Pathophysiology of COPD

Learning Objectives

This module will provide you with a brief overview of the pathophysiology of COPD.

By the end of this module you will be able to:

- Explain the difference between healthy lungs and lungs with COPD
- Describe the changes that occur in the lungs due to emphysema
- Describe the symptoms that are characteristic of chronic bronchitis
- Identify other respiratory conditions that may be confused with COPD
- Recognise the links between other chronic conditions and COPD.

What is COPD?

Chronic Obstructive Pulmonary Disease (COPD) is an umbrella term for a group of obstructive airway disorders including chronic bronchitis, emphysema, small airways disease and chronic asthma (1).

COPD is defined as a disease which is mainly preventable and treatable, and associated with significant extra-pulmonary consequences that may contribute to severity or outcomes (1). The pulmonary component of COPD is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive with an abnormal inflammatory response of the lungs to noxious particles (2). In Australia this is mainly caused by cigarette smoking (1). In COPD the airflow limitation is not fully or substantially reversible and is due to a combination of airway and parenchymal damage. (Roll over to define parenchymal: Parenchymal refers to the functional tissue of the lung (alveoli, alveolar ducts and bronchioles) as distinguished from connective or support tissue.)

Clinical features

The clinical features and pathophysiology of COPD can overlap with chronic bronchitis, emphysema and asthma. The inter-relationship of these conditions with airflow obstruction and COPD can be illustrated by this Venn diagram (3).
Spirometry testing will assist in differentiating asthma from COPD. Results that are fully reversible after the administration of a bronchodilator are indicative of asthma and in this circumstance should be treated as asthma and not COPD. There are similarities in the signs, symptoms and physiology between asthma and COPD (1).

Patients with small airways disease, bronchiectasis and interstitial lung disease may also present with similar symptoms to patients with COPD, sometimes with partially reversible airflow limitation (1).

**Inflammation in COPD**

COPD is a complex disease with many inflammatory pathways that initiate and potentiate the disease process (4).

In Australia, smoking is the major cause of the inflammatory process leading to COPD. Passive smoking in childhood, indoor air pollution, genetic factors, such as alpha 1 antitrypsin deficiency, and chronic asthma can also cause the disease.
Neutrophils, macrophages and CD8+ T-lymphocytes are the key inflammatory cell types involved in COPD (1) (4) (5) (6).

Airway inflammation in COPD is characterized by a neutrophilic inflammation with increased numbers of macrophages and CD8+ T-lymphocytes. These cells release chemokines, cytokines and proteases that are instrumental in producing a chronic inflammatory state (1) (4) (6) (5).

**Bronchoconstriction in COPD**

The autonomic nervous system regulates the contraction and relaxation of smooth muscle thus controlling the diameter of the bronchioles, the rate of breathing and regulating the rate of airflow.

The autonomic nervous system is further divided into the sympathetic nervous system and parasympathetic nervous system (as well as the enteric nervous system). In the respiratory system, the sympathetic and parasympathetic systems have opposing actions.

Stimulation of the sympathetic nervous system (SNS) causes the smooth muscle of the bronchi and bronchioles to relax, causing bronchodilation, whereas stimulation of the parasympathetic nervous system (PNS) causes smooth muscle to contract, leading to bronchoconstriction (7).

Impaired lung function in COPD is caused by structural narrowing of the airways combined with the effects of cholinergic vagal bronchoconstrictive tone and decreased elastic recoil (8).

Bronchodilators improve the airflow limitation observed in patients with COPD by producing airway smooth muscle relaxation, although beta₂-agonists and anticholinergics achieve this effect through different mechanisms (9).

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The following are images of small airway obstructions (10).

(A) Normal small airway.
(B) Small airway containing plug of mucus with relatively few cells, which could have been produced in the glands of the larger airways and aspirated into the smaller airways.
(C) Inflamed airway with thickened wall in which the lumen is partly filled with an inflammatory exudate of mucus and cells, which has probably been produced in the small airway.
(D) Airway surrounded by connective tissue, which appears as if it might restrict normal enlargement of the lumen and unfolding of the epithelial lining that occurs with lung inflation.

(10)
Airflow limitation and air trapping

One consequence of chronic airflow obstruction in COPD is air trapping and subsequent hyperinflation.

The x-rays show normal lungs and lungs that are hyper-inflated.

Posteroanterior chest radiograph findings consistent with COPD and hyperinflation may include:

- hyperlucency, indicated by the top arrow (hyperlucency on x-ray refers to less density compared to a normal lung)
- a low-set or flat diaphragm, indicated by the bottom arrows
- a long, narrow heart shadow, indicated by the circle
- a widened or barrel-shaped chest.

This patient is unable to exhale all the air from their lungs. The trapped air generates an internal pressure in the lungs, which makes it difficult for patients with COPD to breathe in. The air left behind in the lungs takes up space in the thoracic cavity and pushes the diaphragm down. This reduces efficiency of the diaphragm in its function as an inspiratory muscle. Patients with advanced COPD can be very breathless due to the difficulty with inspiration as a result of this hyperinflation.

Emphysema

In emphysema the alveoli are damaged resulting in a significantly reduced surface area for gas exchange to occur (12).

In the aveoli, macrophages and neutrophils try to phagocytose toxic particles (such as smoke particles) to prevent them causing damage. The neutrophils are, however, killed off in this process leading to a series of events in which proteolytic enzymes (e.g. elastase) are released. These enzymes destroy the walls of the airsacs, which break down into larger air spaces, resulting in the destruction of the lung parenchyma and the formation of a

“bulla”. These bullae are less efficient in gas exchange than normal lung. The lungs are normally protected against proteolytic enzymes by alpha-1-antiprotease, but toxins such as tobacco smoke can destroy this protein causing a loss of this normal defence process.

The loss of elasticity in the lung parenchyma due to the destruction of elastin by the proteolytic enzymes also causes airway collapse contributing to air trapping and hyperinflation of the lungs which may clinically manifest as a “barrel chest”.

The combination of the mismatch between the blood flow and the airflow to the damaged aveoli affects gas exchange. This compromises the performance of the respiratory pump, mainly the respiratory muscles, due to the over-inflation and airway narrowing. This results in hypoventilation and the feeling of breathlessness.

**Chronic bronchitis**

In chronic bronchitis there is persistent inflammation and irritation of the bronchi and bronchioles, and increased mucus production (12).

Chronic bronchitis is diagnosed if a patient experiences signs and symptoms for 2 consecutive years. These signs and symptoms are sputum production on most days for 3 months (12). Other symptoms of chronic bronchitis may include wheezing and/or shortness of breath.

Airway obstruction occurs in chronic bronchitis due to chronic inflammation of the airway mucosa causing airway narrowing of the airways. Airways constriction is a result of swelling and excessive mucus production and/or increased vagal tone.

Frequent infections occur due to impaired clearance of secretions by the airway cilia (fine “hairs” on the luminal surface of larger bronchi which are damaged by toxic stimuli such as cigarette smoke) and altered function of the lung macrophages. Macrophages are inflammatory cells that play an important role in destroying foreign particles, including bacteria.

**Asthma**

Asthma is a chronic inflammatory condition of the airways. Eosinophils are the predominant cell in the inflammatory process (13).

Exposure to triggers results in increased inflammation, excessive mucus hypersecretion and bronchoconstriction. These changes produce airway obstruction, chest tightness, breathlessness, coughing and wheezing. Acute exacerbations can be rapid or gradual in onset, and may be severe and potentially life threatening (13). Asthma (both in the steady state and during exacerbations) is usually responsive to medicines that relax bronchial wall smooth muscle and/or reduce/control the inflammation.
COPD is commonly confused with or co-exists with asthma. This will be discussed in more detail later in the training.

The following table provides a summary of the signs, symptoms and pathophysiology of the conditions included in COPD.

<table>
<thead>
<tr>
<th>Signs, Symptoms, Pathophysiology</th>
<th>Emphysema</th>
<th>Chronic Bronchitis</th>
<th>Chronic Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of Breath</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chronic Cough</td>
<td></td>
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<tr>
<td>Excessive Mucus Production</td>
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<tr>
<td>Frequent infections</td>
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<td>✓</td>
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<tr>
<td>Alveolar destruction</td>
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<tr>
<td>Airway narrowing</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Air trapping and hyperinflation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Loss of elasticity</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation and swelling of airways</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Other Respiratory Conditions

In addition to asthma, other lung conditions that may co-exist with COPD are bronchiectasis and interstitial lung disease (14).

Several studies have identified airflow obstruction as a risk factor for lung cancer, therefore patients with COPD have a higher risk of developing lung cancer (15).

Bronchiectasis is a lung condition involving the permanent damage of the airways’ inner lining causing dilation of the bronchi and bronchioles. It is usually accompanied by increased or excessive sputum production. It is most often caused by a previous severe infection of the lungs such as pneumonia in childhood, not by cigarette smoking (13).

Bronchiectasis may also be found in people with a range of immune deficiencies.
Bronchiectasis is a chronic condition characterised by repeated episodes of acute bronchial infection with increased coughing and mucus production (13).

In bronchiectasis, sputum becomes difficult to clear. Sputum can be trapped in “pockets” within the airways, which can lead to further infections and damage to the airways (13).

The diagnosis is usually made by high resolution chest CT scan.

The principal management strategies for bronchiectasis include:

- Regular airway clearance to loosen and clear sputum (using positive end-expiratory pressure devices and also huffing techniques)
- Vaccination against influenza and pneumococcal infection
- Avoiding known irritants (especially cigarette smoke)
- Using bronchodilator therapy and antibiotics (14)
- Pancreatic enzyme supplements if cystic fibrosis is present.

**Interstitial Lung Diseases** are a group of rare lung conditions that cause chronic breathlessness. Generally the causes of these diseases are unknown (13).

There are many different types of interstitial lung disease and distinguishing them is often difficult. Some disorders such as pulmonary fibrosis, only affects the lungs. Some medicines can trigger pulmonary fibrosis, including amiodarone, nitrofurantoin, sulfasalazine and some cytotoxic agents (e.g. bleomycin and methotrexate). (a full listing is provided by Bauman and Chan 2010) (16)

Other forms of interstitial lung disease occur as part of other conditions that affect other parts of the body. For example, sarcoidosis and some of the other connective tissue disorders such as rheumatoid arthritis and scleroderma (13).

**Genetic factors** may also play a role in a person developing COPD. Some families may be more susceptible due to a lack of the protein alpha-1 antitrypsin (AAT). AAT is a protease inhibitor, produced primarily in the liver, which protects the lungs and liver from the inflammatory enzyme elastase. Elastase destroys elastin which maintains the elasticity of alveolar walls. With the resultant loss of this elasticity, emphysema is likely to develop (17).

Normally AAT circulates in the blood and slows or stops the action of elastase. Cigarette smoke directly inactivates AAT, so in the AAT deficient patient smoking is particularly harmful leading to an increased risk of COPD and emphysema (17).

The prevalence of AAT Deficiency is estimated to affect approximately 1 in 2000 to 1 in 5000 individuals (18).

**COPD – A multi-component disease**

COPD is no longer considered a disease of the lung alone. It is recognized as a chronic, systemic inflammatory syndrome that may involve other organs requiring independent diagnosis and
treatment. Inflammation in the respiratory system may be accompanied by inflammation in the cardiovascular, skeletal and nervous systems (19). These systemic consequences have a significant impact on symptom burden, quality of life and outcomes. In addition to respiratory morbidities such as lung cancer, increased risk of pneumonia, respiratory failure and end-stage lung disease, co-morbidities include:

- Cardiovascular disease (coronary artery disease and chronic heart failure)
- Nutritional abnormalities and weight loss
- Hypoxaemia
- Skeletal muscle wasting
- Depression & anxiety
- Osteoporosis
- Diabetes
- Gastrointestinal disorders (notably gastro-oesophageal reflux disease)
- Worsening of other conditions such as anaemia.

This diagram is representative of the changes that occur in patients with COPD, which may all arise in part from the inflammatory processes (19) (20).

As there is a high prevalence of co-morbid conditions in COPD, the assessment of this condition needs to be multidimensional and include a screening for other complicating factors. Similarly it is important to screen for COPD using spirometry in people with other conditions who complain of breathlessness.
References


