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Review Article

Phenotypic Heterogeneity of Chronic Obstructive Pulmonary Disease

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ABSTRACT

A functional definition of chronic obstructive pulmonary disease (COPD) based on airflow limitation has largely dominated the field. However, a view has emerged that COPD involves a complex array of cellular, organic, functional, and clinical events, with a growing interest in disentangling the phenotypic heterogeneity of COPD. The present review is based on the opinion of the authors, who have extensive research experience in several aspects of COPD. The starting assumption of the review is that current knowledge on the pathophysiology and clinical features of COPD allows us to classify phenotypic information in terms of the following dimensions: respiratory symptoms and health status, acute exacerbations, lung function, structural changes, local and systemic inflammation, and systemic effects. Twenty-six phenotypic traits were identified and assigned to one of the 6 dimensions. For each dimension, a summary is provided of the best evidence on the relationships among phenotypic traits, in particular among those corresponding to different dimensions, and on the relationship between these traits and relevant events in the natural history of COPD. The information has been organized graphically into a phenotypic matrix where each cell representing a pair of phenotypic traits is linked to relevant references. The information provided has the potential to increase our understanding of the heterogeneity of COPD phenotypes and help us plan future studies on aspects that are as yet unexplored.

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La heterogeneidad fenotípica de la EPOC

Palabras clave:
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RESUMEN

La definición funcional de la enfermedad pulmonar obstructiva crónica (EPOC), basada en la limitación al flujo aéreo, ha predominado durante largo tiempo en el ámbito de la neumología. Sin embargo, ha surgido una nueva perspectiva que establece que en la EPOC tiene lugar una compleja variedad de manifestaciones celulares, orgánicas, funcionales y clínicas, y se ha incrementado el interés por desentrañar la heterogeneidad fenotípica de dicha enfermedad. La presente revisión se basa en la opinión de unos autores que tienen una amplia experiencia en la investigación de los diversos aspectos de la EPOC. La revisión parte de la base de que el conocimiento actual sobre la fisiopatología y el cuadro clínico de la EPOC permite clasificar la información fenotípica en función de las siguientes dimensiones: síntomas respiratorios y estado de salud, exacerbaciones agudas, función pulmonar, cambios estructurales, inflamación local y sistémica, y efectos sistémicos. Se han identificado 26 rasgos fenotípicos que se han asignado a alguna de las 6 dimensiones. Para cada dimensión se proporciona un resumen de la mejor evidencia sobre la relación existente entre los rasgos fenotípicos —en concreto, entre aquellos que corresponden a diferentes dimensiones— y sobre la relación entre dichos rasgos y las manifestaciones relevantes en la evolución natural de la EPOC. Toda la información se ha organizado gráficamente en una matriz fenotípica donde cada celda que representa un par de rasgos fenotípicos está vinculada a referencias bibliográficas relevantes. La información podría ayudar a comprender mejor la heterogeneidad de los fenotipos de la EPOC y a planificar estudios futuros sobre aspectos que todavía no se han investigado..

A Historical View of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and mortality. Most COPD is attributable to smoking, whose elimination would be sufficient to drastically reduce occurrence. COPD has been predicted to become the fifth leading cause of disability and mortality worldwide by the year 2020,[1] yet, surprisingly, research on this disease has received little attention until recently. The need for a better understanding of the defining phenotypic characteristics of COPD has been targeted as a research priority by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[2,3]

COPD is a relatively recent term resulting from the convergence of 2 historical perspectives. One, predominant in the United Kingdom, saw chronic bronchitis as a progressive disease leading to chronic, irreversible airflow limitation. Another, more prevalent in the United States, considered chronic bronchitis a benign condition, but pointed to emphysema as the underlying disorder leading to persistent irreversible airway obstruction. A third school of thought, the Dutch hypothesis, emerged in the 1960s to posit that asthma and COPD could be 2 extremes of the same developing condition. More recently, COPD has been defined as a usually progressive, although not fully irreversible airflow limitation that brings about changes in the central airways, peripheral bronchi and bronchioles, and lung parenchyma.[4,5]

During the last few decades, the diagnosis of COPD both in clinical practice and in research has been based on the presence of a reduction in expiratory flow as measured through the forced expiratory volume in 1 second (FEV_1) and its ratio to forced vital capacity (FVC). However, despite wide agreement on this functional definition of COPD, which has dominated the field, certain phenotypes have traditionally been considered different COPD entities for various reasons. Dornhorst[6] described 2 extreme clinical phenotypes of respiratory insufficiency: *a)* acyanotic dyspneic emphysema (of the so-called pink puffer) with muscle wasting and *b)* cyanotic congestive chronic bronchitis (of the so-called blue bloater) with right congestive heart failure. Airway changes and loss of alveolar walls could be present in both.[7] Today, such extreme phenotypes are rare,[7] probably thanks to advances in treatment.[2] Burrows et al[8] made a further proposal to distinguish between different phenotypes within COPD based on prognosis. Two forms of chronic airflow limitation were defined: one is emphysema (in nonatopic smokers with no history of asthma), in which mortality is higher and lung function poorer, and the other is asthmatic bronchitis (in atopic subjects or nonsmokers with known asthma). The overlap between asthma and COPD has never been resolved and has recently gained prominence because of studies which show that chronic persistent asthma may be associated with airflow limitation that is only partially reversible despite high doses of corticosteroids.[9] In addition, asthmatics lose lung function much faster than healthy individuals,[10] and those asthmatics who smoke and are nonatopic are at higher risk of loss.[11] Although asthma can usually be distinguished from COPD and there are differences in airway inflammation between the 2 diseases,[12] they often co-occur.

The term overlap syndrome was used by Flenley[13] to describe the co-occurrence of sleep apnea and COPD,[14] although a recent large epidemiologic study has shown that an apnea-hypopnea index greater than 10 events per hour was equally frequent in patients with or without COPD.[15] Other potential subtypes of COPD that have attracted clinical attention are bullous disease, α_1-antitrypsin deficiency, early onset COPD, and other less severe diseases of the airway.

The amount of research conducted on COPD has increased over the last decade, leading to an exponential growth in the quantity of information on its clinical and pathophysiologic characteristics. Therefore, the components of the phenotypic heterogeneity of COPD can be more readily understood and there is greater potential for this research to lead to new diagnostic approaches or therapeutic opportunities. As a consequence of this increased knowledge, the view has emerged that COPD involves different target organs and a complex array of cellular, organic, functional, and clinical events,[16] all of which is reflected in the new definitions of COPD.[17] Therefore, it is no surprise that there is emerging interest in disentangling the phenotypic heterogeneity of COPD in order to form new groupings, as is now the case with asthma and other chronic diseases.[18-20] This paper reviews the various phenotypic traits of COPD by focusing on the links between the traits and on how this complex phenotypic information can be better understood.

Table 1
Phenotypic Dimensions and Traits of COPD

Respiratory Symptoms and Health Status
Chronic mucus hypersecretion
Dyspnea
Health-related quality of life
Exacerbations
Worsening
Colonization
Infection
Respiratory function abnormalities
FEV_1, FEV_1/FVC
Severe stage (FEV_1)
Bronchial hyperreactivity
Bronchodilation
Dynamic hyperinflation
Inspiratory capacity
Gas exchange: PaO_2, $PaCO_2$, DLCO
Structural changes
Emphysema
Chronic bronchitis
Bronchiolitis
Bronchiectasis
Local and systemic inflammation
Local inflammation: inflammatory markers or cells in sputum or lung tissue
Systemic inflammation: inflammatory markers or cells in blood or serum
Proteolysis
Oxidative stress
Vascular remodeling
Systemic effects
Nutritional status
Skeletal (respiratory and peripheral) muscles
Exercise capacity
Cardiovascular disorders

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, carbon monoxide diffusing capacity corrected for alveolar volume.

Methods

The present review is based on the opinion of experts involved in a research network in Spain that addresses the question of phenotypic heterogeneity in COPD. An important assumption of this review is that our current understanding of the pathophysiology and clinical features of COPD allows its phenotypic characteristics to be classified in several dimensions: respiratory symptoms and health status, exacerbations, respiratory functional abnormalities (eg, airflow limitation, bronchial hyperresponsiveness, hyperinflation, gas exchange), structural changes (eg, emphysema, respiratory failure), local and systemic inflammation, and other systemic effects. The use of dimensions to classify a large number of clinically related variables has been well developed both conceptually and metrically through tools that measure health-related quality of life.[21]

Members of the Phenotype and Course of COPD (PAC-COPD) working group with research experience in these dimensions have summarized the best evidence about the most important phenotypic traits, the relationships among these traits, and the relationship between phenotypic traits and principal manifestations in the natural history of COPD. Bibliographic searches on the main phenotypic traits were conducted, until a total of 26 were listed and assigned to 1 of the 6 dimensions (Table). Particular interest has been placed on traits associated with severity and mortality. The Table shows both the traits and dimensions.

Because the relationships among the phenotypic traits appear complex and difficult to organize, a multidimensional phenotypic matrix of COPD was developed (Figure). This matrix is a 2-by-2 table that displays the research on interrelationships between traits of the same or different dimensions and also between these traits and the course of disease. The matrix also includes the references that provide evidence for these relationships. In addition to highlighting the presence of links across dimensions, the matrix depicts empty

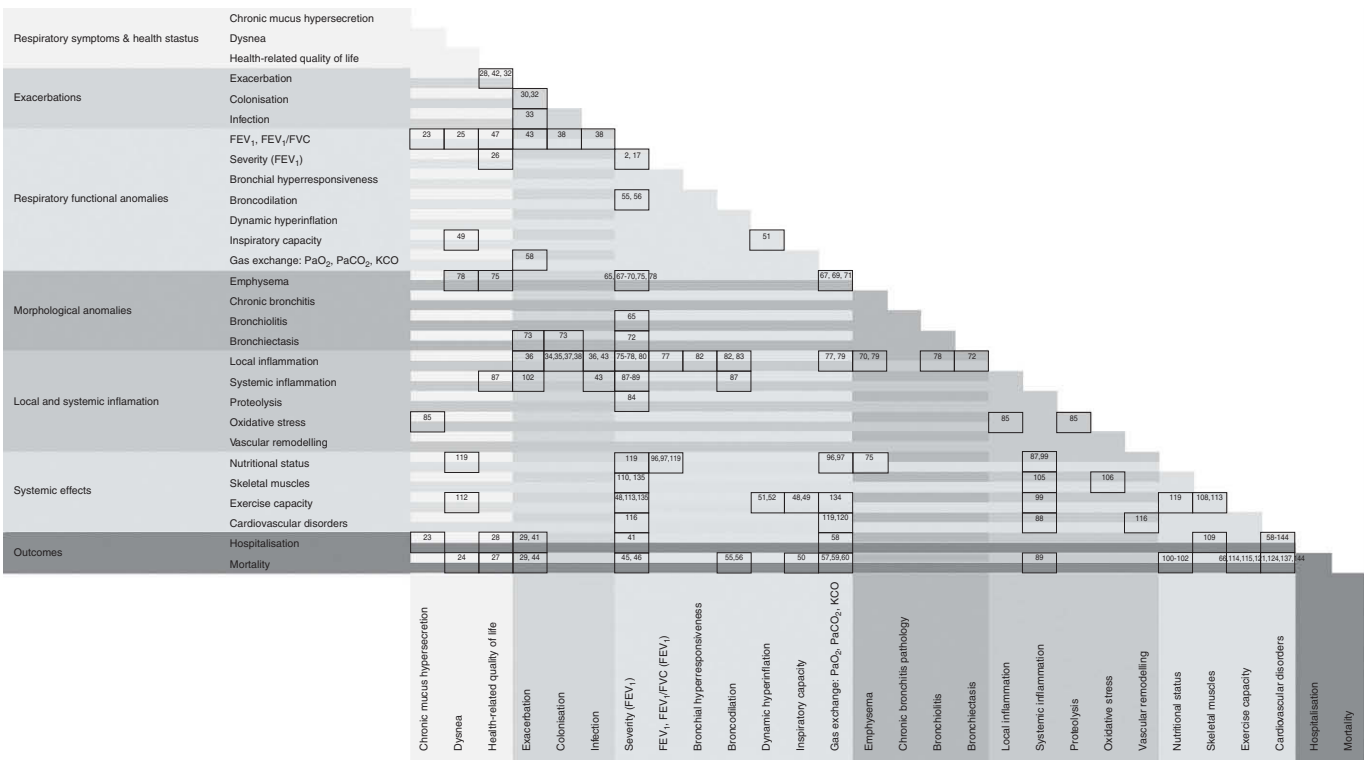

Figure 1. Multidimensional phenotypic matrix of chronic obstructive pulmonary disease. FEV_1 indicates forced vital capacity; DLCO, diffusing capacity of carbon monoxide corrected for alveolar volume.

areas that may be the result of a lack of research and may thus help in planning future studies.

Phenotypic Dimensions and Traits of COPD

Respiratory Symptoms and Health Status

As chronic cough and expectoration are common in COPD, this diagnosis should be considered when these symptoms are present.[17] These signs were originally thought to be benign in smokers, however, and unrelated to COPD.[101] This notion was challenged after an association was found between bronchial hypersecretion, the loss of FEV_1, and hospital admissions due to COPD.[28] COPD patients with chronic bronchitis have been found to have a lower eosinophil count in bronchial biopsies and a higher percentage of eosinophils in sputum than those without symptoms,[84] and dyspnea has been reported to be an important symptom and independent predictor of mortality in moderate-to-severe COPD.[29] However, the severity of dyspnea is highly variable in these patients and only partially correlates with loss of lung function,[33] thus increasing its potential usefulness as a defining phenotypic characteristic of the disease. Furthermore, poor health-related quality of life in COPD correlates well with severity[86] and is associated with both total and respiratory mortality in COPD patients independently of FEV_1, [22] and also with hospital admissions due to exacerbations.[102] In a large sample of patients with severe COPD, the total score on the St George's Respiratory Questionnaire correlated with results of the 6-minute walk test and of the cardiopulmonary exercise test.[25] Functional disability as measured by the Barthel index was associated with a higher risk of death in COPD patients after adjusting for comorbidity.[26]

Acute Exacerbations

Acute exacerbations contribute to deterioration in COPD, since their frequency is associated with a poorer health status,[24,27] a dramatic decline in lung function,[50] and an increased frequency of hospitalization and death.[51] The frequency and severity of exacerbations increase with the severity of COPD, although some patients are more prone than others to recurrent exacerbation. This increased tendency to develop acute exacerbation has been considered a phenotypic characteristic of COPD. Bronchial colonization by bacteria,[49] the appearance of new potentially pathogenic microorganisms in the lower airway,[52,32] and viral infection[103] have all been related to exacerbations. Inflammatory markers in bronchial secretions such as myeloperoxidase, neutrophil elastase, leukotriene-B_4, interleukin (IL) 8, and tumor necrosis factor (TNF) α are related, in a dose-response manner, to the load of pathogenic microorganisms colonizing the bronchi and to bronchial infection.[23,31,104] In addition, the acquisition of a new potentially pathogenic microorganism in the lower airway is associated with an increase in inflammatory markers in sputum (TNF-α and neutrophil elastase) and in serum (C-reactive protein); resolution of the exacerbation is accompanied by a decrease in the levels of inflammatory markers.[86] Airway bacterial load has been associated with a decline in FEV_1 in COPD patients. The inflammatory response and the severity of the exacerbation depend on the nature of the infecting organism, with viral and bacterial coinfections correlating with greater severity.[32,87] In addition to infection, exacerbation has been found to be associated with other factors, such as pulmonary embolism (which has also been identified in a proportion of severe COPD exacerbations of unknown origin[88]), previous hospitalizations due to COPD exacerbations, and long-term oxygen therapy.[30]

Lung Function

FEV_1 and FEV_1/FVC have so far been the defining functional characteristics of COPD and the basis for staging.[17] FEV_1 is strongly related to risk for admission for COPD[88] and for mortality[74] even in the general population.[36] However, the correlation between FEV_1 and symptoms or health-related quality of life is weak.[89] Static lung volumes and inspiratory capacity, an index of lung hyperinflation, may also contribute to a better characterization of the disease. A reduced inspiratory capacity is better predictor of exercise tolerance than a reduced FEV_1 or FVC.[37] Inspiratory capacity also correlates well with improvement in exercise tolerance and dyspnea after inhaled bronchodilators are administered,[57] and its ratio to total lung capacity is an independent risk factor for mortality in these patients.[105] Dynamic hyperinflation during exercise correlates best with resting inspiratory capacity and may help us understand the difficulty of COPD patients in dealing with increased mechanical and metabolic demands during exercise.[34,106]

Airway hyperresponsiveness is another phenotypic trait that may be present in more than half of COPD patients.[35] Early studies pointed to asthmatic bronchitis[8] as a particular phenotype of chronic airflow limitation whose more favorable prognosis may be related to a higher concentration of eosinophils in the bronchial mucosa and secretions.[90] More recent studies have shown that the reversibility of airway limitation is an independent predictor of better survival and slower decline in FEV_1 in this setting.[38,91]

Impaired gas exchange, caused mainly by ventilation-perfusion mismatching, is present in some patients with advanced COPD and has been related to both mortality[92] and admission for exacerbation.[107] Patients with mild daytime hypoxemia may experience severe transient nocturnal hypoxemia and oxygen desaturation during exercise, both of which are related to poor survival.[108] By contrast, patients with nocturnal oxygen desaturation, screened from a large population of patients with COPD, showed similar levels of health status, sleep quality, and daytime function to those of patients without overnight desaturation.[109] Mean pulmonary artery systolic pressure and $PaCO_2$ values have been identified as predictors of severity of nocturnal desaturation.[110] Because of the potential prognostic value of resting and exercise-induced hypoxemia and hypercapnia, these factors are the focus of current studies.[41,95]

Structural Changes

Emphysema, chronic bronchitis, and bronchiolitis are the main conditions involving structural change in COPD.[42,43] However, defining phenotypes on the basis of the predominance of the bronchial or emphysematous component has not been successful,[16] probably because of the limited resolution of chest radiography. Recent developments in high-resolution computed tomography (HRCT),[44] including spiral CT, allow for quantitative assessment of emphysema. Although CT assessment of emphysema correlates well with histology,[45] studies on its relationships with airflow limitation, arterial gas values, and other lung volume parameters have given inconsistent results.[40,44,46-48,111] A recent study that validated measuring emphysema by chest radiography, found that among 458 COPD patients, those with emphysema had a lower body mass index, FEV_1, carbon monoxide diffusing capacity (DLCO), worse quality of life, and greater restriction of physical activity.[53]

The relationship between the presence of emphysema as measured using HRCT and lung function has been the object of study. In general, the more recent studies have found a poorer level of lung function, including DLCO, in patients with a higher degree of emphysema,[39,54,55,60] although in 1 study this relationship was

only found in those COPD patients who had chronic bronchitis.[112] Other traits that have been associated with the presence of emphysema among patients with COPD are elastase in sputum, the BODE index (which combines the body mass index, the degree of obstruction, dyspnea, and exercise capacity), and dyspnea. HRCT may also be helpful for assessing the bronchiolar component of COPD and the presence of bronchiectasis, which has been reported in 30% to 50% of cases.[56,58] The presence of bronchiectasis has been related to more severe exacerbations, lower airway colonization by bacteria, increased levels of inflammatory markers in sputum,[56] and FEV_1.[112]

Local and Systemic Inflammation

To date, 3 different cellular mechanisms—inflammation, proteolysis, and oxidative stress—have been identified in the development and course of COPD. COPD is considered an inflammatory disease of the airways and lung parenchyma that is characterized by an increase in the number of neutrophils, macrophages, and $CD8^+$ lymphocytes.[64] A correlation between local inflammation and the severity of airflow limitation or the course of disease has been reported.[65] Consistent with those results, lung inflammatory mediators such as IL-6 and IL-8[61,113] and inflammatory cells such as $CD8^+$ T lymphocytes and neutrophils have been related to airflow limitation.[63,80] Similarly, an accelerated rate of decline in FEV_1 has been found in patients with higher IL-6 levels and leukocyte counts in sputum.[114] Several markers of inflammation and oxidative stress have been detected in the exhaled air of COPD patients. These include isoprostanes, leukotrienes, cytokines, lipid peroxidation products, and other markers of oxidative and nitrosative stress.[115] The presence of eosinophils in the sputum of COPD patients has been associated with airway hyperresponsiveness,[116] the response to short courses of inhaled corticosteroids,[117,118] and the presence of emphysema as measured by HRCT.[115] Other markers of inflammation in sputum associated with emphysema were matrix metalloproteinase (MMP) 9 and the ratio of MMP-9 to the tissue inhibitor of metalloproteinase 1.[119] Similarly, the imbalance between protease and antiprotease has been related to airflow limitation and is also potentially important.[67] Oxidative stress in the lungs of COPD patients has been related to mucus hypersecretion, proteolysis, and lung inflammation.[68]

At present, the inflammatory process of COPD is thought to extend to other tissue compartments and become systemic. Compared with controls, patients with COPD show higher numbers of circulating white blood cells and elevated levels of biomarkers such as proinflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α), fibrinogen, and C-reactive-protein.[120] In patients with COPD, C-reactive protein—a marker of acute systemic inflammation—has been linked to lung function, health status,[59] 6-minute walk test results and PaO_2,[93] cardiovascular disorders,[94] and mortality[62]; therefore, in combination with symptoms, it could prove to be useful in the diagnosis of exacerbations.[121] C-reactive protein was a strong independent predictor of hospitalization due to COPD and death in a general population-based cohort,[122] and its concentrations have been observed to decrease with inhaled corticosteroids[71] and pravastatin.[72] On the other hand, fibrinogen, but not other biomarkers of systemic inflammation (including C-reactive protein), has been found to be independently associated with recurrent exacerbations in COPD patients in a prospective study.[123] New microarray technologies make it increasingly feasible to test a large number of biomarkers in a single study. Following this approach, 143 different types of biomarkers (chemoattractants, inflammation, tissue destruction, and repair) were recently assayed in serum samples of COPD patients and controls and a final panel of 24 correlated with FEV_1, the 6-minute walk test, DLCO, the BODE index, and the number of exacerbations.[77]

Systemic Effects of COPD: Nutritional Status, Skeletal Muscles, Exercise Capacity, and Cardiovascular Disorders

Recently, the systemic effects of COPD have received considerable attention from researchers.[69,82] Some authors postulate that appropriate management of COPD should consider it a multicomponent disease,[124] and it has been hypothesized that proinflammatory cytokines drive COPD beyond the lungs.[73] Below, we discuss some of the systemic effects that could be considered extrapulmonary components of COPD.

Nutritional Status

Several studies have reported the presence of nutritional abnormalities in patients with COPD.[75,82] The most obvious clinical expression of these nutritional abnormalities is unexplained weight loss. This is particularly prevalent in patients with severe COPD and chronic respiratory failure, found in approximately half,[96] but can also be seen in up to 25% of patients with mild-to-moderate disease.[97] However, its frequency may vary according to the geographic area.[78] Interestingly, there is an association between weight loss and higher TNF-α levels in blood.[125] Weight loss has been related to shorter survival,[66,126] although this association can be reversed with nutritional supplements.[125] The stratification of body mass into fat and fat-free compartments is important for prognosis, as has recently been highlighted by its association with severity[79] and mortality.[127]

Skeletal Muscles

An important systemic component of COPD is skeletal muscle dysfunction. Respiratory muscles suffer a loss of strength and resistance despite several adaptive responses.[128] In the peripheral muscles, especially in the lower extremities, the loss of muscle mass and abnormalities in muscle metabolism are even more evident.[129] Abnormal muscles in COPD patients can show increased levels of proinflammatory cells and molecules,[99] as well as markers of oxidative stress.[130] Muscle abnormalities have been associated with decreased physical activity,[131] reduced exercise capacity,[132] and increased use of health services,[133] but not with the level of airflow limitation.[134]

Exercise Capacity

Decreased exercise capacity is a serious consequence of COPD that results from factors such as ventilatory difficulty (dynamic hyperinflation), gas exchange impairment, decreased cardiac output, abnormalities in both respiratory and systemic muscles, and nutritional impairment.[135] Although dyspnea and leg fatigue seem to be the main causes of limited exercise capacity when COPD patients are compared with healthy controls,[98] muscle strength and lung function show stronger correlations with exercise capacity in patients with more severe disease.[136] The importance of exercise capacity as an independent trait in COPD is supported by its independent association with mortality,[76,137] and this association is stronger than the link with maximal oxygen uptake measured at peak exercise.[70] In a prospective cohort study of COPD patients, a lower FEV_1 was associated with a poorer score in physical fitness tests and a shorter distance covered in the 6-minute walk test.[138]

Cardiovascular Disease

It has been postulated that COPD by itself is an independent risk factor for cardiovascular morbidity and mortality: for every 10% decrease in FEV_1, cardiovascular mortality increases by 28% and nonfatal coronary events increase by almost 20%.[100] It has been hypothesized that this rise in the risk of cardiovascular disorders could be due to COPD-related systemic inflammation.[93] On the other hand, in a large trial including heart failure patients, echocardiography parameters were similar in patients with and without COPD.[139]

Moderate pulmonary hypertension is not uncommon in COPD,[140] and recent findings support the hypothesis that pulmonary hypertension may be the consequence of pulmonary vascular remodeling or cigarette-induced damage,[141] rather than of hypoxemia induced by exercise or developing during sleep.[142,143] The importance of assessing pulmonary hypertension in COPD patients remains unclear, although this condition is independently associated with mortality[83,144] and admission due to COPD.[92] Other cardiovascular abnormalities such as left ventricular dysfunction[145] and arterial hypertension are poorly understood in the context of COPD, but they have significant potential to influence the course of disease. However, COPD was not a predictor of mortality in patients with heart failure.[146]

Other Predisposing Conditions

Cancer,[147,148] Crohn disease and ulcerative colitis,[149] and anemia[150,151] have also been linked to COPD. Anemia was associated with a higher level of health services utilization,[152] a higher level of dyspnea, and a shorter distance in the 6-minute walk test.[153] Depression has been found to be more prevalent in COPD patients than in controls[154] and is associated with a poorer health status.[155] Similarly, comorbidity has been reported to decrease the response to respiratory rehabilitation.[156] For most of these diseases there is insufficient evidence to determine whether their association with COPD corresponds to the expected overlapping distribution in an older population, interrelated phenotypes due to common pathophysiologic pathways, and/or the result of shared environmental determinants.

Understanding Phenotypic Heterogeneity in COPD: A Clinical-Epidemiologic Approach

Several studies have analyzed phenotypic heterogeneity in COPD formally using descriptive statistical techniques such as cluster and factor analysis. These approaches group different correlated variables together into a few conceptually meaningful and statistically independent factors. In fact, this technique has been widely used to explore the dimensions underlying the pathophysiology of COPD.[157-162] Several of these studies have identified at least 3 independent and significant factors: exercise capacity and dyspnea rating, airflow limitation, and lung volume (hyperinflation and air trapping), which together account for more than 60% of the total variance.[156-159] However, when traits such as inflammation and airflow reversibility are considered, a different pattern appears, and the following 3 factors have emerged: airway limitation and lung volume; airflow reversibility, increased immunoglobulin E, and decreased DLCO; and increased exhaled nitric oxide and increased presence of neutrophils and eosinophils in sputum.[161] One of the most important limitations in these studies is that most of them were performed in small nonrepresentative samples and included a small number of COPD traits and dimensions. In addition, part of the variability described may not be related to the heterogeneity of the disease itself, but instead to the fact that patients are at different stages of the natural history of the disease.[163]

Once phenotypic heterogeneity has been expressed as a series of groups of variables that provide different and independent information on the COPD phenotype, the next step involves an assessment of the relationship between the independent phenotypic groupings and manifestations of the disease, in such a way that its relevance for health care and clinical practice can be evaluated. Although the available literature has shown that many phenotypic traits are related to manifestations of the disease, that is, health status measures in COPD patients are associated with mortality related to lung function,[85] these studies have always been based on a very small selection of phenotypic traits, usually different markers of the same phenotypic dimension. One of the few exceptions is the assessment of the prognostic value of a multidimensional COPD score,[164] the BODE score, which has proven to be a better predictor of total and respiratory mortality than the GOLD staging criteria based on FEV_1.

Although these studies about the phenotypic heterogeneity of COPD are a relevant contribution, most of them have only included a limited number of phenotypic traits. In our review, we identified 26 phenotypic traits. These were grouped in 6 different dimensions and have provided information about the interrelationship between these traits and also their relationships with various clinically important outcomes (Figure). This information could prove useful both to integrate the available studies and to design future research. The present review was conducted as part of the PAC-COPD study. An initial cohort of 344 patients from 9 hospitals has been recruited after a first admission for acute exacerbation and followed. The extensive phenotypic evaluation of these patients, together with the information about further hospital admissions and mortality, should enable us to increase our knowledge of the phenotypic heterogeneity of COPD.

This review article has several limitations that should be considered. It is not based on a systematic review of the literature, since we assumed that the scope of research interests of the authors was sufficiently wide to cover the different phenotypic dimensions of COPD. Although some studies may not have been included, this is unlikely to seriously affect the range of phenotypic traits and dimensions we have proposed. A more difficult issue is the internal validity of the studies that have been included. Where possible, we selected longitudinal studies (or cross-sectional ones when appropriate) that included large enough samples. However, the only available information was often from small clinical studies with potentially important selection biases. Therefore, it is possible that in some of the aspects discussed, the conclusions about the interrelationships between phenotypic traits may have been based on biased results. Finally, this review has focused exclusively on the phenotyping of COPD, which we believe is the first necessary step for the investigation of phenotypic heterogeneity. However, other approaches should be considered, particularly the systematic investigation of the genetic mechanisms involved in the expression of phenotypic traits in this disease.[165] While there is little doubt that genetics will help us identify COPD variants,[166,167] using genetics to understand the complexity of COPD phenotypes will require a multidisciplinary effort.[168] New approaches including genome-wide scans and animal models of COPD,[169] as well as proteomic studies,[170] which are becoming increasingly feasible, could help to unravel the genetic heterogeneity of this disease.

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