Chronic obstructive pulmonary disease: aetiology, pathology, physiology and outcome

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Abstract

Chronic obstructive pulmonary disease (COPD) is a physiological diagnosis made on the basis of airflow obstruction. It develops when a genetically susceptible individual encounters a sufficient environmental trigger. Genetic susceptibility is complex and determined by multiple alleles, with the exception of emphysema caused by α_1-antitrypsin deficiency. Cigarette smoke is the usual trigger in the developed world, but globally the burning of biomass fuel in underventilated spaces is important. In individuals susceptible to the effects of smoke, the airway inflammatory response is qualitatively and quantitatively different from that in non-susceptible subjects and is predominantly composed of neutrophils, macrophages and CD8+ lymphocytes. Once established, inflammation can persist even after exposure to smoke has ceased. Airflow obstruction in COPD results from a combination of the airway wall inflammatory response, luminal mucus accumulation and loss of alveolar–airway attachments from coexisting emphysema. The major symptoms are breathlessness, cough and phlegem. Breathlessness is multifactorial, with a contribution from dynamic hyperinflation. Although progressive airflow obstruction is the hallmark of COPD, it is now recognized that it has other important outcomes, notably exacerbations and the development of co-morbidities. In addition, some patient may develop COPD from a normal rate of decline in lung function following submaximal lung growth.

Keywords Chronic bronchitis; chronic obstructive pulmonary disease; COPD; emphysema; exacerbation; spirometry

Key points

- Assessment of severity in COPD should be multifactorial, determined by severity of symptoms, frequency of exacerbations and spirometry
- The progression of airflow obstruction is highly variable between individuals, and accelerated decline of FEV_1 is not always a feature
- Phenotyping of patients using symptoms and physiological and radiological characteristics plays an important role in diagnosis and management

Definitions and diagnosis

The World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD) document[1] defines chronic obstructive pulmonary disease (COPD) as:

> a common preventable and treatable disease, 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.

The most important part of this definition relates to airflow obstruction. Airflow obstruction (a low ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC)) can be detected using spirometry, which is the only way to confirm a diagnosis of COPD. The severity of airflow obstruction (FEV_1) is one component used to grade the severity of COPD: the severity classification used in the GOLD document and National Institute for Health and Care Excellence clinical guideline, currently being updated, is summarized in Table 1. Although other severity assessments such as the multidimensional 'BODE' index – body mass index, airflow obstruction, dyspnoea, exercise capacity – can be a better predictor of outcomes such as mortality, the inclusion of an exercise tolerance assessment in BODE means that it is difficult to integrate into routine clinical practice.

As stated in the GOLD definition, the airflow obstruction in COPD is largely irreversible (in contrast to asthma). However, it is now recognized that the asthma can change from being 'reversible' to 'irreversible' on sequential tests when arbitrary classifications are used. In addition, the presence of reversibility does not predict the clinical response to either inhaled corticosteroids or bronchodilators. Diagnostic criteria are therefore based on post-bronchodilator spirometry, and routine reversibility testing is not recommended. When reversibility testing is performed and shows large changes (e.g. a change in FEV_1 >400 ml), a diagnosis of asthma should be suspected.

Finally, current guidelines recommend using a fixed FEV_1/FVC ratio of <0.7. Although simple to use, the FEV_1/FVC ratio declines with age, risking overdiagnosis of airflow obstruction in the elderly (and underdiagnosis in the young). There is therefore debate about changing to use an FEV_1/FVC ratio based on predicted lower limits of normal for the patient's age, sex, race and height.

COPD, chronic bronchitis and emphysema are not synonymous terms. COPD is a physiological diagnosis. Emphysema is an anatomical (patho-radiological) diagnosis defined as an abnormal and permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. Chronic bronchitis is a clinical diagnosis based on cough productive of sputum for most days of

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Diagnosis and severity classification of airflow limitation in COPD

Stage		Post-bronchodilator FEV_1/FVC ratio	Post-bronchodilator FEV_1 (% predicted)
1	Mild	<0.7	≥80%
2	Moderate	<0.7	50–79%
3	Severe	<0.7	30–49%
4	Very severe	<0.7	<30% (or <50% with respiratory failure[a])

[a] Respiratory failure is defined as a partial pressure of oxygen in arterial blood <8.0 kPa (60 mmHg) with or without a partial pressure of carbon dioxide in arterial blood >6.7 kPa (50 mmHg) while breathing air.

Table 1

the week, in ≥3 months of ≥2 consecutive years (and the absence of another specific diagnosis such as bronchiectasis). Many patients with COPD have varying degrees of both, producing disease heterogeneity and specific 'phenotypes' that have historically included emphysematous 'pink puffers' and bronchitic, hypercapnoeic 'blue bloaters'. Our understanding of phenotypes in COPD and ability to define them is now much more sophisticated. Grouping individuals according to physiological, radiological or other characteristics helps to predict prognosis and treatment response. For example, lung volume reduction surgery is recommended only for patients with COPD who have upper-lobe-predominant emphysema and a poor response to pulmonary rehabilitation.

Many cigarette smokers meet the definition of chronic bronchitis without having airflow obstruction (COPD); this is termed simple chronic bronchitis. Finally, some patients with chronic asthma can develop fixed airflow obstruction that is clinically indistinguishable from COPD.

Aetiology

The GOLD definition of COPD makes reference to an abnormal inflammatory response of the lung to noxious particles or gases.[1] The aetiology of COPD therefore requires an inflammatory insult to the lung. In the developed world, this is usually exposure to cigarette smoke. Globally, exposure to biomass fumes in underventilated spaces is important. Biomass is burned in stoves for cooking and heating, so in the developing world women are at particular risk of COPD. It is important to ask about other domestic, recreational and occupational exposures: use of drugs such as marijuana can result in accelerated disease.

Historically, about 15–20% of smokers develop COPD, although the figure is likely to be higher. This highlights that exposure alone is not sufficient to cause disease, which only occurs in individuals with a susceptible genetic background. Some people exposed to significant environmental tobacco smoke exposure (passive smoke) are also at increased risk, which has been a major driver for tobacco control legislation. The best-defined genetic determinant is α_1-antitrypsin deficiency, although this is an uncommon cause of COPD (1% in the UK). Further candidate susceptibility genes have been suggested by genome-wide association studies in COPD; one large study has noted particularly strong associations between severe disease and loci near *HHIP* (coding for the HHIP signalling protein) and *CHRNA3* (a nicotinic acetylcholine receptor subunit). These data and others suggest that genetic susceptibility to COPD is complex and probably determined by many alleles.

Historically, the aetiology of COPD was described by two hypotheses: a 'British hypothesis' that airflow obstruction results from multiple episodes of airway infection in patients with chronic bronchitis, and a 'Dutch hypothesis' that placed COPD on a spectrum of airway disorders with asthma. Components of both theories remain valid.

The fact that COPD requires a sufficient exposure to respiratory insults implies that it is preventable. Long-term efforts to reduce the global and individual burden of COPD require effective tobacco control measures.

Pathology

Exposure to tobacco smoke results in an airway inflammatory response. In individuals genetically susceptible to the effects of smoke, the inflammatory response is qualitatively and quantitatively different from that in non-susceptible people. Hence, the GOLD definition of COPD[1] makes reference to an abnormal inflammatory response, which can persist after smoking cessation.

The major site of physiological airflow obstruction in COPD is the small airways (defined as <2 mm in internal diameter). Pathological changes are also seen in the large airways and lung parenchyma. As the severity of airflow obstruction increases (reflected in a higher GOLD stage), there is an increase in the volume of inflammatory cells in the airway wall and accumulation of mucus in the airway lumen. The inflammatory infiltrate includes macrophages, neutrophils, CD8+ lymphocytes and, in GOLD stages 3 and 4, lymphoid follicles (Figure 1). This suggests an adaptive response to a self or microbial antigen and could explain the persistence of inflammation after smoking cessation.

In addition to the increase in volume of the airway wall and luminal mucus filling, there is a loss of airway attachments resulting from destruction of alveolar septa. Alveolar destruction (emphysema) results from an imbalance between pro- and anti-inflammatory mechanisms, as shown by α_1-antitrypsin deficiency. This autosomal co-dominant condition is associated with a reduced serum concentration of α_1-antitrypsin, the major defence against neutrophil elastase; unopposed action of the latter in the alveoli causes accelerated and extensive emphysema.

As COPD becomes more severe, bacterial colonization becomes important. Modern molecular methods have transformed our understanding of the airway microbiome, and it is now clear