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

Dheera RDD Dissanayake
John R Hurst

Dheera RDD Dissanayake MB BS is a Medical Officer at University Hospital Kotelawala Defence University, Sri Lanka. Competing interests: none declared.

John R Hurst PhD FRCP is Professor of Respiratory Medicine at University College London, UK. He has clinical and research interests in the diagnosis and management of COPD. Competing interests: JRH has received personal payment and payment to his institution for educational and advisory work, and support to attend meetings, from pharmaceutical companies that make medicines to treat COPD.

Abstract
Chronic obstructive pulmonary disease (COPD) is diagnosed on the basis of airflow obstruction, although the definition also encompasses emphysema. It develops when someone with an (often undefined) genetic susceptibility encounters sufficient inhaled triggers. Genetic susceptibility is complex and determined by multiple alleles; α_1-antitrypsin deficiency is best example of genetic risk. Cigarette smoke is the most common trigger in high-income countries, but globally important contributors include the burning of biomass fuel in under-ventilated spaces, and systematic disadvantage across the life-course affecting lung growth and development. The natural history of lung function decline and maximal lung function attainment is fundamental to understanding COPD. In individuals susceptible to the effects of smoke, the pulmonary inflammatory response is qualitatively and quantitatively different from that in non-susceptible individuals. Once established, inflammation persists even after exposure has ceased. Airflow obstruction in COPD results from a combination of airway wall inflammatory response, luminal mucus accumulation, destruction of small airways and loss of alveolar–airway attachments from emphysema. The major symptoms are breathlessness, cough and sputum expectoration. Breathlessness is multifactorial, but primarily driven by hyperinflation. Although progressive airflow obstruction is the hallmark of COPD, other outcomes are also important, notably exacerbations and the development of co-morbidities.

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

Key points
•Assessment of severity in chronic obstructive pulmonary disease should be holistic, determined by the severity of symptoms, frequency of exacerbations and extent of spirometric impairment, together with co-morbidities
•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, updated in 2023,[1] defines chronic obstructive pulmonary disease (COPD) as:
'*a heterogeneous lung condition characterised by chronic respiratory symptoms due to abnormalities of the airways and/or alveoli that cause persistent, often progressive, airflow obstruction*'.

Destruction of the alveoli is termed emphysema, and there is a disconnection between the more comprehensive GOLD definition above, which includes alveolar abnormalities, and the absolute requirement in GOLD to have demonstrated airflow obstruction to make a diagnosis of COPD. Emphysema may or may not be associated with 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, but only later in the course of disease. A FEV_1/FVC ratio <0.7 confirms the diagnosis of COPD.

The severity of airflow obstruction (FEV_1) is one component used to grade the severity of COPD: the severity classifications used in the GOLD document and National Institute for Health and Care Excellence (NICE) clinical guideline are summarized in Table 1. Although other severity assessments such as the multidimensional 'BODE' index – Body mass index, airflow Obstruction, Dyspnoea, Exercise capacity – are better predictors of outcomes such as mortality, the inclusion of a measurement of exercise capacity in BODE means that it is difficult to integrate into routine clinical practice.

Airflow obstruction in COPD is largely irreversible, in contrast to the classic picture of asthma. In addition, the presence of reversibility does not predict the clinical response to either inhaled corticosteroids or bronchodilators. Diagnostic criteria for COPD are based on post-bronchodilator spirometry. 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.

Current guidelines from both GOLD and NICE recommend using a fixed FEV_1/FVC ratio of <0.7. Although simple to use, the FEV_1/FVC ratio declines with age because of changes in the mechanical properties of the chest wall, risking the overdiagnosis of airflow obstruction in elderly individuals (and underdiagnosis in the young). It has therefore been suggested that the lower limit of normal FEV_1/FVC ratio, which is adjusted for the person's age, sex, race and height, should be used as the diagnostic criterion.

COPD, chronic bronchitis and emphysema are not synonymous. As described above, emphysema is an anatomical (patho-radiological) diagnosis; it is 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 the week, in ≥3 months for ≥2 consecutive years (and the absence of another specific diagnosis such as bronchiectasis).

Many individuals with COPD have varying degrees of both emphysema and chronic bronchitis, 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 more sophisticated, and grouping individuals according to physiological, radiological or other characteristics helps to predict the 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 demonstrable airflow obstruction; 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 development of COPD is usually thought to require an inflammatory insult to the lung. In high-income countries, this is usually linked to exposure to cigarette smoke. Globally, exposure to biomass fumes in underventilated spaces is important, and most COPD deaths in the world occur in low- and middle-income countries. Since biomass is commonly burned in stoves for cooking and heating, in such countries women are at particular risk of COPD. Other domestic, recreational and occupational exposures are also acknowledged: the use of drugs such as marijuana can result in accelerated disease.

There are other causes of the airflow obstruction that characterizes COPD, particularly in low-income settings, including poor lung growth and development through the life-course, and acute and chronic infections such as tuberculosis. Whether these are true causes of COPD in the sense of an inflammatory lung disease, or other conditions that result in airflow obstruction, remains debated. GOLD currently considers these alternative causes of airflow obstruction as COPD 'aetiotypes'.

Historically, about 15–20% of smokers were thought to develop COPD, although the true proportion is probably higher. That only a minority of smokers develop COPD emphasizes the principle that exposure to smoke is necessary but 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 of COPD, 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. Further candidate susceptibility genes have been suggested by genome-

wide association studies (GWASs) in COPD; a recent meta-analysis of GWASs from the UK Biobank and the International COPD Genetics Consortium identified 82 loci associated with COPD, 35 of which had not previously been described. Fourteen of these loci were shared with asthma and pulmonary fibrosis, and many of the loci identified clustered into groups based on co-morbidities such as coronary artery disease and type 2 diabetes mellitus.

These data and others suggest that genetic susceptibility to COPD is complex and probably determined by many alleles. Current research efforts are focused on understanding the longitudinal patterns of disease, as well as the reasons why COPD patients have such a variable presentation. By doing this, and by using increasingly sophisticated genomics techniques, researchers are hoping to find more and better genetic associations with COPD.

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 pertinent.

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

Pathology

Exposure to 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. This abnormal inflammatory response can persist after smoking cessation.

The major site of pathological 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, as measured by the FEV_1, there is an increase in the volume of inflammatory cells in the airway wall and the accumulation of mucus in the airway lumen. The inflammatory infiltrate includes macrophages, neutrophils, CD8+ lymphocytes and, in GOLD stages 3 and 4, lymphoid follicles (see Further reading). This suggests an adaptive response to a self or microbial antigen and could explain the persistence of inflammation after smoking cessation. Less is known about the pathology of biomass-driven COPD.

In addition to the inflammatory increase in volume of the airway wall and luminal mucus filling, there is a loss of airway attachments resulting from the destruction of alveolar septa. Alveolar destruction and emphysema result from an imbalance between pro- and anti-inflammatory mechanisms, as in 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, alterations in airway bacteria occur that contribute to disease pathogenesis. Modern molecular methods have transformed our understanding of the airway microbiome, and it is now clear that the old view of the airway as sterile in health is incorrect.[2] What used to be considered the development of colonization in COPD is now thought to represent a change in colonizing species called 'dysbiosis'.

Individuals colonized with bacterial species such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* are known to have an accelerated decline in lung function and more frequent acute respiratory infections called COPD exacerbations. *Pseudomonas aeruginosa* and atypical *Mycobacteria* can be seen in advanced COPD. There may be an interaction between acute viral and bacterial pathogens, with rhinovirus infection leading to an outgrowth of *H. influenzae* from existing colonies in COPD but not in health. This may help to explain the severity of the response to common pathogens during COPD exacerbations.

Physiology

Figure 1 shows a flow–volume loop from a patient with COPD, at baseline and with an additional demand such as exercise or exacerbation. In COPD, the inspiratory curve is normal or near normal. However, shortly after reaching the peak expiratory flow, collapse of the medium and small airways results in a reduction in airflow. This gives the characteristic 'scalloped' shape of the expiratory portion of the loop, compared with the more gradual decline from a slightly higher peak expiratory flow in health, which produces a smooth curve.

Dynamic hyperinflation puts an additional load on the respiratory muscles, which can already be weakened by the skeletal muscle weakness that can accompany COPD. Dynamic hyperinflation is the term used to describe additional gas trapping within the chest that occurs in expiratory flow-limited individuals upon increasing their respiratory rate. This can occur, for example, on exercise, during exacerbations or with anxiety-related hyperventilation.

Outcomes

The classic description of the natural history of lung function in COPD is derived from the work of Fletcher and Peto,[3] suggesting an accelerated decline of lung function in smokers susceptible to the effects of cigarette smoke. It is now acknowledged that this model does not account for insults that can affect attaining maximal lung capacity in early adult life. These insults might include starting smoking in adolescence (which is common), or paediatric disease such as the bronchopulmonary dysplasia observed in the survivors of preterm birth. Lower baseline lung capacity in these individuals is not necessarily accompanied by an accelerated decline in FEV_1, despite accounting for previous smoking exposure.[4]

It is now recognized that the rate of FEV_1 decline is highly variable, with some COPD patients exhibiting a slower decrease than others. The decline in lung function, as measured by FEV_1, is faster in patients with emphysema and – most importantly – current smokers. This is shown in Figure 2, and describes a number of different patient phenotypes. Overall, it is clear that smokers with COPD who are unable to quit smoking (or those remaining exposed to other pollutants) continue to experience an accelerated decline in lung function; this is associated with progressive symptoms and functional limitation, the development of respiratory failure and death.

In addition to decline in lung function, exacerbations are important events. Exacerbations are characterized by deteriorations in respiratory symptoms, principally increased breathlessness, and/or a change in the character of expectorated sputum. Most exacerbations are caused by episodes of tracheobronchial infection with bacteria or respiratory viruses. Other causes of symptom changes, for example heart failure and pulmonary emboli, should be considered and excluded. Although exacerbations generally become more frequent and more severe as the underlying COPD becomes more severe,[5] they do occur in less severe disease.

Severity of exacerbation is a difficult concept, representing both the severity of the underlying disease and the exacerbation trigger. Susceptibility to exacerbations varies between patients, and the best predictor of how many exacerbations a person will experience in the current year is how many they experienced the previous year.[5] Exacerbations and hospitalizations are associated with much of the healthcare cost attributable to COPD. Exacerbation of COPD is one of the most common reasons for emergency hospital admission. Patients susceptible to frequent exacerbations have a poor quality of life, accelerated decline of lung function and greater mortality. Prevention of exacerbations is therefore a key goal of COPD management strategies.

The GOLD definition of COPD also references the extrapulmonary effects of COPD. Because COPD is associated with cigarette smoke and increasing age, common risk factors for multimorbidity, co-morbidities that are more common in COPD patients than smoking- and age-matched controls can be thought of as extrapulmonary effects of COPD. A common mechanism could be the increased systemic inflammation seen in COPD. Such systemic manifestations include an increased risk of cardiovascular disease, lung cancer, cachexia, osteoporosis, skeletal muscle weakness and depression.

Addressing co-morbidities in COPD is important because many patients with COPD die from such conditions rather than from airway disease, and co-morbidities such as anxiety and depression can have a profound effect on quality of life. Health status can be ascertained using the COPD Assessment Test, a score of >20 indicating a high impact on daily living. This and other parameters can be used to categorize patients, as shown in Figure 3.

COPD remains a major health challenge in the UK and more widely. Around 1 in 20 people >40 years of age are diagnosed with COPD in the UK, and its prevalence is increasing. It kills 25,000 people annually in England and Wales alone, and across the UK it is estimated that there are 835,000 patients in whom the condition has been diagnosed and perhaps 2,200,000 more in whom it remains undiagnosed. Understanding effective prevention, identification and management of COPD is therefore a core skill required across the spectrum of primary and secondary care, in general and specialist areas.

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Diagnosis and severity classification of airflow limitation in COPD

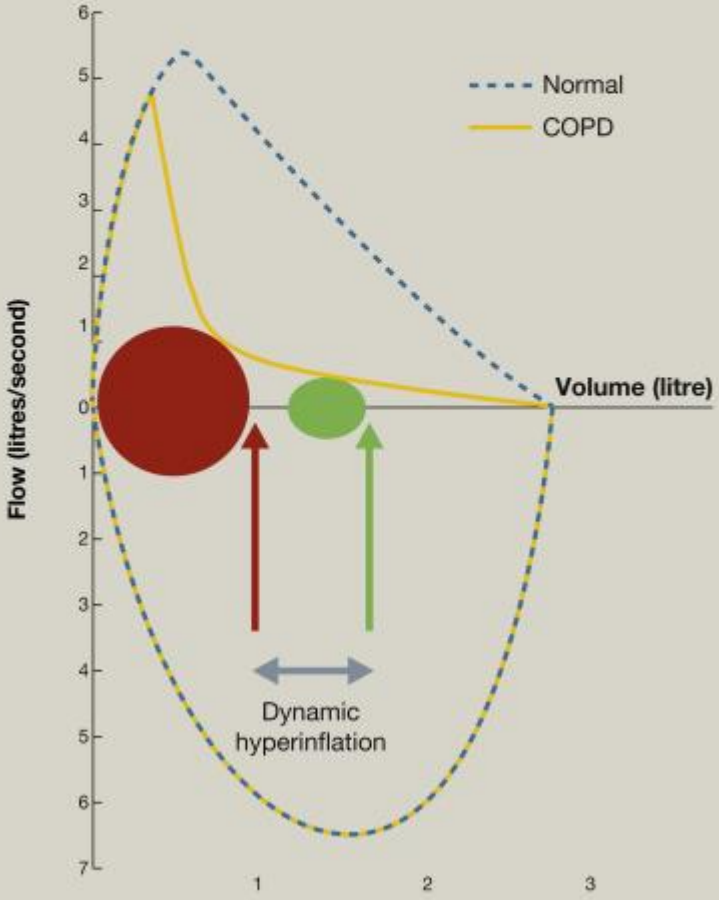
NICE/GOLD stage		Post-bronchodilator FEV_1/FVC ratio	Post-bronchodilator FEV_1 (% predicted)
1	Mild	<0.7	≥80%
2	Moderate	<0.7	50–79%
3	Severe	<0.7	30–49%
4	Very severe	<0.7	<30% (or <50% with respiratory failure[a])

[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.

A flow–volume loop from a patient with COPD

Positive flow (above the *x*-axis) is expiratory and negative flow (below the *x*-axis) inspiratory. On expiration, collapse of the small airways results in a reduction of airflow and the characteristic 'scalloped' shape. At rest, ventilatory requirements in milder disease may be maintained (green circle). At times of additional demand (such as exercise or exacerbation) patients become expiratory flow-limited and develop progressive dynamic hyperinflation and breathlessness.

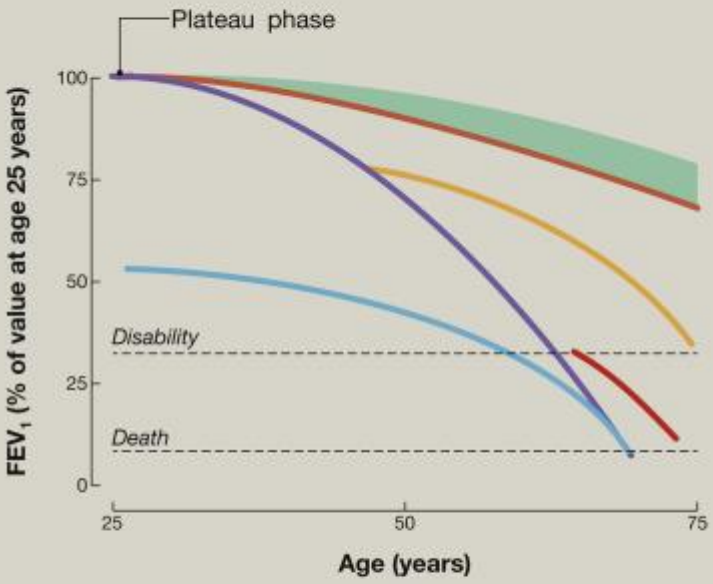


COPD, chronic obstructive pulmonary disease.

Figure 1

The natural history of chronic airflow obstruction

Smokers susceptible to the effects of cigarette smoke (purple line) lose lung function (FEV_1) more rapidly than those not susceptible or non-smokers (green range). Smoking cessation does not reverse the FEV_1 loss but does reduce the accelerated rate of lung function decline (yellow and red lines).

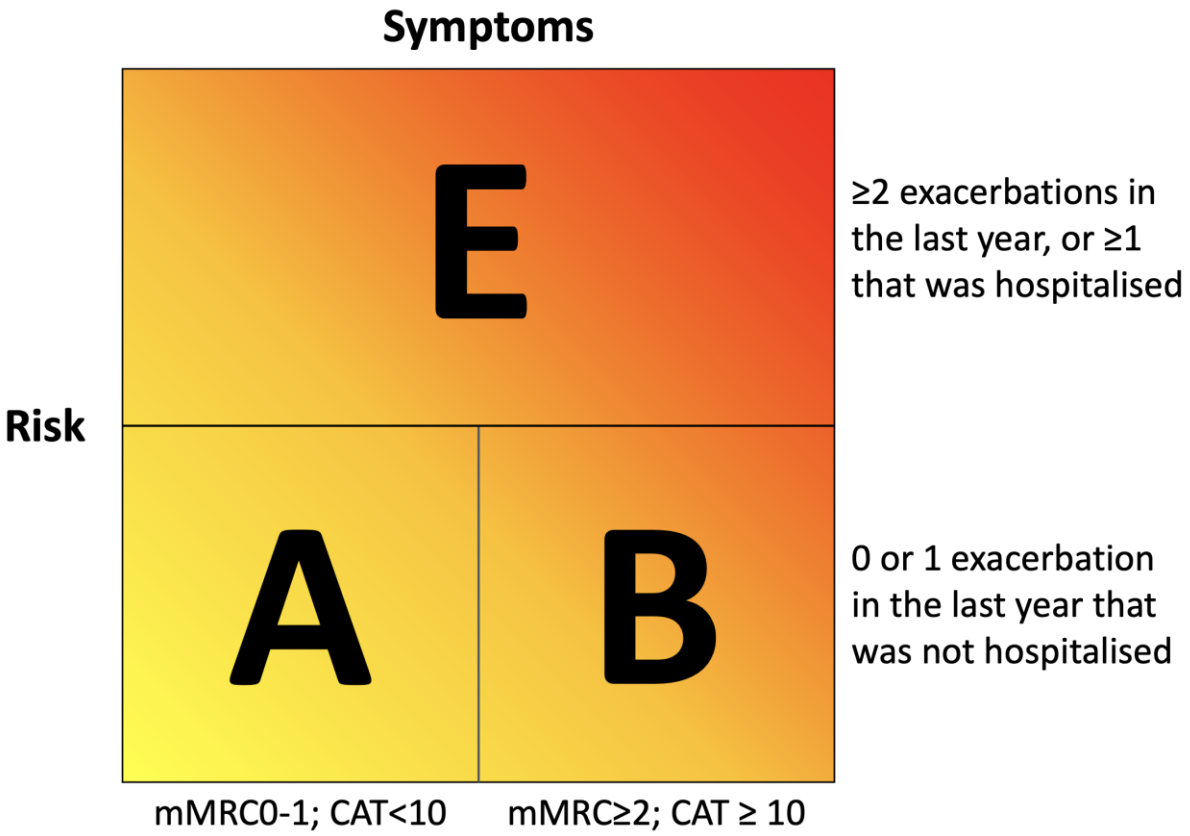


- Never smoked or not susceptible to smoke
- COPD diagnosis, but reduced decline
- Smoked regularly and susceptible to its effects
- Stopped smoking at 45 years
- Stopped smoking at 65 years
- Reduced baseline FEV_1, normal decline

On stopping smoking, the subsequent decrease in FEV_1 is similar to that seen in healthy non-smokers.

Adapted from: Fletcher C *et al. The natural history of chronic bronchitis and emphysema. An 8-year follow-up study of working men in London*. Oxford: Oxford University Press, 1976.

Figure 2



Combined COPD assessment
A more comprehensive assessment of the impact of COPD on the individual at first diagnosis can be made by considering the level of symptoms (measured using the 5-item modified Medical Research Council (mMRC) breathlessness questionnaire, or the 8-item COPD Assessment Test (CAT) questionnaire) and the risk of future exacerbations (based on the past exacerbation history). This can be used to guide first-line pharmacological therapy (e.g. a dual long-acting β-adrenoceptor agonist/long-acting muscarinic antagonist bronchodilator is recommended for GOLD group B). Adapted from the Global Initiative for Chronic Obstructive Lung Disease document.[1]

Figure 3

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