Introduction to the respiratory system
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Functions of the Respiratory System
Functions of the respiratory tract include:
- Gas exchange
- Host defence
- Metabolism of endogenous and exogenous molecules
- Repair
- Vocalisation

Gas exchange
- Oxygenation of the blood and the removal of excess carbon dioxide is the most important function of the respiratory tract.
- Apart from the special case of the placenta (which is produced by the foetus), it is the only organ which can carry out this crucial function.
- The need to carry out gas exchange places a number of anatomical and physiological requirements on the respiratory tract:
  - It must open to the atmosphere
  - It requires a mechanism to warm and humidify atmospheric gases
  - It needs an effective system for gas delivery to the alveoli (respiratory pump)
  - It must have a large gas-permeable surface
  - It needs a large de-oxygenated blood supply in close apposition to the gas-permeable surface.

Host defence
- The anatomical and physiological requirements of the gas exchange mean that the respiratory tract is vulnerable to environmental agents. These include organic and inorganic particulates, spores, pollens, fungi, viruses and bacteria.
- Protection from these is provided by a combination of physiological and cell biological mechanisms:
  - Particle trapping and removal systems in the upper airways.
  - Resident cells able to produce mediators able to attack invading organisms.
  - Migratory cells – macrophages, lymphocytes, neutrophils from the marginated pool “on standby” in the pulmonary vasculature.

Metabolic functions
- The metabolic functions of the lung are performed by specialised epithelial cells and by endothelial cells in the pulmonary capillary network.
- As well as the capacity to metabolise many different inhaled compounds, a variety of endogenous substances are metabolised in the respiratory tract or in its specialist blood supply including:
  - Local hormones: Angiotensin I conversion to Angiotensin II
  - Inflammatory mediators: Bradykinin and prostaglandin degradation
  - Neurotransmitters: Noradrenaline, serotonin.

Development, growth and repair
- Repair is an important function for all organs, particularly the lung which is:
  - Crucial to life
  - Open to the atmosphere and therefore vulnerable to attack and damage
Some insults can be repaired without any evidence of permanent damage e.g. pneumococcal pneumonias
Other insults can lead to loss of lung function due either to the formation of fibrotic “scars” e.g. paraquat poisoning or to the degradation of gas exchanging units (emphysema) e.g. cigarette smoke.

Vocalisation

The creation of speech is a highly complex process that requires sophisticated neurological control of the airflow across the vocal chords, as well as inputs from cognitive areas of the brain.

The burden of respiratory disease

- Responsible for 20% of deaths in the UK
- Causes of respiratory disease related deaths:
  - Cancers of the respiratory system, e.g. lung cancer
    - Lung cancer is biggest UK cancer killer
    - Greater mortality in woman than breast cancer
    - Very small associated 5 year relative survival rate
  - Pneumonia
  - Chronic obstructive pulmonary disease (COPD)
  - Pulmonary circulatory disease
  - Pneumoconioses
  - Asthma
  - Other respiratory diseases
- Most common reason to visit the GP
  - ~1/3 of people will visit their GP at least once a year because of a respiratory condition
  - Most common chronic illness in children is a condition of the respiratory system

Respiratory diseases

- Airway diseases
  - Localised obstruction –
    - Sleep apnoea
    - Laryngeal carcinoma
    - Thyroid enlargement
    - Vocal cord dysfunction
    - Relapsing Polychondritis
    - Tumours
    - Post tracheostomy stenosis
    - Foreign bodies
    - Bronchopulmonary dysplasia
  - Generalised obstruction –
    - Asthma
    - C.O.P.D.
    - Bronchiectasis
    - Cystic Fibrosis
    - Obliterative Bronchiolitis
- Small lung disorders (restrictive)
  - Disease within the lung –
    - Sarcoidosis
    - Asbestosis
    - Extrinsic Allergic Alveolitis
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- Fibrosing Alveolitis
- Eosinophilic pneumonia

- Disease outside the lung –
  - Pleural effusions
  - Pneumothorax
  - Scoliosis
  - Respiratory muscle weakness
  - Obesity

- Infections
  - Tuberculosis
  - Infective bronchitis
  - Pneumonia
  - Empyema

- Pulmonary vascular disorders
  - Pulmonary emboli
  - Pulmonary hypertension

Trends and burdens

- Airway diseases
  - Foreign bodies – inhalation causes confusion and mistakes in diagnosis in the young and old every year
  - Sleep apnoea – leads to a 6x normal risk of having a road traffic crash
  - Tumours – lung cancer is the commonest cause of cancer deaths in men and women
  - COPD – responsible for 1/8 medical admissions
  - Asthma – prevalence of 5.2 million in the UK

- Small lung disorders
  - Obesity – increasing prevalence causes both increased respiratory workload, but also respiratory dysfunction
  - Mesothelioma – deaths due to asbestosis increasing
    - There is a significant time lag between exposure and disease

- Infections
  - TB – rates of infection rising, especially in London
    - On X-rays, consolidation of the superior parts of each lobe can be seen

- Pulmonary vascular disorders
  - Pulmonary emboli – thrombi in the lungs may complicate immobility and be fatal
    - These are more common >40 yrs of age

Symptoms

- Breathlessness – also known as DYSPNOEA; a sensation of difficult, laboured or uncomfortable breathing
  - Causes:
    - Physiological – strenuous exercise, pregnancy
    - Psychological – stress, anxiety, panic attack
    - Pathological – heart disease, lung disease, pulmonary vascular disease, systemic disorders, respiratory muscle weakness
  - Assessment of a breathless patient:
    - Cause –
      - Lung Disease
      - Heart Disease
      - Pulmonary Vascular Disease
      - Neuromuscular disease (eg diaphragm weakness)
• Systemic Disorders (eg anaemia, hyperthyroidism, obesity)
• {Psychogenic Factors}
  - Enquire about –
    • Onset (acute, gradual)
    • Circumstances (on exertion, at rest, at night, lying flat, associated symptoms?)
    • Degree
  - MRC dyspnoea grade –

1. Normal
2. Able to walk and keep up with people of similar age on the level, but not on hills or stairs.
3. Able to walk for 1.5Km on the level at own pace, but unable to keep up with people of similar age
4. Able to walk 100m on the level
5. Breathless at rest or on minimal effort

• Other symptoms:
  - Cough
  - Sputum production
  - Haemoptysis
  - Chest discomfort
  - Wheeze or musical breathing
  - Stridor
  - Hoarseness
  - Snoring history /Daytime sleepiness
  - (Weight loss. Anorexia, Fever)

Pathophysiology

What are the normal processes disturbed?
• Disturbed gas exchange – small organisms meet their oxygen demand via diffusion, whereas larger organisms eg a resting adult cannot meet their requirements via diffusion alone (require 250ml oxygen/minute)
  - Breathing delivers warmed humidified air to specialised gas exchange surfaces
  - The heart delivers deoxygenated blood to the pulmonary capillaries
  - Gas exchange between the air and blood occurs by diffusion
• Damaged respiratory mucosa – damage to the cilia can occur due to the activity of enzymes such as neutrophil elastase – released from neutrophils which are attracted into the airways by cigarette smoke, bacterial products etc
  - Cell walls of epithelial cells are broken down, damaging and destroying the cilia so patients may have a reduced number of cilia as well as cilia that are not working effectively
  - Damaged cilia are less effective at removing mucus from the airways

Examination of the Respiratory System
• Chest X-ray
• MRI
• Spirometer
Basic structure of the respiratory system
Prof Ceri Davies (c.davies@imperial.ac.uk)

1. Sketch and name the cellular layers separating alveolar air from blood.
2. Define alveoli, bronchioles, bronchi, trachea, larynx, pharynx, and nasal cavities.
3. Outline how the respiratory tract is protected against drying, cold and inhaled particles.
4. Explain how the alveoli and airways resist collapse.
5. Describe and sketch the organisation of the chest using the terms chest wall, diaphragm, mediastinum, pleural cavities, pleura, and lungs.
6. Explain the roles of chest wall muscles, diaphragm, chest wall skeleton, pleural cavities, pleura and lungs in breathing in and out.
7. Outline the blood circulation through the lungs making correct use of the terms double circulation, pulmonary circuit, right atrium, tricuspid valve, right ventricle, pulmonary valve, pulmonary trunk, pulmonary arteries, arterioles, alveolar capillaries, venules, pulmonary veins, left atrium.

Introduction

Overview – starts in the nose and nasal passages, then down to pharynx, larynx + trachea, which branches into the primary bronchi which supply the lungs. The lungs sit in the thorax, and are surrounded by pleura, the diaphragm, intercostal muscles and abdominal muscles. All these components are essential for respiration.

Terminology

- **Airways**: air-filled spaces/tubes which take air from the outside to the alveoli.
- **Alveoli**: microscopic spaces lined by very thin simple squamous epithelium through which oxygen + carbon dioxide exchange takes place. Gas exchange takes place within the blood in a network of alveolar capillaries surrounding the alveoli.
- **Alveolar capillaries**: are on the pulmonary circuit bringing deoxygenated blood from the right ventricle of the heart via the pulmonary trunk and pulmonary arteries.
- **Upper airways**: comprise the nasal cavities, the nasopharynx (above roof of mouth), laryngopharynx (shared by airway + foodway), and the larynx (voicebox/Adam’s apple – valve that allows air into the lower airways but excludes liquids and solids)

Structural Components

*The Nasal Cavities*

- nearly triangular cross-section, with fairly smooth medial and inferior walls but an elaborate lateral wall in which the respiratory epithelium with hairy mucosa covers three scroll-like plates of bones called the **conchae**
- has a complex and important vascular and nerve supply
- inspired air passes through these warm, moist plates, becoming warmed and humidified on the way and so protecting the lower parts of the respiratory tract from cold shock and drying.
- The nasal lining becomes cooled in this process so, during expiration, the nasal lining cools the expired air and also retrieves water by condensation.
- Nasal mucus and hairs help exclude a range of airborne particles – because of this the complex, narrow passages of the nasal cavity have a high resistance to airflow
- During exercise the nasal resistance to flow means that the
respiratory muscles cannot propel air through the nose fast enough so open-mouth breathing takes over with an increased loss of water and exposure to airborne particles.

- Secondary role – sense of olfaction (smell) – olfactory tract has a specialised epithelium with specialised nerve supply

The Paranasal Air Sinuses

- Four sets of blind-ended out-pocketings (i.e. holes) of the lateral walls of the nasal cavities
- The air turnover in these is fairly slow and plays little role in heat and water transfer
- Ideas on their functions include reducing the weight of the facial bones, providing a “crumple zone” in facial trauma, acting as resonators for the voice, and insulating sensitive structures such as dental roots and eyes from the rapid temperature fluctuations in the nasal cavities.
- Infection of the maxillary sinus is common as the opening is high up. All sinuses anterior to the brain have a possible insulating effect on the brain

Lower airways – comprise the trachea, the bronchi and the bronchioles (initially surrounded by smooth muscle but ending as respiratory bronchioles from which alveoli are direct or indirect buds). The walls of the larynx, trachea and bronchi are held open by plates or crescents of cartilage (a non-mineralised connective tissue, supporting but flexible). The nasal cavities and pharynx are held open by attachments to nearby bones. The microscopic air spaces (alveoli and bronchioles) contain a surfactant phospholipid that prevents collapse caused by surface tension forces.

The Pharynx

- After conditioning of the air, air passes down the back of the nasal cavity to the pharynx, which is the final part of the airway proximal to its separation from the oesophagus.
- The pharynx consists of 3 parts:
  - **Nasopharynx** – posterior to the nasal cavity, and is the Eustachian tube opening
  - **Oropharynx** – posterior to the tongue, consists of lymphoid tissue
  - **Laryngopharynx** – after the epiglottis
- Food is channelled posteriorly along the oropharynx to the oesophagus

Larynx

- Cartilagenous structure supported from the roof of the mouth by the hyoid bone.
- Is associated with the lateral carotids
- Superior and posterior to the thyroid gland, superior to the trachea
- Develops differently in men and women
- Entire structure is lined by a membrane, which forms a complete sheath on the inside of the trachea
- Arytenoid cartilage – attached to vocal ligaments which open and close entry to the larynx. This is crucial – act as a sphincter preventing entry into the lower airways. They are open during inspiration and closed during phonation
  - when the vocal folds are partially open, and air is passed through, sound is made – this is the mechanism of vocalisation in the mouth
- Without the larynx, voice would be monotonous, low pitch – i.e. role of larynx is modulation of sound
- Also, closure of vocal folds increases the pressure in the thorax and abdomen. This can lead to an expulsive force e.g. during sneezing, childbirth + vomiting

**Trachea**

- Has a regular cartilage arrangement of ~20 horseshoe shaped cartilage rings which keep the trachea open
- The anterior surface is lined with epithelium
- Posterior surface consists of trachealis muscle, which is anterior to oesophageal muscle and is needed for swallowing
  - Posterior surface is where cartilage ring is not continuous

**The tracheobronchial tree**

- Sternal angle at T4 marks where trachea branches
- There is a dimorphism between the primary bronchi, the right side is larger and more vertical therefore more things are inhaled into the right lung
- The secondary bronchi supply each lung lobe
- Within each lobe, tertiary bronchi then supply each pulmonary segment
- With branching of the bronchi, the number of cartilage rings decrease and the amount of smooth muscle increases
The lungs and pleura

- The lungs lie within two pleural cavities separated by a central partition of tissue called the mediastinum. Inside the mediastinum are the trachea, oesophagus, heart, and large blood vessels. The mediastinum is divided into two by the mediastinal septum.

- Each lung has a convex surface facing the ribs (costal surface), a surface moulded to the mediastinum (mediastinal surface), and an inferior (lower or diaphragmatic) surface. The inferior surface is concave and moulded to the diaphragm, a sheet-like muscle that separates the thoracic and abdominal cavities.

- Each lung is covered by a thin, shiny, moist layer of tissue called the pleura, allowing each lung to slide smoothly within its pleural cavity during breathing.

- The apex of each lung projects 2-3 cm above the clavicle in an adult and really lies in the root of the neck.

- Gas exchange occurs in the alveoli and alveolar capillaries within the bronchopulmonary segments.
  - Alveoli are air sacs close to alveolar capillaries, forming a blood-air barrier.
  - The pressure gradient of oxygen drives oxygen across this barrier.
  - $P_{O_2}$ air = 100 mmHg, $P_{O_2}$ blood = 40 mmHg.

The diaphragm and breathing

- Position of the diaphragm: the margin attached to the costal margin, the centre of the dome bulges up because of the pressure difference between the pleural and abdominal cavities. This bulge (and hence the pressure difference) is highest during expiration.

- Breathing is produced by two main sets of muscles. Contraction of the diaphragm (attached to the costal margin, the lower border of the rib cage) pulls the domed centre of the diaphragm down and increases the height of the pleural cavities. Contraction of the intercostal muscles, which almost fill the spaces between adjoining ribs, pulls the ribs upwards towards the relatively fixed first rib; the ribs slope down towards their anterior (front) ends so the lifting movement of the intercostal muscles increases the depth and width of the pleural cavities.

- Expansion of the pleural cavities produces a drop in the pleural pressure, so air flows through the Airways into the lungs, which expand with the increase in pleural cavity volume. The lower part of each lung expands downwards to occupy much of the costo-diaphragmatic recess (the lowest region of each pleural cavity, which in expiration contains no lung because the margin of the diaphragm is pressed closely against the lower part of the rib cage).

- The phrenic nerve (from C3,4 + 5) supplies motor innervation to the diaphragm.
Lung development

Prof John Warner (jwarner@imperial.ac.uk)

1. To understand the continuum of lung growth and development from conception to adulthood and the factors that interfere with normal development.
2. To understand how congenital lung defects arise.
3. To be able to summarize the morphological and/or cellular events associated with the phases of intrauterine lung development.
4. To understand the early life origins of susceptibility to lung disease.
5. To summarize the main aspects of lung growth and the evolution of lung function in the postnatal period.
6. To be able to give a brief account of the changes in the lungs and circulation that occurs at birth to permit air breathing.
7. To briefly describe the changes that occur at birth that facilitates the transition to air breathing. Comment particularly on the role and fate of lung liquid and the importance of pulmonary surfactant in stabilizing breathing.

NB: Functions of the lung – ventilation, diffusion + perfusion

Embryonic development

- The tracheal bud forms from the foregut at 4-5 weeks of gestation
- By 16 weeks gestation, bronchial branching is complete
  - Pulmonary artery branching then follows this
- Alveolar development continues until 8-10 years of age
- Hypoplastic lung – interruption to bronchial branching → development of small lung with little branching
  - Isotope ventilation scan will show poor air supply to the lung
  - Isotope perfusion scan will show poor artery development

Embryogenesis

- Different tissues develop at different rates
- Bronchial buds are supplied by systemic vessels
  - Systemic vessels regress as the pulmonary artery takes over principle supply
- The bronchial artery development occurs independently from the aorta. Insult to this development (e.g. infection, vascular accident, trauma) may result in malformation depending on the timing of the insult rather than its nature
- Theroretical “insults” to either the dividing bronchus may lead malformations including agenesis (early malfunction), a local lesion (impact to specific area), malformation of systemic supply to “normal” lung or “abnormal” lung, or a malformation in the lung leading to normal pulmonary artery supply to abnormal lung.
Influences on lung development

- Hox genes
- Transcription factors
- Autocrine and paracrine interactions
- Peptide growth factors
- Thoracic cage volume
- Lung liquid positive pressure
- Amniotic fluid volume
- Maternal nutrition e.g. vitamin A
- E.g. of restricted lung volume: Diaphragmatic hernia (of Bochdalek) → hypoplasticity

Airway branching

NB: with regards to the cartilaginous rings in the trachea and bronchi/bronchioles, the only complete ring is the cricoid in the larynx. With increased branching, there are an increased number of alveoli, ducts, neural network and smooth muscle development. This is to allow the necessary bronchoconstriction and dilation.

- There are 25 generations of branching which occurs during pre-natal development.
- Pre-natal development consists of 3 development stages: glandular, canalicular and alveolar.
- The development of a foetal airway at 10 weeks gestation leads to pressure changes in the thorax. This has a trophic effect on development → expression of gene which stimulates the branching of the airway

Respiratory “Insult” during maternal pregnancy - SMOKING

- Causes increased respiratory movements and changes in thoracic pressures, while removing some of the soft tissue support and interstitial tissue development
- Reduces elasticity of alveoli → reduced support
- Reduces airway diameter → reduced support → wheezy infant (4x increased risk of infant wheeze) → COPD at old age
- Summary: reduced lung function at birth

Circulation

Foetal circulation

- Mostly bypasses the lungs, as they are not fully developed
- From placenta, blood enters the left atrium from the right atrium through the open foramen ovale
From the right atrium, enters the right ventricle. From the right ventricle, some goes to the lung via the pulmonary trunk, but most to aorta via the ductus arteriosus. This is because the pulmonary artery pressure is greater than the systemic artery pressure, and the pressure gradient drives the movement of the blood.

- Only approx. 10% of foetal blood is transported to the lungs
- PH of blood =7.2 (norm is 7.4), $PO_2=3.4kPa$ (norm 10), $PCO_2=7-8kPa$

At birth

- Massive CNS stimulation due to change in environment
- Low pressure placental circulation is cut → rise in systemic arterial pressure
- Lung aeration causes fall in pulmonary arterial pressure (as lungs stretch), increasing the $PO_2$ and decreasing the $PCO_2$ → SYSTEMIC PRESSURE > PULMONARY PRESSURE
- Ductus arteriosus closes due to changes in prostaglandins
- An increase in left atrial pressure (due to rise in systemic arterial pressure) causes the foramen ovale to close

First day post birth

- Pulmonary vasodilatation increases 5 –fold, increasing the pulmonary blood-flow
- This resets the chemo-receptors and respiratory centres
- Aeration of the lungs occurs – there is high positive expiratory pressure, and the lung volume rises to optimum
- Within the first 2 hours, airway resistance falls
- However lung compliance rise takes at least 24 hours. Lymphatic system is relied on to remove fluid filling lungs, but this is slow therefore the lungs remain stiff until the fluid is removed.
- $PO_2$ increases, $PCO_2$ decreases → increased PH of blood

NB: how does a foetus cope with the decreased $PO_2$? Hb saturation curve is different, therefore has increased oxygen-binding capacity at lower partial pressures. This is known as the Bohr shift

Obstruction of breathing

- Asphyxia
  - At birth, attempted breathing occurs. With umbilical strangulation, gasp fails. This is called primary apnoea
2nd attempt at breathing (with failure of successful ventilation) results in a decreased blood pressure. Heart rate is relatively maintained. This is known as terminal apnoea.

**Resuscitation**
- Required if delivery of oxygen fails following terminal apnoea
- Results in an increase in heart rate and blood pressure

**Apgar score** – used to determine severity of apnoea and need for resuscitation etc.

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<td>Response to catheter</td>
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<td>Colour of trunk</td>
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What can go wrong?

- In a normal foetal human lung – surfactant (phospholipid produced by epithelial cells) is released from lamellar bodies
  - Once secreted, the lamellar bodies create a force resulting in the distension and maintenance of distension of the airways at lower pressures therefore the airways remain open
  - Surfactant is only generated in the late 2nd and early 3rd trimester; therefore premature babies carry risk of alveolar collapse \(\rightarrow\) hypoventilation and hypoxic acidosis \(\rightarrow\) pulmonary vasoconstriction and right to left shunting
  - This is known as IDIOPATHIC RESPIRATORY DISTRESS SYNDROME – as this starts to develop, the baby will “grunt” to try and raise pressure and hold the airways open when breathing out
  - Continuous ventilation is then required, but now surfactant can be replaced
- Cilia – beat in a coordinated fashion moving material out of the airway to prevent infection
  - Malfunction of movement \(\rightarrow\) right lower lobe collapse, dextrocardia and possible total cytus inversus
  - This is known as Kartagener’s syndrome – or primary cilia dyskinesia
    - Shows that orientation of organ development in utero is dependent on cilia function

NB: **Measuring lung function** - Forced expiratory measurements can be made using a pneumotachograph. Shown in a flow-volume loop; reduced lung function is therefore seen as a change in the loop seen.

**Evolution of post-natal lung function**

- During development from infant to old adult, there is a loss of alveolar elasticity \(\rightarrow\) reduced lung compliance
  - Compliance in infants and elderly is more similar, therefore extremes of age pose an increased susceptibility to problems
- With increasing age, as lungs develop lung function increases. However this is only up to a certain point, where it begins to decrease again. Smoking increases the rate of this decrease
  - Early respiratory disease reduces overall lung function throughout life, therefore a combination of early respiratory disease and smoking will \(\rightarrow\) overall reduced lung function + more rapid deterioration of lung function with increased age
- Increased birth weight results in an increased lung function at late adult life, therefore premature babies carry increased risk of reduced lung function
1. Distinguish between alveolar and pulmonary ventilation.
2. Define the common lung volumes and describe how they alter in restrictive and obstructive disease
3. Define anatomical and physiological dead space and give approximate volumes for both in a typical healthy adult
4. Describe the effect of increased breathing frequency compared with increased depth of breathing on alveolar ventilation
5. Define Fick’s law of diffusion
6. Relate Fick’s law of diffusion to gas exchange in health and disease

Introduction

- Healthy subjects at rest normally breathe at a rate of about 12 to 15 breaths/min, each of about 0.5 L.
- The volume of air entering the lungs each minute is called the minute ventilation \( \dot{V} \). The symbol for ventilation has a dot over the V to show it is a rate.
  - Minute ventilation will be 6.0 L min\(^{-1}\) if breathing at 12 breaths/min (12 x 0.5), or 7.5 L min\(^{-1}\) (15 x 0.5) if breathing at 15 breaths/min. Minute ventilation is also sometimes called total or pulmonary ventilation.
- The volume of air breathed in roughly equals the volume breathed out, so that the net flow over a complete cycle is zero, and is called the tidal volume \( V_t \).
  - If we want to express changes in breathing, for example as a result of exercise or disease, we measure the flow in one direction only, conventionally the volume breathed out per minute ( \( \dot{V}_E \)), to calculate minute ventilation.
- A spirometer is an instrument used to measure changes in lung volumes and consists of a closed space from which the subject breathes.
  - It can come in many forms; one type consists of a hollow bell supported in a trough of water (Fig 1). As the subject breathes in, air is drawn from the bell and it sinks slightly; when the subject breathes out the bell rises.
  - Spirometry can be used to measure most lung volumes.
- The minute volume equals total ventilation and will be 7,500 ml/min (500 x 15) breathing at 15 breaths/min.
  - Of 500 ml inhaled with each breath, 150 ml stays in the anatomic dead space, which represents the volume of the conducting airways.
  - The volume of gas entering the respiratory zone is thus (500-150) x 15, i.e. 5,250 ml/min and is termed alveolar ventilation ( \( \dot{V}_A \)).
  - Alveolar ventilation is defined as fresh inspired air available for gas exchange.
    - Insufficient alveolar ventilation, called hypoventilation, or excess, called hyperventilation, can occur in lung disease.
    - We can also consciously alter the volume of our lungs, but we can’t totally empty our lungs. Alveolar ventilation is extremely important because it determines O\(_2\) and CO\(_2\) levels in alveolar gas. Other factors affecting these levels are the rate of O\(_2\) consumption (VO\(_2\)) and the rate of CO\(_2\) production (VCO\(_2\)).
- Why assess spirometry? Diagnosis of respiratory disease, monitoring disease progression, deterioration, drug efficacy. It is also an efficient drug delivery system.
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**Lung Volumes + Capacities**

**Fig 2.** Spirometric volumes and capacities for an average healthy adult. Factors affecting lung volumes include height, age, gender, muscle training and the presence of disease

- **Tidal volume** ($V_t$) – volume of air inspired during quiet respiration
- **Inspiratory reserve volume (IRV)** – volume of air inspired from $V_t$ to maximal inspiration
- **Expiratory reserve volume (ERV)** – volume of air expelled with forced expiration
- **Functional residual capacity (FRC)** is the lung volume at the end of normal quiet expiration (Fig 2)
- **Residual volume (RV)** cannot be expelled after maximal expiration; this represents the volume of the airways.
- **Total lung capacity (TLC)** - The total possible volume which can be contained within the lungs (from maximal inspiration to residual volume). Maximal expiration from TLC expels IRV, $V_t$ and the expiratory reserve volume (ERV).
- **Vital capacity (VC)** – the total volume that can be taken into the lungs after maximal expiration to maximal inspiration. The sum of two or more volumes is termed a capacity. Thus, $TLC + IRV + V_t + ERV =$ vital capacity (VC).
- Since RV can’t be breathed out, RV and ERV can’t be measured with a spirometer, and therefore neither can be FRC, which is the sum of RV and ERV.
  - They are measured when the subject inhales from RV a known volume of non-absorbable tracer gas (such as helium). Its dilution by the unknown volume in the lungs is then measured and RV calculated.

**Clinical relevance of lung volumes/capacities**

- **Tidal volume** – adequate supply necessary to maintain oxygenation and carbon dioxide clearance
- **Inspiratory reserve volume** – required during cough and exercise
- **Functional residual capacity** – product of the balance of opposing chest wall and alveolar recoil, where the lung is at its most compliant; essential to maintain open distal airways during expiration
- **Residual volume** – may increase due to air trapping in disease, which then may alter lung mechanics
- **Vital capacity** – critical value of 1L used to assess whether patient is able to maintain spontaneous ventilation or requires assistance
Respiratory Disease

- The patient is asked to breathe in as deeply as they can and out as fast as they can for a single breath. This gives the forced expiratory volume in 1 second (FEV₁).
- Forced vital capacity is the total volume of air a patient can breathe out after a maximal inspiration
  - Published tables relate spirometric measurements to a normal subject’s gender and height. Deviations from these ‘normal’ values suggest disease.
- In an obstructive lung disease, airway obstruction causes an increase in resistance.
  - During normal breathing, the pressure volume relationship is no different from a normal lung.
  - However, when breathing rapidly, greater pressure is needed to overcome the resistance to flow, and the volume of each breath gets smaller. The increase in the effort to breathe can cause an over-distention of the lungs.
  - These are characterised by a disproportionate reduction in FEV₁ compared to FVC, reflecting airflow limitation, and an increase in both RV and TLC reflecting hyperinflation
  - Common obstructive diseases include asthma, COPD, bronchitis and emphysema.
- In a restrictive lung disease, the compliance of the lung is reduced which increases the stiffness of the lung and limits expansion. In these cases, a greater pressure than normal is required to give the same increase in volume.
  - The flow volume loop may be characterised by a normal or increased FEV₁/FVC ratio, reflecting preserved airflow, and reduced RV and TLC indicating small lung volumes.
  - Common causes of decreased lung compliance are pulmonary fibrosis, pneumonia and pulmonary edema. Patients whose respiratory muscles are unable to perform normally because of a neuromuscular disease (eg ankylosing spondylitis) or paralysis can show a restrictive pattern.

E.g. of respiratory problems regarding lung volumes

- Bibasal atelectasis - Lack of gas exchange within alveoli, most commonly caused by reduced FRC post-surgery
  - Associated problems: reduced oxygenation, poor CO₂ clearance, V/Q (ventilation/perfusion) mismatch, increased work of breathing, breathlessness, reduced exercise tolerance
- Lung hyperinflation – secondary to air trapping and increased residual volume. Leads to a flattened diaphragm, narrow diameter appearance of heart and mediastinum, increased AP diameter, increased pulmonary vasculature, parenchymal (stromal) or suprapleural (membraneous) blebs (blisters/vesicular spaces) may also occur
  - Associated problems: altered respiratory mechanics, reduced tidal volume, V/Q mismatch, poor gas exchange, increased work of breathing, breathlessness, pursed lip breathing, use of accessory muscles

Dead space

- Not all tidal volume air is used in gas exchange; air that isn’t is known as dead space.
- There are two types of dead space: anatomical + alveolar.
- Anatomical dead space is the volume of an inspired breath which has not mixed with the gas in the alveoli but remains in the conducting zone up to the terminal bronchioles, and it measures the anatomical volume of the conducting airways. In a typical healthy adult it measures 150 ml.
  - This may vary because of the size of subject, tracheal intubation/tracheostomy or hypoventilation
If anatomical dead space increases but tidal volume does not, there is less air available for gas exchange.

- **Alveolar dead space** – contained in alveoli which have insufficient blood supply to permit effective gas exchange. The mismatch between ventilation and perfusion is termed a V/Q mismatch. This should be zero in healthy subjects, but in disease is affected by pulmonary embolism and ventilation of non-vascular air spaces e.g. bullae.

- **Physiological dead space** – the combined total of anatomical and alveolar dead space.
  - In healthy adults, this should equal the anatomical dead space = 150ml
  - Increased in emphysema, pulmonary embolism (Fig 4), and pulmonary fibrosis
  - Decreased during rapid breathing and breathholding

**Fig 4 Example of ventilation: perfusion mismatch in a patient with a pulmonary embolus.**

Perfusion is disproportionately reduced compared with ventilation.

**NB: Alveolar ventilation** – can be seen as tidal volume – anatomical dead space (i.e. is the useful air breathed in)

**Respiratory Rate**

If you double the respiratory rate (hence doubling the minute ventilation – VE) as opposed to doubling the tidal volume with the same respiratory rate, the alveolar ventilation does not increase to the same extent. In exercise both are increased to compensate for the increased oxygen demand.

**Alteration of ventilation**

- **Hypoventilation** – exists when the ratio of carbon dioxide production to alveolar ventilation increases above normal, i.e. inadequate alveolar ventilation
  - May be localised (infection, sputum plug), scattered (COPD, asthma) or generalised (pain, reduced respiratory drive)
  - Increased alveolar CO₂ → increased arterial CO₂ → \( \uparrow \) CO₂ + H₂O \( \leftrightarrow \) H₂CO₃ \( \leftrightarrow \) HCO₃ + \( \uparrow \) H⁺ → decreased PH → acidosis

- **Hyperventilation** – exists when the ratio of carbon dioxide production to alveolar ventilation decreases below normal, i.e. excess alveolar ventilation
  - Cause – anxiety, metabolic disease, airway obstruction, parenchymal lung disease, altitude
  - Opposite therefore increases PH → respiratory alkalosis

- Oxygen and carbon dioxide levels in alveolar gas determined by alveolar ventilation, rate of oxygen consumption, rate of carbon dioxide production, Hb content of blood, Hb affinity, atmospheric pressure of oxygen
Gas exchange

- Takes place across the alveolar membrane – purely result of diffusion in accordance with Fick’s Law
- Fick’s Law – the rate of transfer of a gas through a sheet of tissue is proportional to: area of the tissue, the solubility of the gas in the tissue (diffusion constant) and the difference in gas partial pressure between two sides.
  - Inversely proportional to the square root of the gas’s molecular weight and the tissue thickness
- In accordance with Fick’s law, diffusion is dependent on:
  - Concentration/Pressure gradient – described using term partial pressure; amount of gas dissolved in the plasma. The steeper the difference in partial pressures between gas in alveoli and capillary blood the steeper the diffusion gradient → faster + more efficient diffusion (norm O₂ 100 in alveoli, 40 in pulmonary capillaries).
    - Carbon dioxide diffusion much slower as pp difference much smaller, but diffusion from blood to alveoli much more rapid + efficient (suited to necessity of removing carbon dioxide).
    - In the time available equal amounts of the two gases are exchanged, and have no effect on the pressure of the other (stated by Dalton’s law $P_{gas} = \% \text{ total gas} \times P_{tot}$ – i.e. is dependent on fractional concentration of the gas)
  - Gas solubility – CO₂ 20x more soluble than O₂, BUT CO₂ has a very small diffusion gradient and a heavier molecular weight therefore equal amounts of CO₂ and O₂ diffuse across the membrane in the same time period
    - In disease with diffusion impairment, oxygen more strongly affected because less soluble
  - Thickness of alveolar membrane – 0.5-1 micrometre thick therefore gas exchange rapid and efficient
    - Membrane thickening may occur due to inflammation, infection or fibrosis → inadequate time for Hb saturation → hypoxia. Hypercapnia not caused due to high CO₂ solubility
  - Surface area of alveolar membrane – if reduced, sufficient gas exchange may not be possible despite an adequate diffusion rate. E.g. bronchial obstruction → alveolar collapse → decreased arterial oxygen/increased carbon dioxide and deranged pH. In emphysema, structural breakdown of alveolar walls → formation of fewer larger alveoli instead of more numerous and smaller alveoli → significantly reduced surface area
  - Ventilation-perfusion coupling – V/Q ratio described efficacy of the rate at which air reaches the lungs and blood reaches the lungs. In a normal lung, part of the lung is superior and part inferior to the heart → impact on V/Q ratio as lower (dependent) part is better ventilated and better perfused than the apex. For efficient gas exchange there needs to be max coupling between V + Q, and the ratio can be measured with a ventilation/perfusion scan.

Fig 5) reduced ventilation → reduced oxygen. However Q is maintained → shunt, which further reduces O₂ conc + increases CO₂. Hypoxaemic pulmonary constriction then occurs as well as dilatation of the airways leading to a perfusion defect as well. Diagnosis is a primary ventilatory defect.

Oxygen transport

- Series of steps through components that are in series – air → nasal passages → trachea → lungs → blood → tissues
• Approx. 300 ml of oxygen diffuses from the alveoli into the pulmonary capillary blood every minute.
• Mean alveolar pO$_2$ is $\sim$ 13.3 kPa
• The partial pressure of oxygen in a red blood cell entering a capillary is around 5.3 kPa
• Oxygen therefore diffuses rapidly down a concentration gradient into the blood, to bind with haemoglobin

**Carbon dioxide transport**

• Alveolar pCO$_2$ depends on CO$_2$ production and the mean alveolar pCO$_2$ is around 5.3 kPa.
• Rate of diffusion of CO$_2$ is around 20 times greater than that of O$_2$, so that CO$_2$ elimination is not normally affected by a reduction in diffusion capacity.
• The pCO$_2$ of blood as it enters the pulmonary capillary is around 6 kPa and the pCO$_2$ of alveolar gas is around 5.3 kPa. The time taken to equilibrate is similar to that for oxygen.
• Carbon dioxide is a major product of our metabolism - 200 to 250 ml of CO$_2$ is produced by tissue metabolism each minute. Carbon dioxide is carried in blood in physical solution, as bicarbonate ions, and chemically combined with amino acids in blood proteins including haemoglobin
• Carbon dioxide carried in blood thus alters blood pH. Since CO$_2$ + H$_2$O $\Leftrightarrow$ H$_2$CO$_3$ $\Leftrightarrow$ H$^+$ + HCO$_3^-$, a raised arterial pCO$_2$ indicates a respiratory acidosis and a lowered arterial pCO$_2$ indicates a respiratory alkalosis.
1. Describe the main functions of the airways
2. Describe the structure of the principal cells of the airways (including epithelial cells, smooth muscle cells, submucosal glands, inflammatory cells)
3. Draw a diagram of an airway showing the relative location of the cells
4. Describe the main functions of the airway cells
5. Relate the location of the cells to their function
6. Relate the functions of the airway cells to the overall functions of the airways
7. Describe the humoral control of the function of the airway cells
8. Describe the neuronal control of the function of the airway cells
9. Briefly relate changes in control mechanisms to the pathophysiology of respiratory diseases
10. Briefly outline the altered functions of airway cells to the pathophysiology of respiratory diseases

**Basic structure and organisation**

- Airways are either cartilaginous or alveolar
- Basic function – act as conduit pipes to conduct gas exchange
  - Function facilitated by mechanical stability (cartilage) and control of calibre (smooth muscle)
- 23 generations of branching from trachea to alveolar sacs, consisting of a conducting, transitional and respiratory zone, where cartilage quantity decreases and smooth muscle increases
Cartilage ring incomplete and slightly offset, but smooth muscle and nervous innervation complete

Airway consists of many different categories of cells:

- **Lining** – ciliated, intermediate, brush + basal
- **Contractile** – smooth muscle
- **Secretory** – goblet (epithelium), mucous, serous (glands)
- **Connective** – fibroblast, interstitial (elastin, collagen, cartilage)
- **Neuroendocrine** – nerves, ganglia, neuroendocrine, neuroepithelial bodies
- **Vascular** – endothelial, pericyte, plasma
- **Immune** – mast, dendritic, lymphocyte, eosinophil, macrophage, neutrophil

**Human airway epithelium**

- Consists of ciliated epithelial cells with goblet cells protruding through the layer into the lumen of the airway
- Mitochondria also prominent
- Goblet cells contain mucin granules – contain mucin in a highly condensed form
  - Upon secretion, intra-granular mucin expands using ATP absorbing water and swelling.

**Submucosal glands**

- Acini are functional units of secretory cells present in airways
- Mucous cells secrete mucus
- Serous cells secret antibacterials e.g. lysozyme
- Glands also secrete water and salts e.g. Na⁺ and Cl⁻

**Ciliary structure**

- Apical hook engages with mucus
- 9+2 arrangement allows movement of cilia
- ~200 per ciliated cell
- Cilia beating – engages with mucus when vertical, but otherwise circles back (so as to prevent mucus just being moved back and forth)

**Airway epithelial function**

- **Secretion** of mucus, water and electrolyte components of ‘mucus’ (+ plasma, mediators etc)
- Movement of mucus by cilia – **mucociliary clearance**
- **Physical barrier** to foreign substances
- **Production** of regulatory and inflammatory mediators:
  - NO (by nitric oxide synthase, NOS)
  - CO (by hemeoxygenase, HO)
  - Arachidonic acid metabolites, e.g. prostaglandins (COX)
  - Chemokines, e.g. interleukin (IL)-8
  - Cytokines, e.g. GM-CSF
  - Proteases

**Airway smooth muscle**

**Function**

- Inflammation affects the structure, airway calibre and secretory effects of smooth muscle cells within airways
- Structural effects – hypertrophy
- Airway calibre (tone) – contractile and relaxation effects
- Secretion – mediators, cytokines, chemokines
  - Bacterial products stimulate:
    - NOS → NO release
    - COX → prostaglandin release
    - Cytokine, chemokine + adhesion molecule release → inflammatory cell recruitment

**Airway vasculature**

**Trachea-bronchial circulation**

- 1-5% of cardiac output
- Blood flow to airway mucosa = 100-150 ml/min/100g tissue (amongst the highest to any tissue)
- Bronchial arteries arise from many sites on: aorta, intercostal arteries and others
- Blood returns from tracheal circulation via systemic veins
- Blood returns from bronchial circulation to both sides of heart via bronchial and pulmonary veins

**Functions**

- Good gas exchange (airway tissues and blood)
- Contributes to warming of inspired air
- Contributes to humidification of inspired air
- Clears inflammatory mediators
- Clears inhaled drugs (good/bad, depending on drug)
- Supplies airway tissue and lumen with inflammatory cells
- Supplies airway tissue and lumen with proteinaceous plasma (‘plasma exudation’)
  - Inflammatory mediators (e.g. histamine, platelet activating factor- PAF) transported in the blood to endothelial cells, which stimulates the release of plasma into the layer of epithelial cell
Control of airway function

- **Nerves**
  - Parasympathetic – cholinergic
  - Sympathetic – adrenergic
  - Sensory innervation

- **Regulatory and inflammatory mediators**
  - Histamine
  - Arachidonic acid metabolites e.g. prostaglandins, leukotriens
  - Cytokines
  - Chemokines

- Proteinases e.g. neutrophil elastase

- Reactive gas species e.g. O$_2^-$, NO

**Innervation of the airways**

- Parasympathetic motor pathway (cholinergic) $\rightarrow$ constriction – via vagus nerve
- Sensory innervation to brainstem via nodose ganglion
  - Also via dorsal root ganglion to spinal cord
- Sympathetic innervation from spinal cord via cervical thoracic ganglion (relaxation)
  - Adrenaline from adrenal gland also $\rightarrow$ relaxation

**Cholinergic mechanisms**

- Parasympathetic innervation of submucosal glands, smooth muscle cells (and blood vessels)
- Muscarinic receptors involving acetylcholine
- Activation $\rightarrow$ mucus secretion, airway smooth muscle contraction (and vasodilation)

**Regulatory-inflammatory cells in airways**

- Cells: eosinophil, neutrophils, macrophages, mast cells, T lymphocytes
- Mediators: histamine, serotonin, adenosine, prostaglandins, leukotrienes, thromboxane, PAF, endothelin, cytokines, chemokines, growth factors, proteinases, reactive gas species
- Effects: smooth muscle (both airway and vascular $\rightarrow$ constriction + relaxation), secretion (mucuns, water etc), plasma exudation, neural modulation, chemotaxis, remodelling
- NB: cells produce more than one mediator, and each mediator has more than one effect

**Clinical Correlates: Respiratory diseases with loss of airway “control”**

- Asthma, COPD, cystic fibrosis
- All common conditions
- Cause airway inflammation and obstruction
- Also $\rightarrow$ airway remodelling

**Asthma**

- A clinical syndrome characterised by increased airway responsiveness to a variety of stimuli ($\rightarrow$ airways obstruction)
- Airflow obstruction varies over short periods of time and is reversible (spontaneously or with drugs)
- Dyspnea, wheezing and cough (varying degrees - mild to severe)
- Airway inflammation $\rightarrow$ re-modelling
1. Explain the basic pathogenesis of lung cancer.
2. Describe the link between cigarette smoking and the incidence of lung cancer.
3. Describe the different local and systemic complications of lung tumours.
4. Describe the main histological types of lung cancer, their different biological behaviour, and the significance this has for prognosis and treatment.
5. Explain how the different sites and spread of the initial cancer in the lung can influence the chance of resection.
6. Summarise how lung cancer is staged.
7. Explain the modalities by which lung cancer can be diagnosed.
8. Explain the consequences of the existence of a small proportion of drug resistant cells within a tumour.
9. Explain what is meant by a paraneoplastic syndrome with examples.
10. Describe the risk factors and basic pathology of mesothelioma.
11. Give an approximate value for the survival rate of patients 5 years after the initial diagnosis of lung cancer.

Introduction - Epidemiology

- 3rd most common cause of death in UK
- Mortality rate 40,000 per annum
- 5 year survival rate 5.5%
- 80% die within 1 year of diagnosis
- Causative factor: Tobacco, radon, asbestos
- Carcinogens in tobacco smoke
  - Specific lung carcinogens: polonium-210, nickel compounds, cadmium compounds
  - Tumour promoters: volatile phenols
  - Co-carcinogens: pyrene, methylpyrenes, flubranthene etc
- Smoking – stimulates chromosomal translocation + oncogenic fusion protein via k-ras and Erb B2, and inhibits the natural G1 arrest + apoptosis that occurs following a mutation via p-RB, p53 and box genes.
Prevalence of smoking – overall decrease in prevalence of both male and female smokers since 1950, although peak occurs for all ages in the 1970s.

Trends of mortality – overall increase in mortality of both male and female population, but peaks in mortality correspond to time lag following smoking peaks.

There is also an increased risk of lung cancer in passive smokers, which increases in correlation to an increased number of years spent with the smoker.

The cumulative risk of death from lung cancer decreases for each 10 years earlier the smoker quit, but is greatest for patients who continue to smoke, and least for non-smokers.

Lung cancer

Clinical features

- Haemoptysis (coughing of blood originating from the respiratory tract below the level of the larynx)
- Unexplained/persistent (> 3 weeks) cough, chest/shoulder pain, chest signs, dyspnoea (breathlessness), hoarseness, finger clubbing → urgent referral for a chest x-ray
  - NB: finger nail clubbing seen as an increase in the sponginess of the nail bed, with a change in the superior surface of the finger from a concave to a convex surface
- Also may be asymptomatic – incidental finding of a mass on a chest X-ray

Pathogenesis

- Multistep theory of tumour development: As with the development of other tumours lung cancers arise as a consequence of accumulation of mutations of genes which regulate cell proliferation, invasion, angiogenesis and senescence.
  - Pathway different for different tumour types
- Precursor lesion of some of the major lung cancer types are recognized
- Atypical adenomatous hyperplasia as a precursor of adenocarcinoma. However as yet no precursor for small cell carcinoma has been identified
- Pathway for squamous cell carcinoma: normal epithelium → hyperplasia → squamous metaplasia → dysplasia → carcinoma in situ → invasive carcinoma

- Specific genes mutated at different stages of development.
- Genes and Lung cancer - Increasing recognized that polymorphisms in certain genes affect the risk of developing lung cancer and may help explain why some smokers do not develop lung cancer.
  - Familial lung cancers - are rare, but epidemiological evidence of increased risk for first degree relatives of young age, non-smoking cases
  - Susceptibility genes – nicotine addiction, chemical modification of carcinogens → polymorphisms in cytochrome p450 enzymes and glutathione S transferases which play a role in eliminating carcinogens
**Main types**

**Benign lung tumours** – do not metastasise; can cause local complications e.g. airway obstruction, e.g. chondroma

**Malignant lung tumours** – potential to metastasise, but variable clinical behaviour from relatively indolent to aggressive; commonest are epithelial tumours

- **Squamous cell carcinoma**: 25-40% of lung cancer, strong association with smoking, mainly central arising from bronchial epithelium, distant spread is later than seen in adenocarcinoma
  - Histology – shows evidence of squamous differentiation (keratinisation, desmosomes), variety of sub-types
- **Adenocarcinoma**: 25-40% of lung cancer, incidence increasing, most common type in non-smokers and females, often peripheral
  - Atypical adenomatous hyperplasia – proliferation of atypical cells lining the alveolar walls seen. They increase in size and eventually can become invasive.
  - Cytology – mucin vacuoles seen
  - Histology – extrathoracic metastases common and seen early, evidence of glandular differentiation seen with mucin secretions
  - Molecular pathways – precursor may be type 2 pneumocyte/clara cell
    - In non-smoker, EGFR mutation/amplification
    - In smoker, K ras mutation with DNA methylation of p53 occurs
- **Large cell carcinoma**: poorly differentiation tumour composed of large cells with no histological evidence of glandular or squamous differentiation. Electron microscopy shows evidence of some differentiation, suggesting they are probably very poorly differentiated adeno/squamous cell carcinoma; poor prognosis
- **Small cell carcinoma**: 20-25% of lung cancer, very strong association with smoking, very aggressive behaviour; 80% present with advanced disease and paraneoplastic syndromes

**Cell type**

- May be small cell or non-small cell cancer
- Types include:
  - Squamous cell carcinoma
  - Small cell carcinoma
  - Adenocarcinoma
  - Large cell carcinoma
  - Adenosquamous carcinoma
  - Carcinoid
  - Bronchial gland carcinomas
  - Other

**Importance of histological tumour type**: small-cell lung carcinoma have a survival of 2-4 months if untreated, with only 10-20 months treated with current therapy; treatment is usually chemoradiotherapy as too spread for surgery. In contrast, non-small cell lung carcinoma have a 60% 5yr survival rate after early stage detection, are often suitable for surgical resection and are less chemosensitive.

**Diagnosis**

- Role of pathologist – confirm diagnosis, determine histological type of tumour, determine tumour stage, determine molecular pathology
- **Cytology** – Study of cells: Look for malignant cells shed in sputum, or washed/brushed off airways at bronchoscopy, pleural fluid, endoscopic fine needle aspiration of tumour/enlarged lymph node
Histology – study of tissues: Biopsy tumour at bronchoscopy or via percutaneous CT guidance, mediastinoscopy/lymph node biopsy for staging

Special techniques - Gene profiling.

Staging:
All patients should have cross sectional imaging with a CT scan of the thorax, liver and adrenals for staging purposes. Selected patients may require additional investigations such as a bone scan, or positron emmision tomography (PET scan). Staging is classified according to TNM status (tumour, lymph nodes, and metastases)

Staging – TNM classification

T – Primary tumour
- T1 – tumour \( \leq 3 \)cm diameter without invasion more proximal than lobar bronchus
- T2 – tumour >3cm diameter OR
  o Tumour of any size with the following: invades visceral pleura, atelectasis of less than entire lung, proximal extent at least 2cm from carina (last cartilage ring before trachea divides into bronchi)
- T3 – tumour of any size with any of the following:
  o Invasion of chest wall
  o Involvement of diaphragm, mediastinal pleura, or pericardium
  o Atelectasis involving entire lung
  o Proximal extent within 2cm of carina
- T4 – tumour of any size with any of the following:
  o Invasion of the mediastinum
  o Invasion of heart or great vessels
  o Invasion of trachea or oesophagus
  o Invasion of vertebral body or carina
  o Presence of malignant pleural or pericardial effusion (excess fluid accumulation)
  o Satellite tumour nodule(s) within same lobe as primary tumour

N – Nodal involvement
- N0 – no regional node involvement
- N1 – metastasis to ipsilateral hilar and/or ipsilateral peribronchial nodes
- N2 – metastasis to ipsilateral mediastinal and/or subcarinal nodes
- N3 – metastasis to contralateral mediastinal or hilar nodes OR ipsilateral or contralateral scalene or supraclavicular nodes
- Lymph nodes include: anterior carinal, posterior carinal, right paratracheal, left paratracheal, right main bronchus, left main bronchus, right upper hilar, subcarinal, right lower hilar, sub-sub carinal, left hilar

M – Metastasis
- M0 – distant metastasis absent
- M1 – distant metastasis present (includes metastatic tumour nodules in a different lobe from the primary tumour)
- Metastasis may include: brain, bone, hepatic, superior vena caval obxtruction

Stage groups of TNM subsets:
- IA – T1 N0 M0
- IB – T2 N0 M0
- IIA – T1 N1 M0
- IIB – T2 N1 M0 or T3 N0 M0
- IIIA – T3 N1 M0 or T1-3 N2 M0
- IIIB – Any T N3 M0 or T4 Any N M0
- 1V – Any T Any N M1
Treatment

- The choice of treatment is based on three key factors:
  - Histological cell type
  - The stage of the lung cancer
  - Performance status of the patient

Molecular Therapeutics

- Molecular changes in lung cancer provide prognostic data and therapeutic data (predicted response to conventional chemotherapy and targets for novel drugs)
- Predictors of response to conventional chemotherapy – **Excision Repair cross-complimentation group 1 protein** (ERCCG1) – in advanced stage non-small cell lung carcinoma, if ERCCG1 POSITIVE there is a poor response to cisplatin based chemotherapy

Targets of Treatment – EGFR (epidermal growth factor receptor)

- In healthy cells, membrane receptor tyrosine kinase regulates angiogenesis, proliferation, apoptosis and migration.
- In non-small cell lung carcinoma, mutation/amplification occurs, and this is the target of tyrosine kinase inhibitors which can be used as a treatment

Treatment Summary

![Diagram of FAST TRACK DIAGNOSIS]

Treatment of small cell lung cancer

- Small cell lung cancers are rapidly growing tumours, which are highly responsive to chemotherapy and radiotherapy. However, there is the early development of metastases and most patients present with extensive disease.
- A number of cytotoxic agents are active in small cell lung cancer. Combination chemotherapy including cisplatin would be considered conventional treatment.
The combination of cisplatin and etoposide is thought to be more superior to other commonly used regimes such as cyclophosphamide, doxorubicin, and vincristine.

Sequential regimes of chemotherapy with cycling between agents have failed to show significant advantages and preclude the use of alternative agents for disease relapse.

### Treatment of Non-small cell lung cancer

- In non-small cell lung cancer surgery should be considered in all patients with Stage 1, Stage 2, resectable Stage 3 disease with appropriate cardiovascular reserve. In patients with unresectable Stage 3 disease, multi-modality treatment may offer better survival but most regimes require further assessment.
- The role of neoadjuvant chemotherapy followed by surgery is currently under exploration. A reasonable approach in the meantime would be for patients to be offered at least three cycles of chemotherapy with sequential or concomitant radiotherapy.
- In patients with advanced disease combination chemotherapy for palliation should be considered in those with a reasonable performance status.
- In all other patients best supportive care, and where appropriate, treatment with palliative radiotherapy.

### Complications of lung cancer

- **Local**
  - bronchial obstruction (collapse of lung → shortness of breath, or impaired drainage of bronchus → chest infection)
  - local invasion of local airways (causing haemoptysis), large vessels (SVC syndrome → circulatory collapse), oesophagus (→ dysphagia), chest wall (→ pain) and nerves (Horner’s syndrome)
  - extension through pleura/pericardium (with effusions → dyspnoea and cardiac compromise)
  - diffuse lymphatic spread within lung (with shortness of breath; this is a very poor prognostic feature)
- **Systemic**
  - Metastases – brain→fits, skin→lumps, liver→liver pain + deranged LFTs, bones→bone pain + fractures
  - paraneoplastic syndromes: represent systemic effects of tumour due to abnormal expression by tumour cells of substances (e.g. hormones) not normally expressed by the tissue from which the tumour arose. E.g. Secretion of antidiuretic hormone → hyponatremia
    - may be endocrine (like ADH) or non-endocrine (e.g. haematologic/coagulation defects, skin, muscular or miscellaneous disorders)

### Prognosis/Survival

- Survival rates are related to suitability for surgery, which is considered for stage I, II, III and some IIIa patients
- This highlights the need for early detection
- There is usually a 5% overall surgical risk and 10% risk of major complications

### Natural History

**NB: Malignant pleural tumours – Mesothelioma**

- Aetiology – asbestos exposure
- Responsible for <1% cancer deaths, but incidence increases
- Fatal
- Medicolegal implications of diagnosis – compensation for occupational hazards
Most patients have a history of asbestos exposure, but the tumour usually develops decades after the exposure.

- Incidence in males is 3x females
- Presents with dyspnoea, chest pain

### Lung Cell Biology

**Prof Terry Tetley** ([t.tetley@imperial.ac.uk](mailto:t.tetley@imperial.ac.uk))

1. **Know the structure of the mucosa (epithelium + underlying matrix) from the large conducting airways through to the alveoli.**
2. **Know the cell biology and function of the mucociliary escalator in normal lung defence and against inhaled toxins and micro-organisms.**
3. **Know the role of Clara cells (non-ciliated secretory epithelial cells) and alveolar type II cells in lung defence and repair.**
4. **Know the role of the alveolar macrophage and polymorphonuclear neutrophil in normal lung and after inhalation of cigarette smoke, particles, microbes, noxious gases etc.**
5. **Know the role of the interstitial cells in connective tissue synthesis (brief).**
6. **Know what pathology causes obstructive lung disease, especially the role of uncontrolled inflammation, abnormal tissue repair and mucous production (tutorial).**

**Introduction**

- The structure of the lung is optimised for gas exchange – with surface area approx. size of tennis court
- Gas exchange units form a sponge-like structure which are intimately linked with the airways
- The cross-sectional area of the lung increases peripherally – with up to 23 generations of gas exchange units
- The gas exchange units are lined with a fluid called surfactant; this is secreted in the peripheral link and accounts for ~1 wine glass of fluid – forming a very thin layer covering the respiratory units
  - Without it, the surface tension of the different gas exchange units will increase → collapse of the lung

**Healthy, Normal lung vs. COPD + Emphysema**

- In a healthy lung, the **epithelium** forms a continuous barrier, isolating the external environment from the host
  - It produces secretions to facilitate mucociliary clearance
  - Protects underlying cells as well as maintain reduced surface tension
  - Metabolises foreign + host-derived compounds which may be carcinogenic – this is important for smokers
  - Releases mediators – controls the number of inflammatory cells that reach the lung
  - Triggers lung repair processes
- In COPD, there is an increased number of goblet cells (known as hyperplasia) and increased mucus secretion
  - Between the goblet cells, ciliated cells push the mucus towards the throat

**Goblet cells**

- Normally about 1/5 of the epithelial cells – present in large, central and small airways
- Synthesise and secrete mucus.
- Mucus is complex, very "thin" sol phase overlays cells, thick gel phase at air interface.
- **Mucus** contains:
  - Mucin proteins, proteoglycans and glycosaminoglycans, released from goblet cells and seromucous glands. Give mucus viscoelasticity
Serum-derived proteins, such as albumin and alpha 1-antitrypsin, also called alpha 1-proteinase inhibitor, an inhibitor of polymorphonuclear neutrophil proteases. Combats microorganism and phagocyte proteases

Antiproteases synthesised by epithelial cells e.g. secretory leucoprotease inhibitor. Combats microorganism and phagocyte proteases

Antioxidants from the blood and synthesised by epithelial cells and phagocytes - uric acid and ascorbic acid (blood), glutathione (cells). Combats inhaled oxidants e.g. cigarette smoke, ozone. Also counteracts excessive oxidants released by activated phagocytes.

- In smokers, goblet cell number at least doubles; secretions increase in quantity and are thicker (more viscoelastic). Modified gel phase traps cigarette smoke particles but also harbours microorganisms, enhancing chances of infection.

**Ciliated cells**

- Present in large, central and small airways
- Normally approximately 80% of epithelial cells.
- Cilia beat metasynchronously. Imagine a field of corn with wind blowing to form "flow waves".
  - Push mucus forward, engaging when vertical. Then circle around to original position in order to prevent the movement of the mucus backward as well as forward
  - Tips of cilia in sol phase of mucus pushes mucus towards epiglottis. Usually swallowed, but often expectorated.
- Ciliated cells severely depleted in smokers with bronchitis; they beat asynchronously. Reduced mucus clearance, bronchitis and respiratory infections occur. However, extend into bronchioles of smokers, even though reduced in larger airways. Airways are thus obstructed by mucus secretions
  - Bronchitis is much more easily reversed than other illnesses associated with COPD

**Small airways**

- <2mm in diameter
- Not cartilagenous – held open by elastic walls of alveoli pushing on them
- In COPD, mucus becomes trapped, the airways narrow and they are broken down by enzymes and inflammatory cells
  - This reduces peripheral gas exchange

**Clara cells**

- Non-ciliated secretory bronchiolar epithelial cells
- Present in large, central, small airways, bronchi and bronchioles.
- Although found in most conducting and transitional airways, they increase proportionally distally. The bronchi and bronchioles are enriched by these cells
- Role: metabolism, detoxification + repair
- Contain phase I and phase II enzymes.
  - A major role of these enzymes is in xenobiotic metabolism, i.e. metabolism of "foreign" compounds deposited by inhalation.
  - Phase I enzymes include cytochrome P450 oxidases. Unfortunately, although these enzymes are designed to metabolise foreign compounds into a format that enables phase II enzymes to react and neutralise the toxic agent; they often activate a precarcinogen to a carcinogen
    - e.g: Benzopyrene (BP) is a precarcinogen in the particulate tar phase of cigarette smoke. One cytochrome P450, labelled CYP1A1 (also called aryl hydrocarbon hydroxylase), oxidases BP to benzopyrene diol epoxide (BPDE) which is a potent carcinogen. Smokers with lung cancer
have a polymorphism of CYPIA1 that results in high levels (extensive metabolism \(\rightarrow\) extensive production of potent carcinogen)

- Phase II enzymes include glutathione S-transferase, which enables conjugation of BPDE to a small molecule that neutralises its activity. Some individuals are "null" for glutathione S-transferase i.e. they do not synthesise glutathione transferase and cannot neutralise BPDE.
  - Consequently, if an individual who smokes has the CYPIA1 extensive metaboliser gene and the null glutathione gene they are 40 times more likely to get lung cancer!!
- These cells also make and release high levels of antiproteases e.g. secretory leukoproteinase inhibitor (SLPI)
- They also synthesise and secrete lysosome - enzyme that can lyse microorganisms.
- They synthesis and release antioxidants e.g. glutathione, superoxide dismutase

**Alveoli**

- In susceptible subject smokers, holes in the alveoli may develop – and the alveoli may become larger \(\rightarrow\) reduction in surface area available for gas exchange
  - This can be seen as elastic tissue loss, therefore expansion during breathing is reduced which exacerbates dead space
- Walls consist of two types of epithelial cells, type I and II
- Type II cells are more susceptible to damage than type I, but type I will be damaged more often
- Epithelial type II cells – also called type II pneumocytes found only in the alveoli (cover 5% of alveolar surface)
  - Contain lamellar bodies which store surfactant prior to release onto the air-liquid interface
    - Surfactant is phospholipid-rich surface active material that prevents lung collapse on expiration and has immunological functions.
  - Also synthesise and secrete antiproteases
- Positions in the corners of the alveoli, and are embedded in the interstitium with the apical membranes facing the air
  - Type II cells also very close to the capillaries
- Type II cells are a precursor of alveolar type I cells – they divide and differentiate to replace damaged type I cells

**Alveolar unit**

- Consists of type I and II epithelial cells, stromal fibroblasts, alveolar macrophages and capillary endothelium
- Ratio of TII: TI epithelial cells = 2:1
- Stromal cells – make extracellular matrix; cement of lung tissue. Also make collagen + elastin to give elasticity and compliance. Divide to repair
- Capillary endothelium – close proximity to alveoli to reduce diffusion distance
- Alveolar macrophage – enriched in the lower respiratory tract, but found throughout
  - Form about 90% of total phagocytic cells in normal lung. Increase 5-10-fold in smokers lungs.
  - Important scavenging cells; phagocyte debris and microorganisms.
  - Send "messages" to blood/lymphatic system to sequester other inflammatory cells (e.g. neutrophils, lymphocytes) to lungs during infection or as a result of toxicant deposition/inhalation.
  - Synthesise and secrete proteases to digest unwanted debris, attack organic material etc.
  - Generate oxidants during phagocytosis and on activation to kill infecting organisms etc
  - Generate antioxidants such as glutathione to neutralise oxidative molecules that might be inhaled or generated during infection etc
  - Like Clara and type II cells, contain enzymes that metabolise toxicants.

**NB: Polymorphonuclear neutrophils: found throughout the airways.**

- Usually only about 5% of lower respiratory tract phagocytes.
LSS Respiratory System
Alexandra Burke-Smith

- Increase significantly in number, 5-10-fold and proportionally (up to 30% of total phagocytes) in smokers and more so during infection.
- Higher proportion in conducting/large airways. About 30% of total phagocytes normally, up to 70% in smokers. Absolute number also goes up, about 5-fold.
- Store high levels of potent proteases in granules. These are released on activation. Smoker’s lungs contain high levels of these released proteases.
- Release very potent oxidative molecules such as hydroxyl anions during activation.

**Histopathology of Emphysema**

- Classic emphysema is centre-lobular
- The centre of each lobule marks the site of initial infection
- Fibroblasts lie adjacent to epithelial cells lining the alveoli, and are available for proliferation following infection
- Infection $\rightarrow$ chronic damage (TI cell death) $\rightarrow$ alveolar fibrosis (repair mechanism)
  - Increased type II epithelial cells
  - Increased number of fibroblasts – make lots of connective tissue
    - Communication between the type II cells and fibroblasts determines whether repair mechanisms proceed normally or abnormally (e.g. interstitial fibrosis)
  - Increased collagen deposition
- In normal repair, type I cell death causes growth factor release to increase TII cell proliferation and differentiation
- In abnormal repair, there is excess tissue breakdown and elevated growth factor release (seen at end stages on emphysema) $\rightarrow$ fibrotic effect (increased TII cell, stromal/fibroblast and connective tissue synthesis in interstitial space) – irreversible damage

**Effects of Smoking**

- **Blocks proliferation and differentiation of TII cells into TI cells**, as well stimulating apoptosis/necrosis of both TI and TII cells
  - Also blocks communication between TII cells and fibroblasts, therefore blocking repair mechanisms
- **Increases 10x number of macrophages and neutrophils** – effects include increased phagocytosis, antimicrobial defence, antioxidant synthesis and xenobiotic metabolism
  - Macrophage: neutrophil ratio in non-smokers is 70:30, but this reverses in COPD
  - Secrete serine proteases (e.g. neutrophil elastase) and metalloproteases (e.g. MMP9), which activate other proteinases and activate cytokines/chemokines and other proinflammatory mediators therefore increasing the number of inflammatory molecules within the alveoli $\rightarrow$ alveolar inflammation
  - Also release antimicrobial oxidants – which generate highly reactive peroxides, interacting with proteins and lipids and fragmenting connective tissue $\rightarrow$ damage
  - Macrophages also secrete mediators – growth factors + proteases trigger growth and repair by other cells
- **Contains procarcinogens** which are activated by phase I enzymes
  - In normal metabolism, phase II enzymes then make these water soluble so that they can be metabolised and excreted
  - Smoking overloads the pathway, and may inactivate the enzyme, therefore the carcinogen may undergo DNA binding, adduct formation, no repair and mutation
Lung Mechanics I
Dr Robert Shiner (r.shiner@imperial.ac.uk)

1. Explain what is meant by elastic recoil.
2. Define compliance.
3. Explain how pulmonary versus chest wall compliances can vary in various respiratory diseases.
4. Explain the concept of surface tension and the Law of Laplace.
5. Explain how pulmonary surfactant affects lung volume and airway patency.
6. Describe the relationship between alveolar and atmospheric gas pressures, airway resistance and airflow.
7. Describe the factors that affect airway resistance centrally and peripherally.
8. Name the two major components that contribute to the work of breathing and explain how each may be altered in disease states.
9. Describe the relationship between mechanical work and oxygen cost of breathing in normal patients and patients with respiratory insufficiency.

Elasticity

**Definition:** the property of matter that causes it to return to its resting shape after deformation by an external force. In the lung, the force is indicated by pressure exerted on the lung.

**Elastic resistance**

- Also known as elastance = change in pressure/unit of volume change
- It is the reciprocal of compliance, therefore when elastic resistance is decreased, compliance increases
  - When a spring is easy to distend, it has low elastic resistance and high compliance... and vice versa
- Clinical correlate: emphysema – lung elastic resistance is reduced therefore compliance increases

**Pleural pressure**

- The outer surface of the lungs are covered by visceral pleura, which is in close contact to the parietal pleura which lines the inner surface of the thoracic cage
- The gap between the two pleura is called the pleural cavity
- The lungs tend to pull on the pleura inward away from the chest wall, therefore are more prone to collapse. This is due to the connective tissues, elastin and collagen in the lung, as well as the surface tension generated at the air-liquid interface in the alveoli
- If the thorax is opened, the chest wall volume will increase by 600-1000ml, thus increasing the outward pull of the chest wall and separating the two pleura
- The tendency for the lungs to recoil inward (i.e. elastic recoil of the lungs) can be measured as the pleural pressure, i.e. it is the pressure between the pleural layers
- During normal inspiration, the volume of the thorax increases, but the elastic recoils of the lungs and chest wall are cancelled out as they are equal therefore the lung does not collapse
- There is normally a small amount of fluid present in the pleural cavity that allows the visceral and parietal pleura to slide over each other
  - If this cavity is filled with blood (haemothorax) or air (pneumothorax), the gap may expand increasing the pressure on the lung away from the chest wall, therefore increasing the risk of collapse
Compliance

**Definition:** the expression of pressure-volume characteristic of the respiratory apparatus, i.e. the ability of the lung to stretch

- Lung compliance = \( \frac{C}{L} = \frac{\text{Change in volume}}{\text{change in pressure}} \), i.e. the slope of a pressure volume curve
- High compliance means less change in volume for a given change in pressure, i.e. less stretch
- Non-compliant means that a larger pressure is required to achieve the same volume

**In different conditions**

- **Healthy lungs** – 5cm water pressure \( \rightarrow \) inspiration of 1 litre, therefore \( \frac{1}{5} = 0.20 \text{L/cm H}_2\text{O} \)
- **Emphysema** (loss of elastic recoil) - 5cm water pressure \( \rightarrow \) inspiration of 2 litre, therefore \( \frac{2}{5} = 0.40 \text{L/cm H}_2\text{O} \)
- **Pulmonary fibrosis** (increased elastic recoil) - 5cm water pressure \( \rightarrow \) inspiration of 0.5 litre, therefore \( \frac{0.5}{5} = 0.10 \text{L/cm H}_2\text{O} \)

**Measuring Pleural pressure (Ppl)**

- Directly – insert a needle
- Indirectly – measure pressure in a thin-walled balloon introduced into the middle third of the oesophagus; the airway is anterior to the oesophagus and the surrogate pressure is reflective of the pleural pressure
  - This is because the oesophagus lies between the lungs and chest wall and because the walls of the oesophagus are thin + have little tone so exert little of their own pressure

**Lung pressure-volume curves**

For any given pressure applied, the volume during deflation (expiration) is greater than the inflation (inspiration) – this is known as hysteresis – without any pressure, there is always some volume in the lung due to the volume of air occupied by the airways

**Reasons for elastic recoil**

- Half of the elastic recoil of the lungs comes from the elastic properties of their tissues (think like elastic recoil of an inflated rubber balloon – there is always some air in the lungs therefore they are always slightly inflated)
- The other half comes from their structure and surface – millions of alveoli filled with air, lined by liquid and connected to the atmosphere by bronchial tree – this creates an air-liquid surface tension
  - Filling the lung with fluid (like surfactant) reduces this air-liquid surface tension therefore reducing the elastic recoil making the lungs easier to inflate (this was shown by von Neergaard, 1929)
  - Filling the lung with fluid also removes hysteresis as there is no air left in the lung

**Hysteresis**

- Inflation of the lung follows a different pressure-volume relationship than deflation, i.e. it requires a greater pressure to reach a particular lung volume when inflating (inspiring requires a greater pressure – more active), than to hold is at that volume when deflating it (when expiring)
- Saline inflation removes the effect of the elastic recoil of lung surface/structure, but just shows the recoil of the elastic properties of the lung tissues
Transpulmonary pressure (Ptp)

**Definition**: the pressure difference between the alveoli and pleural cavity, i.e. alveolar pressure – pleural pressure (Palv – Ppl)

- NB: remember the pleural pressure can be measured as the tendency of the lung to recoil away from the chest wall
- The barometric pressure is the atmospheric pressure – can be seen to be the same as in the mouth and trachea

**Inspiration**

- During inspiration, the chest expands and inspiratory muscles contract
- This results in changes in the pressures affecting the respiratory system, which causes air to flow through the system
- The respiratory apparatus (lungs, chest wall, diaphragm, abdominal contents, tracheobronchial tree) has an elastic force which offers resistance to this airflow – i.e. the respiratory apparatus does not want to distend, so offers a counter force which in turn offers resistance to the incoming airflow
  - There is also resistance to airflow caused by the gas already present in the respiratory tract
- In order to overcome the resistance to airflow (which is the point of inspiration, to create airflow into the thorax), force is required
  - This force is the required pleural pressure

**Elastic forces during breathing**

- After quiet expiration, the outward recoil of the chest wall is equal to the inward recoil forces of the lungs; therefore there is no movement/change in pressures. However a small volume of air still occupies the airways – FRC (functional residual capacity)
- **Relaxation pressure** (RP) is the net balance between these two recoil forces and is derived by having a subject relax AGAINST A COMPLETE OBSTRUCTION at different lung volumes
  - The relaxation pressure curve can be determined by considering the combine compliance of the chest wall and lung
- **At FRC**, the recoil forces are equal but in opposite directions, therefore there is no movement of air and the RP is 0 or atmospheric
- **Below FRC**, the recoil of the chest > inward recoil of lungs, therefore RP is negative and inspiration occurs
- **Above FRC**, the inward recoil of lung > recoil of chest, therefore RP is positive and expiration occurs
NB: Chest wall recoil
- Assessed by measuring the pressure exerted by the relaxed respiratory system against an occluded airway over a range of voluntarily achieved vital capacity
- This is unreliable and difficult to do
- The chest wall recoil increases as the chest wall stiffens, which occurs with age, obesity and deformities e.g. ankylosing spondylitis

Why measure residual volume?
- An increased residual volume → increased functional residual capacity
- This suggests air trapping due to an airflow obstruction – result of possible asthma, COPD etc
- This air trapping means that the patient cannot expel as much air, resulting in an increased pressure which is uncomfortable for the patient
- In patients with COPD, the smaller the RV, i.e. the closer the inspiratory-to-total lung capacity is to 1, the lower the risk of mortality

Lung stabilisation

Factors which stabilise the lung

- **Surfactant**
  - Forms relatively late in gestation (approx. 25 weeks)
  - Can be assessed in amniotic fluid
  - Glucocorticoids stimulate type II cells produce surfactant (can accelerate lung maturation)
  - Respiratory distress syndrome (RDS) results from an inadequate amount of surfactant – replacement may improve condition
- **Interdependence of lung units**
  - Adjacent alveoli share a common wall, therefore tendency of one alveolus or lung unit to collapse is opposed by the support of surrounding units

Surface tension

- Definition: the manifestation of attracting forces between atoms and molecules
- Units of force/unit length (dynes/cm)
- May be lowered by certain substances when placed in a liquid (exert less attracting forces) – surfactant or surface active molecules

Pulmonary surfactant

- In lungs of all air-breathing vertebrates
- Formed in cuboidal type II alveolar epithelial cells (stored in osmiophillic lamellar bodies, secreted into lumen)
- Consists of phospholipids (90%) ad specific apoproteins (10%)
- Without surfactant, smaller alveoli would empty into larger ones
- Undergoes a continuous process of synthesis and degradation; its synthesis enhanced by glucocorticoids, c-AMP, oestrogens, thyroid, and inhibited by beta receptor blockade.
  - Fate – most recycled to Type II cells, phagocytosis + degradation by macrophages, intra-alveolar catabolism or removal by mucociliary escalatory
Law of Laplace

- Relationship between wall tension (T) which tends to collapse, and distending pressure (P) necessary to hold the bubble open – therefore surfactant uses the law of Laplace to hold alveoli open during the ventilator cycle (P = 2T/r).
- There is a tendency for the lung to collapse due to the elasticity of the lung parenchyma and the surface tension at the air-liquid interface. If surface tension remains constant, but the alveolar radius is reduced the pressure necessary to prevent collapse increases, therefore alveolar expansion requires a greater force.
- In the lungs, the surface tension decreases with expiration (due to the decrease in alveolar radius), but increases with inspiration. If the surface tension changes, the alveolar pressure (P) must remain constant to prevent alveolar collapse throughout the ventilator cycle. This is the role of surfactant.

Applications →

Airflow resistance

- During breathing, the respiratory muscles encounter a force as a result of the resistive properties of the lung and chest wall – the amount of force applied to breathe thus depends on this resistance.
- This resistance comes from:
  - Resistance of the air already present in the airways and upper-bronchial tree
  - Frictional resistance of tissues sliding over each other in lung parenchyma and chest wall
  - During inspiration – the force is provided by inspiratory muscles
  - During slow expiration – the elastic recoil of the lungs is sufficient to overcome the gas + tissue resistance until the level of FRC. To exhale down to RV, forced expiration is required, which uses the respiratory muscles.
  - At end-inspiration/end-expiration, there is no air-flow, flow-resistance passes through 0, all pressure between airway opening and balloon (representing pleural pressure) is being applied to overcome the elastic resistance.
Transpulmonary pressure (Ptp) is the pressure across the respiratory system, and can be calculated by the alveolar pressure – pleural pressure (measure of the tendency of the lungs to recoil inwards). The degree of stretch of the respiratory system during the ventilatory cycle is indicated by the change in volume (V), therefore compliance can be seen as $\frac{V}{P_{tp}}$

During breathing, resistance must be overcome in order to move air through the respiratory system, whether in or out (inspiration/expiration). This resistance is overcome by the generation of pressure in the pleural cavity by the respiratory muscles. This resistance comes from the elastic forces of the lungs, which resists distension; and the resistance to airflow e.g. turbulence at the back of the throat due to the change in angle of flow.

- During breathing, there are 3 types of pressure which must be considered:
  - The total pressure that must be applied to overcome resistance ($P_{TOTAL}$), which is the sum of:
    - Pressure required to overcome elastic resistance ($P_{El}$)
    - Pressure required to overcome flow resistance ($P_R$)
  - At end-expiration/end-inspiration, there is no airflow, therefore $P_R = 0$ and $P_{TOTAL} = P_{El}$
  - At any other point during the respiratory cycle, we can calculate $P_R$, $P_R = P_{TOTAL} - P_{El}$
  - By measuring the rate of airflow and flow-resistive pressure at the same time, a pressure-flow plot can be derived $\rightarrow$ (2nd graph)

- 1st graph – line to the right (next to red arrow) represents inspiration, as a higher pressure is required to overcome the resistive forces

- 2nd graph – the linear portion of the graph shows a linear relationship between pressure change and airflow. This is due to the laminar resistance of airflow through airways. The deviation from this straight line signifies a disproportionate increase in the pressure required to produce a further increase in airflow due to turbulent resistance in the airways.

- 1st graph – flow resistance can be determined from the simultaneous relationship between volume + transpulmonary pressure during 1 breath. The elastic component of the transpulmonary pressure ($P_{El}$) is derived by joining the points of end-expiration & end-inspiration. The pressure necessary to overcome flow resistance (at any point) is the difference between $P_{TOTAL}$ (transpulmonary) - $P_{El}$

- 2nd graph – when $P_R$ is plotted against the simultaneously measured rate of air flow, the flow resistance can be derived from the gradient of the linear portion of the curve

- Flow resistance can be defined as the pressure required to produce a given rate of airflow (expressed in cmH$_2$O/L/sec) = $P_R/ V$ (dot placed above V to indicate rate, also expressed as Q)

- Continuous measurement of alveolar pressure is not necessary – pressure required to overcome flow resistance can be determined by simultaneous recordings of changes in:
  - Lung volume
  - Airflow
  - Transpulmonary pressure

- In asthma or COPD, this pressure may be increased 10-15x
**Getting air into the lungs**

- Air enters and leaves the lungs due to changes in the intrathoracic pressure
- By increasing the size of the thorax, the inspiratory muscles lower the intrathoracic pressure relative to the atmospheric pressure – this causes bulk flow into the airways
- Resistance to this flow is called flow resistance ($R$)
- $R = \frac{\text{pressure (P)}}{\text{Flow (V with dot/Q)}}$ – once max flow has been achieved, the resistance is directly proportional to the driving pressure generated by the inspiratory muscles

**Expiration**

- Expiration is a passive process up to FRC: this involves passive recoil of the lungs
- Expiration is an active process beyond FRC: this involves expiratory muscles (abdominal muscles)
- **Elastic forces at the end of a normal expiration** (i.e. at FRC):
  o No air moves into or out of the lungs
  o A volume of air (equal to FRC) remains in the lungs

**Dynamic compression**

- On expiration, the intrapleural pressure becomes more positive than the alveolar pressure → pressure tending alveolar + airway collapse (occurs in non-cartilagenous small airways)
- On forced expiration, dynamic compression of the small airways causes an increase in airflow resistance (due to the relation of the inspiratory muscles → reduction in thoracic volume)
- When dynamic compression occurs, the alveoli exhibit elastic recoil to oppose the compression. This acts as a radial traction on the small airways - becoming the driving pressure for air out of the lung
- The elastic recoil pressure of the alveoli can be derived by $P_{\text{Alveoli}} - P_{\text{Pleural}}$
- Along the airways, the pressure drops from alveolar pressure to atmospheric pressure in the mouth
  o At some point along the airways, the intramural and extramural pressures are equal, therefore there is no net transmural pressure – this is known as the equal pressure point (also “choke point”)
  o Further towards the mouth, the intramural pressure may be < extramural pressure, which creates a transmural pressure tending to narrow or close the airway (negative) – at these points, flow limitation occurs and the airways may collapse
  o **Flow-limiting sites** typically are in the 2nd + 3rd generations of airways
- When dynamic compression occurs, the driving force for airflow becomes the difference between alveolar and intrapleural pressure → alveolar recoil pressure. This is NOT determined by the respiratory muscle effort, but rather by the compliance and
volume of the lung (a high lung volume → high lung static recoil pressure)
- In disease, the weakened airways can actually collapse causing air-trapping behind the blockade
- Lip pursing moves the EPP to the mouth, a psychological relief to the patient

Factors affecting dynamic compression
- Airway resistance – increased airway resistance → more rapid alveolar pressure drop → earlier airway collapse
- Compliance – increased compliance of the lung means reduced elastic recoil → reduced driving force for airflow
- Lung volume – reduced lung volume means reduced stretch → reduced recoil → reduced driving force
  - Reduced lung volume also increases airway resistance
  - As lung volume decreases, the flow-limiting site moves peripherally (towards alveoli), therefore in late forced expiration the flow is increasingly determined by the properties of the small peripheral airways

Isovolume Pressure-Flow curves
- For any lung volume: maximum inspiratory flow is effort dependent
- For high lung volumes: maximum expiratory flow is effort dependent
- For low lung volumes: maximum expiratory flow is effort independent
  - i.e. maximum expiratory airflow increases to a maximum; further effort produces no further increase in flow due to airway compression

Asthma
Obstructive disorder, i.e. results in a narrowing of the airways. The aperture of the small airways is completely different, resulting in changes to the FEV-1 (graph 2 – is reduced). The max expiratory flow is reduced, and the effort independent component of expiration (involving dynamic compression and the small airways)

Airways

<table>
<thead>
<tr>
<th>Source of airway resistance</th>
<th>Contribution to airway resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract (nose → larynx)</td>
<td>50%</td>
</tr>
<tr>
<td>Trachea → segmental bronchi</td>
<td>35%</td>
</tr>
<tr>
<td>Distal to the bronchioles (airways &lt; 2 mm)</td>
<td>15%</td>
</tr>
</tbody>
</table>
Factors which affect airway resistance:

- Lung volume
- Airway calibre (diameter of the airway)
- Airway generation
- Airflow profile
- Phase of respiration
- Vagal and sympathetic tone
- Respiratory gases

Flow through airways depends on:
1) airway resistance
2) driving pressure
3) Airway generation
   - Regional airway resistance decreases as a function of airway generation
   - The highest regional resistance is at generation 4 – these are medium sized bronchi of short length and frequent branching → highly non-laminar air flow with extreme turbulence
4) Airflow profile
   - Airflow may be laminar, turbulent or transitional (at a branching)
   - laminar flow occurs at low Reynolds numbers, where viscous forces are dominant, and is characterized by smooth, constant fluid motion
     - small airways (diameter <2mm) tend to show more laminar flow with Re <2000
   - turbulent flow occurs at high Reynolds numbers and is dominated by inertial forces, which tend to produce chaotic eddies, vortices and other flow instabilities.
     - Large airways (diameter >2mm) tend to show more turbulent flow with Re > 2000
   - Reynolds number is used to assess the airflow profile, and is calculated by
     - Re = (airway radius x velocity x density) /viscosity
     - Reduced gas density such as helium will reduce the Reynolds number – helium may be of use in airway obstruction particularly

\[
\dot{V} = \frac{P}{8\eta L}\]

Laminar flow + Poiseuille’s Equation
- I.e. for a given driving pressure under laminar conditions:
  - Doubling the length of the airway will halve the flow rate
  - Halving the tube diameter will decrease the flow 16x
- Therefore tube radius is the dominant factor in determining the resistance to flow (in small airways with diameter <2mm)

5) Phase of respiration – resistance is less in inspiration than in expiration
6) Vagal + sympathetic tone (normal little if any)
   - Cholinergic blockade – decreases pulmonary resistance in both large and small airways
   - Beta2 receptor stimulation – produces bronchodilation + increased airway conductance in both large and small airways
     - NB: conductance is the reciprocal of resistance
   - Beta-blockade – may increase airway resistance, i.e. reduce conductance
7) Respiratory gases
   - Hypocapnia – may cause bronchoconstriction + increase resistance, may also reduce ventilation due to poor perfusion
   - Hypercapnia – no effect on airway conductance
Work of breathing

- Respiratory muscles must perform work in order to overcome the mechanical impedences to respiration offered by the lung and chest wall during breathing.
- In graph A, the mechanical work of breathing necessary to overcome elastic resistance is shown.
- In graph B, this is combined with the work required to overcome flow resistance.
- The expiratory portion of the flow resistance work loop falls within the triangle that represents elastic work.
  - This indicates that expiration is passive and brought about by the elastic recoil of the lung, which was stretched during inspiration.
- The total work performed during inspiration is the sum of the elastic work and that required to overcome inspiratory flow resistance.
- In a healthy individual, the total mechanical work per quite breath = work required to overcome elastic properties (2/3) and flow resistance (1/3).
- NB: The product of pressure and volume also has the units of work.
- When the mechanical properties of the respiratory apparatus are altered by disease or during a forceful expiration, additional expiratory mechanical work is necessary – provided by expiratory respiratory muscles e.g. abdominals.
- **Increased flow-resistive work** - E.g. asthma; Elastic energy stored during inspiration is not enough to produce airflow during expiration, therefore expiratory muscles must do extra work.
  - NB: flow resistive loop falls out of the elastic work area, thus additional work required to overcome flow resistance during expiration.
- **Increased elastic-resistance work** - E.g. pulmonary fibrosis; Work required to overcome flow resistance is not altered, but much more work is required to overcome the high elastic resistance of the “stiff lungs”.

Alveolar ventilation

- Work of breathing can affect the pattern of breathing and therefore the amount of ventilation taking part in gas exchange.
- For any given alveolar ventilation, there is an optimal respiratory rate and tidal volume at which the total mechanical work of breathing is minimal.
- When the respiratory rate is less than optimal, flow-resistive work is less BUT larger tidal volumes are required to achieve a given alveolar ventilation – this increases the work required to overcome the elastic resistance.
- When the respiratory rate is more than optimal, total ventilation must increase if the same alveolar ventilation is to be maintained – this is because more ventilation is wasted when the tidal volume is smaller. Therefore the amount of work required to overcome the elastic resistance is less, BUT the flow-resistive work will increase roughly in proportion to the increase in respiratory rate.
- In pulmonary fibrosis/kyphoscoliosis – the elastic resistance is increased, therefore the mechanical work required to overcome this increases – graph is shifted upwards. The work is minimal at an increased frequency → respirations tend to become rapid and shallow.
- In bronchial obstruction, the flow-resistance is increased, therefore the mechanical work required to overcome this increases – graph shifted upward. The work is minimal at a lower frequency → respirations tend to become slower and deeper.

**Key to summary**
A – Normal
B – Pulmonary fibrosis (increased elastic resistance)
C – Bronchial obstruction (increased flow resistance)
Little arrows indicate respiratory rate at which total work is minimal.

**Oxygen cost**
- In order to perform the work necessary to overcome the mechanical resistances encountered during breathing the respiratory muscles require oxygen.
- Oxygen consumption (VO\(_2\)) increases by about 1ml/litre ventilation when ventilation in a healthy individual is increased to 60+ litres/min.
- At very high ventilations, oxygen consumption increases considerably and may become a significant proportion of the total body oxygen consumption.
- In emphysema, oxygen cost (even at low ventilation rates) may be increased by 4-10x.
- Respiratory insufficiency – oxygen consumption increases disproportionately even at very low ventilation, therefore anything that requires an increase in ventilation (e.g. exercise) → increased oxygen requirements – this needs to be considered when forming management plan.

**Pulmonary Circulation**
Dr Claire Shovlin (c.shovlin@imperial.ac.uk)

1. Compare the systemic and pulmonary circulations with respect to
   a. the structure of the arteries and arterioles
   b. the mean arterial blood pressure and
c. the overall resistance to blood flow.
2. Explain how differences in the arterial blood pressures of the two circulations influence the structure of the two ventricles of the heart.
3. Describe and explain the relative difference in blood flow to the bases and apices of the lungs in a standing human.

4. Explain, with reference to the pulmonary circulation, the meaning of the terms vascular recruitment and hypoxic vasoconstriction.

5. Explain the importance of hypoxic vasoconstriction in the foetus. Give one advantage and one disadvantage of this response in an adult suffering from chronic lung disease.

6. Give two reasons why lung disease may lead to pulmonary hypertension. Explain what is meant by “cor pulmonale”.

7. Explain what is meant by pulmonary oedema. Identify 3 pathophysiological mechanisms that may lead to this state.

8. Explain the term “pulmonary embolism” and state the typical site of origin of such emboli. Describe the consequences of a large embolus with respect to:
   a. the right side of the heart and the pulmonary circulation
   b. the viability of the lung tissue and
   c. the implications for gas exchange.

9. Appreciate, in the context of the pulmonary circulation, the concept of shunting. Identify the potential deleterious effects of an increased pulmonary shunt.

NB: Bronchial circulation
- Systemic supply to lungs – support tissue viability
- Branch from the aorta
- Drain into the bronchial veins + small broncho-pulmonary anastomoses

Pulmonary circulation
- From the left ventricle, receives entire cardiac output each cycle
- Primary function – gas exchange
- Other functions include filtering of small emboli, metabolism of vasoactive substances (angiotensin I, bradykinin, serotonin, noradrenaline, prostaglandins, leukotrienes), and other

Structure/function relationship
- Key point – vast alveolar surface area needs to be supplied (70m² – grows from child to adult), therefore structure needs to optimise diffusion
- From right ventricle – deoxygenated blood – alveoli – oxygenated blood – left atrium
- Has to accommodate the entire cardiac output each cycle, therefore has to be a high capacity low resistance circuit
- The cardiac output may also increase (exercise, pyrexia etc), therefore needs to accommodate these changes
- Spare capacity is also required for its filtratory function

Contrast with systemic circulation
- Pulmonary circulation does not require such high pressures due to close proximity with the heart, therefore does not have the same gravity to overcome like with normal venous return
- This means that the structure of the arteries, veins and capillaries are different
- Arteries/veins: pulmonary – thinner walls, less smooth muscle; systemic- thicker wall with abundant smooth muscle
- Capillaries: pulmonary – very thin walls, mesh provides a thin sheet of blood; systemic- network structure throughout tissues
- Pulse pressures: systemic (120/80mmHg), pulmonary (25/8mmHg) – because wall of right ventricle thinner
Mean systemic = 100, mean pulmonary = 5mmHg

- Pulmonary vascular resistance (= pressure gradient/blood flow = arterial-venous pressure/cardiac output)
  - Therefore PVR = 15 - 5/5 = 2mmHg/l/min.
  - In contrast SVR = 18mmHg/l/min
  - This is due to reduced arterial pressure

Embryological/development

- Development completely separate from systemic circulation
- The dorsal aorta splits → left dorsal aorta + right dorsal aorta
- 6 branchial arches arise from the dorsal aorta
- 1st, 2nd and 5th branchial arches: regress on both sides
- 3rd branchial arch: gives rise to the common carotid arteries on both sides
- 4th branchial arch: gives rise to the aorta
- 6th branchial arch: gives rise to the pulmonary circulation (i.e. pulmonary artery)
  - RHS: loses its link to the aorta
  - LHS: retains its link to the aorta during embryonic life – ductus arteriosus

NB: Foetal circulation:

- Ductus arteriosus: forms the link between the pulmonary artery and the aorta
- Blood flow: RV → ductus arteriosus → aorta → systemic circulation → RA
- Foramen ovale: allows blood to flow from RA to LA
- The placenta is the site of gas exchange; therefore most blood flow (60%) is via the placenta
- The pulmonary circulation forms a high resistance circuit since the lungs are fluid-filled
- In the foetus: the RV is hypertrophied; therefore both ventricles have a similar appearance (the RV regresses after birth)

At birth:
First breath causes the lungs to expand, increases the alveolar pressure and decreasing the pulmonary resistance. This leads to:

- Reflex closure of the foramen ovale and the ductus arteriosus occurs
- This is followed by remodelling and permanent closure of both structures
Regulation of blood flow

- The effects of gravity – blood goes down
- The close proximity of alveoli and capillaries from gas exchange results in the exposure of vessels to alveolar pressure. The distribution of blood-flow in the lungs is then considered to be 3 zone model:
  - Zone 1: PA > Pa > Pv (tend vessel compression)
  - Zone 2: Pa > PA > Pv (tend vessel compression on venous side – this is important because the pulmonary circulation needs to restrict recruit vessels, and it is easy to open the tiny closure; PROGRESSIVE RESTRICTION)
  - Zone 3: Pa > Pv > PA

Effects of progressive restriction of the pulmonary vascular bed:

- Right and left lungs: PAP is normal
- Right lung only: PAP is normal since the right lung has sufficient spare capacity to accommodate the entire cardiac output without an increase in PAP
- Right upper lobe only: PAP increases

Increased capacity of the pulmonary bed (required for increased CO accommodation) can then be achieved by recruitment or distension. Both lead to a fall in pulmonary vascular resistance
- Recruitment is the opening of vessels that were previously closed (Zone 2), via a slight increase in venous pressure which is achieved through the integration of pulmonary and cardiovascular system
- By decreasing the pulmonary vascular resistance, it enables to the pulmonary arterial pressure to remain normal even if the venous pressure increases

NB: Pneumonia - Hypoxic pulmonary vasoconstriction (HPV)

- If alveolar oxygen tension falls, active vasoconstriction of pulmonary arteries may occur (to a diameter of <1000 micrometres)
- This diverts blood to the aerated regions of the lung to find more oxygen to meet metabolic demands
- Regulated by HIF (hypoxia-inducible factor) – regulates systemic changes in haematopoetic, respiratory and cardiovascular physiology that combine to restore adequate oxygenation
  - Act as an alveolar oxygen sensor in pulmonary arterial myocytes which cause temporary vasoconstriction
- HPV in the foetus: this helps to maintain low blood flow to the lungs of the foetus - Therefore blood is directed into the systemic circulation
- HPV in chronic lung disease:
  - Advantage: reduces V/Q mismatch by reducing blood flow to poorly ventilated areas
  - Disadvantage: chronic HPV leads to vascular remodelling
  - This results in a permanent increase in PVR → pulmonary hypertension → right-sided heart failure
Disease states

Pulmonary oedema

**Definition:** fluid infiltration from the pulmonary circulation into the pulmonary interstitium due to a change in the rate of normal dynamic fluid shifts

- Consequences include interstitial oedema and alveolar flooding
- Fluid flux across pulmonary capillaries is caused by the difference between hydrostatic pressure and colloid osmotic pressure
  
  \[
  J_V = K_f \left[ \frac{P_c - P_l}{\sigma} \right] - \Delta \text{colloid osmotic pressure}
  \]

  - Normally, if hydrostatic pressure > colloid osmotic pressure, there is a small fluid flux into the interstitum, but any excess fluid drains into the lymphatics (act as rate limiting step)
  - In pulmonary oedema, the lymphatics become overwhelmed by the higher fluid flux rates \( \rightarrow \) interstitial oedema + alveolar flooding

- **Effects** of pulmonary oedema: impaired gas exchange, reduced lung compliance, increased pulmonary venous pressure
- **Clinical presentation** (often seen following a myocardial infarction): Terrified patient (drowning feeling), Severe breathlessness (work of breathing is very high), Pink frothy sputum (due to high intravascular pressures causing rupture of alveolar vessels), Crackles on auscultation
  - Morphine relieves these clinical symptoms

- **Causes:**
  - Increased hydrostatic pressure due to high pulmonary venous pressure which is caused by: Left heart failure, Mitral stenosis
  - Reduced plasma colloid pressure due to low [plasma protein] which is caused by: Starvation, Abnormal leakage from the kidney or the gut
  - Increased capillary permeability due to endothelial cell damage. This occurs in ARDS (adult respiratory distress syndrome)

Pulmonary embolus

**Definition:** clot formation in the pulmonary circulation

- **Mechanism:**
  - Small clots form in the deep veins of lower limbs
  - These clots enter the pulmonary circulation: they are filtered by spare capacity vessels and broken down by the fibrinolytic system in the lungs
  - If a clot is too big: it obstructs blood flow \( \rightarrow \) pulmonary BP increases rapidly \( \rightarrow \) RV failure

- **Consequences:** a spectrum of consequences exists
  - Major clots: RV failure and circulatory collapse
  - Intermediate clots: pressures on the right side of the heart increase
    - Gas exchange decreases \( \rightarrow \) breathlessness
    - Lung infarction is rare due to the dual blood supply to the lungs (pulmonary circulation and bronchial circulation)
  - Small clots: filtered out of the circulation
**Pulmonary hypertension**

**Definition:** elevation pulmonary artery pressure (PAP), such that it gets closer to systemic pressure

**Mechanism:** Pulmonary arteries become thicker at higher pressure and PAP increases, therefore the right ventricle must pump at a higher pressure → hypertrophy (compensation). Right ventricular failure occurs when the right ventricle can no longer compensate.

**Causes:**
- **Pulmonary arterial hypertension** (primary defect in pulmonary arteries), which may be primary or related to collagen/vascular diseases, congenital heart disease, drugs, toxins, HIV etc
  - elevated PVR
- **Pulmonary venous hypertension** (primary defect usually cardiac), which may be left sided atrial, ventricular or valvular disease
  - elevated pulmonary capillary wedge pressure
- **Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxia**
  - When right ventricular failure develops in the setting of chronic lung disease and hypoxia, it is termed COR PULMONALE
- **Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
- **Pulmonary hypertension associated with miscellaneous disorders**

**Pulmonary Shunts**

- Occurs when the alveoli of the lung are perfused with blood as normal, but ventilation fails to supply the perfused region, i.e. V/Q=0.
- Due to the alveoli filling with fluid, causing parts of the lung to be unventilated though still perfused
- Intrapulmonary shunting is the main cause of hypoxaemia (inadequate blood oxygen)
- The lack of ventilation may lead to hypoxic pulmonary vasoconstriction to divert blood flow to other regions of the lung

**Control of breathing (Awake)**

Dr Shakeeb Moosavi (s.moosavi@imperial.ac.uk)

1. To appreciate the wide variety of function served by respiratory muscle activity.
2. To locate and describe two kinds of ‘controllers’ in the brain that can act independently, interact or compete for control of the respiratory pump.
3. To identify the primary sensory inputs and motor outputs common to both controllers, and to characterise the ventilatory response to various stimuli
4. To define breathlessness (dyspnoea), describe its role in breathing control and appreciate its significant clinical impact
5. Give five examples of respiratory or non-respiratory functions achieved by control of respiratory muscle activity
6. Identify neuronal groups in the brainstem that make up the automatic reflex controller, and structures in higher brain areas that drive behavioural breathing.
7. Distinguish the primary purpose of the automatic reflex controller (regulate gas exchange for metabolic homeostasis) and the behavioural controller (other needs such as speech)
8. Locate sources of sensory input to the respiratory control system (central and peripheral chemoreceptors, lungs, airways and chest wall)
9. Describe the ventilatory response to increased PaCO₂, decreased PaO₂, and moderate exercise
10. Define breathlessness as ‘perception’ of respiratory discomfort. State 2 other terms commonly used for ‘breathlessness’ (‘Dyspnoea’ and ‘Short of breath’)

11. Distinguish the effect on respiratory control of 2 neurological conditions: ‘locked in syndrome’ & ‘congenital central hypoventilation syndrome’

Why do we breathe?

The purpose of control of breathing muscles include:
- Appropriate gas exchange – to maintain metabolic homeostasis
- Defence of lung and airways – i.e. through reflex protective behaviours e.g. cough, sneeze, yawn
- Other functions (non-metabolic) include communication (speech, singing), expressing emotions, non-respiratory behaviours including defecation, posture

Overview of breathing control

There are two separate “controllers” in the brain:
- “automatic” bulbopontine controller (found in the brainstem – within medulla + pons)
- “behavioural” suprapontine controller (widely distributed, but all superior to pons)
- These have a common motor output from a spinal motorneuron pool which → lung inflation and alveolar ventilation

Input

- **Chemoreceptors**
  - Peripheral chemoreceptors are found in the bifurcation of the common carotids (respond to pH, PaCO$_2$, hypoxia), and the aortic arch (respond to PaCO$_2$, hypoxia)
  - Central chemoreceptors are located on the surface of the medulla, respond to PaCO$_2$, but not pH or hypoxia
- **Mechanoreceptors**
  - Within the lung:
    - slowly adapting pulmonary stretch receptors (which respond via inhalation reflex or Hering-Breuer reflex)
    - rapidly adapting pulmonary stretch receptors
    - J receptors (bronchial C fibre receptors)
    - Irritant receptors
  - Within the chest wall:
    - Joint receptors
    - Golgi tendon organs
    - Muscle spindles
- **Sensory input**
  - From nose - trigeminal (V) nerve
  - From pharynx – glossopharyngeal (IX) and vagus (X) nerves
  - From larynx – vagus (X)
  - Lungs – vagus (X)
  - Chest wall – spinal nerves
Neural output

- From diaphragm: Phrenic nerve + Cervical plexus (C3-C5)
- From intercostal muscles: T1 – T12
- Abdominal muscles: T6 – L1

Automatic bulbopontine controller:

Rhythm generation

- the pons can be divided into two different centres: the pneumotaxic centre + the apneustic centre
  - The pneumotaxic centre – found in rostral dorsal lateral pons, antagonizes the apneustic centre cyclically inhibiting inspiration by sending a “switch off” signal to the dorsal respiratory group within the medulla
  - Apneustic centre – found in the lower pons, promotes inspiration by stimulations of the dorsal respiratory group of neurons in the medulla
- Within the medulla, there are two sets of respiratory groups of neurones
  - The dorsal respiratory group (DRG) are inspiratory neurones
  - The ventral respiratory group (VRG) consists of expiratory neurones (which receive input from the DRG) and the pre-Botzinger complex (pre-Bot C) which is a complex of rhythm-generating neurons
- Output from the DRG and VRG → spinal motor neurons → muscles → inspiration/expiration (depending origin of input)
- Ventilation of the lung → stimulation of lung stretch receptors, which then inhibits the inspiratory neurons of the DRG and the Apneustic centre within the pons
- Ventilation also alters the blood gas partial pressures, which stimulates arterial chemoreceptors → stimulation/inhibition of DRG (depending on gas pp)
- Neuron activity is cyclical/rhythmic due to the synaptic interaction between groups of neurons

Automatic reflex drive

- Ventilator response to increased PaCO₂ is linear, due to an immediate response from arterial chemo and mechanoreceptors
- However the ventilatory response to reduced PaO₂ is not immediate or linear
Suprapontine controller

- **Volitional**, wilful drives – (from motor homunculus – motor cortex) wide range of control, precise, subconscious, competes for control of respiratory muscles
- **Emotional** drives – involuntary psychological influences, secondary to the perception of discomfort, music perception, purpose unknown
- **Wakefulness** drives – tonic excitatory drive when awake (inhibitory drive also exists)
- Response to **moderate exercise**
- NB: effect of **sleep** on respiratory muscles is purely autonomic, and has no voluntary or emotional input

Clinical correlates

**Dyspnoea (Breathlessness)**

- Definition: “...a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity”
- Unpleasant sensation
- Common
- More prominent than pain during late-stage cancer
- No treatment known
- Clinical prevalence: present in most respiratory disorders, chronic heart failure, terminal cancer, psychiatric disorders, or other disorders affecting respiratory function, e.g. endocrine or neuromuscular
- Is a subjective perception
- Clinical signs of distress include tachypnoea (rapid breathing), “pursed lips” breathing, hyperinflation, cyanosis (blue/purple discoloration of lips, tongue, skin)
- Distinguishable qualities: “hunger2 for air, sense of effort during breathing, chest tightness
- Link to respiratory control: afferent signals reporting demand from breathing occur, but there is an efferent-reafferent mismatch which occurs
  - Indirect role – elicits behaviours to move the respiratory system away from danger, e.g. to seek medical attention, swim to surface, stop exercise
  - Also involved in establishing a learned breathing response to exercise
- There are also cerebral activations which occur during dypsnoea, which can be seen by a PET scan

**Congenital central hypoventilation syndrome (CCHS)**

- Also known as “ondines curse”
- Lesion of the medulla – effect on automatic reflex controller
- This means the patient only breaths with behavioural controller?
  - Leads to a blunted reflex ventilatory response to PaCO₂
  - Essentially normal response to exercise, as the control of breathing during exercise is behavioural

“Locked in syndrome”

- Discrete lesion of the corticospinal pathway of the ventral pons
- This means that there is no voluntary motor control except for eye-blink
- However automatic brainstem reflexes remain intact, therefore ventilatory response to PaCO₂
Control of breathing (Asleep)
Dr Mary Morrell (m.morrell@imperial.ac.uk)

1. Describe the effect of sleep on breathing and blood gases and in healthy people
2. Specifically how does sleep effect oxygen and carbon dioxide levels. What are the mechanisms that lead to these changes?
3. Describe the apnoeic threshold which, in some people leads to central sleep apnoea.
4. Describe the influences of sleep on the upper airway which, in some people leads to obstructive sleep apnoea.
5. Know at least two upper airway muscles that reduce their activity during sleep.
6. Know the other major cardio-respiratory diseases (one cardiac, one respiratory) that are exacerbated by sleep-related changes in the control of breathing; briefly explain why sleep is detrimental to these patients.

NB: control of breathing during sleep is purely autonomic, i.e. there are no voluntary or emotional influences from the motor cortex or limbic system.

Sleep

- Sleep can be seen on a brain EEG across the general cortical areas, whereby brainwaves are of fast frequency and low voltage
- Consists of 4 stages + REM
  - With each stage, there is an increase in the amplification of the electrical activity coming from the brain
- Stage 1 – transitional, slow rolling eye movements, postural movements, auditory response present
- Stage 4 – no auditory response present
- REM – rapid eye movement, dreaming sleep, all muscles functionally paralysed except eyes and diaphragm
  - REM in-between each stage, circadian rhythm
  - Purpose: consolidate memory
- Hypogram of healthy adult – 90 min schedule, sleep deprivation results in missing of 1st REM cycle
- Control of breathing when awake:
  - Reflex/automatic control (by the brainstem)
  - Voluntary/behavioural control (by the motor cortex)
  - Emotional control (by the limbic system)
- Control of breathing during sleep:
  - Only involves reflex/automatic control
  - Does not involve voluntary/behavioural or emotional control

Reflex/automatic control of breathing: brainstem respiratory neurones

- Pre-Bötzinger Complex: the area in the brainstem which controls respiratory rhythm generation
- It contains 2 types of rhythm-generating neurones: Inspiratory neurones – DRG + Expiratory neurones - VRG
- The inspiratory and expiratory neurones exhibit reciprocal inhibition

Factors of respiratory control which are affected by sleep:
- Respiratory muscles in the upper airway and pump muscles
- Respiratory control centres
- Blood gases and chemosensitivity (i.e. pCO₂ and pO₂)
Breathing during sleep (vs. breathing when awake):
- Minute ventilation and tidal volume (TV) fall by ~10%
- Alveolar ventilation falls by ~15%
- Frequency of breathing and oxygen saturation ($\text{SaO}_2$) do not change

Changes in $\text{SaO}_2$ during sleep:
- Tidal Volume decreases $\rightarrow$ $pO_2$ decreases; therefore $\text{SaO}_2$ remains virtually constant in healthy individuals
- COPD patients live on the steep part of the oxygen-dissociation curve; therefore $\text{SaO}_2$ decreases significantly when $pO_2$ decreases

Changes in $\text{CO}_2$ during sleep:
- TV decreases $\rightarrow$ $pCO_2$ increases by ~3-4 mmHg
- The increase in $pCO_2$ stimulates respiratory centres to continue breathing
- N.B. if $pCO_2$ does not increase during sleep, this results in death

Ventilatory sensitivity to $\text{CO}_2$ during sleep:
- Sensitivity to $\text{CO}_2$ decreases during sleep: this causes ventilation to decrease during sleep
- Decrease in ventilation $\rightarrow$ increase in $pCO_2$ (hypercapnia)
- Hypercapnia is mandatory for breathing during sleep

Apnoea

Definition: cessation of breathing

- **Hypercapnic apnoeic threshold**: the amount of $pCO_2$ which is critical for breathing during sleep
- $pCO_2$ must rise above the hypercapnic apnoeic threshold for regular breathing to continue during sleep
- Respiratory muscles of the upper airway assist breathing; if their activity decreases, this results in obstructive sleep apnoea
- Muscles of the upper airway which reduce their activity during sleep:
  - Tongue (genioglossus)
  - Levator palatini
  - Tensor palatine
- These muscles stiffen the soft palate (in the pharyngeal region at the back of the throat)
  - When they are active: they prevent airway constriction and collapse
  - When they are not active: they airway is prone to collapse
- The airway at the back of the throat (i.e. the pharynx) is distensible since it does not contain cartilage.

Influences of sleep on the airway include:
The muscles of the upper airway relax and the airway constricts
- Pharyngeal resistance increases; therefore ventilation becomes more difficult
- Hence more effort is required to achieve the same amount of ventilation
- N.B. in some people, turbulent airflow is setup over the vocal chords → snoring

**Obstructive sleep apnoea:** results from a mechanical obstruction of the airway during sleep

- Airflow stops; respiratory effort increases
- There is no impairment of respiratory control
- Positive pressure → airway collapse
- **Mechanism:**
  1. Sleep
  2. Upper airway muscle function decreases
  3. Apnoea → hypoxia and hypercapnia → increased respiratory effort
  4. Arousal
- **Consequence:** paradoxical breathing
  - Pressure moves between the thorax and the abdomen during breathing
  - Air does not move, as patient tries to breathe, they expose the thorax to large negative pressures at a time when the O\(_2\) saturation has fallen – this is dangerous for the heart
- **Symptoms:**
  - Loud snoring
  - Partner witnesses lack of breathing
  - Profound sleepiness during the day
- Obstructive sleep apnoea mainly affects middle-aged men

**Central sleep apnoea:** pCO\(_2\) decreases and gets closer to the apnoeic threshold

- Airflow stops; there is no respiratory effort due to lack of brain control
- Rare unless congenital: congenital hyperventilation syndrome
- Most patients with this condition have heart failure

**Cardio-respiratory diseases**

**COPD:**

- Normal changes in breathing during sleep (e.g. reduced ventilation) compromise breathing since the patient is on the steep part of the oxygen-dissociation curve
- Therefore the patient is more likely to encounter respiratory difficulty during sleep since SaO\(_2\) decreases with a decrease in pO\(_2\)

**Heart failure**

- associated with central sleep apnoea
- Mechanism: heart failure → pulmonary congestion → irritation of J-receptors in the lungs → chronic hyperventilation → hypocapnia → patient gets closer to the apnoeic threshold
- When awake: patients have volitional control of breathing; therefore they are sensitive to CO\(_2\)
- During sleep: patients lack volitional control of breathing; therefore they depend on blood gases
- Heart failure patients that breathe poorly at night have a higher mortality than those who breathe normally
Sensory Aspects of Respiratory Disease
Prof Fan Chung (f.chung@imperial.ac.uk)

General:
1. Understand how respiratory symptoms are generated and perceived
2. Discuss the importance of measuring respiratory symptoms in clinical medicine and clinical research
3. Outline the clinical causes and the pathophysiological basis of these respiratory symptoms: cough, chest pain and dyspnea. (Dyspnea will be covered in detail in another presentation).

Cough:
4. Describe the mechanics of a cough with reference to inspiration, expiration and closure of the glottis. Briefly explain how this manoeuvre serves to (i) protect the lungs from inhaled noxious materials and (ii) clear excessive secretions from the lower respiratory tract.
5. Identify the type and location of sensory receptors with the airways indicating how they are stimulated to give rise to cough. Identify the neural pathways which transmit this afferent (sensory) neural information to the brain.
6. Describe in outline which regions in the brain are involved in generating the co-ordinated neural activity that results in the act of cough. Identify the efferent (motor) neural pathways and the main muscle groups which produce cough.
7. Explain the concept of the sensitised cough reflex in disease as the basis for chronic cough.
8. Discuss ways of controlling unnecessary cough.

Chest pain:
9. Identify the type and location of sensory receptors with the thoracic cavity that when stimulated give rise to chest pain. Identify the neural pathways which transmit this afferent neural information to the brain.
10. Describe in outline which regions in the brain are involved in the perception of pain.
11. Discuss the concept of referred pain in the chest.
12. Describe different typical patterns of chest pain that can help in diagnosing the cause of pain.

Dyspnoea:
13. Review the terms used by patients to describe the troublesome symptom of shortness of breath and its measurement.
14. Discuss the main important causes of shortness of breath and approach to management

Introduction to Respiratory disease
- Symptoms – an abnormal/worrying sensation that leads the person to seek medical attention e.g. cough, chest pain, shortness of breath
- Sign – an observable feature on physical examination of the patient, e.g. hyperinflation of the chest wall, dullness on percussion of chest wall, increased respiratory rate, reduced movement of chest wall
- Mechanism of symptom recognition – may be physiologic or pathological stimulus leading to conscious sensation
  - Neurophysiology: sensory stimulus → transducer → excitation of sensory nerve → integration within CNS → sensory impression
  - Behavioural psychology: sensory impression → perception → evoked sensation
- Prevalence of respiratory symptoms
  - Cough – 3rd most common GP complaint, 10-38% of respiratory outpatients
  - Chest pain – most common pain for seeking attention
  - Shortness of breath (SOB/dyspnoea) – 6-27% of general population, 3% A&E visits
Cough

- Epidemiology – most prevalent is chronic cough correlated to smoking, but also associated with current asthma, environmental tobacco smoke exposure – prevalence from 7.2-18%, with a reduced prevalence involving sputum production
- Definition: a crucial defence mechanism protecting the lower respiratory tract from inhaled foreign material and excessive secretion, secondary to mucociliary clearance
  - Important in lung disease when mucociliary clearance is impaired, and mucus production is increased
- The expulsive phase of a cough generates a high velocity of airflow, facilitated by bronchoconstriction and mucus secretion
- Effectively, everyone has a cough – used to remove 30-100ml of fluid from the airways each day – this is to reduce risk of disease
- “cough receptor” – nerve profile situated between a goblet cell and a columnar epithelial cell, when stimulated → cough
  - These are rapidly adapting irritant receptors which are located within airway epithelium, most numerous on posterior wall of trachea
  - At main carina (last cartilage before tracheal bifurcation) and large branching points, less numerous
  - Less numerous in more distal airways – absent beyond respiratory bronchioles
  - Also in the pharynx – possibly also in the external auditory meatus, eardrums, paranasal sinuses, pharynx, diaphragm, pleura, pericardium + stomach
  - Stimuli: larangeal and tracheobronchial receptors response to chemical and mechanical stimuli
  - RARs considered to be cough receptors
- Sensory receptors also present – in the lungs and airways, including slowly adapting stretch receptors, rapidly adapting stretch receptors and C-fibre receptors
  - Slowly adapting stretch receptors – located in the airway smooth muscle, are myelinated nerve fibres predominantly in trachea and main bronchi; mechanoreceptors which respond to lung inflation
  - Rapidly adapting stretch receptors – located in naso-pharynx, larynx, trachea, bronchi; small, myelinated nerve fibres which respond to both mechanical/chemical irritant stimuli + inflammatory mediators
  - C-fibre receptors – are “free” nerve endings found in the larynx, trachea, bronchi and lungs. Are small unmyelinated fibres which respond to chemical irritants + inflammatory mediators by releasing neuropeptide inflammatory mediators: substance B, neurokinin A, calcitonin gene related peptide.
- Stimuli include mechanical irritants (dust, mucous, food, drink) or chemical (noxious, intrinsic inflammatory agents)

Nerve pathways

- Afferent pathways for the stimuli from lungs via Vagus nerve (X), and from throat via superior laryngeal nerve
  - Both stimulate “cough centre” in medulla → pathway to cerebral cortex
- Central pathways- Cough centre in brain stem is probably diffusely located
  - Vagal afferents relay impulses to an area near the nucleus tractus solitarius, then is integrated in a “cough centre” in the medulla oblongata
    - This is distinct from the respiratory centre – bulbopontine controller
  - Possible neurotransmitters involved: 5-hydroxytryptamine, gamma-amino-butyric acid
    - Opiates work centrally in suppressing cough, acting on the cough centre in the medulla
- Efferent pathways – cerebral cortex → cough centre → glottis, diaphragm + expiratory muscles, i.e. motor neurones to respiratory muscles
Mechanics

- Inspiratory phase: negative airflow occurs
- Glottic closure: subglottic pressure increases, while the glottis is closed
- Expiratory phase (explosive): airflow increases rapidly → sound

Causes

- **Acute infections** – tracheobronchitis, bronchopneumonia, viral pneumonia, acute-on-chronic bronchitis, bordetella pertussis
- **Chronic infections** – bronchiectasis, tuberculosis, cystic fibrosis
- **Airway diseases** – asthma, chronic bronchitis, chronic post-nasal drip
- **Parenchymal diseases** – interstitial fibrosis, emphysema
- **Tumours** – bronchogenic carcinoma, alveolar cell carcinoma, benign airway tumours
- **Foreign body**
- **Cardiovascular** – left ventricular failure, pulmonary infarction, aortic aneurysm
- **Other diseases** – reflux oesophagitis, recurrent aspiration
- **Drugs** – angiotensin converting enzyme

Type

- **Acute** - < 3 weeks, most commonly due to common cold (involves cough, post-nasal drip, throat clearing, nasal blockage and nasal discharge)
- **Chronic persistent** - >3 weeks on presentation to respiratory clinic
  - Asthma + eosinophil associated
  - Gastro-oesophageal associated
  - Rhinosinusitis (post-nasal drip)
  - Chronic bronchitis (“smokers cough”)
  - Bronchiectasis, Drugs, Post-viral, Idiopathic + other causes
**Gastro-oesophageal reflux: reflux of gastric contents (pH ~ 2 or 3)**

3 mechanisms:
1. Oesophageal bronchial reflex: activation of cough receptors occurs due to interconnecting neurones between the trachea and oesophagus
2. Direct action of protons on cough receptors: protons travel to the pharynx and stimulate cough receptors
3. Activation of brainstem cough centres
   - 3rd mechanism = neural mechanism
   - Plasticity of neural mechanisms: The nervous system is plastic: i.e. its sensitivity can be increased by chemical mediators
   - Chemical mediators (e.g. prostaglandin E$_2$) increase the excitability of afferent nerves
   - The number of receptors and voltage-gated channels increases, e.g. TRPV-1 (transient receptor potential vaniloid-1: calcium-permeable, non-selective cation channel)
   - Neurotransmitter levels increase e.g. neurokinins in brain stem

Chronic cough indicates that patients have increased cough reflex
- Indications of chronic cough:
  - Irritation in the throat or upper chest
  - Cough paroxysms are difficult to control
- Triggers of chronic cough include: deep inhalation; laughing; talking too much; vigorous exercise; smells; cigarette smoke; eating crumbles; cold air; lying flat

**Complications of cough**
- Pneumothorax with subcutaneous emphysema
- Loss of consciousness (cough syncope)
- Cardiac dysrhythmias
- Headaches
- Intercostal muscle pain
- Rupture of rectus abdominis muscle
- Social embarrassment
- Urinary incontinence
- Wound dehiscence

**Treatments**
- Inhaled corticosteroids + inhaled beta-adrenergic agonists - For asthma, cough-variant asthma + eosinophilic bronchitis
- Topical steroids, topical vasoconstrictors - For rhinosinusitis (post-nasal drip)
- Proton-pump inhibitors, medical therapies - For gastro-oesophageal reflux
- Stop ACE inhibitor – for ACE inhibitor cough
- Antitussives:
  - Opiates – codeine, pholcodeine, dextromethorphan
  - Demulcents
  - Aromatics

**Targets for treatment**
- Acid pH inhibitors e.g. PPIs – airway epithelium + periciliary fluid
- Opioids – CNS + vagus nerve
- Bronchodilator: beta2-agonists + anticholinergics – airway smooth muscle
- Anti-inflammatories: corticosteroids, leukotriene antagonists + Cox inhibitors – blood vessel-eosinophil communication
Chest pain

- Sensory input
  - Nose: trigeminal nerve (V)
  - Pharynx: glossopharyngeal nerve (IX); vagus nerve (X)
  - Larynx: vagus nerve (X)
  - Lungs: vagus nerve (X)
  - Chest wall: spinal nerves

Nerve pathways

Pain pathway:
- Pain receptors: Aδ and C-fibres
- Nerve fibres cross at the spinal level and synapse in the thalamus
- Nerves travel to the primary somatosensory cortex

Touch pathway:
- Touch receptors: Aα and Aβ
- Nerve fibres cross at the medullary level and synapse in the thalamus
- Nerves travel to the primary somatosensory cortex

Conscious sensation of pain
- Neurophysiology: sensory stimulus → transducer → excitation of sensory nerve → integration within CNS → sensory impression
- Behavioural psychology: sensory impression → perception → evoked sensation

Types of pain

- **Visceral + somatic**
  - Visceral mechanisms less well understood, vagueness also causes overlap of location
  - Difficulty in diagnosis of visceral pain level
  - **Chronic** pain – more complicated than **acute** pain and depends on poorly defined neural mechanisms within the brain

Chest pain in respiratory disorders:
- Chest wall- muscular or rib fracture
- Pleural pain
- Deep-seated, poorly-localised pain
- Nerve-root pain/intercostal nerve pain
- Referred pain: shoulder-tip pain of diaphragmatic irritation

Chest pain in non-respiratory disorders
- CVD – myocardial ischaemia/infarction, pericarditis, dissecting aneurysm
- Gastrointestinal disorders – oesophageal rupture, gastrooesophageal ferlux
- Psychiatric disorders – panic

Brain imaging during pain

Can be seen by positron emission tomography (PET) scans – Location of electrical activation is related to graded pain intensity

1. **Somatosensory processing** – primary + secondary somatosensory cortex, posterior insular cortex
2. **Motor processing** – cerebellum, putamen, ventral premotor cortex
3. **Affective processing** – anterior cingulate cortex, insular cortex
4. **Attentional processing** – anterior cingulate cortex, primary somatosensory cortex, ventral premotor cortex
5. **Autonomic function** – anterior cingulate cortex, anterior insular cortex

**Treatment**

- Treat the cause, not just the symptoms
- Chronic pain is more difficult to manage, although analgesics may reduce symptoms
- Pain can be severe and refractory, in which case it is best dealt with at “pain clinics”

**Dyspnoea**

**What is shortness of breath?**

- Symptom reported by patient - occurs at inappropriately low levels of exertion and limits exercise tolerance
- Unpleasant and frightening experience
- Can be associated with feelings of impending suffocation
- Poor perception of respiratory symptoms and dyspnoea may be life-threatening

**Assessing dyspnoea**

**NB: Different scales used to assess dyspnoea**

**Clinical dyspnea scale (American Thoracic Society)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 None</td>
<td>Not troubled by breathlessness except with strenuous exercise</td>
</tr>
<tr>
<td>1 Slight</td>
<td>Troubled by shortness of breath when hurrying or walking up a slight hill</td>
</tr>
<tr>
<td>2 Moderate</td>
<td>Walks slower than people of same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level</td>
</tr>
<tr>
<td>3 Severe</td>
<td>Stops for breath after walking about 100 yards or after a few minutes on the level</td>
</tr>
<tr>
<td>4 Very Severe</td>
<td>Too breathless to leave house or breathless when dressing or undressing</td>
</tr>
</tbody>
</table>

**Respiratory descriptors** - Used in conjunction with scales when assessing SOB

<table>
<thead>
<tr>
<th>Air-hunger cluster</th>
<th>Work/effort cluster</th>
<th>Tightness cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunger for more air</td>
<td>Breathing requires effort</td>
<td>Tightness/constriction in my chest</td>
</tr>
<tr>
<td>Urge to breathe more</td>
<td>Breathing requires work</td>
<td>Heaviness in my chest</td>
</tr>
<tr>
<td>Starved for air</td>
<td>Breathing is uncomfortable</td>
<td></td>
</tr>
<tr>
<td>Suffocation/smothering</td>
<td>Feels like heavy exercise</td>
<td></td>
</tr>
<tr>
<td>Short of breath</td>
<td>Size of breaths feel too large</td>
<td></td>
</tr>
<tr>
<td>Breaths feel too small</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary of ways of assessing SOB

- Volunteered comments & clinicians’ assessment
- Subjective rating scales
  - Visual analogue
  - Modified Borg
- Questionnaires
  - Exercise tolerance related - Eg. Baseline Dyspnea Index, Shortness of Breath Questionnaire
  - Quality of life - Eg. SF36, St George's Respiratory Questionnaire
- Exercise testing
  - 6 minute walk test
  - Shuttle test

Chronic dyspnoea

Some disorders present with chronic SOB, including:

- **Impaired pulmonary function**
  - Airflow obstruction eg Asthma, COPD, tracheal stenosis
  - Restriction of lung mechanics eg idiopathic pulmonary fibrosis
  - Extrathoracic pulmonary restriction eg Kyphoscoliosis, pleural effusion
  - Neuromuscular weakness eg Phrenic nerve paralysis
  - Gas exchange abnormalities eg Right to left shunts
- **Impaired cardiovascular function**
  - Myocardial disease leading to heart failure
  - Valvular disease
  - Pericardial disease
  - Pulmonary vascular disease
  - Congenital vascular disease
- **Altered central ventilatory drive or perception**
  - Systemic or metabolic disease
  - Metabolic acidosis
  - Anaemia
- **Physiologic processes** eg deconditioning, hypoxic high altitude, pregnancy, severe exercise
- **Idiopathic hyperventilation**

General treatment

- Treat the cause, e.g. lung/cardiac
- Treatment of dyspnoea itself is difficult
- Therapeutic options include:
  - Add bronchodilators e.g. anticholinergics or b-adrenergic agonists
  - Drugs affecting brain e.g. morphine, diazepam
  - Lung resection (e.g. lung volume reduction surgery)
  - Pulmonary rehabilitation (improve general fitness, general health, psychological well-being)
Hypoxia in Health and Disease
Prof Stephen Semple (s.semple@imperial.ac.uk)

1. Oxygen delivery to the body tissues. Relationship of oxygen delivery to tissues and oxygen consumption. The development of tissue hypoxia when delivery fails to meet demand with onset of anaerobic metabolism (lactic acid production)

2. Haemoglobin and blood gas transport.

3. Definition and causes of hypoxaemia.

4. The relationships between content and gas tension in blood for oxygen (O\textsubscript{2}) and carbon dioxide (CO\textsubscript{2}) i.e. the O\textsubscript{2} and CO\textsubscript{2} dissociation curves. Factors affecting these curves with particular reference to oxygen uptake in the lung and the downloading of oxygen in the tissues.

5. The ventilatory and symptomatic effects of moving from sea level to high altitude. Description of the process of acclimatization on ascent to high altitude.

6. Definition of respiratory failure and effect on arterial gas tensions.

7. The relationship between CO\textsubscript{2} tension (PCO\textsubscript{2}) and arterial oxygen tension (PO\textsubscript{2}) within the lung. The effect on the relationship of changes in alveolar ventilation and ventilation / perfusion relationships within the lung

**NB: Oxygen delivery calculations**
- Oxygen delivered = cardiac output (litres/min) x oxygen content (ml/litre)
- Oxygen uptake/consumption = cardiac output (litres/min) x arterio-venous difference (60ml)
- Respiratory quotient (R.Q) = carbon dioxide output/ oxygen uptake

Intro to hypoxia

- **Hypoxia:** lack of oxygen
- **Hypoxaemia:** reduced arterial oxygen (also known as hypoxic hypoxia)
  - Arterial PO\textsubscript{2} < 10.7kPa, 80mmHg
  - Arterial O\textsubscript{2} saturation < 93%
  - Arterial O\textsubscript{2} content reduced (i.e. the ml O\textsubscript{2} per 100ml blood reduced)
- **Cause:** alveolar hypoventilation – this may be due to impaired gas exchange in the lung, or reduced barometric pressure (which occurs at high altitude)
- There are other causes of hypoxia where the arterial PO\textsubscript{2} oxygen saturation and content are normal (i.e. non hypoxaemic hypoxia). These include:
  - Anaemic hypoxia
  - Stagnant hypoxia
  - Histotoxic hypoxia
- **Compensatory mechanisms** of the body for hypoxia include:
  - Alveolar hyperventilation
  - Increased cardiac output
  - Improved pulmonary perfusion
  - Changes in regional blood flow
  - Polycythaemia
  - Anaerobic metabolism
**Gas transport + exchange in the red blood cell**

Oxygen is transported around the body in red blood cells, bound with Hb to form HbO$_2$.

Some carbon dioxide is sequestered in red blood cells and bound with Hb to form HbCO$_2$, but most CO$_2$ is transported in blood plasma as bicarbonate ions (HCO$_3^-$).

**In the lungs:**

O$_2$ IN
- inhaled O$_2$ diffuses across from the alveolar wall across the pulmonary capillary wall and is taken up by red blood cell
  - It is then bound with Hb (previously bound to a H$^+$ ion) to form HbO$_2$, displacing the H$^+$ ion

CO$_2$ OUT
- CO$_2$ bound with Hb is released from the Hb molecule and the red cell, diffusing across the pulmonary capillary wall into the alveolus, where it is then exhaled
- HCO$_3^-$ ions that have been transported in the blood plasma from the tissues is taken up by the red cell. The H$^+$ ion (that was previously displaced from the HbH molecule on oxygen binding) then binds with the bicarbonate ion to form H$_2$CO$_3$ (hydrogen bicarbonate)
  - This is then dehydrated by carbonic anhydrase to form CO$_2$ and H$_2$O
  - Via coupled transport, using the chloride shift of Cl$^-$ ions into the red cell, this CO$_2$ is then released from the red cell back into the plasma, where it diffuses across the pulmonary capillary wall into the alveolus where it is exhaled

**In the tissues:**

O$_2$ OUT
- H$^+$ ion displaces oxygen from oxyhaemoglobin
  - It is then released from the red cell into the blood plasma where it diffuses across systemic capillary walls into the tissue cell

CO$_2$ IN
- CO$_2$ diffuses out of the tissue cell, across the systemic capillary wall across the blood plasma, where coupled with the chloride shift, it is taken up by the red cell
  - Some of the CO$_2$ is then sequestered by haemoglobin to form carbamino-Hb – this reaction releases oxygen from the Hb molecule
  - The rest of the CO$_2$ then binds with a water molecule to form H$_2$CO$_3$ (involves carbonic anhydrase)
    - This hydrogen bicarbonate then dissociates to form HCO$_3^-$ + H$^+$ ions
The HCO₃⁻ are then released by the red cell into the blood plasma, where they are transported back to the lungs.

**Haemoglobin**

- Molecular weight 64,500
- Globular protein – consists of two alpha and two beta polypeptide globin chains
  - Each chain has an associated haem molecule comprising a prophyrin + ferrous ion (Fe²⁺)
- Each haemoglobin molecule can combine with 4 molecules of oxygen
- In deoxyhaemoglobin, there are tight electrostatic bonds between the globin chains. The haem molecules are placed in crevices within the tight conformational shape, and have a low affinity for oxygen. This means that at low surrounding partial pressures of oxygen, the increase in Hb oxygen uptake for increased oxygen pp is small!
- However, once one molecule of oxygen is taken up, there is a conformational change in the Hb molecule – this renders the other oxygen binding sites very easily accessible → steep increase in Hb oxygen uptake for small pp oxygen increases → sigmoid shape of oxygen dissociation curve
- Other factors leading to changes in the binding of oxygen to the haem group are: pH, pCO₂, temperature, concentration of 2,3-diphosphoglycerate (DPG)
- Oxygen dissociation curve:
  - **Bohr effect** – shown by the red line on the graph; a decrease in oxygen affinity of deoxyhaemoglobin is seen when pH decreases or pCO₂ increases
  - **Haldane effect** – describes how O₂ displaces CO₂ from Hb, i.e. oxygenated blood has a reduced carbon dioxide carrying ability, and vice versa

**Oxygen affinity**

<table>
<thead>
<tr>
<th>Factors which decrease oxygen affinity</th>
<th>Factors which increase oxygen affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓pH</td>
<td>↑pH</td>
</tr>
<tr>
<td>↑pCO₂</td>
<td>↓pCO₂</td>
</tr>
<tr>
<td>↑temp</td>
<td>↓temp</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Store blood</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Foetal blood</td>
</tr>
<tr>
<td>↑2,3-bisphosphoglycerate (leads to a shift in O₂ dissociation curve to the right)</td>
<td>↓2,3-bisphosphoglycerate (leads to a shift in O₂ dissociation curve to the left)</td>
</tr>
</tbody>
</table>

**Effect of exercise**

- The increased production of CO₂ with exercise leads to an increase in the tissues of PCO₂ and fall in pH.
- This reduces oxygen affinity and increases oxygen release.
- The disadvantage of this change in affinity leads to a reduction in oxygen uptake in the lung, and a fall in arterial PO₂.
  - Disadvantage is offset by the increase in ventilation associated with exercise which reduces a rise in alveolar PO₂ and prevents a fall in oxygen saturation.
Effect of carbon monoxide (CO)

- Carbon monoxide affinity for Hb is 250 times higher for Hb than Oxygen.
- In the presence of CO the oxygen dissociation curve is shifted to the left (high affinity) impairing oxygen unloading in the tissues, therefore leading to ischaemia (DANGEROUS)
- Note the lower affinity in anaemia (low Hb) and the difference in shape.

High altitude

Hypobaric hypoxia

An increase in altitude → decrease in oxygen partial pressure → decrease in pp of alveolar + arterial oxygen → reduced oxygenation of arterial blood

Respiratory response

- To ensure an adequate uptake of oxygen in the lungs at the reduced PaO$_2$, alveolar ventilation increases and there is an increased arterial oxygen affinity
  - This leads to a fall in PaCO$_2$, with an associated rise in pH
- The rise in pH is known as respiratory alkalaemia, and its effect is to stop the respiratory response to hypoxaemia
  - This means that over the next few days at high altitude renal compensation for the alkalaemia leads to a return of the pH to normal, removing the inhibition of breathing.
- The result is a further increase in alveolar ventilation and rise in PaO2. Oxygen affinity tends to return to the same level as that which operated at sea level due to correction of the alkalaemia due to renal compensation, and increased production of 2-3,DPG.

Role of 2-3 bisphoglycerate

Binds deoxyhaemoglobin in the tissues leading to its increased production via bisphoglycerate synthase → accumulation in red cells

Acclimitisation of Lowlanders

- In Lowlanders (residents at sea level) the ventilatory response to hypoxia at altitude does not restore the Pa,O$_2$ to sea level → hypoxaemia → unwell with headache, anorexia, photophobia and poor sleep. These symptoms are often mild but when severe the condition is referred to as Acute Mountain Sickness (AMS)
Acclimatisation occurs over the next 2 to 10 days with resolution of symptoms and improved physical and mental performance. It is associated with a gradual rise in ventilation and Pa, O₂.

At altitudes above about 5500m (18,000ft) the strength of the hypoxic stimulus leads to a marked respiratory alkalaemia with increased oxygen affinity and uptake of oxygen in the lung. However this impairs unloading of oxygen in the tissues and limits exercise capacity.

The initial unpleasant effects of ascent to altitude can be improved by slowing the ascent. Drug prophylaxis against the unpleasant effects is achieved with acetazolamide leading to a mild metabolic acidosis with respiratory compensation and a rise in Pa,O₂.

High altitude pulmonary oedema (HAPE) + high altitude cerebral oedema (HACE)

- serious medical emergencies - untreated mortality of about 50%
- Approximately 1% of lowlanders suffer from these conditions usually proceeded by AMS.
- Patients with HAPE suffer from severe breathlessness, dry cough, chest pain and occasionally with haemoptysis. A chest X-ray shows patchy pulmonary oedema.
  o The alveolar hypoxia leads to reflex pulmonary artery constriction and pulmonary hypertension which may lead to right heart failure.
  o It is assumed that the oedema is due to “Capillary Leak” due to endothelial damage from hypoxia. There is no evidence of left ventricular failure.
- HACE usually follows AMS with severe headache, impaired cognition and physical function with clouding of consciousness which may proceed to coma. On ophthalmoscopy retinal haemorrhages are often seen and less commonly papilledema (optic disc swelling)
- Successful treatment of HAPE and HACE depend on transferring the patient on oxygen to the lowest possible altitude in the shortest possible time. Nifedipine is used in HAPE because it leads to relaxation of pulmonary artery smooth muscle and reduction in pulmonary artery hypertension

Respiratory Failure

RF is associated with a failure of alveolar ventilation and/or gas exchange. The limits defining failure are an arterial oxygen tension, less than 60 mmHg (8 kPa) and a carbon dioxide tension above 50 mmHg (6.7 kPa), the patient being at rest and breathing air.

Respiratory failure can be classified into 3 groups:

- **Type 1 Hypoxaemic failure** - is a disturbance of ventilation to perfusion relationships (gas exchange problem) within the lung, whilst overall alveolar ventilation remains normal (point B)
  o low PaO₂
  o normal (or low) PaCO₂
- **Type 2 Ventilatory failure** - condition results from alveolar hypoventilation
  o Raised PaCO₂
  o Low PaO₂ (point A)
- **Type 3 Combined hypoxaemic and ventilatory failure** in which features of type 1 and 2 are mixed, the defect including both alveolar hypoventilation and a disturbance of ventilation – perfusion relationships within the lung.
  o Raised PaCO₂
  o Low PaO₂ (point C).
- In a normal ventilated lung, the arterial PO₂ and PCO₂ are inversely proportional, a result of which is the linear relationship shown on the graph.
- Therefore if PCO₂ goes up due to alveolar hypoventilation, PO₂ goes down (vice versa for hyperventilation) – this allows type R failure to be identified easily as it will fall on the same linear relationship
NB: if PCO₂ and PO₂ are added at any point on the graph, they will come to the same value (approx. 16kPa) – this is very useful for characterizing type 2 failure

**Ventilation-perfusion relationship**

**NB: V/Q**
- "V" – ventilation – the air which reaches the alveoli
- "Q" – perfusion – the blood which reaches the alveoli

**Carbon dioxide dissociation**
- The increase in partial pressures of CO₂ → increase in PaCO₂
- This relationship is nearly linear
- N is the PCO₂ and CO₂ content of blood leaving a normal lung with normal V/Q ratios averaged at 0.8 (see N in fig)
- In disease of the lung there are low V/Q areas (H) and normal and high V/Q areas (L). When blood from these areas mix in the left side of the heart the areas of high V/Q compensate for the low V/Q areas.
- This results in an arterial PCO₂ that is slightly raised by within the normal range. This normality is achieved because the CO₂ dissociation curve is nearly linear and also because any rise in PCO₂ stimulates the chemoreceptors leading to an increase of ventilation of the high V/Q areas.

**Oxygen dissociation**
- Consider two equal volumes of blood with the same gas with Po₂ of 80 mmHg (10.7 kPa) - each aliquot will have an oxygen saturation of 95% (point N)
- Equilibrate one with a gas of Po₂ of 40 mmHg (5.3 kPa) and the other with a Po₂ of 120 mmHg (16 kPa); the mean tension is still 80 mmHg (10.7 kPa)
- If the O₂ dissociation curve was linear, one would expect that when the two bloods were mixed the resulting tension and saturation would be 80 mmHg (10.7 kPa) and 95%
- However, an increase in PO₂ to 120mmHg only raises the saturation by 4% (point H), and a decrease to 40mmHg lowers the saturation by 20% (point L)
- When the two equal volumes of NEW blood (point H + L) are mixed anaerobically, the O₂ tension (pressure) and saturation of the mixture are 53 mmHg (7.1 kPa) and 86.5% respectively (point F).
  - This is because the increase in oxygen saturation, and, therefore, oxygen content (ml of O₂ per 100ml of blood) of sample H is less than the fall in O₂ saturation of sample L.
  - This result outside the normal range is due to the sigmoidal shape of the oxygen dissociation curve.

**Extra note: Air travel**
- pressurisation of cabins is equivalent to breathing 15% of oxygen at sea level
- This has no adverse effects in people free of respiratory and cardiovascular disease. In patients with lung disease or respiratory muscle weakness it may be necessary to arrange for in-flight O₂ availability
- Assessment for need of in-flight oxygen is usually based on the arterial oxygen saturation (measured by pulse oxymeter) and the FEV1. The recommendations of The British Thoracic Society are (at sea level)
  - O₂ sat >95% - not required
O₂ sat 92-95%, with FEV₁ > 50% Predicted – not required
O₂ sat 92-95%, with FEV₁ < 50% Predicted – perform hypoxic challenge test
O₂ sat <92% - O₂ required

- Hypoxic challenge test: patient breathes an inspired O₂ of 15% through a mask for approximately 20 min with arterial blood gases measured at the start and end.
  - If the oxygen saturation falls to 85% and the PaO₂ to below 6.6 kPa in-flight O₂ is recommended.
  - No in-flight oxygen is required if the PaO₂ remains above 7.4 kPa.
  - This leaves a borderline range of 6.6 to 7.4 kPa when it is helpful to add one of the walk tests to the assessment of the need for in-flight oxygen. A walk test, which is judged as satisfactory on clinical grounds, would obviate the need for in-flight oxygen.

Lung Immunology – Allergic airway diseases
Prof Barry Kay (b.kay@imperial.ac.uk)

1. To define "Allergy" and to distinguish it from related terms such as "Intolerance", "Atopy" and "Hypersensitivity".

Hypersensitivity – and exaggerated response that may be immunological or non-immunological
- Immunological – i.e. allergy; may be IgE-mediated (e.g. atopic diseases including hayfever, eczema, asthma) or non—IgE-mediated (e.g. farmers lung)
- Non immunological – intolerance (e.g. food), enzyme deficiency (e.g. lactase DH), pharmacological (e.g. aspirin hypersensitivity)

Allergy – an exaggerated immunological response to a foreign substance (allergen) which is either inhaled, swallowed, injected, or comes in contact with the skin or eye
- An allergy is a mechanism, not a disease, but the mechanisms often play a temporary or permanent role in disease
- Can be subdivided into different categories:
  - Asthma
  - Drug reactions
  - Food reactions
  - Rhinitis
  - Eczema, urticaria (hives), angioedema (swelling similar to hives, but not on surface of skin)

Atopy – “out of place”; the hereditary predisposition to produce IgE antibodies against common environmental allergens
- The atopic diseases are allergic rhinitis, asthma + atopic eczema
- Allergic tissue reactions in atopic subjects are characterised by infiltration of Th2 cells and eosinophils
- The term “allergic match” is used to describe the common progression from atopic dermatitis to allergic asthma

2. To understand the fundamental immunological mechanisms operative in the major forms of allergic airway diseases (i.e. allergic rhinitis, asthma and extrinsic allergic alveolitis)

IgE-mediated allergic reactions in the upper and lower airways
- May present with either acute or chronic symptoms of allergy
Acute symptoms result from the binding of allergen to IgE-coated mast cell, which causes mast cell degranulation and histamine release.

Chronic symptoms present from the interaction of the allergen with antigen-presenting-cells – involving the release of Th2 cytokines and chemokines.

**Th2 responses**

- Involves the collaboration between innate and adaptive immune responses
- PAMPs present on allergen interact with barrier cells e.g. epithelial cells lining airway - stimulates secretion of IL-33 and IL-25
- Interleukins attract natural helper cells, nuocytes and MPType2 cells (which differentiate to form mast cells, basophils + macrophages)
- These cells then secrete IL-4, IL-5 + IL-13, which induces Th2 cell differentiation, B1 cell proliferation and anti-allergen effector functions – this is where the adaptive immune response is involved
- Th2 cell is CD4+, therefore releases:
  - IL-4 \(\rightarrow\) IgE synthesis
  - IL-5 \(\rightarrow\) Eosinophil development
  - IL-9 \(\rightarrow\) Mast cell development
  - IL-13 \(\rightarrow\) IgE synthesis + airway hyperresponsiveness

**Allergic diseases**

**Allergic diseases include:**

**Atopic allergy (IgE mediated)**
- Allergic asthma – including occupational
- Allergic rhinitis – including hay fever
- Anaphylaxis - e.g. food, insect stings, drugs, latex
- Skin allergies – e.g. urticaria, angioedema, atopic eczema

**Non-atopic allergy (IgG mediated/T-cell mediated)**
- Contact dermatitis
- Extrinsic allergic alveolitis
- Coeliac disease

**Non-allergic hypersensitivity/intolerance responses:**
- Usually apply to food intolerance
- Non-immunological mechanisms
- E.g. include enzyme deficiency (Lactase DH), migraine (triggered by coffee, wine), IBS (exacerbated by various foods), bloating due to wheat intolerance
- Also idiopathic environmental intolerance (also known as multiple chemical hypersensitivity – cause unknown)

**Allergic rhinitis**
- can be either seasonal or perennial (triggered indoors) – prevalence up to 17% of the population
- characterised by a blocked or runny nose, sneezing, itching and streaming eyes
- Seasonal allergic rhinoconjunctivitis (more commonly referred to as hayfever), is caused by allergenic substances contained within pollen.
  - Commonly the causative factor is grass pollen but allergy to tree and weed pollen is also on the increase.
- Worst symptoms usually at the height of summer when vast clouds of grass pollens become airborne. Due to mild winters and warmer springs, pollination of grasses in the United Kingdom is now starting earlier.
therefore the worst symptoms can be well established by the first week in June and tend to peak around mid-June to early July.

- When the pollen counts are very high, some wheeziness can also co-exist with rhinitis, in a condition known as seasonal allergic asthma.
- Perennial allergic rhinitis involves troublesome chronic symptoms such as a blocked, runny nose and sneezing.
- Can have non-allergic causes of perennial rhinitis such as infection and structural abnormalities, and a small minority of patients have underlying immunodeficiency problems too.
- Allergy to the house dust mite (*Dermatophagoides* species) and allergens derived from animals such as cats, dogs, horses and pet rodents are the most important causes.

**Asthma**

**Definition:** chronic disorder characterized by episodes of wheezy breathlessness, but which may also present as an isolated cough, particularly in children – affects 8-12% population

**Aetiology** - still uncertain, but the pathology involves inflammation of the large and small airways (bronchi and bronchioles).

- The consequence is an irritable or twitchy airway in which airflow obstruction results from exposure to a variety of non-specific irritants (bronchial hyper-responsiveness).

**Clinical presentation:** A wide clinical spectrum of asthma symptoms result, ranging from mild occasional wheezing, which is usually controlled by the occasional use of inhaled bronchodilators, through to severe intractable disease which requires treatment using systemic corticosteroids.

**Relationship to allergy:** Allergy can trigger an attack in around 75 per cent of asthmatics, and this is most commonly due to sensitivity to house dust mites or pollen. However, even in patients who suffer from allergic asthma, there are usually other triggers such as viral infections, exercise, exposure to fumes and other irritants such as tobacco smoke, and certain drugs (especially aspirin and related compounds). Food allergens and additives are rarely responsible but can also occasionally be implicated in triggering asthmatic symptoms. In a few cases, the role of allergy in asthma is obvious, such as in patients who wheeze when the pollen count is high but not at other times of the year. But in many cases it is difficult to determine the exact role of allergy in asthma. A significant proportion of asthmatics (about 25 per cent) are not sensitised to common airborne allergens, and so are ‘non-atopic asthmatics’. Their disorder often starts in later life and can be more severe than those who have asthma which begins in childhood.

- In intermittent, mild asthma – allergy frequently very important
- In persistent but manageable asthma – allergy sometimes important
- In chronic, severe asthma – allergy less important, but infection is important

**General anaphylaxis**

**Symptoms:**

- Dizziness, seizures, loss of consciousness
- Anxiety, sense of gloom
- Arrhythmia
- Vomiting, diarrhoea, pain
- Urticaria/hives
- Tingling in hands and feet
- Bronchoconstriction
- Laryngeal oedema
LSS Respiratory System

- Lip, tongue swelling

**Causes:**
- Drugs, e.g. penicillin
- Foods, e.g. peanuts, tree nuts, milk, eggs, fish, shellfish, sesame seeds, soybeans, celery, celeriac
- Insect stings e.g. bees, wasps, hornets
- Latex

**Treatment:** use of an EpiPen

*Extrinsic allergic alveolitis (EAA)*

**Definition:** Extrinsic allergic alveolitis (EAA) or hypersensitivity pneumonitis (HP) is a non-IgE T cell mediated inflammatory disease effecting the alveoli and interstitium – Affects 0.1% population

**Cause:** It occurs in susceptible people following the repeated inhalation of certain antigens. These antigens typically include bacterial or fungal microorganisms in the workplace or bird antigens. Some antigens that cause asthma such as the mold, alternaria, can also induce EAA.

**Examples of extrinsic allergic alveolitis:**
- Farmer’s lung – moudly hay
- Bird fancier’s lung – bird droppings
- Air conditioner lung – air conditioner moulds
- Mushroom workers lung – mushroom compost
- Malt works lung – moudly malt or barley
- Coffee works lung – unroasted coffee beans
- Millers lung – infested flour
- Hot tub lung – bacterial contamination

The prevalence of EAA varies and is related to the particular antigen and the host immune response. Studies have shown that, a minority of individuals exposed develop disease. Cytokine gene polymorphisms in the TNF-alpha promoter region appear to be a host susceptibility factor.

Establishing the diagnosis of EAA is challenging requiring a high index of suspicion, a thorough history, careful examination, complete pulmonary function tests and radiographic studies.

- The histology reveals a lymphocytic infiltrate with a predominance of CD8+ lymphocytes, “foamy” alveolar macrophages, and granulomas consistent with nonspecific interstitial pneumonia.
- Early identification of patients with EAA with subsequent avoidance of the causative antigen is the key to a successful outcome.

Pharmacologic treatment for acute EAA is limited to oxygen and oral corticosteroids. Oral steroids may not affect the long-term outcome. The prognosis is generally favorable if intervention takes place before pulmonary fibrosis occurs.

3. To appreciate the scope and burden of allergic airway disease
Overlap of atopic disease

Prevalence

- 5.7 mil diagnosed with asthma at some point
- 1/15 people recorded diagnosis of allergic rhinitis
- 117% increase in no suffering from peanut allergy from 2001-2005
- No of hospital admissions due to anaphylactic shock increased 7x from 1990-2000

Trends

- Decrease in infectious diseases (e.g. hep A, TB, measles, rheumatic fever) mirrors an increase in allergy and autoimmune disease (e.g. MS, Crohn’s disease, T1 diabetes, asthma)
- Increase in hospital admission rates for urticaria, food allergy and anaphylactic shock among children <15 yrs

Burden

- Allergic disorders can make social interactions difficult as even simple everyday activities can pose a major health risk
- On a national scale, the treatment of allergy patients forms a significant part of the work of the health care providers and the number of allergy-related work absences represents a large cost to the economy
- Allergies affect all aspects of a patient’s life. Hayfever symptoms disrupt children’s sleep and often impair their performance at school and asthma has been associated with school absenteeism.
- Allergy patients often find it difficult to live a normal life. This is especially apparent in children, where special care has to be taken whilst engaging in everyday activities which in turn induces anxiety and impairs the quality of life.
- The prevalence of allergic disease has markedly increased over recent years. In the UK, by 2004, the scale of the “allergy epidemic” was such that 39 per cent of children and 30 per cent of adults had been diagnosed with one or more of asthma, eczema and hayfever, and 38 per cent of children and 45 per cent of adults had experienced symptoms of these disorders in the preceding 12 months.
- In fact by the end of 2005, approximately one in nine people had a recorded diagnosis of “any allergic disease,” including any one of asthma, hayfever, eczema, anaphylaxis or peanut allergy.
- Asthma, eczema and allergic rhinitis often occur together and this co-morbidity, or multiple allergic disease, often requires multiple referrals to different organ specialists

4. To understand possible reasons for the rising trends in allergic disease.

- Marked increase in prevalence indicates importance of environmental influences in addition to genes
- Hygiene hypothesis: developing immune system is deprived of the microbial antigens that stimulate Th2 cells, because the environment is relatively clean and because of childhood vaccinations and the widespread use of antibiotics for minor illnesses in early life. This is in addition to a genetic predisposition to asthma involving chromosome 5,6,11,12 + 14
  - Atopy and allergic asthma were less frequent in people exposed to agents in soil, air and water such as H. pylori, T. gondii, hepatitis A virus.
  - Also a traditional lifestyle with a high gut bacterial turnover rate and intestinal colonisation with lactobacilli and bifidobacteria protect against allergy. Such a lifestyle is usually associated with "organic" food including spontaneously fermented vegetables.
- Other related factors which may encourage the Th2 phenotype include a date of birth around the pollen season, and alterations in infant diet.
Furthermore, atopic allergic diseases are less common in younger siblings and larger sibships and in those who have had measles and hepatitis A indicating that repeated “immune stimulation” (e.g. by viruses) may be protective.

The development of specific allergic diseases may be related to alterations in the target organ. For example, the co-factors required for the development of an asthmatic attack may include respiratory virus infections and exposure to increased allergens, tobacco smoke, and air pollutants. These factors alone, or in combination, may alter immunoregulatory mechanisms at mucosal surfaces in ways that promote a Th2 cell-mediated allergic inflammatory response.

5. Outline the principles of treatment of allergic airway diseases, including allergen specific immunotherapy.

- Consists of: allergen avoidance, anti-allergic medication + immunotherapy (also called desensitisation/hypersensitisation)
- Anti-allergic medication: antihistamines used to relieve rhinitis symptoms, and topical corticosteroids (anti-inflammatory).
  - Histamine1-receptor antagonists less sedative + more selective than old antihistamines

**Immunotherapy:** administering increasing concentrations of allergenic extracts over long periods of time.

- Advantages – effective and produces long lasting immunity
- Disadvantages – risk of developing anaphylaxis (particularly during induction), time consuming, standardisation problems
  - Attempts to minimize systemic reactions include pre-treatment of allergen extracts with agents like formaldehyde (→ allergoids). However this results in reduced immunogenicity as well as a decrease in IgE binding.
- Indications for use: gass/tree pollen allergic rhino-conjunctivitis uncontrolled by medication, bee/wasp sting anaphylaxis at risk for repeats
- Mode of action is complex, but central to its principle is down-regulation and up-regulation:
**Blood Gases and Acid-based Data**

Prof Stephen Semple ([s.semple@imperial.ac.uk](mailto:s.semple@imperial.ac.uk))

1. **Describe the qualitative changes in arterial blood pH, PCO\(_2\) and Base Excess in the following acid-base disturbances:**
   
   i. **Acute respiratory acidosis**
   
   ii. **Acute respiratory alkalosis**

2. **For (i) and (ii) above, describe the qualitative changes in arterial blood pH, PCO\(_2\) and Base Excess following renal compensation.**

3. **Describe the qualitative changes in arterial blood pH, PCO\(_2\) and Base Excess in the following acid-base disturbances:**
   
   i. **Metabolic acidosis with respiratory compensation**
   
   ii. **Metabolic alkalosis with respiratory compensation**

4. **Comment on the mechanism whereby metabolic changes in acid-base status lead to alteration in ventilation and hence respiratory compensation.**

5. **Describe the qualitative changes in arterial blood pH, PCO\(_2\), Base Excess and PO\(_2\) in a patient with (i) Type I respiratory failure (ii) Type II respiratory failure, in each case after full renal compensation.**

**Normal Ranges**

**Measured:**

- Hb 13.3-17.7 g/dl
- pH 7.37-7.45 units
- pCO\(_2\) 4.7-6.4 kPa (35-48 mmHg)
- pO\(_2\) >10.7 kPa (80mmHg)

**Calculated:**

- base excess -2 \(\rightarrow\) +2 mmol/l

**Acid-base status of the patient:** determined by balance between input/loss of acids + bases from the patient (via lungs and/or kidneys), as well as the products of metabolism – reflected by changes in arterial blood partial pressures

- **Changes in arterial pCO\(_2\)** should produce changes in alveolar ventilation such that the pCO\(_2\) remains within the normal range, thus a normal pCO\(_2\) implies a normal alveolar ventilation and chemical control of CO\(_2\)
  
  o High pCO\(_2\) indicates alveolar hypoventilation
  
  o Low pCO\(_2\) indicates alveolar hyperventilation

**Acute Respiratory acidosis (uncompensated)** – insufficient ventilation

- pCO\(_2\) ↑
- pH ↓
- pO\(_2\) ↓
- base excess – within normal range

**Acute Respiratory alkalosis (uncompensated)** – over ventilation

- pCO\(_2\) ↓
- pH ↑
- pO\(_2\) normal (although high, there is no upper limit on normal range)
- base excess – within normal range
Changes in the \([HCO_3^-]\) due to metabolic acids and acid excretion by the kidneys also affects the acid-base status. \([HCO_3^-]\) is one of two variables that determine \([H^+]\) or pH of the blood.

The factors which affect the \([HCO_3^-]\) in the blood are:
- Gaseous - \(pCO_2\)
- Metabolic - the \([HCO_3^-]\) falls when metabolic acids (e.g. lactic acid) is buffered
- Renal - the \([HCO_3^-]\) rises when acid excretion increases, and vice versa

**Base excess** determines how much of a disturbance to the acid-base status is due to:
- Changes in production/ingestion of metabolic acid
- Changes in excretion of acid by kidneys

The actual \([HCO_3^-]\) is measured from the patients pH and \(Pco_2\) and the difference between this value and the theoretical \([HCO_3^-]\) (calculated from the patients \(Pco_2\) assuming no metabolic or renal disturbances) is the base excess – any change present is solely due to metabolic or renal disturbances.

Therefore if the \(Pco_2\) is above or below normal, but the base excess is close to zero (or within the normal range), there is a purely respiratory disturbance.

**Renal compensation** – if there is increased metabolic acid levels, \([HCO_3^-]\) ions buffer this increase. This results in a decrease in \([HCO_3^-]\) levels in the blood. The kidneys then compensate for this loss, but producing \(CO_2\) which forms carbonic acid; this then dissociates into a \([HCO_3^-]\) ion and a \(H^+\) ion (the \(H^+\) ion is then transported into the glomerular filtrate, and the bicarbonate ion into the blood).

A rise in base excess is due to:
- an increase in renal excretion of carbonic acid
- drug administration of a base
- loss of acid from vomiting
  - result: metabolic alkalosis

A fall in base excess is due to:
- overproduction of metabolic acids
- ingestion of an acid
- reduction/failure of renal acid excretion
  - result: metabolic acidosis

**Metabolic alkalosis (with respiratory compensation)** – seen by an increase in base excess, with a corresponding increase in pH. The \(pCO_2\) is also increased as it tries to compensate for the increased pH, which would have been higher if not for this (due to reduced alveolar ventilation).
- \(pCO_2\) ↑
- pH ↑
- \(pO_2\) normal
- base excess ↑

**Metabolic acidosis (with respiratory compensation)** – seen by a decrease in the base excess with a corresponding fall in pH. The \(pCO_2\) is also reduced as it tries to compensate for the reduced pH (increased alveolar ventilation).
- \(pCO_2\) ↓
- pH ↓
- \(pO_2\) normal
- base excess ↓
Chronic respiratory acidosis (with renal compensation) – seen by a rise in CO₂ with only a slight drop in pH accompanied with an increased base excess and reduced pO₂. This suggests chronic hypoventilation, which caused the drop in pO₂ and rise in pCO₂. However due to this chronic respiratory acidosis, there is an additional acid excretion by the kidney, which accounts for the high base excess and only slightly reduced pH. Often associated with patient reduced consciousness and reduced ventilation rate.

- pCO₂ ↑
- pH ↓ (only slight)
- pO₂ ↓
- base excess ↑

Chronic respiratory alkalosis (with renal compensation) – seen by a drop in pCO₂ with corresponding increase in pH. However increase in pH only slight due to reduced acid excretion by kidneys in order to try and compensate for the alkalosis. Often associated with hyperventilation + anxiety etc.

- pCO₂ ↓
- pH ↑ (only slight)
- pO₂ normal
- base excess ↓

Ventilatory failure

Type II respiratory failure: high pCO₂ indicates inadequate alveolar ventilation, with corresponding reduced arterial pO₂. Base excess is normal.

Type I respiratory failure: pCO₂ normal (adequate ventilation), but reduced pO₂ (arterial hypoxaemia due to inadequate oxygenation and hence perfusion). Base excess and pH are normal.

Combined respiratory failure: high pCO₂ (not as high as in type II), but greatly reduced pO₂ (more than type I and type II)

Lung Infection

Dr R Wilson (r.wilson@imperial.ac.uk)

1. To learn about the healthy lungs defences against infection. We are continually exposed to infectious agents during breathing, but the healthy lung is sterile from the first bronchial division.
2. To understand how the host defences can be compromised; congenital or acquired. Three examples: primary ciliary dyskinesia, viral infection, cigarette smoking.
3. To understand the differences in pathogenesis between acute and chronic lung infections. Two examples: pneumococcal lobar pneumonia and bronchiectasis.

Lower Respiratory tract infections

- There is a large clinical iceberg of LRTIs present in the community →
- Patients with infection severe enough to be admitted to hospital are the tip of the iceberg
- The majority of infections are trivial and do not require treatment
- This is because lung infections are very common – while breathing we are constantly exposed to potential infectious agents
• However despite medical advances about 5 percent of those admitted to hospital with pneumonia die
• However we do have a multi-layered defence mechanism of the respiratory tract against these infections:
  o Mechanical – URT filtration, mucociliary clearance, cough, surfactant, epithelial barrier
  o Local – BALT (Bronchiole-associated lymphoid tissue), siG, lysozyme, transferrin, antiproteinases, alveolar macrophages
  o Systemic – polymorphonuclear leucocytes, complement, immunoglobulins
• The healthy lung is also sterile from the first bronchial division

*Mucociliary clearance*

• Cilia are an example of mechanical defence – they are part of the mucociliary system which protects the upper and lower airways all the way distally to the respiratory bronchioles
• Ciliated layer lies beneath the sticky mucus layer, surrounding by a watery fluid known as periciliary fluid
• Each epithelial cell has 200 cilia, with tight junctions sealing the gaps between the cells acting as a barrier protecting the airways
• Each cilium has a coordinated beating movement, consisting of a stiff downstroke which propels mucus forward, and a curved backstroke within the periciliary fluid underneath the fluid. This ensures mucus is propelled in one direction only. Each cilium beats about 14 times per second, and engages with the mucus with its claws only when at full vertical height.
• Each cilium and its surrounding neighbours beat in an ordered fashion, known as metchronal rhythm
• Each cilium also has an individual ultra-structure which can be examined under EM.
  o Consist of 9 doublets + 2 central microtubules, which slide up and down each other to cause ciliary movement
  o ATPase in the dynein arms provides the energy for movement

*Why do we get infections?*

• When an infection occurs either the infectious agent overcomes the lung defences (is virulent enough) or the defences are weakened in someway to allow the infectious agent in. this weakness may be:
  o Inherited – e.g. immunodeficiency
  o Acquired – e.g. through smoking
• Most commonly, it is a combination of both inherited and acquired susceptibility which leads to infection
• **Effect of smoking**: cigarettes perturb mucociliary clearance, by destroying the cilia (seen by biopsy), and changing the nature of airways to stimulate increased mucus production (causing morning cough). Is also makes the mucus produced more viscous and difficult to move by any remaining cilia
• Effect of viruses: also perturb mucociliary clearance by destroying cilia, stimulating the production of more, and more watery mucus (leading to a runny nose). The cilia therefore do not have a grip on the mucus, making it difficult to get rid of.
  o In addition viruses separate the tight junctions between airway epithelium and destroy epithelial cells.

*Respiratory infection syndromes*

• Due to a congenital abnormality, which results in weak defences
• Indications that something is wrong with lung defences:
  o Incidence of virulent infections
  o Recurrent infections, especially pneumonia
  o Chronic infections: if the body is unable to get rid of the infection even with the help of treatment
• These are hereditary (as well as acquired through viruses, cigarette smoking) causes of reduced lung defences
• Examples include Kartegener’s syndrome (dextracardia, bronchiectasis, sinusitis), primary ciliary dyskinesia
• PCD – cilia don’t beat properly so mucociliary clearance doesn’t work
  o Some men are infertile because sperm tails are cilia, so they do not move successfully to reach the ovum
  o Cilia present with absent dynein arms, no energy, no movement
  o Other ultrastructural abnormalities involve the microtubules, which perform disorganised beating
• Diagnosis of abnormal cilia is through “painless” nasal brushing
  o However Nitric oxide levels also provide an excellent screening test and is less painful for patient

### Bacterial infections

• Broadly speaking, bacterial pathogens of the lung fall into two groups:
  o Virulent species – cause pneumonia e.g. streptococcus pneumonia
  o Less virulent species – cause bronchitis, are equipped to chronically infect airways in which the host defences have been compromised e.g. unencapsulated haemophilus influenzae

### Influenza

• Haemophilus influenza is the commonest cause of airway infections; about a ¼ of smokers have this bacterium chronically infecting their airways
• Bacteria has hair-like projections called fimbriae which anchor the bacterium to epithelial cells to stop the bacteria being moved away by ciliary beat
• In an infected bronchial mucosa, the bacterial infection stimulates more mucus production, and the bacteria bind avidly to mucus
• In an episode of bronchitis, the inflammatory response and antibiotics help clear the infection from the airway. However bacteria are equipped with ways of avoiding elimination by the body’s defences.
  o They either produce factors which impair the defences, or find ways of “hiding” from the defences
• Bacterial strategies to avoid clearance from the airways include:
  o Exoproducts which impair mucociliary clearance – by slowing and disorganising ciliary beat, stimulating mucus production, affecting ion transport + damaging epithelium
  o Enzymes – break down local immunoglobulins
  o Exoproducts – impair neutrophil, macrophage + lymphocyte function
  o Adherence is increased by epithelial damage and tight junction separation
  o Avoid immune surveillance – using surface heterogeneity, biofilm formation, surrounding gel and endocytosis

### Pneumonia

• Infection of the alveoli, which is a much more serious illness than infection of the airways
• 5% mortality rate from hospital admissions
• Clinical features: cough, sputum, fever, dyspnoea, pleural pain, headache
  o Consolidation of lung seen on x-ray
• Histology: alveoli filled with inflammatory cells, fibrin, cell debris and bacteria
  o Most common cause is streptococcus pneumoniae – this a virulent bacterium produces a toxin called pneumolysin which punches holes into cell membranes killing the cell, therefore when studies under EM; dead cells seen with invading bacteria between them
Bronchiectasis

- Case history: breathing difficulties as baby, recurrent childhood chest infections, purulent sputum daily
  - Lung infections from childhood suggests a problem with lung defences
- Diagnosis: idiopathic bronchiectasis
  - Bronchiectasis is dilated airways in which the structural proteins have been damaged → chronic productive cough
- Management includes: physiotherapy (postural physiotherapy helps get phlegm out of the lungs) + many different medications
- Common complaints from bronchiectasis patients: cough + sputum, recurrent infections, breathlessness, fatigue
- Causes of chronic bronchial sepsis:
  - Congenital – e.g. pulmonary sequestration, bronchial wall abnormalities
  - Mechanical obstruction – e.g. foreign body, tumour, lymph node
  - Inflammatory pneumonitis – e.g. gastric contents, caustic gas
  - Fibrosis – e.g. CFA, sarcoid
  - Postinfective – e.g. TB, pneumonia
  - Immunological – e.g. ABPA, post-transplant
  - Impaired mucociliary clearance – e.g. CF, PCD, Youngs
  - Immune deficiency e.g. hypogammaglobulinaemia
- Bronchiectasis forms a viscous cycle of infection + inflammation – microbial infection → inflammation → tissue damage → impaired lung defences → more infection
- Chronic infection also involves a protease/antiprotease balance – when phagocytes engulf bacteria they spill a little protease enzyme which is normal inside the cell to kill the bacteria. This is usually neutralised by antiproteases in the mucus
  - In chronic infection, so much protease is spilled it overwhelms the ability of the antiproteases to neutralise it
  - The proteases then digest the epithelial cells, damaging them
- In a bronchiectatic airway wall, the structural protein elastin has been digested away by protease enzymes released by neutrophils as they are attracted into the airway lumen by bacteria
- Treatment is used to improve lung function

LECTURER’S NOTES

Primary ciliary dyskinesia is rare and is thought to be an autosomal recessive condition with incomplete penetrance.

- Ultrastructural abnormalities in the cilia, causing them to be immotile, or to move in a slow disordered fashion
- Absence of one or both of the dynein arms, but abnormalities of the microtubules or radial spokes have also been reported
- The cause of the disease in these patients is uncertain, and it may be that the ultrastructural abnormality is beyond the resolution of the electron microscope. Ciliary disorientation, which means that the cilia beat in different directions, has been described in such patients but, since this abnormality can occur at sites of inflammation in chronic rhinosinusitis and following viral infections its relevance is uncertain, and it may be a secondary phenomena.

Cilia line the nose, paranasal sinuses, middle ear and eustachian tube, and bronchi as far as the respiratory bronchioles, and also form the tail of spermatozoa. Impaired ciliary function occurs at all these sites, and diffuse bronchiectasis is usually associated with chronic sinusitis, middle ear disease, and often but not invariably, male infertility. The condition may present in the neonatal period with pneumonia or segmental collapse due to mucus impaction, or more commonly in childhood with recurrent infections. About 50% of cases have dextrocardia and a
smaller percentage full situs inversus, which is thought to be due to abnormal cellular microtubules that are involved in rotation of the organs in the embryo. When primary ciliary dyskinesia causes the clinical triad of bronchiectasis, dextrocardia and chronic sinusitis the condition is known as Kartagener’s syndrome after the German paediatrician who first described it.

Effects of viral infection and cigarette smoking on mucociliary clearance – viral infection leads to loss of ciliated cells and increased watery secretions that are not easily moved by ciliary beat; cigarette smoke also kills ciliated cells and causes increased sticky secretions that are not easily moved by cilia

The outcomes of a bacterial infection are –

- the host defences win: bacterial eradication
- The bacterium wins: serious illness or death
- Bacterial persistence: lung abscess or chronic airway infection
- Antibiotics kill large numbers of bacteria, but are dependent on the host defences to mop up those bacteria that remain
- Chronic airway infection leads to chronic inflammation. This causes progressive damage to the airway wall leading to bronchiectasis
- The vicious circle hypothesis proposes that bacteria stimulated host-mediated inflammation causes progressive lung damage – see text

Mucus is poorly cleared from the bronchiectatic areas for several reasons. There is pooling in the abnormal dilated airways; ciliated cells are lost when the epithelium is damaged; the mucus is less elastic and more viscous making it difficult to clear by ciliary beat or cough. Bacteria adhere avidly to mucus where they multiply so that bacterial counts in sputum often exceed $10^9$-colony forming units (cfu) per millilitre. Large number of neutrophils are attracted from the bloodstream into the bronchial lumen in response to bacterial infection, by chemotactic products of bacteria themselves and also mediators from host cells (e.g. interleukin-8, C5a, leukotriene B4). Serum levels of the adhesion molecules E-selectin, intercellular adhesion molecule (ICAM)-1 and vascular adhesion molecule (VCAM)-1 are elevated, suggesting that endothelial activation occurs, probably within the lung. The failure of the inflammatory response to eradicate the infection once it is established in patients with bronchiectasis is due to a combination of impaired local host defences, some properties of bacteria themselves and the high bacterial number.

Although local host defences are impaired, in most patients the systemic inflammatory response is intact and persistent bacterial infection leads to exuberant chronic inflammation which damages the lung. Neutrophils spill proteolytic enzymes such as elastase and reactive oxygen species during phagocytosis that cause tissue damage in the affected area. The infection and inflammation may spread to involve adjacent areas of normal bystander lung, in time causing extension of the bronchiectasis. Immune complexes are formed between antibodies that are produced locally, and those arriving via transudation, and bacterial antigens. These stimulate other inflammatory processes. The lung defences are weakened by the damage caused by inflammation, and this in turn promotes continued infection which perpetuates the inflammatory response. Epithelial cells, lymphocytes and macrophages release cytokines and other factors which orchestrate and perpetuate this sequence of events which has been termed a "vicious circle". Bronchiectatic secretions have increased amounts of interleukin (IL)-1α and IL-1β, tumour necrosis factor α, IL-6, IL-8 and granulocyte colony-stimulating factor. The levels of IL-8 are particularly high.
Respiratory System Practical 1: Respiratory Muscles

Identify the principal muscles associated with inspiration and expiration:

- The inspiratory muscles include:
  - The diaphragm
  - The accessory muscles, which include:
    - External intercostals (infero-medial direction)
    - Scalene
    - Sternocleidomastoid

- The expiratory muscles include:
  - Internal intercostals (infero-lateral direction)
  - The internal and external oblique
  - Rectus abdominis

Understand the additional non-respiratory actions of these muscles.

- Accessory muscles control air movement during other behaviours such as speech, laughter, coughing, sneezing, and vomiting
- The diaphragm is an essential muscle in childbirth and is also used when vomiting
- The rectus abdominis is used during laughing and coughing
- The sternocleidomastoid is involved in movement of the head

Understand how contraction of inspiratory muscles causes the chest wall to expand and the lungs to enlarge:

- The diaphragm contracts and is pulled downwards, increasing the super-inferior dimensions of the thorax
- The external intercostals contract, pulling the ribs up and out, increasing the antero-posterior dimensions of the thorax
- The increased volume decreases the pressure, causing a pressure gradient; air rushes into the lungs, filling them

Understand how contraction of expiratory muscles causes the chest wall to contract and the lungs to reduce in size:

- The internal intercostal muscles, along with the oblique muscles and rectus abdominis causes the ribs to be pulled in and down decreasing the antero-posterior dimensions of the thorax
- The diaphragm relaxes and is pushed upwards, decreasing the supero-inferior dimensions of the thorax
- A pressure gradient is generated and so air is pushed out
Recognise that these muscles will be differentially activated during different breathing states; more specifically, identify which muscles will be active during quiet breathing; identify which muscles will be active when ventilatory demand is increased such as during exercise or during lung disease:

- The diaphragm alone is used in quiet breathing
- The external intercostals are used on increased demand
- The scalene, sternocleidomastoid and accessory expiratory muscles only are used in exercise or during high demand

In addition to their primary role in maintaining alveolar ventilation, know that respiratory muscles will control air movement during other behaviours including, speech, laughter, coughing, sneezing and vomiting.

**Respiratory System Practical 2: Lung Volumes**

Describe how to measure the respiratory volumes and capacities of the lung:

- Lung volumes are measured by spirometry
- Height and weight of the subject are recorded first, followed by a minute of breathing at rest
- The subject then breathes from the spirometer wearing a nose clip for 30 seconds; after a few normal breaths, a maximum inspiration and a slow maximum respiration are measured
- This should ideally be repeated in different postures
- The spirometer cannot be used to measure the residual volume (RV), and therefore cannot measure either the functional residual capacity (FRC) or the total lung capacity (TLC)
- These values must be obtained by the inert gas dilution technique
  - A tracer gas (helium) is used, which mixes with the air in the lungs but does not diffuse out; the volume is then determined by the amount that this gas is diluted as it mixes with the air in the lungs

Be aware of approximate values for these in a young healthy adult:

<table>
<thead>
<tr>
<th>Volume/Capacity</th>
<th>Definition</th>
<th>Approximate Value (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Volume ($V_T$)</td>
<td>The volume of air inspired in a single spontaneous breath</td>
<td>500</td>
</tr>
<tr>
<td>Inspiratory Reserve Volume (IRV)</td>
<td>The additional volume that could be maximally inspired after a tidal volume inspiration</td>
<td>3100</td>
</tr>
<tr>
<td>Expiratory Reserve Volume (ERV)</td>
<td>The additional volume that could be maximally expired after a tidal volume expiration</td>
<td>1200</td>
</tr>
<tr>
<td>Vital Capacity (VC)</td>
<td>The volume of air that is possible to maximally exhale following a maximal inspiration ($IRV+V_T+ERV$)</td>
<td>4800</td>
</tr>
<tr>
<td>Inspiratory Capacity (IC)</td>
<td>The volume of air that it is possible to inspire at the end of a normal quiet expiration ($V_T+ERV$)</td>
<td>3600</td>
</tr>
<tr>
<td>Residual Volume (RV)</td>
<td>The volume of air remaining within the lungs and airways at the end of a normal quiet expiration</td>
<td>1200</td>
</tr>
<tr>
<td>Functional Residual Capacity (FRV)</td>
<td>The volume of air contained within the lungs and airways at the end of a tidal volume expiration; this is the equilibrium volume at which elastic recoil exactly balances the chest wall forces (RV+ERV)</td>
<td>2400</td>
</tr>
<tr>
<td>Total Lung Capacity (TLC)</td>
<td>The volume of air contained within the lungs and airways at the end of a maximal inspiration (RV+ERV+$V_T+IRV$)</td>
<td>6000</td>
</tr>
</tbody>
</table>
Be aware that body height, weight, age and gender influence the values of these volumes, and can be used to predict these values:

- These volumes can be influenced by body weight, height, age and gender
- There will be charts that help predict these values
- However there will be inter-subject variability

Be aware which can, and which cannot be measured by the use of a simple spirometer:

- As stated previously, the spirometer cannot be used to measure the residual volume (RV), and therefore cannot measure either the functional residual capacity (FRC) or the total lung capacity (TLC)

Be able to describe the principle of measurement for those lung volumes/capacities that CANNOT be measured by the use of a simple spirometer:

- The inert gas dilution technique is used

Be aware how these volumes may change during exercise.

- During exercise the ventilation rate is increased, so the tidal volume will be increased; the tidal volume is the main value that changes
- ETV, IRV, FRC and the IC all change
- The values of RV, TLC and VLC cannot be changed at all

Be able to state which lung volumes/capacities (including RV, FRC, VC, TLC) are changed from normal for: (1) a severe chronic restrictive lung disorder (2) a severe chronic obstructive pulmonary disorder, and be able to give reasons for these changes:

**Severe chronic obstructive disease:**

- VC would either be decreased or would remain constant
  - TLC could decrease based on the VC changes
- FRC would increase, as would RV
- In an obstructive disease, the patient has hyper-inflated lungs from which it is difficult to expel air

**Severe chronic restrictive disease:**

- RV would be unchanged, whilst a decrease in VC (and TLC by extension) would occur
- FRC would be significantly reduced
- In restrictive conditions, the patients cannot fill their lungs as they cannot expand them enough; this consequently lowers vital capacity greatly
Respiratory System Practical 3: Assessment of Airway Resistance

Briefly describe two methods that can be used (indirectly) to evaluate airways resistance:
- Forced expiratory volume (FEV₁) is measured using a vitalograph
- Peak expiratory flow rate (PEFR) is measured using a peak flow meter

Define FVC and FEV₁:
- Forced vital capacity (FVC): the maximum volume of air expired as forcefully and rapidly as possible following a maximum inspiration
- Forced expiratory volume (FEV₁): the volume of gas expired in the first one second of this manoeuvre

Explain why FEV₁ may be reduced in both obstructive and restrictive lung disease:
- FEV₁ may be reduced in both obstructive and restrictive lung disease
  - In restrictive disorders, there is a low compliance, so the vital capacity is much compromised
  - Although vital capacity can be normal in obstructive disorders, airway narrowing results in a high resistance, which slows expiration

Explain the significance of the ratio FEV₁/FVC and state an approximate normal value in a young healthy subject:
- The ratio FEV₁/FVC is an estimate of airway resistance
- The ratio should normally be around 1, as a healthy subject would be able to breathe out the air in his/her lungs within the first second of forced expiration

Predict and explain the change (if any) in the ratio FEV₁/FVC in obstructive lung disease:
- Vital capacity may be normal, but FEV₁ is reduced due to airway resistance and so the ratio decreases

Predict and explain the change (if any) in the ratio FEV₁/FVC in restrictive lung disease:
- Vital capacity is reduced dramatically, but airway resistance is normal, so both values decrease and the ratio stays the same

Explain why the Wright Peak Flow meter may be particularly useful for patients with asthma or COPD:
- It is small, inexpensive, and easy to use, which means that peak flow can be monitored at home
- Patients can be educated to recognise when the values change to a degree that they should seek medical advice

State which values for FVC, FEV₁, FEV₁/FVC, and PEFR generally increase with increase in subject size as measured by the subject’s height:
- FVC, FEV₁, FEV₁/FVC ratio, and PEFR generally increase with increased subject size, as measured by height

State which values for FVC, FEV₁, FEV₁/FVC and PEFR generally decrease with age after peaking at about 20 years:
- FVC, FEV₁, FEV₁/FVC ratio, and PEFR generally decrease with age after peaking at 20

State which values for FVC, FEV₁ and PEFR are lower in females than in males of the same age and height:
- FVC, FEV₁, FEV₁/FVC ratio, and PEFR are generally lower in females than in males of the same age and height

These changes in structure and function may increase airway resistance:
- Bronchoconstriction
  - Smooth muscle contracts in the wall of the airways
  - This is frequently the case in asthmatics
- Physical blockage
  - An example is increased mucus secretion
  - This leads to more viscous mucus, which is more difficult to remove and thus forms mucus plugs in airways
- Loss of radial traction (outward pull)
- Change to the airway wall structure
  - The lumen can narrow, which occurs frequently in asthmatics
- Airway inflammation
  - This leads to swelling of tissue and a reduction in luminal diameter
Respiratory System Practical 4: Breath Holding

Indicate what happens to arterial PO$_2$, PCO$_2$ and O$_2$ saturation during breath holding:
- Arterial PO$_2$ decreases
- Arterial PCO$_2$ increases
- Consequently, oxygen saturation of the blood falls
  - There is less oxygen for the haemoglobin to carry
  - Carbon dioxide now binds to the haemoglobin to be carried back to the lungs to be removed

Indicate what effect the following manoeuvres have on arterial PO$_2$, PCO$_2$ and O$_2$ saturation:

Over-breathing of room air:
- Arterial PO$_2$ increases
- Arterial PCO$_2$ decreases
- O$_2$ saturation remains constant

Normal breathing of oxygen:
- Arterial PO$_2$ increases greatly
- PCO$_2$ remains constant
- O$_2$ saturation rises slightly

Over-breathing of oxygen:
- Arterial PO$_2$ increases even more greatly
- PCO$_2$ goes down
- O$_2$ saturation rises slightly

Briefly explain why the changes in arterial PO$_2$ and PCO$_2$ during a breath-hold eventually lead to an inability to sustain the breath hold:
- Increased PCO$_2$ and decreased PO$_2$ stimulates the central and peripheral chemoreceptors, which instigate nervous impulses from the respiratory centre that overcome voluntary suppression by the apneustic centre
  - This forces the subject to stop holding his/her breath and take another breath of fresh air to bring oxygen levels back up and lower carbon dioxide levels

Identify the relative importance of changes in arterial PO$_2$ and PCO$_2$ in determining how long a breath can be held following normal breathing (i.e. from normal blood gas levels). Comment on the main reason for this:
- Ventilation increases linearly with PCO$_2$, but a marked fall in PO$_2$ must occur before there is a noticeable rise in ventilation
  - This means that if the arterial PO$_2$ falls significantly during breath-hold, the various responses will cause the ventilation rate to be increased and so the breath can no longer be held

Explain why breath-holding time may alter if PO$_2$ and PCO$_2$ are changed immediately before a breath hold:
- If PCO$_2$ is reduced immediately before breath hold, stimulation of the chemoreceptors will occur in the required degree at a later time, thereby allowing the breath to be held for longer
- There is, however, little effect if the PO$_2$ is changed before the breath hold

Identify what factors other than PCO$_2$ and PO$_2$, may influence breath-holding time:
- Neural stimuli from the chest wall and lung receptors induce chest expansion and thus influence breath holding time
Respiratory System Practical 5: Gas Exchange/Oxygen Transport

Understand the factors that determine alveolar PO₂ and PCO₂:

- The factors that determine alveolar PO₂ and PCO₂ are:
  - Composition of inspired air
  - Alveolar ventilation
  - Metabolic rate (O₂ use and CO₂ production)

Define hypoventilation and hyperventilation. Distinguish between the latter and the raised level of ventilation (hyperpnoea) observed during exercise:

- Hypoventilation: breathing at an abnormally shallow and slow rate, resulting in increased PCO₂
- Hyperventilation: breathing at an abnormally rapid rate (at rest) leading to a decreased PCO₂
- Hyperpnoea: rapid ventilation appropriate for a metabolic acidotic state, as observed in exercise

Understand the relationship between alveolar PO₂ and PCO₂ and end-pulmonary capillary PO₂ and PCO₂. Explain the consequences of this for systemic arterial PO₂ and PCO₂:

- Alveolar PO₂ and PCO₂ and end-pulmonary PO₂ and PCO₂ should be the same respectively due to the efficiency of the diffusion process

Know how (if at all) a reduction in Hb concentration in the blood (anaemia) affects arterial PO₂, PCO₂ and oxygen content. Explain the effectiveness (or lack of it) of breathing an oxygen-enriched gas mixture in correcting any abnormalities associated with anaemia:

- A reduction of haemoglobin concentration in the blood, or anaemia, does not affect arterial PO₂ or PCO₂
- However, anaemia drastically decreases oxygen content
- Hyperventilation with oxygen-rich gas will improve PO₂ will improve PO₂, but since the haemoglobin present is already 97% saturation, it will not cause a significant rise in oxygen content

Know how (if at all) a reduction in ventilation rate below normal (hypoventilation) affects arterial PO₂, PCO₂ and oxygen content. Explain the effectiveness (or lack of it) of breathing an oxygen-enriched gas mixture in correcting any abnormalities associated with hypoventilation:

- Hypoventilation causes a decrease in PO₂ and oxygen content, and a rise in PCO₂
- Breathing an oxygen-enriched gas will improve PO₂ and return oxygen content to normal, but will also reduce PCO₂

Give normal values for arterial PO₂, PCO₂, Hb saturation, and Hb concentration:

- PO₂: 13.3 kPa
- PCO₂: 5.3 kPa
- Hb saturation: 97%
- Hb concentration: 15 g/dl
Mr Jones is 62 years old and was diagnosed with chronic obstructive pulmonary disease (COPD) five years ago, when he gave up smoking. He used to smoke 20 cigarettes a day, and smoked for 30 pack years altogether. Unfortunately, he still has COPD. He regularly visits his GP and the GP has asked him if he would like to participate in a trial of a new drug that will be administered by inhalation.

The new drug has dual action – it is a bifunctional protease inhibitor. It can inhibit the activity of serine proteinases as well as matrix metalloproteinases, one site with the inhibitory capacity of alpha-1 antitrypsin (AAT; also called alpha-1 proteinase inhibitor) and the other site with the inhibitory capacity of tissue inhibitor of metalloproteinases (TIMP). In order to assess the efficacy of this drug, prior to the study patients will have lung function tests, bronchoalveolar lavage and high resolution CT scanning. If they have any other unrelated conditions they will not be allowed to proceed with the study. Having been included, they will be asked to inhale the drug (or placebo if in the control group) twice daily (as demonstrated by the research nurse). Patients will be monitored at regular intervals (e.g. lung function, bronchoalveolar lavage and CT scanning every 6 months) for up to two years. It is important that the patients do not start smoking again.

COPD can consist of three pathological conditions, bronchitis, emphysema and small airways disease, but people with COPD do not necessarily have all three conditions.

What level of the respiratory tract is affected by each of these conditions?

**Bronchitis:**
- This affects the bronchi mainly and generally not the bronchioles
- The bronchi here are cartilaginous as they are part of the large airway path compared to the non-cartilaginous bronchioles which are part of the small airway

**Emphysema:**
- This mainly affects the respiratory bronchioles, especially of smokers
- It leads to the loss of the connective tissue scaffold, basement membrane and normal cell organisation
- There is also a loss of surface area and elastic recoil of alveoli, which compromises gas exchange

**Small airways disease:**
- This affects the bronchioles and other non-cartilaginous regions of the airways

Why does the assessment include lung function?
- Lung function tests measure FEV₁, vital capacity, and so on to obtain a baseline level of measurements to measure against
- These tests will be repeated after the trial and a comparison of the two results will be done

Why does the assessment include bronchoalveolar lavage?
- An endoscope is passed through the respiratory tract and then into the lungs, in through the bronchioles and alveoli
• The endoscope aspirates a sample of tissue and other material, much like in a biopsy; the sample is then analysed
• The material aspirated is known as a peripheral wash and contains:
  o Surfactant, found in the epithelia and produced by Type II cells
  o Macrophages
  o Neutrophils
• The number of these inflammatory cells (neutrophils and macrophages) is analysed
  o In healthy lungs, there should be a ratio of 70% macrophages to 30% neutrophils
  o In COPD, there is a ratio of 70% neutrophils to 30% macrophages
• The purpose of the bronchoalveolar lavage is to obtain a cell count of inflammatory cells

Why does the assessment include high resolution CT scanning?
• High resolution CT scans offer a far more detailed scan than regular CT, allowing things to be seen on a micro scale
• With bronchitis, the small airways would appear to be denser in number on the scan
• With emphysema, there would be many holes in the small airways of the lungs
• With COPD, the small airways would again seem to be denser

What happens to the structure of the lung during emphysema?
• There are many holes in the small airways of the lungs, which are the result of an endogenous immune response
• The macrophages and neutrophils contain proteases, which are released during the inflammatory phase of emphysema
• These proteases break down the host tissue in order to help cell migration and break down any particulate matter deposited in the lungs
• The neutrophils release many oxygen free radicals, which are very toxic
  o These reactive oxygen species are secreted to kill any infecting microbes
• The macrophages also secrete many chemicals prior to the phagocytosis of the foreign or infecting microbe
  o Lysozymes within the macrophage complete the digestion of the microbe
• However, if either the oxygen free radicals, lysozymes, or proteases leak out of the inflammatory cell, they cause irreversible damage to the host tissue
  o It is basically protease secretion overload that causes tissue destruction in emphysema
• Emphysema is far more prevalent in smokers
  o This is due to a deficiency in the enzyme α-1-antitrypsin, which circulates in the blood and is able to mop up all the excess proteases

Why do the small airways collapse, become obstructed and stenosed?

Obstruction:
• Small airways are easily obstructed by particular matter and mucous
• Smokers inhale cigarette smoke, which contains many harmful particles that obstruct their airways
  o This leads to the “smoker’s cough”, as coughing is the only way smokers can manage to remove some of these trapped particles

Stenosis:
• The airway becomes damaged in some way, either due to the endogenous immune response or by cigarette smoke
• As it is repaired, the airway narrows as new tissue grows to replace the old, damaged tissue
• The scar tissue remains and narrows the airway
LSS Respiratory System

Alexandra Burke-Smith

What are the changes in epithelial cell profile and secretions during bronchitis?

- Excess mucous is produced by the goblet cells as the number of goblet cells increases; at the same time, the number of ciliated cells decreases
- Consequently the trapped particles cannot be removed by the cilia, as there are not enough of them, and they tend to beat in a disordered fashion
- Coughing is the only way possible to attempt to clear the blocked airways, leading to the characteristic smoker’s cough
- As the mucous traps particles, dirt, and foreign microbes, the inflammatory cell number also increases
- In the peripheral lung, there are likely to be deposits of particle matter
- In conducting lung airways, there are likely to be deposits of foreign infecting cells and so many neutrophils will be found here

Why would a protease inhibitor help treat COPD?

- A protease inhibitor inhibits the action of the secreted proteases
- It is only given to people who stop smoking completely as inhaled cigarette smoke will tend to inhibit protease inhibitors

Why don’t endogenous inhibitors work?

- An example of an endogenous inhibitor is a tissue inhibitor of metalloproteinases (TIMP)
- Endogenous inhibitors do not work as there is proteolytic overload
  - Too many protease enzymes have been released into the lungs, causing damage
- An endogenous inhibitor would not remove any of the protease already present
- The oxidants in cigarette smoke also prevent endogenous inhibitors from working

Why use a dual inhibitor?

- A dual inhibitor would be effective, as the protease inhibitor would inhibit the protease already present in the lungs and the endogenous inhibitor would act by preventing the release of more protease
- There would be a synergistic effect in limiting the protease action

What might cause problems with the efficacy of inhaled therapy? Could this be problem be solved?

- The excess mucous present in the lungs would not allow inhaled therapy to be effective
- Some of it would be coughed up in order to try and remove it, but not enough would be removed
- The method of massaging the chest may also help to remove some of the mucous
- Administration of mucolytic, which breaks down mucous, would be the only effective way of removing the excess mucous

Would Mr. Jones feel better if he used a bronchodilator?

- A bronchodilator would help, as it makes breathing easier
  - The airways would be dilated
- However, if the airways are constricted due to reasons other than bronchoconstriction, the effectiveness of the bronchodilator would be lessened

Post-treatment:

- The LFT should show improvement
  - FEV₁ should increase
  - V₅ should increase
- Bronchoalveolar lavage should show a drop in inflammatory cell numbers
- CT scan would not show a decrease in the number of holes in the lungs
  - Some may appear to have been healed, but this will not be functional tissue; rather, it is scar tissue
  - If therapy was successful, there should not be any more holes in the lung walls than before the treatment
Respiratory System Practicals 7 & 8: Lung Histology I and II

Identify the following structures/cells on a histological section, photomicrograph or electron micrograph of normal lung tissue: bronchiole; pulmonary artery; alveolar duct; alveolus; ciliated epithelial cell; goblet cell, clara cell, type 1 pneumocyte; type 2 pneumocyte; alveolar macrophage:

- Bronchiole
- Pulmonary artery
- Alveolar duct
- Alveolus
- Ciliated epithelial cell
- Goblet cell
- Clara cell
- Type 1 pneumocyte
- Type 2 pneumocyte
- Alveolar macrophage

Define the difference between metaplasia and dysplasia and be able to differentiate between them in a histological section of lung tissue:

- Metaplasia: the reversible change in differentiation from one fully differentiated type to another
- Dysplasia: an abnormal pattern of growth in which some of the histological features of malignancy are present
- Hyperplasia: an increase in size of a tissue or organ resulting from an increase in the number of cells
- Hypertrophy: an increase in size of a tissue or organ resulting from an increase in size of individual cells
State what is meant by the terms lobectomy and pneumonectomy with respect to the lungs:

- Lobectomy: removal of a lung lobe
- Pneumonectomy: removal of a complete lung

Briefly describe, in terms of respiratory anatomy/pathology what is meant by the following medical terms:

- Emphysema: destruction of the walls of the alveoli, producing abnormally large air spaces
- Pleural effusion: accumulation of fluid in the pleural space, possible causing pleurisy
- Atelectasis: incomplete expansion of the lung or portion of the lung due to airway obstruction, lung compression or inadequate pulmonary surfactant
- Haemoptysis: coughing up of blood

Identify, with reference to the picture of the lung section, the macroscopic characteristics of emphysema:

- Pictures A and D represent normal lung
- Pictures B and E represent a lung with emphysema
State in a few words what is meant by each of the following terms and indicate which is a sign and which is a symptom:

**Signs:**
- Finger clubbing: increased nail bed sponginess, which leads to a loss of angle between the nail and the nail bed
- Hyperinflation: increased volume and hyper-expansion of the thorax due to expiratory airflow limitation
- Central cyanosis: a bluish tongue that indicates a low $\text{PO}_2$ of around 7 – 8 kPa
- Tachypnoea: an increase in respiratory rate to maintain $\text{PCO}_2$ and $\text{PO}_2$ within normal range

**Symptoms:**
- Dyspnoea: shortness of breath or an unpleasant awareness of breathing
- Cough: a rapid expiratory manoeuvre due to stimulation of irritant receptors in the respiratory tract membrane
- Haemoptysis: the coughing up of blood from the nose, nasopharynx, vocal cords or lower respiratory tract
- Chest pain: pain in the thorax, attributable to various causes:
  - Pleural pain is due to infection, infarction, and connective tissue disease
  - Mediastinal pain is due to a large pulmonary embolism or mediastinal lymphadenopathy
  - Chest wall pain is due to rib fracture, nerve root pain, or costochondritis, which is the inflammation of the junction between the bone and cartilage

When a patient states they are breathless, what simple assessment would you want to perform, and what physical sign would you be looking for?
- Breathlessness can be tested during a shuttle walking test
- Signs include tachypnoea
  - Tachypnoea is an appropriate involuntary response in which the respiratory rate is increased to maintain $\text{PO}_2$ and $\text{PCO}_2$
  - Hyperventilation is instead a voluntary increase in the minute ventilation that results in a fall in arterial $\text{PCO}_2$
- Other signs include a sense of doom, wheezing, chest pain, cold, clammy skin and central cyanosis

State what is meant by the term central cyanosis and briefly explain why it is assessed by looking at the tongue. Distinguish between central and peripheral cyanosis:

**Peripheral cyanosis:**
- Peripheral cyanosis can be indicated by a bluish colour of the hands
- However, a bluish colour of the hands could also indicate poor peripheral circulation

**Central cyanosis:**
- Central cyanosis is often due to a circulatory or ventilatory problem that leads to poor oxygenation of blood in the lungs
- Assessment of the tongue colour is preferred
- A bluish tongue indicates a low arterial $\text{PO}_2$ of 7-8kPa

Describe how hyperinflation is assessed (i) on physical examination (ii) from the results of lung function testing. Briefly explain why hyperinflation commonly accompanies COPD
- Hyperinflation commonly accompanies COPD, as the predominant problem in COPD is expiratory flow limitation
- Expiratory flow is limited, resulting in air trapping and therefore an increased volume of air in the lungs at the end of expiration
- Signs present upon examination include:
Indicate the respiratory characteristics that can be assessed by palpation and percussion of the chest:

**Palpitation:**
- Reduced overall movement of chest wall: Hyperinflation
- Reduced local chest wall movement: Consolidation
- Deviation of the trachea to: Collapse
- Deviation of the trachea away: Tension pneumothorax

**Percussion:**
- Note reduced: Lung collapse, effusion, or consolidation
- Note increased: Pneumothorax

**Briefly describe what is meant by the terms “wheeze” and “crackles”. Indicate what conditions are associated with these breath sounds:**

**Wheeze:**
- Wheeze is a musical sound that reflects the airways narrowing
- It can be caused by a generalised disease such as asthma, COPD, or pulmonary oedema, or by a localised factor such as a tumour or foreign body

**Crackle:**
- Crackle is the equalization of the intra-luminal pressure of the collapsed small airways during inspiration
- This occurs in Acute Respiratory Distress Syndrome (ARDS), pulmonary fibrosis, and bronchiectasis.

**Describe the physical characteristics of pitting oedema. Give one example of a respiratory disorder that could be associated with this:**
- Pitting oedema is the accumulation of fluid within the connective tissue of the skin in a gravitational distribution
- An indentation remains after gentle pressure is applied over a bony prominence
- It may arise in conditions like COPD or pulmonary hypertension

**Outline what physical characteristics of sputum are indicative of respiratory pathology, briefly stating why:**

**Colour:**
- Clear/white: Chronic obstructive pulmonary disease (COPD)
- Green: Chest infection
- Blood-stained red: Pulmonary embolism
- Blood-stained rusty red: Pneumonia
- Blood-stained pink: Pulmonary oedema

**Consistency:**
- Mucoid: Chronic obstructive pulmonary disease (COPD)
- Thick: Cystic fibrosis
- High volume of clear sputum: Asthma

**Volume:**
- Over 20ml/day: Bronchiectasis, cystic fibrosis

**Smell:**
- Foul smelling: Anaerobic chest infection