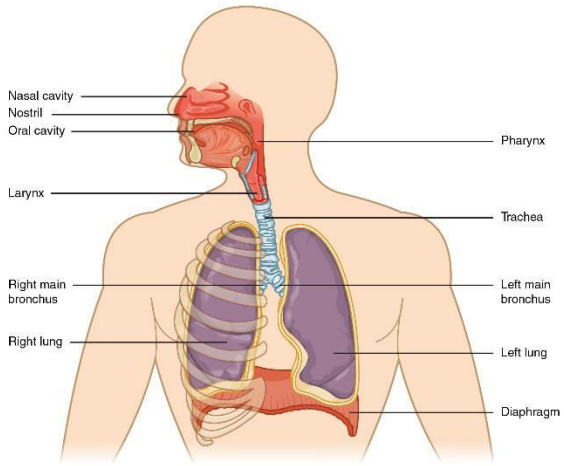
Anatomy and Physiology of the Lung.

Anatomy:

The respiratory system is everything from the nose to the diaphragm.

Divided to the conducting zone; where air goes in and out of the lungs.

And the Respiratory zone: the part of the lungs where the gas exchange occurs.



Conducting Zone:

Large Airways:

Trachea

Right + Left Main Bronchus

Bronchioles

Terminal bronchioles

Respiratory Zone

Respiratory bronchioles (branch off from a terminal bronchiole to the alveolar sacs)

Alveoli.

Basics

Location: Thoracic Cavity, Lungs, and most of the cells within the body (cells with mitochondria.) The exchange of gases in the lungs is **external respiration.** The production of energy from biomolecules is **internal respiration.**

Active or passive: Both.

Voluntary/involuntary: Both. We can consciously control the rate of breathing, but we usually do not have to.

Normal ventilation: **Frequency:** At rest, 12 breaths per minute.

Volume: About 0.5 L of gas per breath.

An overview of respiration

External Respiration: Exchange of oxygen and carbon dioxide between atmosphere and body tissues, e.g inhalation and exhalation.

Internal Respiration: Aerobic metabolism i.e Oxidative Phosphorylation, where the glucose is broken down to make energy.

External Respiration.

External respiration is comprised of 4 steps.

1. **Pulmonary Ventilation.**

Air (gases) move in and out of the lungs by bulk pressure. Pressure is increased or reduced by contraction or relaxation of the diaphragm, which forces air out and into the lungs.

2. **Exchange of O_2 and CO_2 between lungs and blood.**
3. **Transportation of the O_2 and CO_2 in blood.**

Requires circulation in order to transport gases within a system, in order to reach tissues.

In pulmonary circulation, the blood flows from heart, to the lungs, back to the heart. The heart takes deoxygenated blood to the lungs. Oxygenated blood then returns to the heart.

The oxygenated blood is carried by the systemic circulation. This carries oxygenated blood to all functioning parts of the body. These use oxygen in the blood to carry out internal respiration.

Exchange of O_2 and CO_2 between blood and body tissues.

Diagnostic Tests for Pathophysiology.

1. X-Ray: Bones show as white, with muscles showing more opaque white.

X-Rays allow us to examine the bones of the thoracic cavity, the heart, and the conducting airways, for deviation from normal, collapsed lungs (pneumothorax) or liquid, that may allow for diagnosis.

TC Scan: Allows us to examine the areas of the thoracic cavity, at different views and at different "cuts" i.e. every 2 mm.

2. Endoscope; Bronchoscopy.: Tube with optical fiber and light is inserted down the pharynx into the bronchus, allowing us to visualise the inside of the lung, or take samples e.g. infection fluid or tumour tissue; using a brush extension.

Most people are awake during a bronchoscopy. Before the procedure, a doctor sprays a local anesthetic into the nose and throat to numb the area. Many people also take a sedative to help them relax.

Doctors only recommend a general anesthetic in rare cases, when they will be using a rigid bronchoscope.

Once the anesthetic takes effect, the doctor will usually insert a flexible bronchoscope tube through the nose and throat and into the bronchi. As the tube moves into the lungs, a person may feel a pressing or tugging sensation.

Some people initially cough or gag, but this usually subsides quickly. A doctor may administer oxygen throughout the procedure may to aid breathing.

The bronchoscope's light and camera help the doctor to see the airways clearly, even around bends.

If a doctor needs to insert a stent or take a biopsy, they can pass brushes, needles, and other instruments through a channel in the bronchoscope. A stent is a small tube that helps to keep blocked or narrow airways open.

A doctor sometimes sprays a saline solution through the airways, in a process called bronchial washing, or lavage, to collect cells and fluids. The doctor will later examine them under a microscope.

During the bronchoscopy, a doctor may take an ultrasound, to get a clearer picture of the lymph nodes and tissues in and around the bronchi.

Common Chronic Diseases of the Respiratory System; Asthma, COPD.

Other common diseases include chronic cough, chronic allergic rhinitis, and membrane hyaline syndrome.

Asthma.

High prevalence in Ireland; one of the highest in Europe and the world.

Asthma is a chronic **inflammatory** disorder of the airways; inflammation is the cardinal symptom.

Patient suffers from exaggerated responses to a wide variety of exogenous and endogenous stimuli; resulting in a potent bronchoconstriction. Stimuli can be allergenic or non-allergenic.

Leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughin, particularly at night or the early morning.

General and *variable* airflow obstruction usually reversible, either spontaneously or with appropriate treatment.

Asthma; Obstruction is **reversible**. COPD: Obstruction is **irreversible.**

Chronic Obstructive Pulmonary Disease

Airflow limitation that is *not reversible*; no obstruction = no COPD.

Tobacco smoking is a predisposing factor.

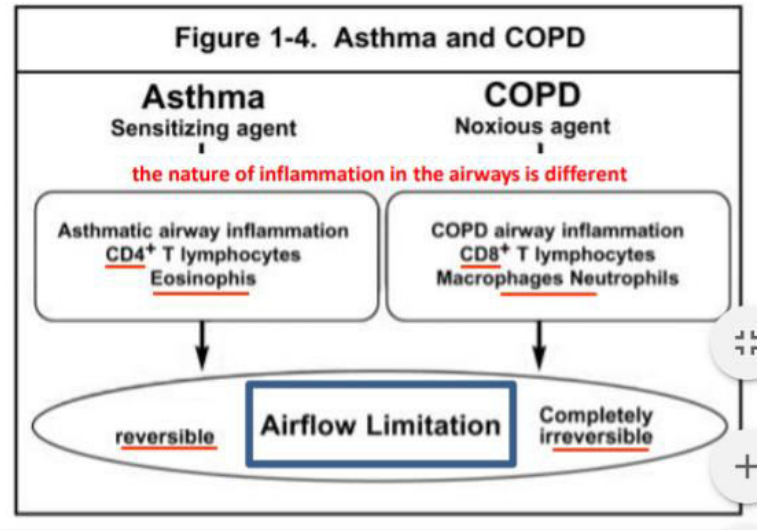
Symptoms; Dyspnea; shortness of breath that is *constant*, cough, sputum production

Airflow limitation is progressive.

Usually sputum in a persistent cough.

Asthma vs. COPD.

They have common symptoms, inflammation, and bronchoconstriction.



Airways Resistance:

Due to bronchial smooth muscle tone and inflammation? May also be mucousal build up.

Use a spirometer to measure this.

Spirometry: Diagnosis and monitoring patients in clinic. *Not portable; cannot be done at home.*

Peak flow meter: Diagnosis, particularly in asthma, but mainly used by patient for self-monitoring.

Spirometry.

Most common of the pulmonary function tests.

Measures volume or flow of forced expiration.

Used for diagnostic purposes rather than monitoring.

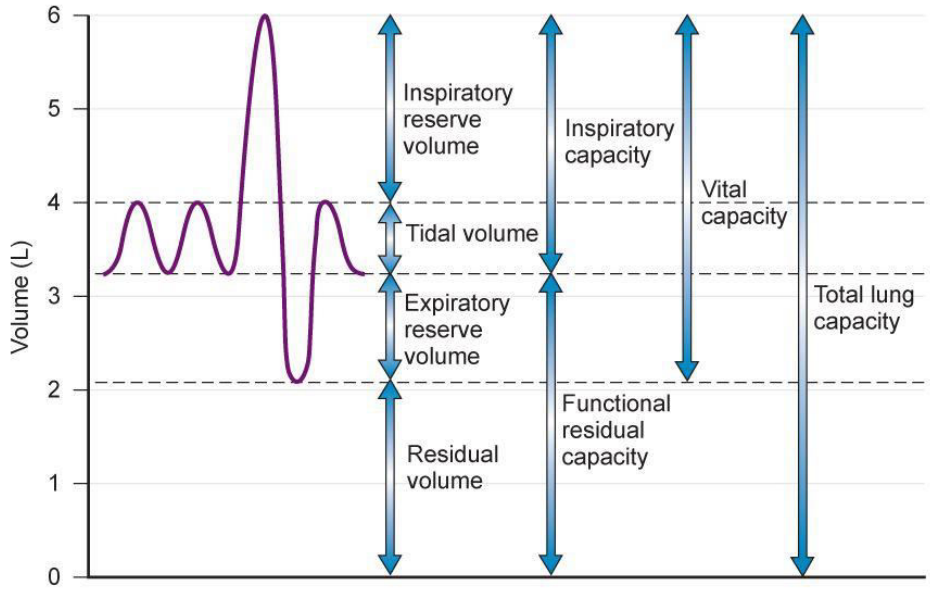
From maximal inspiration, exhale into the spirometer as fast and completely as possible.

Allows us to measure:

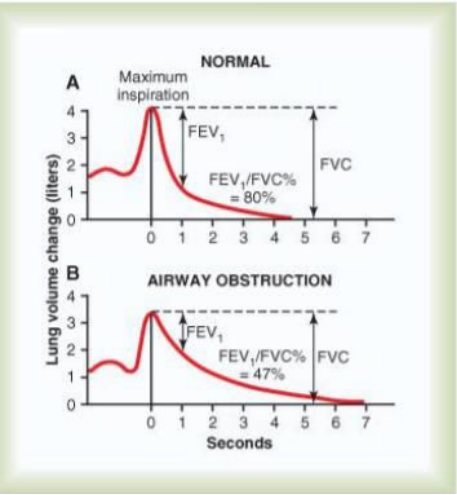
Forced Vital Capacity: The total air a patient can move.

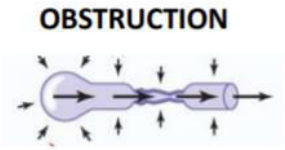
FEV1: Forced expiratory volume in one second; the amount of air a patient can exhale in one second.

Typical Spirogram;



Diagnosis using Spirometry. Spirometry = measure the degree of obstruction.





FOR COPD.

Using a standard spirograph comparison*; based on the patients age/weight/race etc*, we compare that to us.

Ratio of FEV1 to FVC is approx. 80%.

In an obstruction: FEV1/FVC = less than 70%.

Depending on their FEV1, we can determine the severity of the obstruction.

This is because when there is an obstruction, air can enter, but cannot leave the alveolus.

For Asthma

We see if this obstruction is reversible. We do this by using an agent to open the lungs, and repeating the test. If the improvement is 12% or 200 mL or higher, then it is asthma.

To ensure accurate diagnosis, it is important for the patient to not take any bronchodilating medicines within 24 hours of the test. Ideally, we should test the patient while they are not being medicated; to prevent under-diagnosis or over-treating.

Peak Flow Meter. = Monitor progression.

Patients can be provided a peak flow meter and peak flow diary.

The doctor specifies a green, yellow and red zone of Peak Flow Rate (dependent on the person's age, weight, size, etc.). The doctor has a table that will specify ideal peak flow rates for the patient's demography.

When using a peak flow meter, the test is done three times, and the highest value is used

Respiratory Therapy.

The distinction between

Long Term Treatment: Drugs used for the management of *chronic* but *stable* disease.

and

Short Term Treatment: Management of *acute situations.* E.g. in an asthma attack, or a COPD patient with a cold that aggravates the obstruction.

Is crucial.

Relievers: Bronchodilators that are short acting; drugs that open the airways to allow for easier breathing.

Preventers: Anti-inflammatory agents or long-acting bronchodilators that will prevent or help prevent an aggravation of the disease.

Some medicines have both bronchodilatory **and** anti-inflammatory effects.

Bronchodilators.

These drugs increase the airway calibre.

They relax airway smooth muscles.

Can be

(Always know which is for Asthma only, which is for COPD only, and which is for both.)

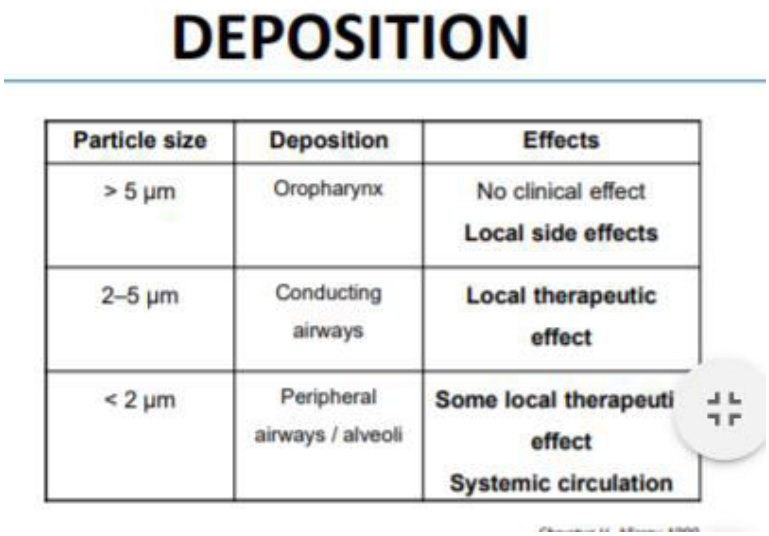
- Sympathomimetics
- Antimuscarinics
- *Methylxanthines: these are both relievers and preventers.*

Routes of Administration.

Can be inhaled, enteral or parenteral.

e.g. Salbutamol solution, salbutamol pMDIs.

IV Routes used in extreme acute exacerbations.



Preventers

Mainly anti-inflammatory agents:

- Methylxanthines e.g. Theophylline
- Corticosteroids e.g. Beclomethasone
- Leukotriene antagonists e.g. Monteleukast, Zilueton (Inhibitor of production by Lipoxygenase)
- Inhibitors of mast cell degranulation e.g. Cromoglycate
- Omalizumab (Anti IgE MAB.)
- Phosphodiesterase type-4 inhibitors (e.g. Roflumilast)
- Anti Interleukin antibodies e.g. Mepolizumab, Benralizumab

2. PHU33110 Drug Delivery by Inhalation

Pharmaceutical Aerosols.

In order to be presented to the respiratory system by inhalation; a drug must be introduced to the lung as a pharmaceutical aerosol.

An aerosol is a 2-phase system consisting of a gaseous continuous phase (usually air) and a discontinuous phase of individual particles/droplets. The disperse phase can consist of solid particles or liquid droplets.

Aerosols can be used for local delivery, or to achieve systemic delivery.

Local:

- Topical delivery.
- Oral inhalations that work *in* the respiratory tract. E.g. Bronchodilators
- Nasal inhalations to have an effect in the nasal passages e.g. nasal decongestants.

Systemic Delivery

- Glyceryl Trinitrate sublingual spray → Absorbed through mucosa under tongue.
- Salmon Calcitonin → Nasal Spray (For osteoporosis.)
- Desmopressin → Nasal Spray (For Diabetes Insipidus.)
- Insulin (Exubera [discontinued]/Afrezza) DPI
- Levodopa (Inbrija) [EMA Approved 2019.] DPI.

Benefits of Systemic delivery via inhalation: The lungs have a huge surface area, particularly in the alveoli. If a drug can reach this deep into the lungs, it will have approx. 100 m^2 available for absorption.

Aerosol generation/Aerosol devices.

Aerosols can be generated by different mechanisms.

The pressurised aerosol is the most widely used aerosol system for medicinal products (particularly for orally inhaled drugs.)

Therapeutic aerosols can also be generated from aqueous systems (nebulisers) and dry powder inhaler (DPI) devices.

pMDIs ➔ Require a propellant.
DPIs ➔ Flow aid may be needed.
Nebulisers ➔ Require the nebulising equipment.

Powder systems: Dry Powder Inhalers.

For **all inhaled systems;** the API aerodynamic particle size is *critical*!

It requires an "aerodynamic particle diameter" of 0.5 to 5 micrometres. The aerodynamic particle diameter is **not** the same as it's geometric size; the aerodynamic size takes into account the way the particle behaves in an airstream. It equates this behaviour, to the size. A geometrically large particle may be very low density. In an inhaled airstream, they will be more easily carried, and so they

behave like smaller particles. As such, their aerodynamic particle diameter may be much smaller than their geometric size.

If particles are too large – they will impact with the back of the throat and be swallowed, and not reach the respiratory tract.

If particles are too small- they won't deposit in the lungs; they have insufficient inertia, don't settle and so are exhaled upon exhalation.

Methods for Micronising Powders:

- Milling: Fluid Energy Mill
- Evaporation: Spray drying (often results in amorphous material.) Amorphous = more hygroscopic. More sticky. More aggregating. Can be bad, because it ruins the aerodynamics of particles.
- Controlled precipitation/crystallisation (harder to control fully.).

After we get tiny powders: we need to keep them that way.

Tiny powders = high surface area = high surface free energy = high tendency to stick together; disrupting flow.

Dry Powder Inhalation formulation.

Drugs delivered by DPIs may be formulated as pure drug, such as the Pulmicort Budesonide turbohaler. These particles are agitated in such a way during processing, that they form "spheroids". Tiny particles aggregate in almost perfectly shaped spheres. Upon inhalation through the device, the spheres break, and the particles release individually allowing for their inhalations.

This spheroid technology isn't possible for all drugs; they must be quite hydrophobic so that their cohesive forces don't stick them together and allow them to dissociate upon force of inhalation.

More commonly, a drug is mixed with an inactive excipient; a carrier or flow-aid.

Flow Aids:

Alpha-lactose monohydrate.

These are larger particles.

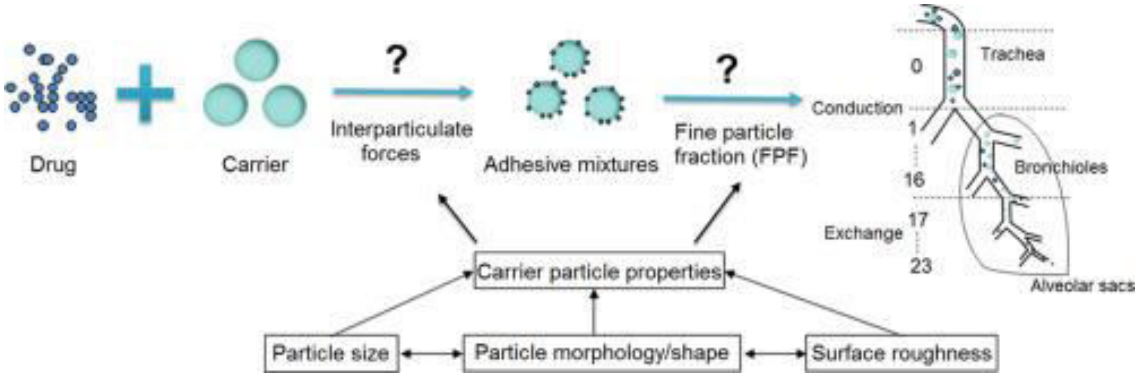
The drug particles preferentially adhere to the flow-aid particle, in a weak way.

Upon inhalation, the drug and carrier particles separate due to different movement and deposition characteristics. Drug particles are inhaled and the carrier particle impacts with the throat and is swallowed.

Weight ratio of carrier to drug is typically 100:1 to 50:1.

Sometimes, a fine fraction of lactose will be mixed with coarse lactose carrier particles. This fine lactose will occupy the highest energy sites on the carrier; to prevent strong adhesion that would prevent detachment of the active.

i.e. The fine fraction "smooths" the surface of the coarse carrier, to allow for easier detachment.



Factors affecting drug-carrier adhesion.

- Surface properties of drug and carrier.
- Rugosity = coarseness. Reduced by using the fine particle fraction.
- Drug carrier ratio.
- Particle size of components.
- Relative humidity: adsorbed moisture may produce liquid bridges that reduces detachment.
- Electrostatic forces can also reduce the detachment from drug and carrier.

The downside of using a flow aid; it increases the amount of powder that a patient has to inhale to get a dose.

There is (obviously) a maximum amount of powder one person can inhale in a breath, e.g. 10-30 mg. If we try to inhale more than this, it can cause irritation, pain, bronchoconstriction; bad.

Therefore, in order to increase the dose of a drug we can give, by removing the need for a carrier, we can use some new upcoming pharmaceutical technology, such as *pulmosphere technology.*

Pulmosphere.

Spray drying of an emulsion of *perfluorooctyl bromide (Perflubron)* and *Distearoylphosphatidylcholine,* a natural surfactant found in the lung. The active ingredient is dissolved in the water phase.

The aqueous phase evaporates first upon spray drying, and the active begins to precipitate out.

The oil makes it way to the interface between oil and water.

As the oil begins to evaporate later, the oil “blow holes” into the solid particles; producing super porous particles of API.

Super porous = reduces opportunity for surface-surface action is reduced = less cohesion. (More pores = less chance for a surface and a surface to come together.) = Better flow and better dispersability.