1 Pathophysiology

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COPD: DEFINITION

The definition of COPD that is recognised by both the American Thoracic Society and the European Respiratory Society is that it is a preventable and treatable disease characterised by airflow limitation that is not fully reversible and does not change markedly over several months (American Thoracic Society 1962; 2005). The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.

COPD is an umbrella term that covers many well-known smoking-related lung diseases. They include chronic bronchitis, emphysema and some cases of chronic asthma. Chronic bronchitis is defined clinically as chronic productive cough for three months in each of two successive years in a patient in whom other causes of productive chronic cough have been excluded (American Thoracic Society 1962). Emphysema is defined pathologically as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis (Snider et al. 1985). Patients with COPD have features of both conditions, although one may be more prominent than the other.

RISK FACTORS

SMOKING

Smoking is the main cause of COPD, but other environmental and industrial pollutants can also result in COPD in people who have never smoked. Passive exposure to cigarette smoke also can contribute to respiratory symptoms and COPD.

POLLUTION

Indoor air pollution from some fuels used for cooking and heating in poorly vented dwellings may contribute to airflow limitation.

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With respect to outdoor pollution, studies have shown a relationship between levels of atmospheric pollution and respiratory problems in both adults and children. Therefore, outdoor air pollution adds to the burden of inhaled particles, although to what degree is unknown. It is mainly comprised of particulates and gases. The particulates mainly originate from the incomplete combustion of solid fuels and diesel, ash and fine dusts. The main gaseous components are the various oxides of sulphur, nitrogen and carbon, again from the combustion of fossil fuels, hydrocarbons and ozone. The role of outdoor air pollution in the evolution of COPD remains controversial.

OCCUPATION

Any occupation in which the local environment is polluted with gases and particles increases the risk of developing COPD. There is evidence that cadmium and silica also increase the risk of COPD particularly in smokers. At-risk occupations include coal miners, metal workers, grain handlers, cotton workers and workers in paper mills.

INFECTION

The role of viral infections of the upper and lower respiratory tract in the pathogenesis of COPD is still unclear. Respiratory infections in early childhood also are associated with reduced lung function and increased respiratory problems in adulthood, which may lead to COPD. Once COPD is established, repeated infective exacerbations of airflow obstruction, either viral or bacterial, may accelerate the decline in lung function.

INHERITED

There also is a rare, inherited form of emphysema known as alpha-1-antitrypsin deficiency, which causes COPD. This mainly results in panacinar emphysema that largely affects the lower lobes.

GENDER

It is frequently stated that COPD is more prevalent in men. However, when smoking and occupational exposure are taken into account, the relative risk of developing COPD is not significantly higher in men than women.

SOCIO-ECONOMIC STATUS

In studies conducted in the UK in the 1950s and the 1960s, there is a clear social class gradient for COPD with a higher prevalence in the lower socio-economic groups. There is also a higher prevalence of smoking in the lower
socio-economic strata, and they are more likely to be employed in jobs where they may be at risk from occupational exposure. Poorer housing conditions and use of fossil fuels for heating without adequate ventilation may also be important contributory factors.

**PATHOLOGY**

The pathogenic mechanisms causing COPD are not clear but are likely to be diverse. The increased number of activated polymorphonuclear leukocytes and macrophages release elastases in a manner that cannot be counteracted effectively by antiproteases, resulting in lung destruction. Pathological changes in COPD occur in the large (central) airways, the small (peripheral) bronchioles, lung parenchyma and pulmonary vasculature. These will now be described in turn.

**CENTRAL AIRWAYS**

The central airways include the trachea, bronchi, and bronchioles greater than 2–4 mm in internal diameter. In patients with chronic bronchitis, the epithelium and associated ducts are infiltrated with an inflammatory exudate of fluid and cells (Mullen et al. 1985; O'Shaughnessy et al. 1997). The predominant cells in this inflammatory exudate are macrophages and CD8+ T lymphocytes (Saetta et al. 1993; O'Shaughnessy et al. 1997).

Chronic inflammation in the central airways is also associated with an increase in the number of goblet and squamous cells; dysfunction, damage, and/or loss of cilia; enlarged submucosal mucus-secreting glands (Reid 1960); an increase in the amount of smooth muscle and connective tissue in the airway wall (Jamal et al. 1984); degeneration of the airway cartilage (Thurlbeck et al. 1974; Haraguchi et al. 1999); and mucus hypersecretion. The various pathological changes in the central airways are responsible for the symptoms of chronic cough and sputum production, which identify people at risk for COPD and may continue to be present throughout the course of the disease.

**PERIPHERAL AIRWAYS**

The peripheral airways include small bronchi and bronchioles that have an internal diameter of less than 2 mm. The early decline in lung function in COPD is correlated with inflammatory changes in the peripheral airways, similar to those that occur in the central airways: exudate of fluid and cells in the airway wall and lumen, goblet and squamous cell metaplasia of the epithelium (Cosio et al. 1978), oedema of the airway mucosa due to inflammation, and excess mucus in the airways due to goblet cell hyperplasia.
However, the most characteristic change in the peripheral airways of patients with COPD is airway narrowing. Inflammation initiated by cigarette smoking (Niewoehner et al. 1974) and other risk factors (Pride & Burrows 1995) leads to repeated cycles of injury and repair of the walls of the peripheral airways. Injury is caused either directly by inhaled toxic particles and gases such as those found in cigarette smoke, or indirectly by the action of inflammatory mediators; this injury then initiates repair processes. It seems likely that disordered repair processes can lead to tissue remodelling with altered structure and function. Cigarette smoke may impair lung repair mechanisms, thereby further contributing to altered lung structure (Laurent et al. 1983; Osman et al. 1985; Nakamura et al. 1995). Even normal lung repair mechanisms can lead to airway remodelling because tissue repair in the airways, as elsewhere in the body, may involve scar tissue formation. This injury and repair process results in increasing collagen content and scar tissue formation that narrows the lumen and produces fixed airways obstruction (Matsuba & Thurlbeck 1972).

The peripheral airways become the major site of airways obstruction in COPD, and direct measurements of peripheral airways resistance (Hogg et al. 1968) show that the structural changes in the airway wall are the most important cause of the increase in peripheral airways resistance in COPD.

Inflammatory changes such as airway oedema and mucus hypersecretion also contribute to airway narrowing in COPD as does the loss of elastic recoil, but fibrosis of the small airways plays the largest role (Figure 1.1).

![Figure 1.1. Pathophysiology of COPD](image-url)
LUNG PARENCHYMMA

The lung parenchyma includes the gas-exchanging surface of the lung (respiratory bronchioles and alveoli) and the pulmonary capillary system.

The most common type of parenchymal destruction in COPD patients is the centrilobular form of emphysema, which involves dilatation and destruction of the respiratory bronchioles (Leopold & Geoff 1957). These lesions occur more frequently in the upper lobes. In advanced disease they may appear diffusely throughout the entire lung and also involve destruction of the pulmonary capillary bed.

Panacinar emphysema, which extends throughout the acinus, is the characteristic lesion seen in alpha-1 antitrypsin deficiency and involves dilatation and destruction of the alveolar ducts and sacs as well as the respiratory bronchioles. It tends to affect the lower more than upper lung regions. Because this process usually affects all of the acini in the secondary lobule, it is also referred to as panlobular emphysema. The primary mechanism of lung parenchyma destruction, in both smoking-related COPD and alpha-1 antitrypsin deficiency, is thought to be an imbalance of endogenous proteinases and antiproteinases in the lung.

PULMONARY VASCULATURE

Pulmonary vascular changes in COPD are characterised by a thickening of the vessel wall that begins early in the natural history of the disease, when lung function is reasonably well maintained and pulmonary vascular pressures are normal at rest (Wright et al. 1983). Endothelial dysfunction of the pulmonary arteries occurs early in COPD (Peinado et al. 1998). Since endothelium plays an important role in regulating vascular tone and cell proliferation, it is likely that endothelial dysfunction might initiate the sequence of events that results ultimately in structural changes. Thickening of the intima is the first structural change (Wright et al. 1983), followed by an increase in vascular smooth muscle and the infiltration of the vessel wall by inflammatory cells, including macrophages and CD8+ T lymphocytes (Peinado et al. 1999).

These structural changes are correlated with an increase in pulmonary vascular pressure that develops first with exercise and then at rest. As COPD progresses, greater amounts of smooth muscle and collagen (Riley et al. 1977) further thicken the vessel wall. In severe disease, the changes in the muscular arteries may be associated with emphysematous destruction of the pulmonary capillary bed.

PATHOPHYSIOLOGY

Pathological changes in COPD lead to corresponding physiological abnormalities that usually become evident first on exercise and later also at rest.
Physiological changes characteristic of the disease include: mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension, and cor pulmonale, and they usually develop in this order over the course of the disease. In turn, the various physiological abnormalities contribute to the characteristic symptoms of COPD – chronic cough and sputum production and dyspnoea.

MUCUS HYPERSECRETION AND CILIARY DYSFUNCTION

Mucus hypersecretion in COPD is caused by the stimulation of the enlarged mucus-secreting glands and increased number of goblet cells by inflammatory mediators such as leukotrienes, proteinases, and neuropeptides. Ciliated epithelial cells undergo squamous metaplasia leading to impairment in mucociliary clearance mechanisms. These changes are usually the first physiological abnormalities to develop in COPD, and can be present for many years before any other physiological abnormalities develop.

AIRFLOW LIMITATION AND PULMONARY HYPERINFLATION

Expiratory airflow limitation is the hallmark physiological change of COPD. The airflow limitation characteristic of COPD is primarily irreversible, with a small reversible component. Several pathological characteristics contribute to airflow limitation and changes in pulmonary mechanics.

The irreversible component of airflow limitation is primarily due to remodelling (Hogg et al. 1968; Matsuba & Thurlbeck 1972; Cosio et al. 1978; Mullen et al. 1985; Matsuba et al. 1989; Kuwano et al. 1993), fibrosis and narrowing of the small airways that produces fixed airways obstruction and a consequent increase in airways resistance. The sites of airflow limitation in COPD are the smaller conducting airways, including bronchi and bronchioles less than 2 mm in internal diameter.

Parenchymal destruction (emphysema) plays a smaller role in this irreversible component but contributes to expiratory airflow limitation and the increase in airways resistance in several ways. Destruction of alveolar attachments inhibits the ability of the small airways to maintain patency (Dayman 1951). Alveolar destruction is also associated with a loss of elastic recoil of the lung (Butler et al. 1960; Mead et al. 1967), which decreases the intra-alveolar pressure driving exhalation.

Although both the destruction of alveolar attachments to the outer wall of the peripheral airways and the loss of lung elastic recoil produced by emphysema have been implicated in the pathogenesis of peripheral airways obstruction (Dayman 1951; Lane et al. 1968), direct measurements of peripheral airways resistance show that the structural changes in the airway wall are the most important cause of the increase in peripheral airways resistance in COPD.
Airway smooth muscle contraction, ongoing airway inflammation, and intraluminal accumulation of mucus and plasma exudate may be responsible for the small part of airflow limitation that is reversible with treatment. Inflammation and accumulation of mucus and exudate may be particularly important during exacerbations (Burnett & Stockley 1981).

Airflow limitation in COPD is best measured through spirometry, which is key to the diagnosis and management of the disease. The essential spirometric measurements for diagnosis and monitoring of COPD patients are the forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC). As COPD progresses, with increased airway wall thickness, loss of alveolar attachments, and loss of lung elastic recoil, both FEV₁ and FVC decrease. A decrease in the ratio of FEV₁ to FVC is often the first sign of developing airflow limitation. FEV₁ declines naturally with age, but the rate of decline in COPD patients is generally greater than that in normal subjects.

With increasing severity of airflow limitation, expiration becomes flow-limited during tidal breathing. Initially, this occurs only during exercise, but later it is also seen at rest. In parallel with this, functional residual capacity (FRC) increases due to the combination of the decrease in the elastic properties of the lungs and premature airway closure.

As airflow limitation develops, the rate of lung emptying is slowed and the interval between inspiratory efforts does not allow expiration to the relaxation volume of the respiratory system; this leads to dynamic pulmonary hyperinflation. The increase in FRC can impair inspiratory muscle function.

These changes occur as the disease advances but are almost always seen first during exercise, when the greater metabolic stimulus to ventilation stresses the ability of the ventilatory pump to maintain gas exchange.

**AIRFLOW RESISTANCE**

Resistance is defined as the pressure required to produce flow. In emphysema, the destruction of collagen and elastin fibres leads to a reduction in the radial traction of the airways, which in turn leads to a reduced airway calibre. Chronic bronchitis is associated with a chronic inflammatory process that consists of cellular infiltration and airway wall oedema; this along with the mucus in the lumen leads to a further reduction in airway calibre. Chronic inflammatory process develops into granulation tissue and peribronchial fibrosis. These irreversible changes initially start in the small airways but can and often do progress into the larger airways. Consequently the reduced airway calibre results in increased airways resistance and therefore airflow resistance. During expiration there is increased pressure around the airways that increases the tendency for the airways to collapse. Increased airways resistance is indicated by a reduced forced expiratory volume FEV₁/FVC ratio and increased expiratory time. In the normal lung, resistance of the smaller airways makes up a small percentage of the total airways resistance (Hogg et al. 1968). But in patients
with COPD the total lower airways resistance approximately doubles, and most of the increase is due to a large increase in peripheral airways resistance (Hogg et al. 1968). There is wide agreement that the peripheral airways become the major site of obstruction in COPD.

COMPLIANCE

**Lung compliance** is defined as change in volume per unit change in pressure. This measurement represents the relationship between the volume of the respiratory system and the recoil pressures of the lungs and chest wall. **Lung recoil pressure** comprises two components:

1. Tension of the elastic fibres and connective tissue network of the lungs.
2. Surface tension at the air–liquid interface in the alveoli; at FRC the lung recoil pressure is equal to the outward recoil pressure of the chest wall.

Low compliance infers that the lungs are stiff in that for a given pressure a small volume change is achieved; a high value of compliance indicates that the lungs inflate easily as for a given pressure there is a large volume change. The pressure–volume relationship of the respiratory system is shown in Figure 1.2.

In health, breathing occurs over the linear part of the curve, i.e. between FRC and FRC + 500 mls, where the compliance values are high and the work of breathing least.

**PEEP**

Dynamic airway collapse and insufficient tidal expiratory time result in the end-expiratory lung volume rising above the FRC, leading to dynamic hyper-inflation. This in turn means that due to end-expiratory elastic recoil the alveo-
lar pressure remains positive at the end of expiration. Therefore before the inspiratory muscles can create a negative pressure in the central airways and produce inspiratory flow, they must overcome this positive end expiratory pressure (PEEP) in the alveoli, termed intrinsic PEEP (IPEEP).

**GAS EXCHANGE ABNORMALITIES**

In advanced COPD, the combination of peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduces the lung’s capacity for gas exchange, producing hypoxaemia and in advanced disease, also hypercapnia. The correlation between routine lung function tests and arterial blood gases is poor, but significant hypoxaemia or hypercapnia is rare when FEV₁ is greater than 1.00 L (Lane et al. 1968). Hypoxaemia is initially only present during exercise, but as the disease continues to progress it is also present at rest.

Inequality in the ventilation/perfusion ratio (VA/Q) is the major mechanism behind hypoxaemia in COPD, regardless of the stage of the disease. Chronic hypercapnia usually reflects inspiratory muscle dysfunction and alveolar hypoventilation.

**PULMONARY HYPERTENSION AND COR PULMONALE**

Pulmonary hypertension develops late in the course of COPD usually after the development of severe hypoxaemia (PaO₂ < 8.0 kPa or 60 mm Hg) and often hypercapnia as well. It is the major cardiovascular complication of COPD and is associated with the development of cor pulmonale and with a poor prognosis (MacNee 1994). However, even in patients with severe disease, pulmonary arterial pressure is usually only modestly elevated at rest, though it may rise markedly with exercise. Pulmonary hypertension in COPD is believed to progress rather slowly even if left untreated. Further studies are required to firmly establish the natural history of pulmonary hypertension in COPD.

Factors that are known to contribute to the development of pulmonary hypertension in patients with COPD include vasoconstriction; remodelling of pulmonary arteries, which thickens the vessel walls and reduces the lumen; and destruction of the pulmonary capillary bed by emphysema, which further increases the pressure required to perfuse the pulmonary vascular bed.

In advanced COPD, hypoxia plays the primary role in producing pulmonary hypertension, both by causing vasoconstriction of the pulmonary arteries and by promoting remodelling of the vessel wall.

Pulmonary hypertension is associated with the development of cor pulmonale. Cor pulmonale is defined as right ventricular failure resulting from diseases affecting the function and/or structure of the lungs, except when these pulmonary alterations are due to diseases that primarily affect the left side of the heart, as in congenital heart disease.
The prevalence and natural history of cor pulmonale in COPD are still to be clarified. Pulmonary hypertension and reduction of the vascular bed due to emphysema can lead to right ventricular hypertrophy and right heart failure, but right ventricular function appears to be maintained in some patients despite the presence of pulmonary hypertension (Biernacki et al. 1988). Right heart failure is associated with venous stasis and thrombosis that may result in pulmonary embolism and further compromise the pulmonary circulation.

Severe stable COPD is associated with severe derangement in respiratory mechanics and abnormal V/Q ratios. During an exacerbation the inflammatory process in the airways further impairs the respiratory mechanics as well as further challenging the gas exchange process.

During an exacerbation the increase in airflow resistance results in an increase in the work of breathing of the inspiratory muscles and also reduces the rate of lung emptying. The presence of expiratory flow limitation means that there is insufficient tidal expiration time to empty the lungs; consequently the end-expiratory lung volume rises above the FRC, leading to dynamic hyperinflation. This in turn means that due to end-expiratory elastic recoil, the alveolar pressure remains positive at the end of expiration. Therefore, before the inspiratory muscles can create a negative pressure in the central airways and produce inspiratory flow, they must overcome this positive end-expiratory pressure in the alveoli, termed intrinsic peep (IPEEP). This intrinsic PEEP adds to the resistive load. So an acute exacerbation of COPD is associated with an increase in the resistive and elastic loads by an increase in the inspiratory workload. Additionally, dynamic hyperinflation decreases the overall pressure generating capacity by the inspiratory muscles. This is due in part to the shortening of the inspiratory muscles and the alteration in the geometric interaction between the muscle groups.

In patients with chronic obstructive pulmonary disease, a thorough understanding on the clinician’s part of the pathophysiologic basis of airflow limitation greatly enhances decisions regarding patient care.

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