Chapter

New Perspectives in Pharmacological Therapy for COPD: Phenotype Classification and Corticosteroids with Bronchodilators

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Abstract

Chronic obstructive lung disease (COPD) is heterogeneous and complex. Symptoms and pathophysiological disorders overlap between COPD and asthma. To progress the management of COPD, patients with COPD should be classified by distinct clinical phenotypes. These groupings derived from multiple dimensions including clinical, physiologic, imaging, and endotyping determine clusters of patients with common characteristics that relate to clinically meaningful outcomes such as symptoms, exacerbations, response to therapy, and disease progression (stratified medicine). Moreover, since several phenotypes can coexist in individual patients with COPD, an approach due to therapeutic target identified phenotypes and endotypes (treatable traits) has been proposed as an advanced therapy recently (precision medicine). Airway eosinophilia and airway hyperresponsiveness, which are hallmarks of asthma, are developed in some patients with COPD, independent of asthma. It is perhaps meaningful to classify COPD according to airway eosinophilia and airway hyperresponsiveness as phenotypes and to put these phenotypes into focus as treatable traits. These phenotypes are closely related to frequency of exacerbations and reactivity to inhaled corticosteroids with bronchodilators in therapy for COPD. Hence, research for phenotype classification can play a fundamental role for development of the management and treatment for COPD.

Keywords: COPD, phenotypes, treatable traits, airway eosinophilic inflammation, airway hyperresponsiveness

1. Introduction

Chronic obstructive lung disease (COPD) is defined as a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms (shortness of breath, chronic cough, sputum production) and by airway obstruction (airflow limitation) that will not return to the normal range [1]. It is considered that COPD is

complex and heterogeneous in symptoms, disease progression, functional outcomes, and response to therapies based on the etiology, pathogenesis, and type of lung pathology [2]. To address this complexity and heterogeneity, it is desirable to meaningfully identify and classify groups of patients with similar clinical characteristics, prognosis, and/or therapeutic needs, referred to as clinical phenotypes. However, it has not established to classify patients with COPD into defined subtypes according to distinct phenotypes. The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) study, which is a longitudinal cohort study of more than 10,000 smokers, is being carried out to identify the etiology, progression, and heterogeneity of COPD. This cohort study is probably useful for research and development of treatable trait toward precision medicine or personalized medicine for COPD [3–5].

Chronic lung inflammation, which is caused by cigarette smoke and other environmental exposures (biomass fuel, air pollution etc.), contributes to the pathogenesis of this disease. This chronic lung inflammation related to neutrophils and macrophages is normal response in many people, but appears to be modified in patients who develop COPD, leading to emphysema and small airway fibrosis, which are essential characteristics in pathology of this disease. COPD is diagnosed only by persistent airflow limitation in spirometry, but other variables in lung function test may be relevant to diagnosis and prognosis of this disease. Since not only FEV_1 but also FEV_1/FVC physiologically decreases with age, the fixed cutoff point for FEV_1/FVC ratio may be inaccurate to use for diagnosis of COPD. Airflow limitation is progressive, and a decline of FEV_1 varies in each patient.

The pathological alterations cause not only airflow limitation mediated by the loss of alveolar attachment to the small airways but also gas trapping (an increase in residual volume (RV) or a decrease in inspiratory capacity (IC)). Moreover, these structural alterations also cause a decrease in lung elastic recoil (a reduction in dynamic elastance). Since COPD is associated with not only small airway but also alveolar disease [6], some patients with COPD have a low diffusing capacity of the lung for carbon monoxide (DL_{CO}). It has been recognized that chronic airflow obstruction could be seen in a variety of overlapping conditions among airway diseases, most notably in patients with COPD and asthma [7, 8]. The overlap of asthma and COPD has been proposed as a distinct COPD phenotype, refers to a set of observable characteristics of an organism.

When infections or heart failure occurs in patients, the stable periods of COPD may be interrupted by acute worsening of respiratory symptoms (exacerbations). Moreover, significant chronic diseases are concomitant with most patients with COPD (comorbidity) [9]. The prognosis of each patient with COPD is probably dependent on frequency of exacerbations and coexisting diseases. Hence, COPD is a heterogeneous disease in symptoms, exacerbations, disease progression, functional outcomes, and response to therapies (clinical phenotypes) [10]. A unique phenotype, which has similar underlying biologic (physiologic or molecular) mechanisms that define subtypes (referred to as "endotypes") to guide the development of therapy, is sheared between COPD and asthma [11]. In COPD, individual patients with similar degrees of airflow limitation most likely are different in terms of symptoms, exercise capacity, and exacerbation risk. Ever since 2011, Global Initiative for Chronic Obstructive Lung Disease (GOLD) states a multidimensional assessment of patients with COPD that includes two new dimensions: symptoms experienced by the patient and the risk of future exacerbations [1].

Since COPD is heterogeneous, patients with this disease can be stratified according to clinical phenotypes [3, 4, 10]. However, different clinical characteristics are mixed in various proportions in individual patients with COPD. This chapter

describes multiple dimensions including clinical, physiologic, imaging, and endotyping dimensions in COPD [9]; moreover, describes effectiveness of corticosteroids with bronchodilators to patients with COPD who have airway eosinophilia and airway hyperresponsiveness as phenotypes in order to search treatable trait for COPD [12].

2. COPD pheotypes

Multiple disease characteristics have been termed COPD phenotypes up until now; and individual patients with COPD can be grouped by phenotypes (phenotypic grouping). These groupings are proposed to determine clusters of patients with common characteristics that relate to clinically meaningful outcomes such as symptoms, exacerbations, response to therapy, and rate of disease progression, or death (stratified medicine) [10, 13]. This more focused definition allows for classifications of patients to distinct prognostic and therapeutic subgroups for both clinical and research purposes as a heterogeneous disease in COPD. The earliest phenotypic classification of COPD was separated into two groups based on physical examination, the "Pink Puffers" and the "Blue Bloaters" [14]. Airflow limitation detected by the routine use of spirometry is insufficient to distinguish COPD from asthma and other airway diseases (chronic bronchitis, pan bronchiolitis, bronchiectasis, etc.). It is especially difficult to distinguish between COPD and asthma. More than 50 years ago, Dutch hypothesis argued that bronchodilator responsiveness was an overlapping feature shared by various forms of obstructive lung diseases, including asthma [15]. In contrast, the British hypothesis argued that bronchodilator responsiveness in patients with COPD was due to concomitant asthma [16]. Hence, multivariable approaches to deal with diseases probably provide relevant information that can characterize different subtypes of COPD. Multiple dimensions for COPD assessment can include clinical, physiologic, imaging, and endotyping dimensions (**Figure 1**) [9]. Data from each dimension support the relevance of specific variables to diagnosis and prognosis for COPD. However, very few and limited combinations of these variables and dimensions have been studied and validated. Therefore, various classification systems for COPD have established taking into phenotypes and endotypes to allow categorization of patients in meaningful methods.

2.1 Clinical dimension

2.1.1 Symptoms

Symptoms (dyspnea, cough, sputum production) and signs (wheezing, prologued exhalation) overlap between COPD and other airway diseases, but with a decline in body mass index (BMI), very little overlap between COPD and asthma. The GOLD Report initially stated a classification system based on reduction in FEV_1 [1]. However, FEV_1 is no clearly associated with symptom severity, functional status, and prognosis [17, 18]. Symptom severity has been shown to be better predictor of mortality than FEV_1 alone in patients with COPD [19]. Health questionnaires such as COPD Assessment Test (CAT) scores and St George Respiratory Questionnaire (SGRQ) scores have been used to understand the relationship between symptoms and quality of life [20]. As an approach includes more variables, a multidimensional grading system including body mass index (BMI), obstruction in the airway (FEV_1), dyspnea, and exercise ability (BODE index) has shown to be better than FEV_1 alone in predicting mortality in patients with COPD [21].

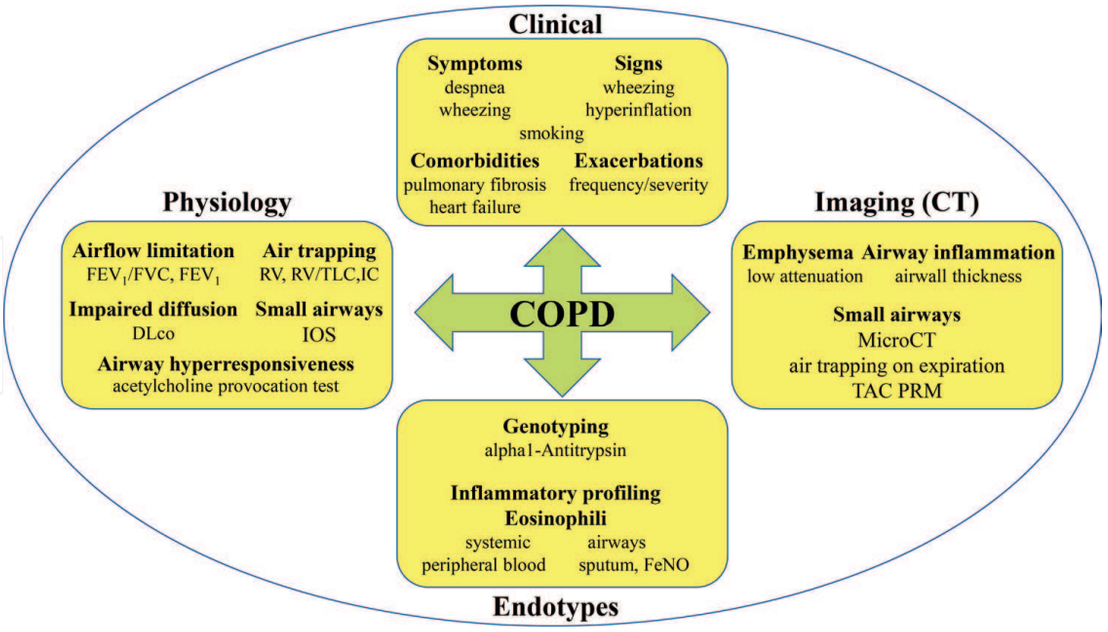

Figure 1.
A Schema of multiple dimensions for assessment of COPD phenotypes. Squares represent dimensions, which is consist of clinical, physiology, imaging CT, and endotypes; and enclose variables with defined or possible relevance to diagnosis, prognosis, or potential therapy in patients with COPD. Illustrated based on ref. [1, 9].

2.1.2 Exacerbations

COPD exacerbations perhaps result in rapid decrease of lung function (FEV_1), deterioration of quality of life, and escalation of healthcare cost [22]. Clinical studies have demonstrated that severe COPD exacerbations are associated with a high mortality [23], and that COPD exacerbations are independent risk factor for morbidity in the disease [24]. Frequent exacerbators are a group of subjects with two or more exacerbations per year [25]. Although recent data suggest that the frequent exacerbator phenotype is quite infrequent in a large cohort study, this phenotype seems to be quite stable over time because the best predictor for exacerbations is history of prior exacerbations [26]. In the recent GOLD Report, the stage of COPD is classified by percentage predicted FEV_1 (Grades I–IV), and separately dyspnea severity and exacerbation history are incorporated into a 2 × 2 grid to form four groups A – D [1]. This assessment approach will guide more precise treatment for individualized patient with COPD. However, this classification is insufficient to seize accurately the heterogeneity of COPD.

During a COPD exacerbation, bacteria, viruses, or both are detected from lower airway secretions in two-thirds of patients, and bacterial/viral coinfection is present in one-fourth [27]. *Hemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis* are isolated as the most common bacterial pathogens during COPD exacerbations. Acquisition of a new bacterial strain precedes exacerbations [28]. Rhino virus is most frequently associated with exacerbations [29], whereas coronavirus, parainfluenza, adenovirus, and influenza virus are less prevalent.

2.1.3 Smoking

Cigarette smokers have a higher prevalence of respiratory symptoms, and impaired lung function, a greater annual rate of decline in FEV_1, and a greater rate of COPD mortality than non-smokers [1]. As shown in the SPIROMICS cohort,

respiratory symptoms are present in half of cigarette smokers with preserved lung function. When compared with asymptomatic cigarette smokers, these symptomatic smokers have greater limitation of physical activity, lung function abnormalities (although still within the limits considered as normal), and evidence of airway wall thickening on CT imaging of the chest [30]. Importantly, cigarette smokers with preserved lung function and respiratory symptoms have higher rates of exacerbations than asymptomatic cigarette smokers.

2.1.4 Comorbidity

Patients with COPD have a high prevalence not only of other pulmonary disease (lung cancer, pulmonary hypertension, pulmonary fibrosis, etc.) but also extrapulmonary diseases (cardiovascular diseases, diabetes mellitus, hyperlipidemia, etc.) [31]. This is very important because approximately two-thirds of patients with COPD die from these other diseases, and comorbidities have a significant effect on prognosis or mortality [32, 33]. Recent investigations using network analysis of comorbidities in patients with COPD demonstrate that the presence of hubs of comorbid conditions is highly associated with this disease beyond lung cancer and cardiovascular disease (COPD comorbidity network). Prognosis of patients with COPD is most likely affected by larger number of multiple interlinked morbidities, and their clustering pattern suggests common pathobiological pathways [34].

Combined pulmonary fibrosis and emphysema (CPFE), which is defined by CT imaging of the chest, is closely associated to a history of cigarette smoking. CPFE is characterized by exertional dyspnea, emphysema in the upper lobe, and fibrosis in the lower lobe of the lungs. Patients with CPFE have preserved lung volume (total lung capacity, forced vital capacity) and severely diminished carbon monoxide diffusion capacity of the lung (DLco), moreover, have high prevalence of pulmonary hypertension, and poor prognosis [35]. Survival rate in CPFE is worse than that expected for emphysema without fibrosis; in contrast, survival rate in CPFE is better than that in usual interstitial pneumonia diagnosed by pathological findings. It is still unknown whether the therapy for COPD or pulmonary fibrosis/usual interstitial pneumonia is effective for CPFE. Corticosteroids do not have significant benefit to patients with CPFE.

2.2 Physiological dimension

2.2.1 Airflow limitation

Diagnosis of COPD is based on the physiologic criteria of fixed obstruction in forced expiratory flow (0.7 as cutoff point for FEV_1/FVC ratio); however, the use of a fixed cut point like this probably misclassifies some older patients as developing COPD (more frequent diagnosis of COPD in elderly subjects), compared with the use of a cutoff point derived from the lower limit normal (LLN) for FEV_1/FVC ratio. On the other hand, the use of this fixed cutoff point for FEV_1/FVC ratio results in less frequent diagnosis of COPD in younger adults, compared with that of the LLN. Since the LLN for FEV_1/FVC ratio decreases with age, the accuracy of these diagnostic criteria also should be changed with age [36]. The use of the LLN affects the establishment of early diagnosis for COPD in younger adults. Criterion used in the LLN would be a more desirable parameter that increases the accuracy of diagnosis in this disease. However, those values are dependent on the reference population and are unlikely to

accurately reflect the normality of many different ethnic groups. Moreover, there are no longitudinal studies available validating the use of the LLN.

FEV_1 also normally decreases with age, and FEV_1 (% of the predicted value) is used as an indicator for staging of COPD. However, FEV_1 is not always associated with shortness of breath, exercise tolerance, and quality of life [17, 18]. The rate of decrease is probably an important indicator of disease progression in patients with COPD. However, the rate of lung function decrease (a decline of FEV_1) is not also considered for diagnosis or stage classification of this disease. In these approaches using spirometry (the physiologic criteria), first-line medications have been applied consistently in the condition that COPD is once diagnosed without much consideration of possible distinct phenotypes of COPD.

2.2.2 Impaired diffusion

Diffusing capacity derived from DL_{CO} can estimate the potential of gas exchange of the lung [37]. DLco is frequently reduced in patients with established COPD. There is also a subset of cigarette smokers with normal spirometry (FEV_1/FVC ratio > 0.7), who have a low value of DL_{CO}. Decreased DL_{CO} in smokers is pathologically correlated to the destruction of the pulmonary capillary bed, and a low value of DL_{CO} in the context of a normal total lung capacity (TLC) probably indicates alveolar destruction, i.e., emphysema [37, 38] and possibly small airway disease, both of which are components of COPD [39, 40]. Clinical trials have reported a significant correlation between reduced DL_{CO} and emphysema on CT imaging of the chest [41, 42]. Decreased DL_{CO} has also been correlated with dynamic hyperinflation caused by the presence of severe expiratory airflow limitation derived from emphysema and small airway diseases, independent of decreases in FEV_1/FVC or FEV_1 [43]. Moreover, smokers with normal post-bronchodilator FEV_1 but low DL_{CO} have a higher risk of developing COPD with airflow limitation, compared with those with normal post-bronchodilator FEV_1 and normal DL_{CO} [44]. Hence, DL_{CO} measurement is useful for early diagnosis of COPD who are cigarette smokers without airflow limitation. However, this examination is not part of the GOLD criteria and is currently not used as a routine screening tool [45, 46].

2.2.3 Airway trapping

Gas trapping develops in patients with COPD from the early stages of this disease. Gas trapping results in a rise in residual volume (RV), and static hyperinflation, which is an increase in TLC, as airflow limitation worsens. Lung volume such as RV and TLC is impossible to measure by spirometry in the routine use, and these alterations are estimated by body plethysmography and helium dilution lung volume measurement. RV and TLC are probably helpful to characterize the severity of COPD; however, these are not generally used for management of this disease.

Patients with COPD show widely variable exercise capacities. It is recently considered that FEV_1 was a poor predictor of exercise capacity, and that dynamic hyperinflation, which is a concomitant with decreases in inspiratory capacity (IC) and inspiratory reserve volume (IRV), is more closely related to exercise tolerance than FEV_1 [47]. Dynamic hyperinflation is defined as the variable and temporary increase in end expiratory lung volume (EELV) above its baseline value, which occurs when ventilatory demand is acutely increased during exercise [48, 49]. This phenomenon results from gas trapping in the airways. This is usually measured by IC, which

accurately reflects changes in EELV provided that TLC remains unaltered. During exercise, in normal subjects, the tidal volume (VT) is markedly increased at the expense of both the IRV and the expiratory reserve volume. In contrast, since airflow is limited and RV is increased in patients with COPD, VT is only a little increased at the expense of their reduced IRV. Therefore, a reduction in IC causes impaired exercise tolerance in patients with this disease. IC can be measured using spirometry, but IC is currently not used as a clinical predictor of exercise capacity.

2.2.4 Small airway obstruction (less than 2 mm diameter)

The current approach to diagnosis and staging of COPD is based on post-bronchodilator FEV_1/FVC ratio, and FEV_1 (% of predicted value) in spirometry, even though this disease is considered generally to begin in the small airways [50]. This area is classically recognized to be the "quiet zone" or "silent zone" because it cannot be easily assessed by means of spirometry alone [51]. The forced oscillation technique, such as impulse oscillation system (IOS) or MostGraph, was been developed to compute the respiratory system impedance that reflects the mechanical properties (resistance and reactance) of the respiratory system [52]. Higher oscillation frequencies (approximately 20 Hz) reflect large airways, and lower oscillation frequencies (<10 Hz) reflect the entire respiratory system, including the small airways. Abnormalities with low oscillation frequencies can be related to disorders in the small airways. However, the forced oscillation technique has not yet been established as clinical test to estimate the small airway function.

Although little is currently known about the clinical relevance of the small airway dysfunction, abnormalities in this area are probably correlated with magnitude of inhaled toxin exposure, severity of respiratory symptoms, response to therapy, presence of systemic inflammation. When the presence of respiratory symptoms in patients is unexplained by using routine clinical evaluation because chest CT and spirometry findings are within the normal range, these results may indicate that small airway disorders develop despite normal airflow on spirometry [53].

2.2.5 Airway hyperresponsiveness

It is classically considered that sensitivity to muscarinic activation is a hallmark of asthma, referred to as airway hyperresponsiveness (AHR). However, recent reports have demonstrated that AHR also develops in as set of COPD [12, 54–56]. Awareness of this paradigm shift is gradually increasing. To evaluate AHR, acetylcholine inhalation challenge is carried out according to the standard method of the Japanese Society of Allergy (Acetylcholine provocation test) [57], which is a modified method reported by Hargreaves and coworkers [58]. The provocation test is ended at a concentration of acetylcholine where FEV_1 is reduced by more than 20% from its baseline value. Threshold values are expressed as a minimal concentration of acetylcholine that reduces FEV_1 by more than 20%. AHR is generally defined as threshold values of less than 8 mg/ml of acetylcholine [56, 59]. Acetylcholine provocation test is most reliable for diagnosis of asthma because this clinical examination has great sensitivity and specificity to diagnosis of asthma [60]. Clinical reports have indicated that AHR is complicated by ~60% or ~ 94% of patients with COPD [61, 62]. Since airway narrowing occurs in COPD because of airflow limitation, exclusion criteria should be established to maintain the accuracy of this provocation test for COPD. Recently, acetylcholine provocation test was carried out for subjects who have FEV1 ≥ 70%

predicted values not only to avoid false positives but also to secure safety in this examination [63]. Moreover, the patients with COPD were enrolled in the study and do not have past history of asthma and no clinical features of asthma. As a result, AHR developed in approximate 50% of the patient with COPD excluded asthma [12].

2.3 Imaging dimension

2.3.1 Emphysema

COPD, which is diagnosed in routine use of spirometry, contains both with and without emphysema. Emphysema, which can be easily detected by chest CT, occurs in a significant proportion of cigarette smokers that might not fit the COPD spirometric criteria [64]. Emphysema can be divided into with and without airflow limitation (FEV_1/FVC ratio < 0.7); COPD also can be divided into with and without emphysema. Multiple different phenotypes of emphysema have been described, i.e., centrilobular, panlobular, and paraseptal phenotypes. Some differences are shown among these phenotypes. The centrilobular phenotype is associated with greater smoking history, whereas the panlobular phenotype is associated with reduced body mass index, independent of FEV_1 [65]. Paraseptal emphysema is associated with fewer symptoms and less physiologic impairment. In the analysis of different emphysema patterns based on the Fleischer Society grading system, Kaplan–Meier survival curves demonstrate that patients with absent and trace emphysema have the best survival; those with moderate centrilobular emphysema have intermediate survival; and those with confluent or advanced destructive emphysema have poor survival [66]. However, little is known what determines the distribution of the emphysema. Phenotyping based on the anatomic distribution may result in important therapeutic implications that lung volume reduction surgery may be beneficial to patients with upper-lobe emphysema and low exercise capacity [67].

2.3.2 Small airway

The narrowing and loss of terminal bronchioles occur before the development of emphysema. Assessment of small airway disease is probably useful to identify COPD at an early stage [64, 68]. However, small airways are less than 2 mm in diameter [69]. Because this size falls below the resolution limit of chest CT for direct evaluation, small airways are not imaged directly using routine CT scan. For this reason, novel methods using CT have been devised to evaluate small airways diseases. Micro-CT studies, which are 3D imaging techniques utilizing X-rays to see inside an object, have demonstrated that both total bronchiolar area and the number of small conducting airways are reduced in the early stage [68]. Measures of air trapping on expiratory CT have been used to estimate functional small airway disease, including the ratio of expiratory to inspiratory mean lung density [70, 71], the expiratory to inspiratory relative volume change of voxels with attenuation between 2860 and 2950 HU, and the percentage of voxels below 2856 HU in expiration. However, these imaging techniques have their advantages and limitations. CT total airway count (TAC), which is measured as well as airway inner diameter and wall area using anatomically equivalent airways, reflects the airway-related disease changes in the "quiet" zone (small airways) [72]. A significant decrease in TAC may be observed in early stage of COPD; and that can predict a rapid decline of lung function [72]. The parametric response

mapping (PRM), a technique pairing inspiratory and expiratory CT, has been developed to assess small airway diseases. That images to define emphysema (PRM^{emph}) and functional small airways disease (PRM^{fSAD}), a measure of nonemphysematous air trapping [64, 73–76]. These techniques will allow for more accurate diagnosis of individual patients complementing standard clinical examinations to estimate COPD phenotypes. Analysis methods for CT imaging in COPD are making progress to establish novel phenotypes for development of precision medicine according to the results derived from the COPDgene study [75, 76].

Small airways disease occurs in the early stage of COPD and becomes more widespread over time as this disease progresses to more severe. Airway remodeling is observed in this peripheral area in patients with COPD, and pathological findings of that are characterized by goblet cell hyperplasia, mucous gland enlargement, peribronchiolar wall infiltration with inflammatory cells, and bronchiolar smooth muscle hypertrophy [77, 78]. The therapeutic relevance of this phenotype can include use of therapies that allow the small airways to be targeted pharmacologically [79]. However, it is not so easy to estimate accurately diagnosis and treatment outcome in the small airway disease of COPD.

2.4 Endotyping dimension

2.4.1 α_1-Antitrypsin deficiency

It is well known that α_1-antitrypsin is a proteinase inhibitor that protects lung tissue from damage by neutrophil elastase. An imbalance between proteinases and antiproteinases causes destruction of elastin fibers, which affects the elastic recoil of the lung and brings about parenchymal destruction (emphysema). This imbalance between proteinases and antiproteinases seems to be less evident in patients with other forms of emphysema. This condition of α_1-Antitrypsin deficiency is observed less than 5% of patients with COPD and presents in younger subjects compared with the rest of the COPD population [80]. Mutation of the α_1-antitrypsin gene results in a much higher risk of COPD in cigarette smokers and workers exposed to environmental particules. Homozygous α_1-antitrypsin deficiency occurs in 1–4.5% of patients with COPD; in contrast, the heterozygous form occurs in 17.8% of patients with COPD [81]. Previous clinical trial may provide the therapeutic relevance that intravenous augmentation with pooled human α_1-antitrypsin may be beneficial to subjects with severe α_1-antitrypsin deficiency [82].

2.4.2 Inflammatory profiling

It is classically considered that asthma is characterized by eosinophil inflammation in the large airways with Th2 phenotype, om the other hand, that COPD is characterized by initial macrophage, neutrophil, and CD8 lymphocyte inflammation in the small airways [83]. However, it is recently proven that eosinophil and non-TH2 related inflammation is involved not only in the large airways but also the small airways in patients with asthma; on the other hand, eosinophil inflammation is involved in the large airways in patients with COPD. Blood eosinophil counts are increased in COPD patients compared with healthy controls, even when atopic patients are removed from the analysis [84]. This paradigm shift in the approach to this disease is generally recognized. Hence, airway inflammatory profiling is not so useful for differential diagnosis between COPD and asthma since eosinophil inflammation overlaps with

these two diseases. The eosinophil count in the peripheral blood may be beneficial as a predictor of the frequency of exacerbations and response to corticosteroid in the management of COPD [85–88]. The increased blood eosinophil numbers may be a reason for increased lung eosinophil numbers observed in a subgroup of COPD patients [89, 90]. According to these reports, it has been assumed all along that blood eosinophilia is a faithful representation of tissue eosinophilia. However, this assumption has not been proven conclusively [91]. The eosinophil count in the peripheral blood does not always correspond to the eosinophil count in the lung tissue. Furthermore, high numbers of blood eosinophils are not associated with frequency of exacerbations [92]. It remains to be solved whether useful blood eosinophil counts are useful as a predictor of the management of COPD. COPD with airway eosinophilia in the tissue probably is a subgroup (phenotype) of this disease, since this phenotype has unique pulmonary and systemic manifestations and a differential response to drugs [87, 88, 93]. This phenotype of COPD probably has a good response to corticosteroids [89]; and sputum examination is probably most reliable as a clinical test to detect eosinophil inflammation in the airways, blood test is not. Blood eosinophilic phenotype was associated with PH. Eosinophilic COPD was associated with higher mPAP and PVR and increased likelihood of PH. More studies are needed to further explore this finding [94].

3. Treatable traits and precision medicine of airway diseases

3.1 Overlap of symptoms and airflow limitation between COPD and asthma

COPD and asthma are the two most prevalent human airway diseases. Although COPD and asthma are pathologically entirely different diseases, it is not so easy to clearly distinguish between these two diseases. In patients with COPD, the initial pathological alterations occur in bronchioles less than 2 mm in diameter ("silent zone" in spirometry). Disorders in the bronchioles are followed by parenchymal remodeling [68], which is different from asthma. On the other hand, disorders in bronchioles probably cause wheezing, which is characteristic to asthma. Clinical manifestations and airflow limitation overlap with COPD and asthma; moreover, eosinophilia and hyperresponsiveness in the airways, which are classically considered to be characteristic of asthma, also overlap with these two diseases. In patients with asthma who have a history of smoking, a differential diagnosis between asthma and COPD can be difficult just in the routine use of spirometry. In these cases that fit the pyrometric criteria for COPD, it may be hard to distinguish clearly between asthma and COPD because of the LLN for FEV_1/FVC ratio and the low incidence (approximately 15%) of COPD in smokers. In patients with COPD who have eosinophilia and hyperresponsiveness in the airways, it is also can be difficult to accurately distinguish between COPD and COPD with asthma even though they have symptoms with variability (cough, dyspnea, wheezing), which are clinical features of asthma, but overlap between COPD and asthma.

3.2 Asthma-COPD overlap

The term asthma-COPD overlap (ACO), which is a phenotype of COPD, is used to identify patients with airway diseases that combine clinical features of both

asthma and COPD [8, 95]. However, diagnosis of ACO may be unclear because COPD and asthma may be unclear because these two diseases are heterogeneous. It is also unclear to accurately distinguish between ACO and COPD with eosinophilia in peripheral blood. There is still disagreement with ACO; and the concept of ACO remains quite controversial [11, 96]. ACO is diagnosed for a patient who has characteristic of COPD, namely persistent airflow limitation as well as features of asthma [8]. Features of asthma develop in between approximately 15% of patients with COPD as well [8, 97]. ACO is not a single uniform entity but consists of multiple sub-phenotypes, such as asthma with irreversible airway obstruction due to structural changes, or smoke or predominantly neutrophilic inflammation, and COPD with eosinophilic inflammation [97]. It is generally considered that patients with ACO appear to have more symptoms, more frequent exacerbations, increased risk of hospitalization, and a worse quality of life [98]; on the other hand, patients with ACO appear to have a lower mortality [95]. The identification of ACO is important because corticosteroids are beneficial to patients with ACO, regardless of FEV_1 or exacerbation frequency [99]. The responsiveness to corticosteroids is due to feature of asthma in ACO.

3.3 Airway eosinophilia and airway hyperresponsiveness as phenotypes of COPD

Since airway eosinophilia and AHR overlap between COPD and asthma, the differential diagnosis between COPD, asthma, and ACO can be unclear in cases with eosinophilia and AHR in the airways. It also still unclear to distinguish accurately between eosinophilic COPD and COPD with asthma [100]. A previous report that examined airway eosinophilic inflammation using sputum induction and examined AHR using methacholine provocation test in 21 cases of COPD has indicated that 41.4% had AHR, 31.0% had increased sputum eosinophils, and that cases with AHR had higher sputum eosinophils than cases without AHR and those with sputum eosinophils more than 3% had more exacerbations in the previous year [55]. In another study, 203 patients with COPD who have no symptoms and past history related to asthma were enrolled to examine role of eosinophilic inflammation and AHR in the airways as phenotypes of COPD [12]. These subjects were diagnosed as COPD based on lung function test and smoking history. Eosinophils in the sputum were observed in 65 (50.4%) of 129 subjects using qualitative analysis; in contrast, lower grade (more than 0%, less than 3%) and higher grade (3% or more) were observed in 15 (20.3%) and 25 (33.8%) of 74 subjects using quantitative analysis [12]. Exacerbations occurred much more frequently in lower-grade airway eosinophilia without inhaled corticosteroid than in higher-grade airway eosinophilia with inhaled corticosteroid [12]. Regulation of airway eosinophilia is associated with a reduction in exacerbations of COPD (**Figure 2**) [101]. AHR developed in 46.9% of these subjects with sputum eosinophils; but grade of airway eosinophilia was not associated with development of AHR. AHR also significantly increased frequency of exacerbations in COPD with both lower and higher grade in airway eosinophilia [12]. This clinical report demonstrates that airway eosinophilia and AHR cause in COPD, independent of asthma, and that these phenotypes of COPD are closely related to symptom stability (exacerbations). Moreover, AHR is associated with mortality in COPD [102–104]. These essential results derived from these clinical studies are summarized in **Figures 2**, **3** and **Table 1**.

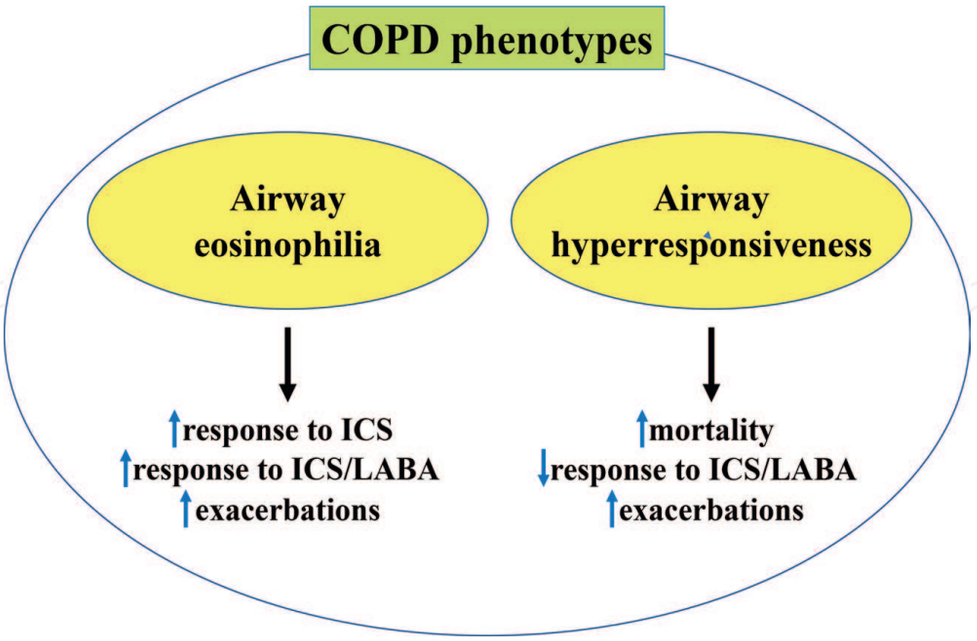

Figure 2.
Clinical characteristics caused by airway eosinophilia and airway hyperresponsiveness as phenotypes of COPD. Illustrated based on ref. [12, 55, 89, 101–109].

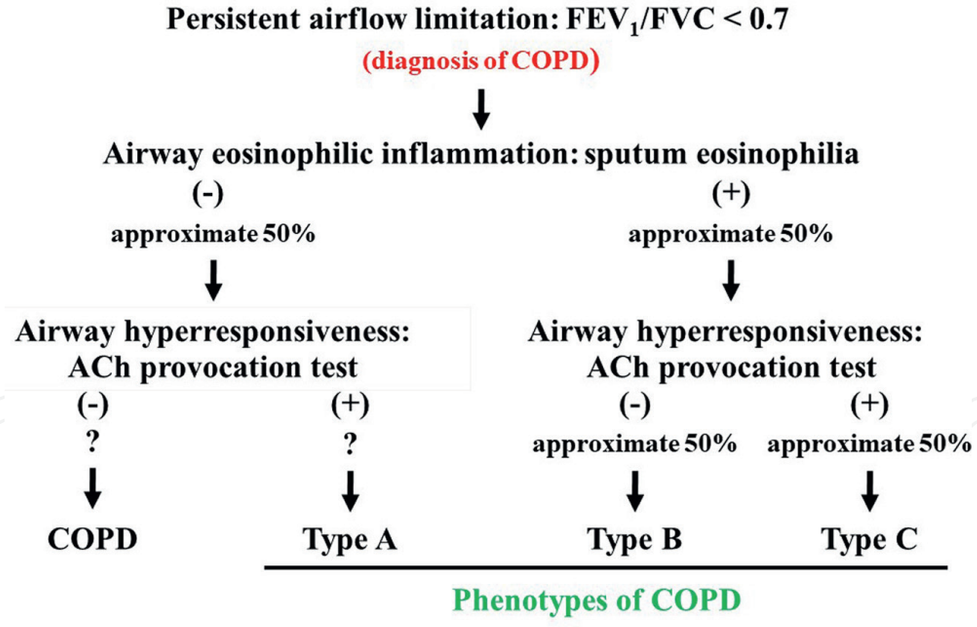

Figure 3.
Phenotypes of COPD classified into airway eosinophilia and airway hyperresponsiveness. Illustrated based on ref. [12, 55].

3.4 Phenotypes and response to corticosteroids with bronchodilators

COPD with peripheral blood eosinophilia may have a particularly favorable response to inhaled corticosteroid (ICS)/long-acting β_2-adrenergic agonist (LABA) therapy, perhaps because of the inflammation profiling that responds well to corticosteroids. However, prospective studies are required to evaluate the role of blood

	Phenotypes of COPD		
Treatable traits	**Type A**	**Type B**	**Type C**
FEV_1/FVC <0.7	+	+	+
Sputum eosinophils	−	+	+
ACh provocation PC_{20} < 5000 μg/mL	+	−	+
Stability and therapy	**Type A**	**Type B**	**Type C**
Frequency of exacerbations	+	++	+++
Response to ICS with LABA	unknown	more potent	less potent

Table 1.
Effects of airway eosinophilia and airway hyperresponsiveness as treatable traits on the management of COPD. Illustrated based on refs. [12, 55].

eosinophils as a biomarker of inhaled therapy response in COPD [110]. Eosinophil counts in the peripheral blood are not always associated with those in the airways. For this reason, patients with COPD who have sputum eosinophilia were enrolled to examine involvement of eosinophilic inflammation in response to corticosteroids and LABA [12, 55, 105, 106]. Inhaled indacaterol (a LABA) caused a greater increase in FEV_1 [107] and IC [108] in these patients than those shown in other previous reports. Addition of inhaled ciclesonide (a corticosteroid) to indacaterol caused much higher increases in FEV_1 and IC, and values of CAT score and frequency of on demand use of procaterol (a short-acting β_2-adrenergic agonist) were markedly reduced (**Table 1**) [12]. These results indicate that not only ICS but also LABA is effective in improving lung function, symptoms, and quality of life in COPD with airway eosinophilia [109]. Since airway inflammation induced by neutrophils and oxidative stress may be the main pathogenesis of COPD, ICS is generally considered to be not so beneficial to this disease. However, ICS/LABA is beneficial to airway eosinophilic inflammation in COPD, similar to that in asthma. Indacaterol, a strong partial β_2-adrenergic agonist, is probably effective for COPD because of higher values of its intrinsic efficacy close to a full agonist [111–115]. In these patients with COPD who have sputum eosinophilia, there was no deference in response to indacaterol for FEV_1 and IC between these subjects with and without AHR; in contrast, addition to ciclesonide caused greater increases in FEV_1 and IC in these subjects without AHR than in these subjects with AHR [12]. However, mechanisms underlining this reduced responsiveness to corticosteroids in COPD with AHR have not been investigated in detail. Therefore, airway eosinophilia and AHR affect symptom suitability (exacerbations) and responsiveness to corticosteroids and β_2-adrenergic agonists in COPD (**Table 1**, **Figure 2**).

4. Conclusions

Although it is generally considered that COPD has heterogeneity, COPD is currently diagnosed based on physiologic criteria using spirometry. Hence, individual patients with COPD should be classified by distinct phenotypes (stratified medicine). Research for characterization of different subtypes COPD has been conducted on according to multivariable approaches to address disease using multiple dimensions including clinical, physiologic, imaging, and endotyping [1, 9] (**Figure 1**). However, possible distinct phenotypes have been not yet established up to today. Recently,

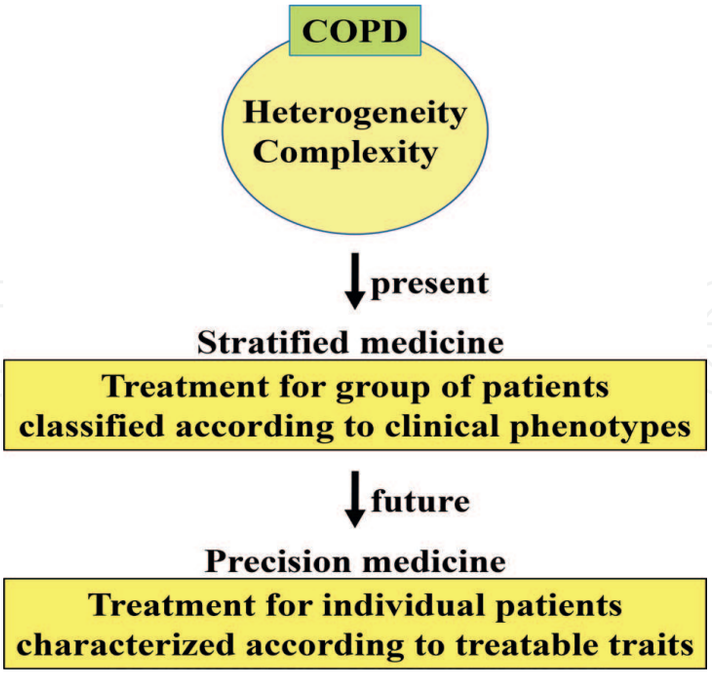

Figure 4.
A direction to aim for the management of COPD. Precision medicine of personalized medicine is suitable for a heterogeneous disease. Illustrated based on refs. [1, 3, 5].

precision medicine due to treatable trait has been proposed as aimed treatment for COPD in near future [3–5] (**Figure 4**). It is defined as treatments targeted to the needs of individual patients based on genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations (personalized medicine) [116–119].

Conflict of interest

Hiroaki Kume: none.
Ryuki Yamada: none.
Yuki Sato: none.

DOI: http://dx.doi.org/10.5772/intechopen.106949

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