COPD: Definition and Phenotypes

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KEYWORDS

• COPD • Definition • Diagnosis • Lung function • Chronic inflammation

KEY POINTS

- The definition of chronic obstructive pulmonary disease (COPD) is pragmatic and highlights the chronicity, the enhanced inflammation, and the importance of exacerbations and comorbidities.
- For the clinical diagnosis of COPD, exposures, symptoms, and airflow limitation are all required.
- Phenotypes are distinct COPD subgroups that deserve attention because they have either specific outcomes or require specific management.
- The frequent exacerbator is an important phenotype with higher future risks and a requirement for preventive treatments.

The definition and phenotypes in chronic obstructive pulmonary disease (COPD) are important topics. Not only should the definition clearly outline the disease but it is also, to a large extent, the conceptual framework on which we build the diagnostic criteria for the disease. *Phenotype* is a more recent term in COPD; however, the notion of COPD consisting of several subgroups is not new at all. In fact, it is often stated that COPD is a syndrome rather than a disease. Snider[1] has dealt with this COPD nosology quite extensively, and this article only deals briefly with these concepts. More space is devoted to the operationalization of the definition, diagnostic criteria, and phenotypes.

DEFINITION

Several definitions of COPD exist, and it would be wrong to say that one is clearly superior to another. The first definitions arising from working groups of the major respiratory societies came in 1995 from the American Thoracic Society (ATS)[2] and the European Respiratory Society (ERS).[3] Significant national guidelines have subsequently adopted and modified these definitions. The ATS and ERS definitions are shown in **Box 1**.

Neither of these definitions is particularly precise and can easily include disease entities that are not usually regarded as COPD, such as cystic fibrosis, sarcoidosis, and bronchiectasis. Importantly, neither of these definitions differentiates COPD from chronic asthma with airway remodeling. There are reasons for this; there is a significant overlap, and as acknowledged by the ATS mentioning airway hyperreactivity, one of the hallmarks of asthma, some patients with COPD do have features that make it difficult to separate them from patients with chronic ongoing asthma.

In 2001, the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) was launched; in their seminal document from 2001,[4] COPD is

Disclosure of Interests: J. Vestbo has received honoraria for advising Bioxydyn, Chiesi, GlaxoSmithKline, Novartis, Syntaxin, and Takeda. J. Vestbo has received honoraria for presenting from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Takeda. J. Vestbo is a member (vice-chair) of the Board of Directors of the Global Initiative for Obstructive Lung Diseases (GOLD), and he is the chair of the GOLD Scientific Committee.

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Clin Chest Med 35 (2014) 1–6
http://dx.doi.org/10.1016/j.ccm.2013.10.010

Box 1
COPD definitions from the ATS and ERS 1995

ATS 1995

"Chronic obstructive pulmonary disease is defined as a disease state characterized by the presence of airflow obstruction caused by chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible."[2]

ERS 1995

"COPD is defined as a disorder characterized by reduced maximum expiratory flow and slow forced emptying of the lungs, features which do not change markedly over several months. Most of the airflow limitation is slowly progressive and irreversible. The airflow limitation is due to varying combinations of airway disease and emphysema; the relative contribution of the two processes is difficult to define *in vivo*."[3]

defined as "a disease state characterized by airflow limitation that is not fully reversible. The airflow obstruction is usually both progressive and associated with an abnormal response of the lungs to noxious particles or gases."[4]

This definition differs fundamentally from those of the ATS and ERS in its inclusion of inflammation as well as the disease being a consequence of external stimuli (ie, noxious particles and gases). The GOLD document has been revised twice, in 2006 and 2011. On both occasions, the definition has been changed. In 2006[5] it was changed as follows:

> *Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.*[5]

The phrase *preventable and treatable* was also included in the definition proposed by the joint ATS/ERS document from 2004 and reflects an attempt to leave previous therapeutic nihilism regarding COPD behind. Importantly, this definition includes extrapulmonary effects as a contributor to severity in individual patients. These extrapulmonary effects were, however, not clearly defined; subsequently, many of these effects were seen as comorbidities. This point is reflected in the most recent GOLD definition[6] and is shown in **Box 2**.

The most recent changes reflect the increased knowledge of the disease that had accumulated since 2006. It has become clear that calling airflow limitation reversible in asthma and irreversible in COPD is too simplistic because patients with COPD can show significant reversibility with bronchodilators. However, airflow is never normalized; the airflow limitation was, thus, described as persistent. Similarly, we have seen that the chronic inflammation in airways and lung parenchyma does not have any specific abnormal characteristics. Rather, it seems that patients with COPD are unable to switch off inflammation; it was, therefore, thought that the phrase *enhanced inflammation* was a better descriptor. Extrapulmonary effects were replaced by comorbidities, and it was thought that the importance of exacerbations for individual patients was sufficient to warrant the inclusion of the term *exacerbations* in the definition.

DIAGNOSTIC CRITERIA

Is the current definition as proposed by GOLD ideal? The many different suggestions for a definition probably illustrates that this is not the case. The most important limitation is probably that it seems difficult to directly translate the definition into diagnostic criteria. In particular, we have no means of easily measuring the enhanced inflammation that we think is the basis for COPD. For this reason, our diagnostic criteria have heavily relied on the physiologic ascertainment of airflow limitation in patients with relevant exposure presenting to a physician.

In the GOLD 2011 revision,[6] the main section on diagnosis states that

> *A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the*

Box 2
COPD definition according to GOLD 2011

"Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients."[6]

disease. Spirometry is required to make the diagnosis in this clinical context; the presence of a post-bronchodilator [forced expiratory volume in the first second of expiration/forced vital capacity] FEV_1/FVC <0.70 confirms the presence of persistent airflow limitation and thus of COPD.[6]

It is important to note that the aforementioned definition relates to a clinical diagnosis (ie, a doctor making a diagnosis in a patient). Although this is clearly the most important aspect of a diagnosis, the epidemiology of COPD has for decades relied on field measurements of lung function using spirometry and simple questions excluding asthma and sometimes other respiratory disease. It may seem trivial, but this distinction has significant implications, not the least of which is for the discussion on the spirometric criteria for airflow limitation. In epidemiology, there is no proxy for patients going to a doctor; diagnostic criteria in epidemiology, therefore, resemble the criteria that would be used for screening, a tool not advocated by any major respiratory society or body.

However, the devil is often in the details. Importantly, in the 2013 update,[7] the terms *and/or* in the second line have been substituted by the term *and* as shown in **Box 3**.

In simple words, this means that in patients with relevant exposure and respiratory symptoms, a spirometry should be obtained; if airflow limitation (here defined as a postbronchodilator FEV_1/FVC <0.70) is found, this constitutes a diagnosis of COPD unless patients have other respiratory conditions, such as asthma, bronchiectasis, stenosing bronchial tumor, and so forth. Using the aforementioned strategy for COPD case finding will often result in a favorable yield; in Denmark, programs using this approach have resulted in diagnoses in 20% to 30% of those fulfilling the criteria for spirometry.[8]

Unfortunately, most of the debate on diagnostic criteria has focused on the choice of an FEV_1/FVC of less than 0.70 as the defining cutoff for airflow limitation. This cutoff is somewhat arbitrary, and opponents often argue that it has no scientific validity; instead, the lower limit of normal (LLN) is proposed.[9] There is little doubt that in most populations, the fixed 0.70 cutoff will result in more abnormal FEV_1/FVC ratios in the elderly and fewer in patients younger than 50 years.[10] This has led to a heated debate that seems futile because no gold standard exists; therefore, little real evidence exists in this area. In the epidemiologic setting, LLN should be preferred,[11] although great care should be taken when selecting reference values. In the clinical setting, no comparative studies exist. The virtue of the fixed 0.70 cutoff is simplicity and familiarity, and this is the reason why GOLD[7] and the UK National Center for Clinical Excellence have kept this criterion. The LLN is the physiologists' choice because it is anchored in our usual scientific definition of normality. However, this author really does not think it matters in clinical practice, and it seems that far too much energy has been spent on this issue considering the underrecognition, underdiagnosis, and undertreatment of COPD globally.

The probably most critical issue with the current diagnostic criteria is that they do not capture patients with pure emphysema until relatively late in the course of the disease. With an increasing focus on early diagnosis, the lack of sensitivity to a major COPD component – such as emphysema – reliance on simple spirometry for diagnosis may no longer be sufficient.

Box 3
COPD diagnostic criteria according to GOLD 2013

"A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context; the presence of a post-bronchodilator FEV_1/FVC <0.70 confirms the presence of persistent airflow limitation and thus of COPD."[7]

CONSIDERATIONS FOR FUTURE DIAGNOSTIC CRITERIA

So, because the current diagnostic criteria are far from ideal and the spirometric criteria are frequently the topic of futile debates, it may be worth considering if it is time to rethink diagnosis. When comparing with another chronic illness that in many ways resembles COPD, heart failure, it is clear that others have avoided debate on very specific cutoff values.[12] If we were to transfer similar thinking to COPD as that of the cardiologists when diagnosing heart failure, future COPD diagnostic criteria could take the shape of 'Symptoms and clinical features compatible with COPD in an individual with relevant exposures, where either physiologic measures or imaging support the presence of functional or structural abnormalities supporting a diagnosis of COPD.'

With the very general definition of COPD and the debated diagnostic criteria, those favoring the use of diagnoses such as emphysema and chronic bronchitis (the splitters) instead of COPD (the

lumpers) may wish to go back to the time before the umbrella term *COPD* was launched. But there is little doubt that COPD has come to stay. However, the splitters can comfort themselves in the fact that most COPD researchers and many clinicians find increasing value in splitting COPD into subgroups, into *phenotypes*.

COPD PHENOTYPES

A phenotype is usually considered the physical appearance or biochemical characteristic resulting from an interaction between its genotype and the environment. In COPD, whereby the underlying genes are mainly unknown or poorly characterized, *phenotype* has become almost synonymous with *clinical subgroup*. Several researchers have come up with a consensus definition of phenotypes[13] as shown in **Box 4**. This definition emphasizes that a phenotype has to be a subgroup that impacts on the outcome, that is, that having a particular phenotype means a different prognosis, a higher risk of exacerbation, a better response to a particular therapy, and so forth.

There are a few important issues regarding the concept of phenotypes. One phenotype is unlikely to be unique to one patient. In Snider's[14] original nonproportional Venn diagram, several overlapping subgroups were presented; subsequent studies trying to implement Snider's diagram to patients and populations showed that the overlap was indeed substantial. In addition to belonging to several phenotypes, patients can also have phenotypical traits. Considering emphysema as a phenotype, a patient could have mild emphysema and quite significant airflow limitation; one could speculate if emphysema had any importance in this particular patient. Also, specific combinations of phenotypes could be more important than others. Finally, in asthma, there is a move away from phenotypes toward endotypes,[15] whereby an endotype is basically a phenotype defined by a distinct pathophysiologic mechanism.

SPECIFIC COPD PHENOTYPES

The classic phenotypes of Snider's[14] diagram are asthma, emphysema, and chronic bronchitis. Asthma is likely to be considered a disease entity of its own, or a separate syndrome, despite the significant clinical overlap and the fact that asthma can be regarded as a risk factor for persistent airflow limitation. Features of asthma, such as airway hyperresponsiveness and reversibility, have been associated with a worse prognosis in some studies[16,17]; but particularly reversibility seems to be a very instable phenotype in COPD.[17]

Emphysema is a significant component of COPD and the extent of emphysema increases with increasing severity of airflow limitation. Emphysema is associated with a significantly increased decline in FEV_1, the hallmark of COPD.[18] Emphysema is a stable phenotype. The same can be said for chronic bronchitis, which in some studies has been associated with excess FEV_1 decline, particularly in younger adults,[19] with hospital admission as well as mortality.

Many other phenotypes are likely to exist as suggested in **Box 5**.

Having frequent exacerbations is a feature that has attracted considerable attention in recent years. Several studies have shown that only some patients with COPD experience exacerbations. But with the analyses of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study,[20] it became evident that having 2 or more exacerbations per year seemed a stable phenotype. This has significant implications. First, exacerbations are associated with a poor prognosis[21] and an excess FEV_1 decline[18,22]; secondly, several treatments are aimed at reducing exacerbations.[7] It can be argued whether 2 annual exacerbations is the right threshold for defining the frequent exacerbator, but at least the current literature seems to support this cutoff.

Another characteristic that has attracted attention lately is the presence of systemic inflammation. Early studies saw systemic inflammation as

Box 4
Phenotype definition

"A COPD phenotype is 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)."[13]

Box 5
Features of suggested phenotypes in COPD

Asthma
Bronchial hyperresponsiveness
Bronchodilator reversibility
Emphysema
Hyperinflation
Cachexia
Chronic bronchitis
Frequent exacerbations
Systemic inflammation

a feature of COPD; but with larger patient cohorts studied, we have learned more. First, not all patients with COPD have elevated markers of systemic inflammation. The markers most frequently measured have been C-reactive protein (CRP) and fibrinogen, and both are associated with subsequent hospital admission and death.[23] Recent analyses from the ECLIPSE study showed that multiple markers were likely to provide more relevant information than single markers,[24] and an epidemiologic study has shown that the use of 3 biomarkers (CRP, fibrinogen, and white blood cell count) seemed to provide prognostic value regarding incident comorbidities.[25] However, we currently have no treatment aimed at systemic inflammation in COPD.

Several other phenotypes exist and could be discussed. They are all based on our understanding of the disease, and most of them rely on single observational characteristics. Several groups have made an attempt at developing phenotypes based on an unbiased approach, including machine learning. They have been applied in both stable COPD and exacerbations; but, to date, the value of these approaches is difficult to evaluate.

Thus, the whole concept of COPD as a syndrome with specific entities is constantly evolving. The current definition has changed only a little over the last decade. It is likely to change within the coming decade. Whether the concept of phenotypes will evolve and be included in future standards for diagnosis and management remains to be seen.

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