoracic blood volume, left and right diastolic ventricular volume indexes, cardiac index and stroke volume index in patients with hyperinflation [87]. In this study, the correlation between intrathoracic blood volume and left ventricular end diastolic volume index highlights the role of decreased ventricular preload in the lower cardiac function in hyperinflated patients.

Vassaux et al. showed that severe resting hyperinflation (IC/TLC < 0.25) was associated with decreased exercise capacity and a lower peak oxygen pulse, and that IC/TLC was strongly correlated (r = 0.95) to peak oxygen pulse across disease severity, both in COPD patients and in controls [88]. Watz et al. similarly showed that static hyperinflation (evaluated using IC/TLC, FRC and RV) correlated better with the size of the cardiac chambers than the degree of airflow obstruction or DLCO [89]. Left ventricular diastolic dysfunction [90] and left atrial size [91] were also reported as being altered in patients with hyperinflation.

Whether the cardiopulmonary effects of hyperinflation are related to clinical outcome in patients with the EH phenotype in unclear, but there is evidence supporting the fact that the decrease in hyperinflation induced by bronchodilator therapy can improve right ventricular function [92]. In addition, as several large trials have reported trends for a decrease in mortality with the use of bronchodilators and lung volume reduction surgery (LVRS) in COPD, it is possible that part of this effect was related to a bronchodilator- or surgery-induced decrease in hyperinflation and consequent unloading of the cardiocirculatory system [13, 93–97]. In addition, the decrease in hyperinflation induced by bronchodilator therapy has been shown to improve right ventricular function

Prognosis

In a large multicenter cohort of patients with COPD ($n = 689$) followed for a mean of 34 months, an IC/TLC ratio < 0.25 was a significant and independent predictor of mortality, and globally performed better than FEV1 alone, although not better than the BODE index [98]. Although this study underscored the importance of the IC/TLC ratio as a prognostic marker in a general COPD population, the precise proportion of "EH" or other phenotypes in this COPD cohort was not reported.

In the medical treatment arm of the NETT study [21], high-risk patients (defined as FEV1 < 20 % predicted and either DLCO < 20 % predicted or homogenous emphysema of CT) had a higher mortality rate. In a multivariate mortality model, RV was among the independent predictors of mortality in this cohort, as were the presence of a low BMI, DLCO, and others. In this subgroup of patients with very severe disease, IC/TLC was only associated with mortality in univariate analyses [99].

Other characteristics of the EH phenotype have been shown to be independent predictors of mortality, such as CT-assessed emphysema [100], a higher dyspnoea level [9], low BMI [100–102] and exercise (in)tolerance [99, 103, 104].

Concerning disease evolution, emphysema [105] and CT-derived hyperinflation [106, 107] have been shown to be related to a faster FEV1 decline and to an increased exacerbation frequency in some [108], but not all studies [109].

Treatment

Smoking cessation remains the first and foremost therapeutic intervention in patients with COPD, and can significantly reduce disease progression [110–112].

As reviewed, hyperinflation is closely related to dyspnoea and exercise capacity, and as such is an attractive treatment target in patients with EH phenotype. In recent years, many pharmacological studies have included the evaluation of clinically relevant outcomes other than FEV_1 such as hyperinflation and/or exercise capacity. However, it is important to note that most pharmacological-related studies have been conducted in COPD patients with no specification of their underlying phenotype.

Bronchodilators, both short- and long-acting beta-agonists and anticholinergics, significantly decrease static and dynamic hyperinflation, improve IC during exercise (delaying the reaching of a critical IRV), improve dyspnoea and increase forced expiratory flows and exercise capacity. Some also have a positive effect on exacerbation rates, healthcare utilisation and, possibly, mortality [93, 94, 96, 113–118]. One study highlighted the fact that bronchodilators predominantly exert their effects on measures of resting hyperinflation, even when little or no change in FEV1 is observed [37]. In addition, a study investigating the predictors of improvement in exercise tolerance following treatment of short-acting bronchodilator (ipratropium bromide, three times a day for a 3-week period) found that an increased resting IC was the best predictor of change in endurance time following bronchodilation, and that the change in FEV1 was not [119].

Long-acting beta-agonists such as salmeterol and formoterol have been shown to decrease resting and dynamic hyperinflation and increase exercise performance [120–124], although this improvement did not always

reach clinical significance. Indacaterol, tiotropium, glycopyrronium bromide and aclidinium bromide also showed their ability to positively impact hyperinflation and improve exercise capacity [92, 125–133].

The use of a combination of long-acting bronchodilators is suggested in patients on mono-therapy who still experience significant symptoms [134], and could be routinely considered in patients with the EH phenotype. The addition of a second bronchodilator provides improvements in lung function, symptoms and exercise capacity compared with placebo or monotherapy, with little increase in side effects [115, 135, 136].

The advent of new fixed-dose once-daily dual bronchodilator options such as indacaterol-glycopyrronium, vilanterol-umeclidinium, olodaterol-tiotropium and (twice-daily) formoterol-aclidinium bromide provide clinicians and patients with effective and simpler options for maximisation of bronchodilation. These combinations are at least as effective as the simultaneous use of their individual components (possibly via a synergistic effect [137, 138]) and significantly improve lung function compared with monotherapy [139–145]. A positive effect on exercise tolerance has also been demonstrated for indacaterol-glycopyrronium and vilanterol-umeclidinium compared with placebo [146, 147], although the magnitude of this effect was less when compared to monotherapy with tiotropium.

Inhaled corticosteroids (ICS), on the other hand, have not consistently been associated with improvements in lung function and hyperinflation [148]. The combination of fluticasone and salmeterol was found to be superior to placebo in increasing exercise endurance time and decreasing hyperinflation, but was similar to salmeterol alone [149]. However, another study described the greater effect of combined budesonide-formoterol on exercise endurance time compared to formoterol alone. In addition, the addition of high-dose fluticasone to standard bronchodilator therapy resulted in a large clinically significant increase in endurance time and decrease in hyperinflation [150].

The NETT trial [21] showed that, in patients with severe emphysema, LVRS conferred a 5-years survival advantage (risk ratio for death 0.86, $p = 0.02$) compared with optimal medical therapy [151]. The LVRS group also showed a decrease in exacerbation frequency [152], improved exercise tolerance and quality of life through 3 and 4 years respectively. Patients with upper-lobe predominant emphysema and low exercise capacity were the ones in which LVRS was most beneficial, whereas those with very severe lung disease (FEV1 < 20 % predicted and either homogenous emphysema of DLCO < 20 % predicted) showed higher mortality rates in the perioperative period. Bronchoscopic lung volume reduction (BLVR) techniques such as endobronchial one-way valves and coils, instillation of biological agents and thermal vapour ablation are currently under investigation as promising non-surgical approaches to emphysema treatment [153].

Finally, comprehensive pulmonary rehabilitation (PR) remains a cornerstone of the management of patients with COPD [134, 154] and has a significant impact on dyspnoea, exercise tolerance, exacerbation rates, health-care utilization and hyperinflation [154–156]. Improvements in exercise capacity are enhanced when PR is coupled with bronchodilator therapy [157], emphasizing the importance of a multimodal approach to therapy.

Conclusion

The use of clinically relevant phenotypes in COPD allows for more coherent understanding of this heterogeneous disease. In this review, we highlighted the main characteristics of the EH phenotype in COPD: a heightened level of dyspnoea, marked exercise intolerance related to a critical constraint on lung volume expansion and hemodynamic consequences of hyperinflation, metabolic wasting and an adverse prognosis that is related to the degree of air trapping. As suggested by the Spanish GesEPOC guidelines, the management of patients with COPD can also be addressed in the light of the clinical phenotypes. In patients with EH, treatment should primarily focus on smoking cessation, the combination of maximal bronchodilation and pulmonary rehabilitation, while LVRS and BLVR techniques remain an option in highly selected patients.

Abbreviations

ADL: Activities of daily living; BLVR: Bronchoscopic lung volume reduction; BMI: Body mass index; BODE index: Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity index; COPD: Chronic obstructive lung disease; CT: Computed tomography; DH: Dynamic hyperinflation; D_LCO: Diffusion capacity of the lung for carbon monoxide; DNAH5: Dynein, axonemal, heavy chain 5; ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; EELV: End-expiratory lung volume; EH: Emphysema-hyperinflated phenotype; EPHX1: Microsomal epoxide hydrolase; FEV_1: Forced expiratory volume in 1 s; FRC: Functional residual capacity; FVC: Forced vital capacity; GOLD: Global initiative for Obstructive Lung Disease; GSTP1: Glutathione S-transferase P1; IC: Inspiratory capacity; ICS: Inhaled corticosteroids; IRV: Inspiratory reserve volume; LVRS: Lung volume reduction surgery; NETT: National Emphysema Treatment Trial; PR: Pulmonary rehabilitation; RV: Residual volume; SNP: Single nucleotide polymorphism; TLC: Total lung capacity; ULN: Upper limit of normality; VO_2: Oxygen uptake.

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

All authors participated to the drafting of the manuscript, drafting of the figures and have given final approval of the final form of the manuscript.

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References

1. Gershon AS, Warner L, Cascagnette P, Victor JC, To T. Lifetime risk of developing chronic obstructive pulmonary disease: a longitudinal population study. Lancet. 2011;378(9795):991–6.
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(9589):741–50.
3. Chronic obstructive pulmonary disease among adults–United States, 2011. Morb Mortal Wkly Rep (MMWR). 2012;61(46):938–43. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6146a2.htm
4. Barnes PJ, Kleinert S. COPD–a neglected disease. Lancet. 2004;364(9434):564–5.
5. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–65.
6. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010;11:122.
7. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. A 15-year follow-up study. Am Rev Respir Dis. 1979;119(6):895–902.
8. Celli BR, Cote CG, Marin JM, Casanova C, Oca MM, Mendez RA, et al. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2004;350:1005–12.
9. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest. 2002;121(5):1434–40.
10. Dornhorst AC. Respiratory insufficiency. Lancet. 1955;268(6876):1185–7.
11. Burrows B, Fletcher CM, Heard BE, Jones NL, Wootliff JS. The emphysematous and bronchial types of chronic airways obstruction. A clinicopathological study of patients in London and Chicago. Lancet. 1966;1(7442):830–5.
12. Snider GL. Chronic obstructive pulmonary disease: a definition and implications of structural determinants of airflow obstruction for epidemiology. Am Rev Respir Dis. 1989;140(3 Pt 2):S3–8.
13. Miravitlles M, Calle M, Soler-Cataluna JJ. Clinical phenotypes of COPD: identification, definition and implications for guidelines. Arch Bronconeumol. 2012;48(3):86–98.
14. Agusti A. The path to personalised medicine in COPD. Thorax. 2014;69(9):857–64.
15. Segreti A, Stirpe E, Rogliani P, Cazzola M. Defining phenotypes in COPD: an aid to personalized healthcare. Mol Diagn Ther. 2014;18(4):381–8.
16. Kim V, Criner GJ. The chronic bronchitis phenotype in chronic obstructive pulmonary disease: features and implications. Curr Opin Pulm Med. 2015;21(2):133–41.
17. Vestbo J. COPD: definition and phenotypes. Clin Chest Med. 2014;35(1):1–6.
18. Parr DG. Patient phenotyping and early disease detection in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2011;8(4):338–49.
19. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010;182(5):598–604.
20. Miravitlles M, Soler-Cataluna JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. A new approach to grading and treating COPD based on clinical phenotypes: summary of the Spanish COPD guidelines (GesEPOC). Prim Care Respir J. 2013;22(1):117–21.
21. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med. 2003;348(21):2059–73.
22. DeMeo DL, Hersh CP, Hoffman EA, Litonjua AA, Lazarus R, Sparrow D, et al. Genetic determinants of emphysema distribution in the national emphysema treatment trial. Am J Respir Crit Care Med. 2007;176(1):42–8.
23. He JQ, Ruan J, Connett JE, Anthonisen NR, Pare PD, Sandford AJ. Antioxidant gene polymorphisms and susceptibility to a rapid decline in lung function in smokers. Am J Respir Crit Care Med. 2002;166(3):323–8.
24. Ishii T, Matsuse T, Teramoto S, Matsui H, Miyao M, Hosoi T, et al. Glutathione S-transferase P1 (GSTP1) polymorphism in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(8):693–6.
25. Sandford AJ, Chagani T, Weir TD, Connett JE, Anthonisen NR, Pare PD. Susceptibility genes for rapid decline of lung function in the lung health study. Am J Respir Crit Care Med. 2001;163(2):469–73.
26. Hersh CP, Demeo DL, Lazarus R, Celedon JC, Raby BA, Benditt JO, et al. Genetic association analysis of functional impairment in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;173(9):977–84.
27. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, et al. Genetic epidemiology of COPD (COPDGene) study design. COPD. 2010;7(1):32–43.
28. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J. 2008;31(4):869–73.
29. Grydeland TB, Dirksen A, Coxson HO, Pillai SG, Sharma S, Eide GE, et al. Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking. Eur Respir J. 2009;34(4):858–65.
30. Lee JH, McDonald ML, Cho MH, Wan ES, Castaldi PJ, Hunninghake GM, et al. DNAH5 is associated with total lung capacity in chronic obstructive pulmonary disease. Respir Res. 2014;15:97.
31. O'Donnell DE, Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. Eur Respir Rev. 2006;15(100):61–7.
32. Aliverti A. Chest Wall Mechanics in COPD. Curr Respir Med Rev. 2008;4:240–9.
33. Rossi A, Aisanov Z, Avdeev S, Di Maria G, Donner CF, Izquierdo JL, et al. Mechanisms, assessment and therapeutic implications of lung hyperinflation in COPD. Respir Med. 2015;109(7):785–802.
34. Langer D, Ciavaglia CE, Neder JA, Webb KA, O'Donnell DE. Lung hyperinflation in chronic obstructive pulmonary disease: mechanisms, clinical implications and treatment. Expert Rev Respir Med. 2014;8(6):731–49.
35. Pellegrino R, Viegi G, Brusasco V, Crapo R, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–98.
36. Smith BM, Hoffman EA, Basner RC, Kawut SM, Kalhan R, Barr RG. Not all measures of hyperinflation are created equal: lung structure and clinical correlates of gas trapping and hyperexpansion in COPD: the Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study. Chest. 2014;145(6):1305–15.
37. Deesomchok A, Webb KA, Forkert L, Lam YM, Ofir D, Jensen D, et al. Lung hyperinflation and its reversibility in patients with airway obstruction of varying severity. COPD. 2010;7(6):428–37.
38. Sun XW, Gu SY, Li QY, Ren L, Shen JM, Wan HY, et al. Pulmonary Function Parameters in High-resolution Computed Tomography Phenotypes of Chronic Obstructive Pulmonary Disease. Am J Med Sci. 2015;349(3):228–33.
39. Gould GA, Redpath AT, Ryan M, Warren PM, Best JJ, Flenley DC, et al. Lung CT density correlates with measurements of airflow limitation and the diffusing capacity. Eur Respir J. 1991;4(2):141–6.
40. Marsh S, Aldington S, Williams MV, Nowitz M, Kingzett-Taylor A, Weatherall M, et al. Physiological associations of computerized tomography lung density: a factor analysis. Int J Chron Obstruct Pulmon Dis. 2006;1(2):181–7.
41. Kitaguchi Y, Fujimoto K, Kubo K, Honda T. Characteristics of COPD phenotypes classified according to the findings of HRCT. Respir Med. 2006;100(10):1742–52.
42. Boschetto P, Miniati M, Miotto D, Braccioni F, De Rosa E, Bononi I, et al. Predominant emphysema phenotype in chronic obstructive pulmonary. Eur Respir J. 2003;21(3):450–4.
43. Krowka MJ, Enright PL, Rodarte JR, Hyatt RE. Effect of effort on measurement of forced expiratory volume in one second. Am Rev Respir Dis. 1987;136(4):829–33.
44. Pellegrino R, Crimi E, Gobbi A, Torchio R, Antonelli A, Gulotta C, et al. Severity grading of chronic obstructive pulmonary disease: the confounding effect of phenotype and thoracic gas compression. J Applied Physiol (Bethesda, Md : 1985). 2015;118(7):796–802.
45. O'Donnell D, Revill S, Webb K. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164:770–7.
46. O'Donnell DE, Parker CM. COPD exacerbations, 3: Pathophysiology. Thorax. 2006;61:354–61.

47. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006;3(2):180–4.
48. 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(3):753–62.
49. Hudson AL, Laveneziana P. Do we "drive" dyspnoea? Eur Respir J. 2015;45(2):301–4.
50. Laviolette L, Laveneziana P, Faculty ERSRS. Dyspnoea: a multidimensional and multidisciplinary approach. Eur Respir J. 2014;43(6):1750–62.
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(12):1367–73.
52. Hannink JD, van Helvoort HA, Dekhuijzen PN, Heijdra YF. Dynamic hyperinflation during daily activities: does COPD global initiative for chronic obstructive lung disease stage matter? Chest. 2010;137(5):1116–21.
53. Diaz O, Villafranca C, Ghezzo H, Borzone G, Leiva A, Milic-Emil J, et al. Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. Eur Respir J. 2000;16(2):269–75.
54. 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(9):1452–9.
55. Guenette JA, Webb KA, O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? Eur Respir J. 2012;40(2):322–9.
56. Snider G, Kleinerman J, Thurlbeck W, Bengally Z. The definition of emphysema. Report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases workshop. Am Rev Respir Dis. 1985;132(1):182–5.
57. Lee JS, Ra SW, Chae EJ, Seo JB, Lim SY, Kim TH, et al. Validation of the lower limit of normal diffusing capacity for detecting emphysema. Respiration. 2011;81(4):287–93.
58. West WW, Nagai A, Hodgkin JE, Thurlbeck WM. The National Institutes of Health Intermittent Positive Pressure Breathing trial–pathology studies. III. The diagnosis of emphysema. Am Rev Respir Dis. 1987;135(1):123–9.
59. Morrison NJ, Abboud RT, Ramadan F, Miller RR, Gibson NN, Evans KG, et al. Comparison of single breath carbon monoxide diffusing capacity and pressure-volume curves in detecting emphysema. Am Rev Respir Dis. 1989;139(5):1179–87.
60. Berend N, Woolcock AJ, Marlin GE. Correlation between the function and structure of the lung in smokers. Am Rev Respir Dis. 1979;119(5):695–705.
61. Gelb AF, Schein M, Kuei J, Tashkin DP, Muller NL, Hogg JC, et al. Limited contribution of emphysema in advanced chronic obstructive pulmonary disease. Am Rev Respir Dis. 1993;147(5):1157–61.
62. Makita H, Nasuhara Y, Nagai K, Ito Y, Hasegawa M, Betsuyaku T, et al. Characterisation of phenotypes based on severity of emphysema in chronic obstructive pulmonary disease. Thorax. 2007;62(11):932–7.
63. Fan L, Xia Y, Guan Y, Zhang TF, Liu SY. Characteristic features of pulmonary function test, CT volume analysis and MR perfusion imaging in COPD patients with different HRCT phenotypes. Clin Respir J. 2014;8(1):45–54.
64. Soejima K, Yamaguchi K, Kohda E, Takeshita K, Ito Y, Mastubara H, et al. Longitudinal follow-up study of smoking-induced lung density changes by high-resolution computed tomography. Am J Respir Crit Care Med. 2000; 161(4 Pt 1):1264–73.
65. Izquierdo-Alonso JL, Rodriguez-Gonzalezmoro JM, de Lucas-Ramos P, Unzueta I, Ribera X, Anton E, et al. Prevalence and characteristics of three clinical phenotypes of chronic obstructive pulmonary disease (COPD). Respir Med. 2013;107(5):724–31.
66. Gouzi F, Abdellaoui A, Molinari N, Pinot E, Ayoub B, Laoudj-Chenivesse D, et al. Fiber atrophy, oxidative stress, and oxidative fiber reduction are the attributes of different phenotypes in chronic obstructive pulmonary disease patients. J Appl Phycol (Bethesda, Md: 1985). 2013;115(12):1796–805.
67. Albuquerque AL, Nery LE, Villaca DS, Machado TY, Oliveira CC, Paes AT, et al. Inspiratory fraction and exercise impairment in COPD patients GOLD stages II-III. Eur Respir J. 2006;28(5):939–44.
68. Lahaije AJ, van Helvoort HA, Dekhuijzen PN, Vercoulen JH, Heijdra YF. Resting and ADL-induced dynamic hyperinflation explain physical inactivity in COPD better than FEV1. Respir Med. 2013;107(6):834–40.
69. Garcia-Rio F, Lores V, Mediano O, Rojo B, Hernanz A, Lopez-Collazo E, et al. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. Am J Respir Crit Care Med. 2009;180(6):506–12.
70. Marquez-Martin E, Ramos PC, Lopez-Campos JL, Serrano Gotarredona Mdel P, Herrero SN, Aguilar RT, et al. Components of physical capacity in patients with chronic obstructive pulmonary disease: relationship with phenotypic expression. Int J Chron Obstruct Pulmon Dis. 2011;6:105–12.
71. Mair G, Maclay J, Miller JJ, McAllister D, Connell M, Murchison JT, et al. Airway dimensions in COPD: relationships with clinical variables. Respir Med. 2010;104(11):1683–90.
72. Gea J, Agustí A, Roca J. Pathophysiology of muscle dysfunction in COPD. J Appl Physiol. 2013;114:1222–34.
73. Yende S, Waterer GW, Tolley EA, Newman AB, Bauer DC, Taaffe DR, et al. Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. Thorax. 2006;61(1):10–6.
74. Debigare R, Cote CH, Maltais F. Peripheral muscle wasting in chronic obstructive pulmonary disease. Clinical relevance and mechanisms. Am J Respir Crit Care Med. 2001;164(9):1712–7.
75. Eid AA, Ionescu AA, Nixon LS, Lewis-Jenkins V, Matthews SB, Griffiths TL, et al. Inflammatory response and body composition in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(8 Pt 1):1414–8.
76. Huertas A, Testa U, Riccioni R, Petrucci E, Riti V, Savi D, et al. Bone marrow-derived progenitors are greatly reduced in patients with severe COPD and low-BMI. Respir Physiol Neurobiol. 2010;170(1):23–31.
77. Huertas A, Palange P. Circulating endothelial progenitor cells and chronic pulmonary diseases. Eur Respir J. 2011;37(2):426–31.
78. Vassilakopoulos T, Roussos C, Zakynthinos S. The immune response to resistive breathing. Eur Respir J. 2004;24(6):1033–43.
79. Miller M, Cho JY, Pham A, Ramsdell J, Broide DH. Adiponectin and functional adiponectin receptor 1 are expressed by airway epithelial cells in chronic obstructive pulmonary disease. J Immunol. 2009;182(1): 684–91.
80. Miller M, Pham A, Cho JY, Rosenthal P, Broide DH. Adiponectin-deficient mice are protected against tobacco-induced inflammation and increased emphysema. Am J Physiol Lung Cell Mol Physiol. 2010;299(6): L834–42.
81. Carolan BJ, Kim YI, Williams AA, Kechris K, Lutz S, Reisdorph N, et al. The association of adiponectin with computed tomography phenotypes in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;188(5):561–6.
82. Bai P, Sun Y, Jin J, Hou J, Li R, Zhang Q, et al. Disturbance of the OPG/RANK/RANKL pathway and systemic inflammation in COPD patients with emphysema and osteoporosis. Respir Res. 2011;12:157.
83. Bon J, Kahloon R, Zhang Y, Xue J, Fuhrman CR, Tan J, et al. Autoreactivity to glucose regulated protein 78 links emphysema and osteoporosis in smokers. PLoS ONE. 2014;9(9):e105066.
84. Chubachi S, Nakamura H, Sasaki M, Haraguchi M, Miyazaki M, Takahashi S, et al. Polymorphism of LRP5 gene and emphysema severity are associated with osteoporosis in Japanese patients with or at risk for COPD. Respirology. 2015;20(2):286–95.
85. Ohara T, Hirai T, Muro S, Haruna A, Terada K, Kinose D, et al. Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD. Chest. 2008;134(6):1244–9.
86. Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med. 2010;362(3):217–27.
87. Jorgensen K, Muller MF, Nel J, Upton RN, Houltz E, Ricksten SE. Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema: an MRI study. Chest. 2007;131(4):1050–7.
88. Vassaux C, Torre-Bouscoulet L, Zeineldine S, Cortopassi F, Paz-Diaz H, Celli BR, et al. Effects of hyperinflation on the oxygen pulse as a marker of cardiac performance in COPD. Eur Respir J. 2008;32(5):1275–82.
89. Watz H, Waschki B, Meyer T, Kretschmar G, Kirsten A, Claussen M, et al. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest. 2010;138(1):32–8.
90. Malerba M, Ragnoli B, Salameh M, Sennino G, Sorlini ML, Radaeli A, et al. Sub-clinical left ventricular diastolic dysfunction in early stage of chronic obstructive pulmonary disease. J Biol Regul Homeost Agents. 2011;25(3):443–51.
91. Cassagnes L, Pontana F, Molinari F, Faivre JB, Santangelo T, Algeri E, et al. Left atrial volume in chronic obstructive pulmonary disease. J Thorac Imaging. 2014;29(4):233–9.
92. Santus P, Radovanovic D, Di Marco S, Valenti V, Raccanelli R, Blasi F, et al. Effect of indacaterol on lung deflation improves cardiac performance in hyperinflated COPD patients: an interventional, randomized, double-blind clinical trial. Int J Chron Obstruct Pulmon Dis. 2015;10:1917–23.
93. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359(15):1543–54.

94. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775–89.
95. Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP, et al. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180(10):948–55.
96. Johnson M, Agusti AG, Barnes NC. Reflections on TORCH: potential mechanisms for the survival benefit of salmeterol/fluticasone propionate in COPD patients. COPD. 2008;5(6):369–75.
97. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19–26.
98. 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(6):591–7.
99. Martinez FJ, Foster G, Curtis JL, Criner G, Weinmann G, Fishman A, et al. Predictors of mortality in patients with emphysema and severe airflow obstruction. Am J Respir Crit Care Med. 2006;173(12):1326–34.
100. Haruna A, Muro S, Nakano Y, Ohara T, Hoshino Y, Ogawa E, et al. CT scan findings of emphysema predict mortality in COPD. Chest. 2010;138(3):635–40.
101. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157(6 Pt 1):1791–7.
102. Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;160(6):1856–61.
103. Waschki B, Kirsten A, Holz O, Muller KC, Meyer T, Watz H, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. Chest. 2011;140(2):331–42.
104. Ringbaek TJ, Lange P. Outdoor activity and performance status as predictors of survival in hypoxaemic chronic obstructive pulmonary disease (COPD). Clin Rehabil. 2005;19(3):331–8.
105. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al. Changes in forced expiratory volume in 1 s over time in COPD. N Engl J Med. 2011;365(13):1184–92.
106. Yuan R, Hogg JC, Pare PD, Sin DD, Wong JC, Nakano Y, et al. Prediction of the rate of decline in FEV(1) in smokers using quantitative Computed Tomography. Thorax. 2009;64(11):944–9.
107. Mohamed Hoesein FA, van Rikxoort E, van Ginneken B, de Jong PA, Prokop M, Lammers JW, et al. Computed tomography-quantified emphysema distribution is associated with lung function decline. Eur Respir J. 2012;40(4):844–50.
108. 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(5):411–4.
109. Han MK, Bartholmai B, Liu LX, Murray S, Curtis JL, Sciurba FC, et al. Clinical significance of radiologic characterizations in COPD. COPD. 2009;6(6):459–67.
110. Mohamed Hoesein FA, Zanen P, de Jong PA, van Ginneken B, Boezen HM, Groen HJ, et al. Rate of progression of CT-quantified emphysema in male current and ex-smokers: a follow-up study. Respir Res. 2013;14:55.
111. Coxson HO, Dirksen A, Edwards LD, Yates JC, Agusti A, Bakke P, et al. The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study. Lancet Respir Med. 2013;1(2):129–36.
112. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med. 2002; 166(5):675–9.
113. Friedman M, Serby CW, Menjoge SS, Wilson JD, Hilleman DE, Witek Jr TJ. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest. 1999;115(3):635–41.
114. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B, et al. Long-term safety and efficacy of indacaterol, a long-acting beta(2)-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest. 2011;140(1):68–75.
115. van Noord JA, Aumann JL, Janssens E, Smeets JJ, Verhaert J, Disse B, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J. 2005;26(2):214–22.
116. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper Jr JA, Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med. 2005;143(5):317–26.
117. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MP, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364(12):1093–103.
118. Bateman ED, Chapman KR, Singh D, D'Urzo AD, Molins E, Leselbaum A, et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). Respir Res. 2015;16:92.
119. 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(2):542–9.
120. Liesker JJ, Van De Velde V, Meysman M, Vincken W, Wollmer P, Hansson L, et al. Effects of formoterol (Oxis Turbuhaler) and ipratropium on exercise capacity in patients with COPD. Respir Med. 2002;96(8):559–66.
121. 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(1):86–94.
122. 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(6):471–6.
123. Akkoca Yildiz O, Onen ZP, Demir G, Eris Gulbay B, Saryal S, Karabiyikoglu G. Is there any difference between effects of ipratropium bromide and formoterol on exercise capacity in moderate COPD patients? Tuberkuloz ve toraks. 2006;54(2):105–13.
124. 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(10):2056–64.
125. 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(5):340–5.
126. 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(7):1030–6.
127. 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(6):832–40.
128. 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(3):1168–78.
129. Travers J, Laveneziana P, Webb KA, Kesten S, O'Donnell DE. Effect of tiotropium bromide on the cardiovascular response to exercise in COPD. Respir Med. 2007;101(9):2017–24.
130. 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.
131. 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(4):580–7.
132. Watz H, Krippner F, Kirsten A, Magnussen H, Vogelmeier C. Indacaterol improves lung hyperinflation and physical activity in patients with moderate chronic obstructive pulmonary disease–a randomized, multicenter, double-blind, placebo-controlled study. BMC Pulm Med. 2014;14:158.
133. Santus P, Radovanovic D, Henchi S, Di Marco F, Centanni S, D'Angelo E, et al. Assessment of acute bronchodilator effects from specific airway resistance changes in stable COPD patients. Respir Physiol Neurobiol. 2014; 197:36–45.
134. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–65.
135. 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(9):1288–96.
136. Wedzicha JA, Dahl R, Buhl R, Schubert-Tennigkeit A, Chen H, D'Andrea P, et al. Pooled safety analysis of the fixed-dose combination of indacaterol and glycopyrronium (QVA149), its monocomponents, and tiotropium versus placebo in COPD patients. Respir Med. 2014;108(10): 1498–507.
137. Cazzola M, Calzetta L, Ora J, Puxeddu E, Rogliani P, Matera MG. Searching for the synergistic effect between aclidinium and formoterol: From bench to bedside. Respir Med. 2015;109(10):1305–11.

138. Calzetta L, Matera MG, Cazzola M. Pharmacological interaction between LABAs and LAMAs in the airways: optimizing synergy. Eur J Pharmacol. 2015;761:168–73.
139. Mahler DA, Decramer M, D'Urzo A, Worth H, White T, Alagappan VK, et al. Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. Eur Respir J. 2014;43(6):1599–609.
140. Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J. 2013;42(6):1484–94.
141. Decramer M, Anzueto A, Kerwin E, Kaelin T, Richard N, Crater G, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. Lancet Respir Med. 2014;2(6):472–86.
142. Maleki-Yazdi MR, Kaelin T, Richard N, Zvarich M, Church A. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. Respir Med. 2014;108(12):1752–60.
143. Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2–4). Eur Respir J. 2015.
144. Singh D, Jones PW, Bateman ED, Korn S, Serra C, Molins E, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. BMC Pulm Med. 2014; 14:178.
145. D'Urzo AD, Rennard SI, Kerwin EM, Mergel V, Leselbaum AR, Caracta CF, et al. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. Respir Res. 2014;15(1):123.
146. Maltais F, Singh S, Donald AC, Crater G, Church A, Goh AH, et al. Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: two randomized, double-blind clinical trials. Ther Adv Respir Dis. 2014;8(6):169–81.
147. 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(4):584–92.
148. Lee JH, Lee YK, Kim EK, Kim TH, Huh JW, Kim WJ, et al. Responses to inhaled long-acting beta-agonist and corticosteroid according to COPD subtype. Respir Med. 2010;104(4):542–9.
149. 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(3):647–56.
150. Guenette JA, Raghavan N, Harris-McAllister V, Preston ME, Webb KA, O'Donnell DE. Effect of adjunct fluticasone propionate on airway physiology during rest and exercise in COPD. Respir Med. 2011;105(12):1836–45.
151. Naunheim KS, Wood DE, Mohsenifar Z, Sternberg AL, Criner GJ, DeCamp MM, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg. 2006;82(2):431–43.
152. Washko GR, Fan VS, Ramsey SD, Mohsenifar Z, Martinez F, Make BJ, et al. The effect of lung volume reduction surgery on chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med. 2008;177(2):164–9.
153. Meena M, Dixit R, Singh M, Samaria JK, Kumar S. Surgical and bronchoscopic lung volume reduction in chronic obstructive pulmonary disease. Pulm Med. 2014;2014:757016.
154. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An Official American Thoracic Society/EuropeanRespiratory Society Statement: Key Concepts and Advances in Pulmonary Rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13–64.
155. Yoshimi K, Ueki J, Seyama K, Takizawa M, Yamaguchi S, Kitahara E, et al. Pulmonary rehabilitation program including respiratory conditioning for chronic obstructive pulmonary disease (COPD): Improved hyperinflation and expiratory flow during tidal breathing. J Thorac Dis. 2012;4(3):259–64.
156. Van Helvoort HAC, Willems LM, Dekhuijzen PNR, Heijdra YF. Pulmonary rehabilitation decreases dynamic hyperinflation during activities of daily life in patients with COPD. Eur Respir J. 2014;44 Suppl 58:622.
157. Casaburi R, Kukafka D, Cooper CB, Witek Jr TJ, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest. 2005;127(3):809–17.