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Respiratory Physiology II

The process of respiration

By the perioperativeCPD team

This module covers the physiological process of respiration, of which breathing is only the first stage. The ultimate function of the respiratory system is gas exchange which consists of supplying the body's tissues with oxygen and removing carbon dioxide, the waste product.

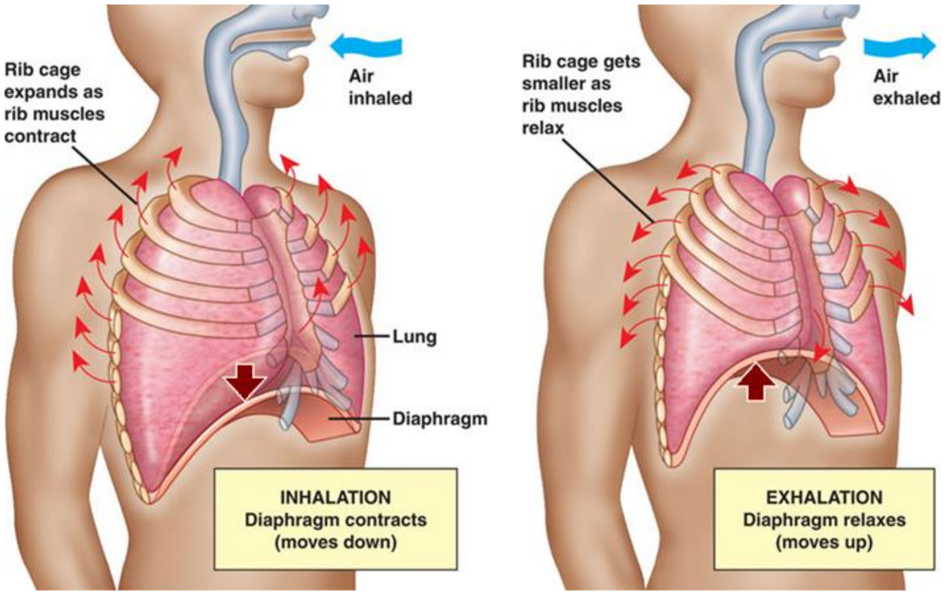
There are four key elements to this process:

1. **Pulmonary ventilation**, inhalation and exhalation or breathing
2. **External respiration**, where gases are exchanged between the lungs and the bloodstream
3. **Internal respiration,** where gases are exchanged between the bloodstream and body's tissues
4. **Transport of gases in the blood** (oxygen and carbon dioxide)

Also covered are the control of respiration, the effects of anaesthetics on respiration and normal lung volumes and capacities.

1. Pulmonary ventilation

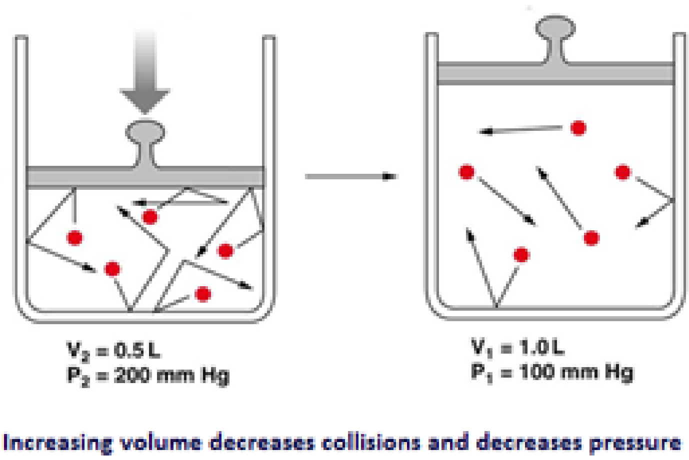
Pulmonary ventilation or breathing involves two stages, inspiration during which atmospheric air is drawn into the lungs and expiration, in which the alveolar air is forced out. Inspiration occurs if the pressure within the lungs is less than atmospheric pressure, i.e., there is a negative pressure in the lungs. Similarly, expiration takes place when the pressure in the lungs is higher than the atmospheric pressure.



As the lungs themselves have no muscle tissue, the ribcage and diaphragm control the lungs expansion and contraction. Inspiration is initiated by the contraction of diaphragm, which moves down, increasing the volume of thoracic cavity. The diaphragm moves from 1cm to 10cm depending on whether there is normal or heavy breathing and contributes most of the volume of a normal breath. Simultaneously, the contraction of external intercostal muscles lifts the ribs up and out further increasing in the volume of the thoracic cavity.

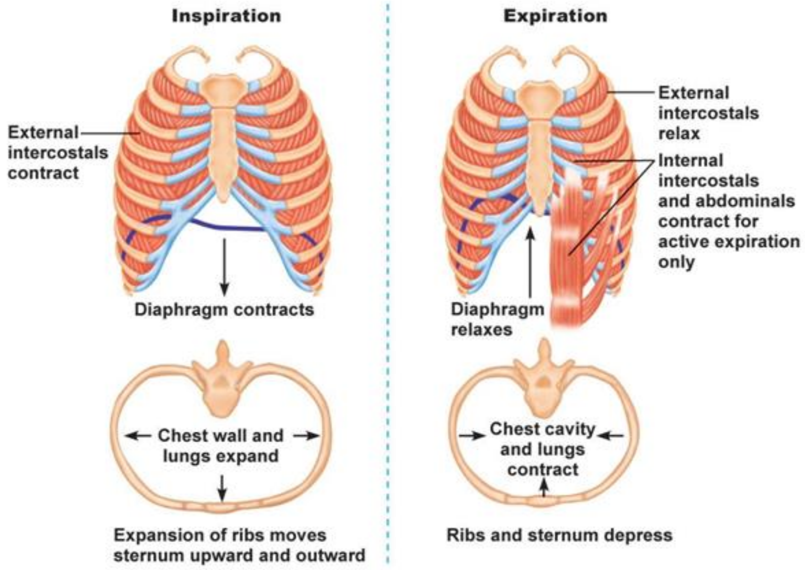
The overall increase in the thoracic volume causes a similar increase in pulmonary or lung volume. This increase in lung volume decreases the pressure in the lungs to less than the atmospheric pressure which results in air being drawn into the lungs i.e. inspiration. The drop in pressure due to increased volume is explained by Boyle's Law.

Boyle's law (see below) states that the pressure of a gas in a closed container is inversely proportional to the volume of the container. If the volume of the container increases, the pressure of the gases decreases proportionally.



Boyle's Law

Relaxation of the diaphragm and the inter-costal muscles returns the diaphragm and ribs to their normal positions and reduces the thoracic volume and thus the lung volume. This leads to an increase in lung pressure to above atmospheric pressure causing the expulsion of air from the lungs, i.e. expiration. During active expiration, when breathing becomes laboured, the abdominal and internal intercostal muscles become involved to help expel the air.

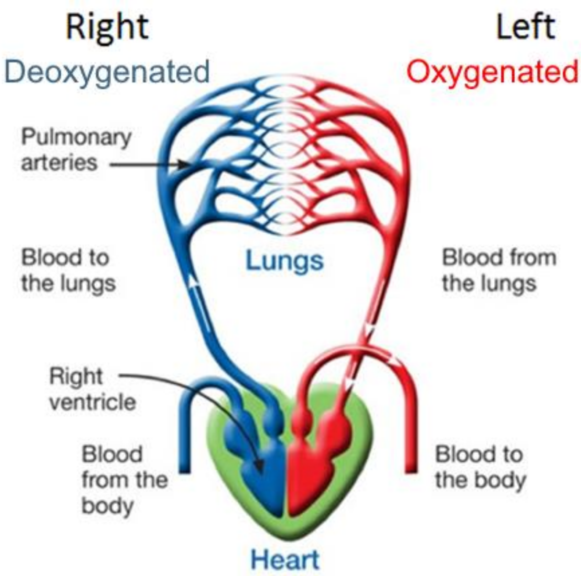


The muscles of breathing

The connective tissue and elasticity of the lungs also causes them recoil to their smallest possible size. The surface tension in the alveoli creates a pull which causes the bronchioles and the alveolar ducts to recoil. Surfactant, a detergent-like complex secreted by certain alveolar cells, reduces surface tension and helps keep the alveoli from totally collapsing.

2. External respiration

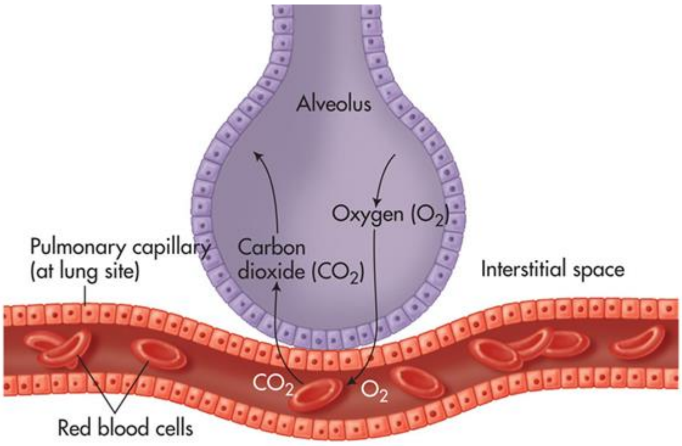
External respiration is the exchange of gases between the alveoli in the lungs and the blood by diffusion. As seen below, deoxygenated blood enters the lungs from the right side of the heart. Oxygenated blood then leaves the lungs to enter the left side of the heart where it is then pumped around the body to the tissues and cells.



Blood supplies to the lungs

The transfer of oxygen from the alveoli into the pulmonary blood supply happens because the concentration, or more correctly partial pressure, of oxygen in venous blood is lower than that in lungs. Because of the pressure gradient oxygen will move from an area of high partial pressure to an area of low partial pressure. In this case, moving from the alveoli across the alveolar wall and into the pulmonary capillaries (see below) where it is picked up and transported by haemoglobin in the red blood cells. There is a lower partial pressure of oxygen within the pulmonary blood supply than in the alveoli because much of the oxygen has been used up by the body's tissues in the creation of energy (cellular respiration).

Note: The partial pressures of gases are governed by Dalton's Law. There are more details on partial pressures and Dalton's Law at the end of the module.

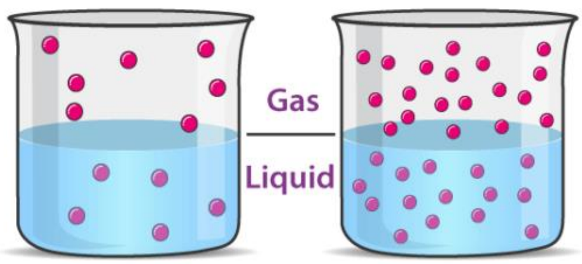


External respiration at the lungs

Conversely, the partial pressure of carbon dioxide in the deoxygenated blood coming back from the tissues is higher than of the air in the alveoli. Remember carbon dioxide (CO2) is a waste product produced by the cells and principally expelled by the body through the lungs.

Again, because of the pressure gradient created, carbon dioxide will therefore move from an area of high partial pressure to an area of low partial pressure. So the carbon dioxide moves from the pulmonary capillaries into the alveoli and is then exhaled.

This movement is governed by Henry's Law. Henry's law describes the behaviour of gases when they come into contact with a liquid, such as blood. Henry's law states that the concentration of gas in a liquid is directly proportional to the solubility and partial pressure of that gas. The greater the partial pressure of the gas, the greater the number of gas molecules that will dissolve in the liquid. The concentration of the gas in a liquid is also dependent on the solubility of the gas in the liquid. For example, although nitrogen is present in the atmosphere, very little nitrogen dissolves into the blood, because the solubility of nitrogen in blood is very low.



Henry's Law

How fast gases diffuse across alveoli membrane into the pulmonary capillaries depends on several factors:

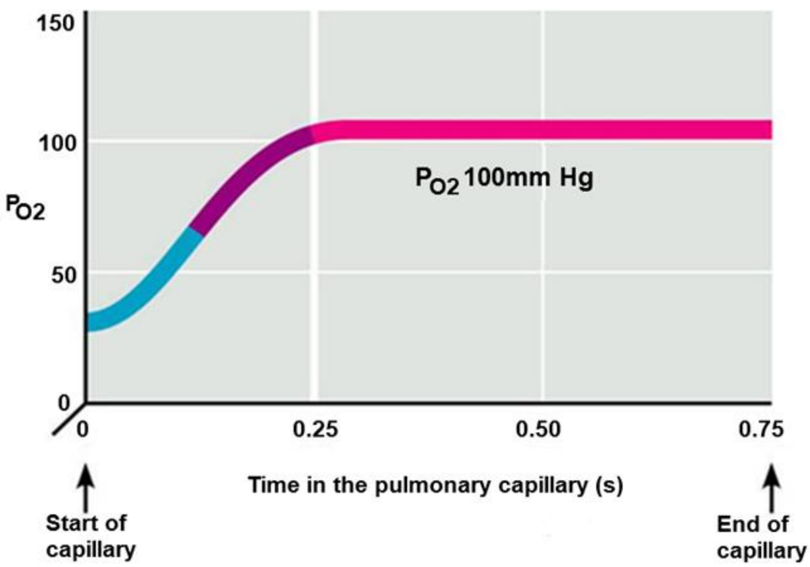
1. The rate of diffusion across any membrane is directly proportional to its surface area. The surface area of the lungs is approximately 70 m^2 (half a tennis court), which provides a large area over which the gas can exchange. If this is surface area is reduced then gas exchange becomes more difficult. An example of a condition which could cause this would be emphysema where the alveoli walls disintegrate and the surface area of the lung is therefore reduced.

2. The thickness of the membrane is also crucial. The thicker the membrane the harder it is for the gas to diffuse across it. This is why the total thickness of the alveoli membranes is only about 0.002 mm (a human hair is 0.075 millimetres wide). Anything which increases this distance will also make gas exchange more difficult. So for example a build-up of fluid or lung secretions as in a severe pneumonia will worsen the gas exchange.

3. The difference in partial pressures between the gases will also affect how fast diffusion can take place.

- The partial pressure of oxygen (PO_2) of venous blood is ~40 mmHg
- The partial pressure of oxygen (PO_2) in the alveoli is ~100 mmHg

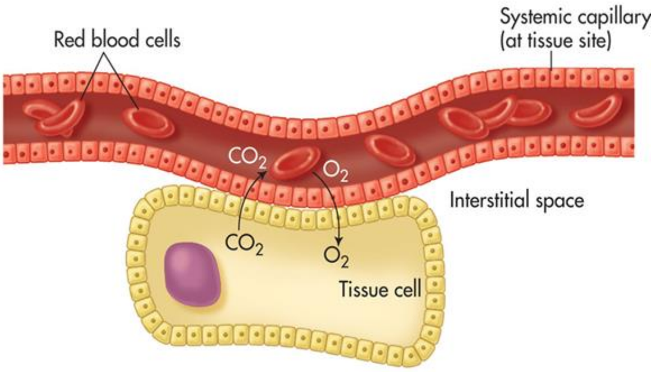
The large pressure difference or gradient allows oxygen to diffuse across rapidly and quickly reach equilibrium (0.25sec) therefore blood can move quickly through the pulmonary capillaries and still be adequately oxygenated (see below).



If the partial pressure of alveoli oxygen is reduced, when for example one goes to a higher altitude, then the rate of gas exchange will slow down giving the typical symptoms of high altitude sickness caused by the low partial pressure of oxygen in the blood.

3. Internal respiration

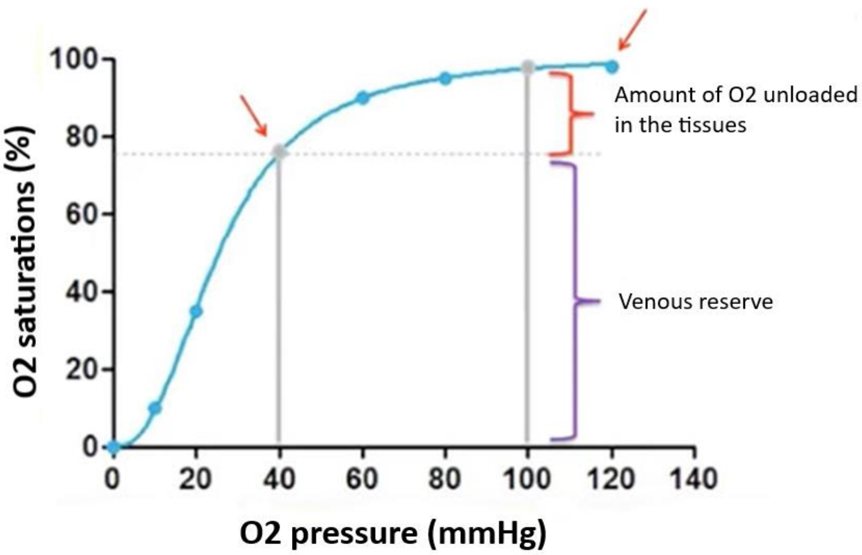
Internal respiration is gas exchange that occurs at the level of body tissues. Similar to external respiration, internal respiration also occurs as simple diffusion due to a partial pressure gradient. However, the partial pressure gradients are opposite of those present at the lungs. The partial pressure of oxygen in tissues is low, about 40 mm Hg, because oxygen is continuously used by the cells. In contrast, the partial pressure of oxygen in arterial blood is about 100 mm Hg. This creates a pressure gradient that causes oxygen to dissociate from haemoglobin, diffuse out of the blood, cross the interstitial space, and enter the tissue.



Internal respiration at the cells

Remember that cells continuously produce carbon dioxide, as the partial pressure of carbon dioxide is lower in the blood than it is in the tissues, this causes carbon dioxide to diffuse out of the tissue, cross the interstitial space, and enter the blood. It is then carried back to the lungs either bound to haemoglobin, dissolved in plasma, or in a converted form. By the time blood returns to the heart, the partial pressure of oxygen has reduced to about 40 mm Hg, and the partial pressure of carbon dioxide has risen to about 45 mm Hg. The blood is then pumped back to the lungs to be oxygenated once again during external respiration.

This means that the O2 levels of venous blood are lower than that of arterial blood and the haemoglobin in the red blood cells contains less oxygen, although still about 75-80% saturated, which gives a significant "reserve capacity" in the oxygen delivery system.



Oxygen disassociation curve

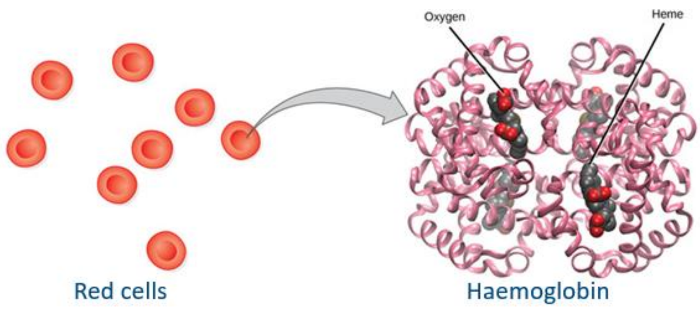
4. Transport of gases in the Blood

The function of respiration is to provide oxygen for use by the body cells and to eliminate carbon dioxide, a waste product, from the body. In order for the exchange of oxygen and carbon dioxide to occur, both gases must be transported between the lungs and the tissues and although carbon dioxide is more soluble than oxygen in blood, both gases require a specialised system for the transport of the majority of the gas molecules.

The transport of oxygen in the blood

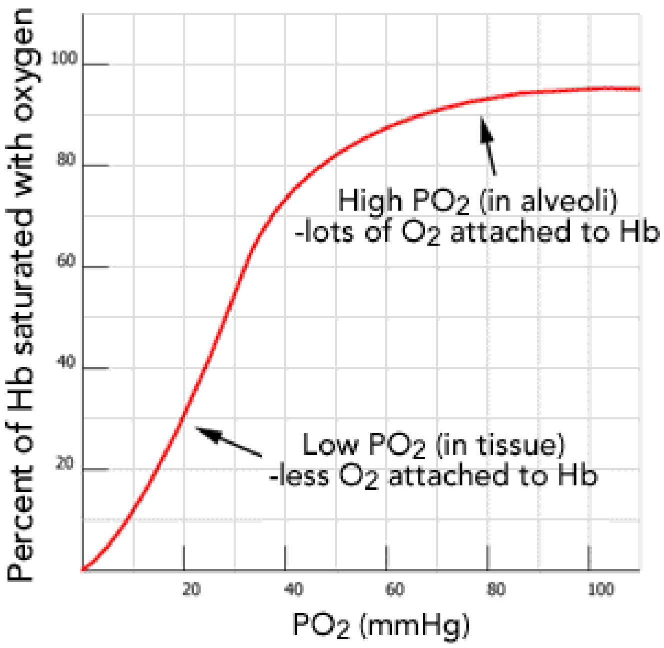
Although oxygen dissolves in blood, only a small amount of oxygen is transported this way. Only 1.5 percent of oxygen in the blood is dissolved directly into the blood itself. Most oxygen, 98.5 percent, is bound to and carried to the tissues by a protein called haemoglobin.

Haemoglobin, or Hb, is found in red blood cells (erythrocytes) and is made of four subunits. Each subunit (heme group) binds one oxygen molecule, allowing each haemoglobin molecule to bind four oxygen molecules.



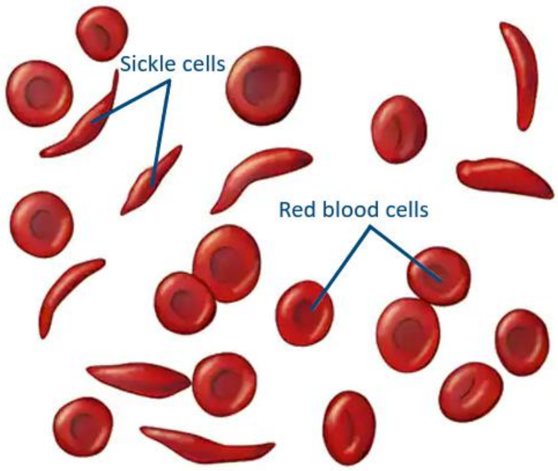
It is easier to bind a second and third oxygen molecule to Hb than the first molecule. This is because the haemoglobin molecule changes its shape, or conformation, as oxygen binds. The fourth oxygen is then more difficult to bind.

The binding of oxygen to haemoglobin can be plotted as a function of the partial pressure of oxygen in the blood (x-axis) versus the relative Hb-oxygen saturation (y-axis). The resulting graph, an oxygen dissociation curve, is sigmoidal, or S-shaped. As the partial pressure of oxygen increases, the haemoglobin becomes increasingly saturated with oxygen.



Factors That Affect Oxygen Binding

The oxygen-carrying capacity of haemoglobin determines how much oxygen is carried in the blood. In addition, diseases (sickle cell anaemia) can also affect oxygen-carrying capacity and delivery; the same is true for changes in the bodies carbon dioxide levels, blood pH, and body temperature.



Sickle cells

Sickle cell anaemia is an inherited red blood cell disorder in which there aren't enough healthy red blood cells to carry oxygen throughout your body. In sickle cell anaemia, the red blood cells are shaped like sickles or crescent moons.

Any increases in carbon dioxide and subsequent decrease in pH reduce the affinity of haemoglobin for oxygen. Therefore, more oxygen is needed to reach the same haemoglobin saturation level as when the pH was higher. A similar shift also results from an increase in body temperature. Increased temperature, such as from increased activity of skeletal muscle, causes the affinity of haemoglobin for oxygen to be reduced.

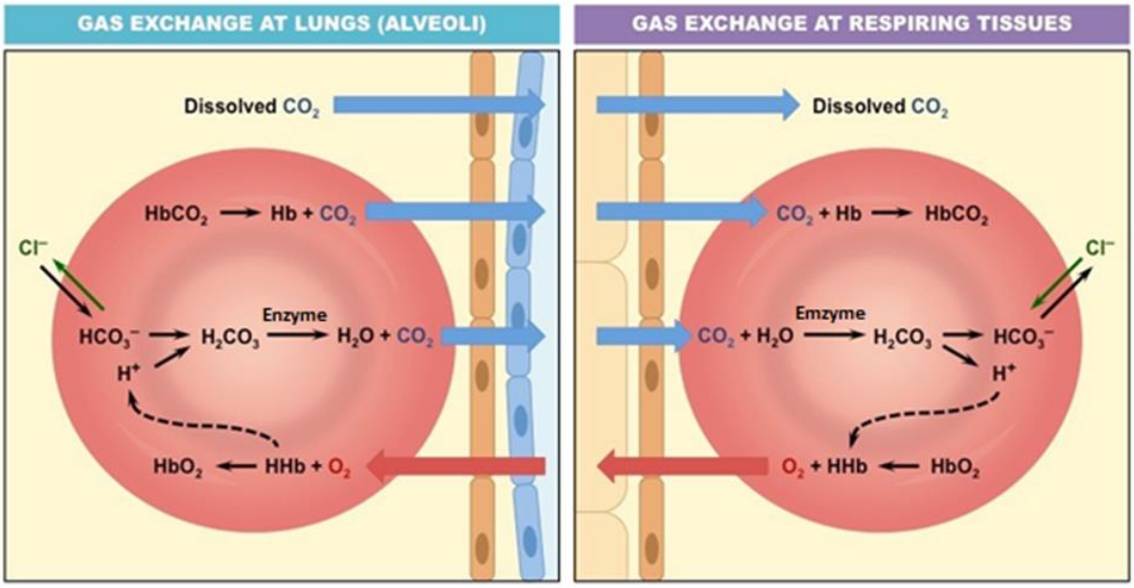
Transport of Carbon Dioxide in the Blood

Carbon dioxide molecules are transported in the blood from body tissues to the lungs by one of three methods:

1. Dissolution directly into the blood
2. Binding to haemoglobin
3. Carried as a bicarbonate ion

Several properties of carbon dioxide in the blood affect its transport. Firstly, carbon dioxide is more soluble in blood than is oxygen. About 5 to 7 percent of all carbon dioxide is dissolved and carried in the plasma. Secondly, carbon dioxide can bind to plasma proteins or can enter red blood cells and bind to haemoglobin. This form transports about 10 percent of the carbon dioxide. Binding of carbon dioxide to haemoglobin is reversible. Therefore, when it reaches the lungs, the carbon dioxide can freely dissociate from the haemoglobin and be expelled from the body.

Thirdly, the majority of carbon dioxide molecules (approx. 85 percent) are carried as part of the bicarbonate buffer system. In this system, carbon dioxide diffuses into the red blood cells. Enzymes within the red blood cells quickly convert the carbon dioxide to carbonic acid which breaks down into into bicarbonate ions ($HCO3^-$) and hydrogen (H^+) ions. Since carbon dioxide is quickly converted into bicarbonate ions, this reaction allows for the continued uptake of carbon dioxide into the blood, down its concentration gradient. It also results in the production of H^+ ions which also binds to the haemoglobin, limiting shifts in pH.



The newly-synthesised bicarbonate ion is transported out of the red blood cell into the liquid component of the blood in exchange for a chloride ion (Cl-); this is called the chloride shift. When the blood reaches the lungs, the bicarbonate ion is transported back into the red blood cell in a reverse exchange for the chloride ion. The H+ ion dissociates from the haemoglobin and binds to the bicarbonate ion which is converted back via carbonic acid into carbon dioxide again through enzymatic action. The carbon dioxide produced is expelled through the lungs during exhalation.

The main implication of this process is that the pH of blood becomes a way of determining the amount of carbon dioxide in blood. This is because if carbon dioxide increases in the body, it will manifest as increased concentrations of bicarbonate and increased concentrations of hydrogen ions will reduce blood pH and make the blood more acidic.

Conversely, if carbon dioxide levels are reduced, there will be less bicarbonate and less hydrogen ions dissolved in the blood, so pH will increase and blood will become more basic or alkaline. Bicarbonate ions act as a buffer for the pH of blood so that blood pH will be neutral as long as bicarbonate and hydrogen ions are balanced.

This connection explains how ventilation rate and blood chemistry are related, as hyperventilation will cause alkalosis, and hypoventilation will cause acidosis, due to the changes in carbon dioxide levels that they cause.

The presence of this bicarbonate buffer system also allows for people to travel and live at high altitudes. When the partial pressure of oxygen and carbon dioxide change at high altitudes, the bicarbonate buffer system adjusts to regulate carbon dioxide while maintaining the correct pH in the body.

Carbon Monoxide Poisoning

While carbon dioxide can readily associate and dissociate from haemoglobin, other molecules, such as carbon monoxide (CO), cannot. Carbon monoxide has a greater affinity for haemoglobin than does oxygen. Therefore, when carbon monoxide is present, it binds to haemoglobin preferentially over oxygen. As a result, oxygen cannot bind to haemoglobin, so very little oxygen is transported throughout the body. Carbon monoxide is a colourless, odourless gas which is difficult to detect. It is produced by gas-powered vehicles and tools.

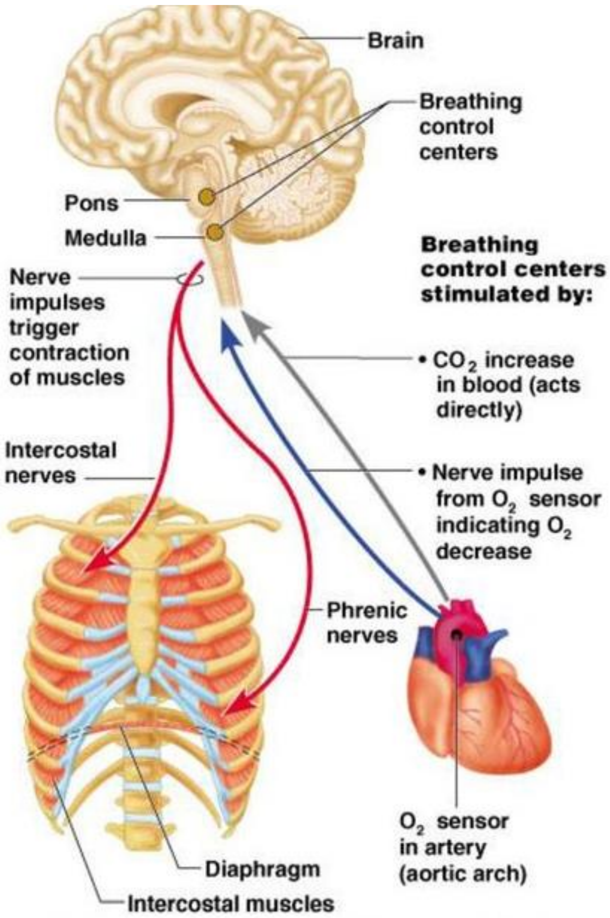
Carbon monoxide can cause headaches, confusion, and nausea; long-term exposure can cause brain damage or death. Administering 100 percent (pure) oxygen is the usual treatment for carbon monoxide poisoning as it speeds up the separation of carbon monoxide from haemoglobin.

5. Control of respiration

There are areas in the brain stem called the respiratory centres. These centres located in the medulla oblongata and the pons send messages via the phrenic and vagus nerves to the respiratory muscles to regulate the rate, rhythm and depth of breathing. This control by the autonomic nervous system involuntary and continuous. You do not have to think about it, it just happens.

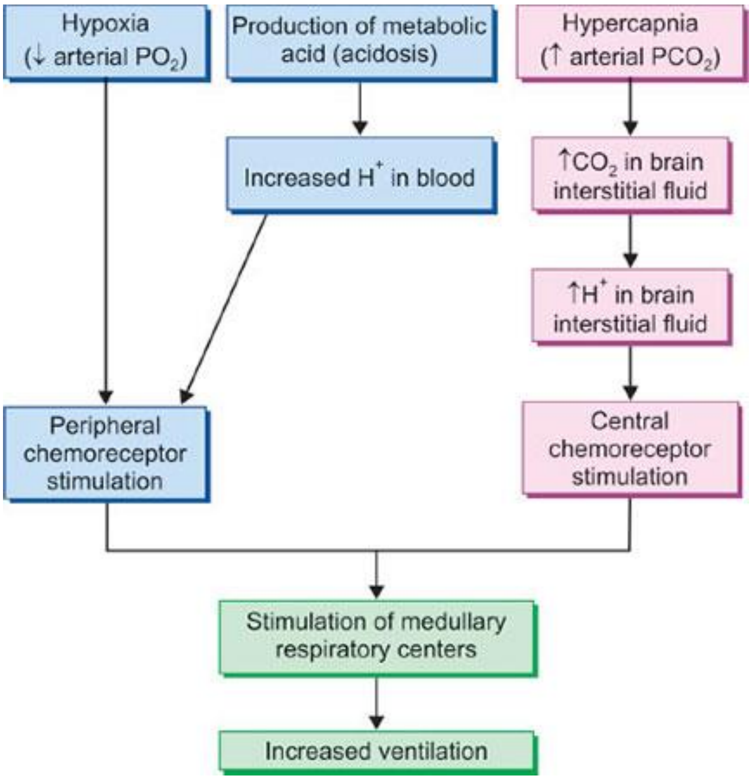
While the respiratory centres establish the basic rhythm of respiration, sometimes we need to consciously modify it. You can voluntarily alter your pattern of breathing, for example, we may need to hold our breath for when putting our head under water. This is behaviour is controlled separately by the cerebral cortex area in the brain.

The respiratory centres receive and act on inputs from chemoreceptors, both central and peripheral. Changes in carbon dioxide levels acting on the central chemoreceptors are the most important single driver of ventilation.



Control of respiration

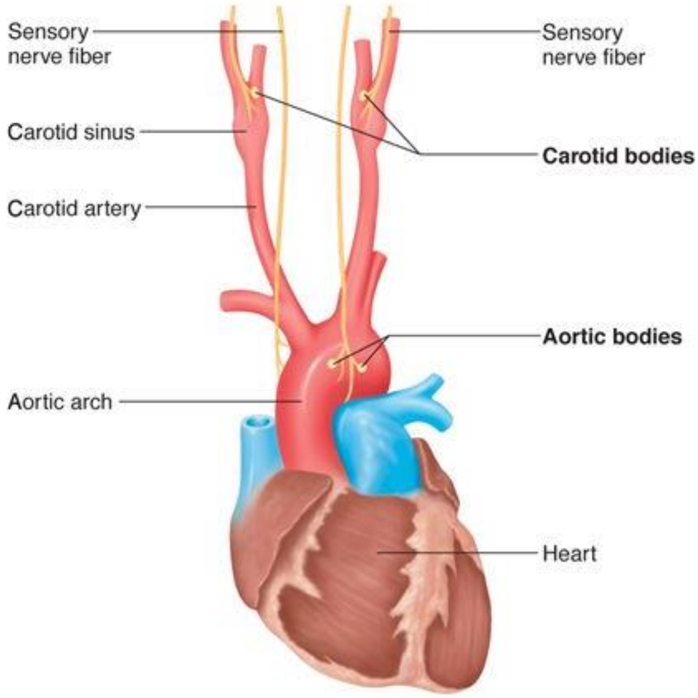
If carbon dioxide levels in the blood increase, the carbon dioxide will diffuse across the blood brain barrier into the cerebrospinal fluid (CSF) increasing the level of carbon dioxide in the CSF. Increased carbon dioxide leads to increased hydrogen ions (H^+) which stimulates the central chemoreceptors to increase the speed and depth of breathing, returning concentrations to normal resting levels. Lowered carbon dioxide and hydrogen ions causes the oppose reaction, a slowing of the respiratory rate and depth.



Control of ventilation

There are more chemoreceptors in the peripheral nervous system which are sensitive to changes in hydrogen ions, carbon dioxide and oxygen levels in the blood. These are located in the carotid (carotid sinus) and aortic bodies (aortic arch). The input from both these areas will also cause the inspiratory area to become active and the rate and depth of breathing will increase. Like the central chemoreceptors, it is mainly changes in carbon dioxide and hydrogen ion levels which stimulate these receptors. The stimulation caused by dropping oxygen levels in the arterial blood only happens at very low levels (i.e. 60 mmHg or an oxygen saturations of less than 90%).

To summarise, the most important single driver of ventilation is CO2 levels, acting on the central chemoreceptors by altering CSF pH. This alters the rate of CO2 removal and returns concentrations to normal resting levels.



Peripheral chemoreceptors

Note: COPD patients tend to have chronically elevated levels of carbon dioxide due to the nature of their illness. Because of this chronically elevated level of carbon dioxide in the chemoreceptors, is has historically been thought they become tolerant of these high levels and therefore the carbon dioxide ceases to be that person's drive to breathe. What therefore drives them to breathe is the hypoxic drive and if you give these patients too much oxygen you blunt their hypoxic drive which can lead to them retaining dangerously high levels of carbon dioxide.

The theory behind this has been disproven but the effects are still valid so it is still recommended that titrated oxygen therapy to achieve saturations of 88% to 92% is given in patients with an acute exacerbation of COPD to avoid hypoxemia and reduce the risk of oxygen-induced hypercapnia.

The effects of anaesthetics on respiration

All modern anaesthetic drugs (except ketamine and nitrous oxide) cause a dose-dependent reduction in breathing. This can be due to either a reduction in the respiratory rate (e.g., opioids), a reduction in the tidal volume (e.g., volatile anaesthetics) or both (e.g., propofol).

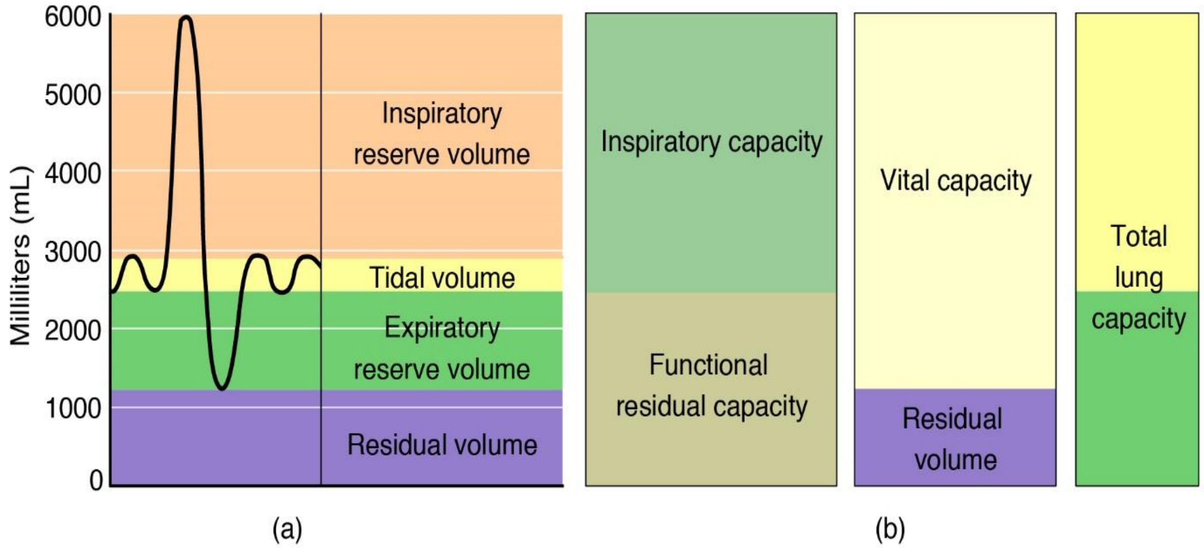
Under normal conditions the CO2 of arterial blood is the predominant factor controlling ventilation. The ventilatory response to carbon dioxide is reduced by virtually all anaesthetic drugs until excessively high concentrations are produced. As a result, anaesthetised patients become hypercapnic if their ventilation is not supported.

In addition, after a period of mechanical ventilation the threshold at which the CO2 stimulates the return of spontaneous ventilation is increased, thus delaying the return of spontaneous ventilation.

Hypercapnia causes vasodilation, tachycardia, arrhythmias, hypertension and in an awake patient, headache, confusion, tremor, sedation and eventually coma (CO2 narcosis). Of equal importance is that the increased CO2 displaces oxygen from the alveoli and this can exacerbate hypoxia. All of these effects can be seen in the postoperative period.

6. Normal Lung Volumes and Capacities

Lung volumes can be measured by an instrument known as a spirometer producing a graph called a spirogram as can be seen below. Inspiration is recorded as an upward deflection and expiration as a downward one.



Respiratory volume is the term used for various volumes of air moved by or associated with the lungs at a given point in the respiratory cycle.
There are four major types of respiratory volumes:

- tidal,
- residual,
- inspiratory reserve,
- expiratory reserve.

Tidal volume (TV)

The volume of air that is inspired in normal, quiet breathing in the healthy lung is approximately 500mls. This will vary depending on the size of the person (6-8mg/kg). This normal volume is called the tidal volume and approximately only 350mls of this actually reaches the alveoli. The rest is in those parts of the lung which do not take part in gas exchange, and is called the dead space of the lung (it is not dead, but physiologically it does not contribute to gas exchange).

Minute volume (MV) **(**not shown above but referred a lot in anaesthetics)

The total amount of air taken in during one minute can be found by multiplying the tidal volume by the number of normal breaths per minute, which is about 12 (MV=TV x RR) this will give a normal minute volume (MV) of about 6 litres.

Inspiratory reserve volume

By taking a very deep breath another 2-3 litres can be taken into the lungs. This is known as inspiratory reserve volume.

Expiratory reserve volume

Expiratory reserve volume is the air you can exhale if you do so forcibly and this volume is approximately 1.2 L.

Residual volume

Even after forced exhalation of air there is still a good volume of our remaining in the lungs which cannot be exhaled. This is known as the residual volume, and usually amounts to about 1.2 L. The residual volume makes breathing easier by preventing the alveoli from collapsing.

Functional residual capacity (FRC)

The sum of the residual volume plus the expiratory reserve volume is otherwise known as the functional residual capacity. FRC is important because it keeps small airways open. The FRC is considerably reduced in an anaesthetised patient. During general anaesthesia FRC is reduced by approximately 20%. The reduction is greater in the obese and in patients with COPD. The most likely mechanism is the loss of inspiratory muscle tone of the muscles acting on the rib cage. Also lying supine reduces the FRC.

It is this capacity that the anaesthetist tries to wash out using oxygen prior to intubation. This ensures that the anaesthetist increases the period of time to intubate the patient before they start to become hypoxic from 2-3 minutes to about 6-7 minutes.

Total lung capacity is the sum of all the volumes and amounts to approximately 6 L.

Respiratory Rates

The normal respiratory rate of a child decreases from birth to adolescence. A child under 1 year of age has a normal respiratory rate between 30 and 60 breaths per minute, but by the time a child is about 10 years old, the normal rate is closer to 18 to 30.

By adolescence, the normal respiratory rate is similar to that of adults, 12 to 18 breaths per minute.

Partial pressures

Why use partial pressures not concentrations

During this module we have presumed that we are at sea level. At sea level, atmospheric pressure is 760 mmHg; therefore, the partial pressure of oxygen would be 160 mmHg, or 760 mmHg x 0.21.

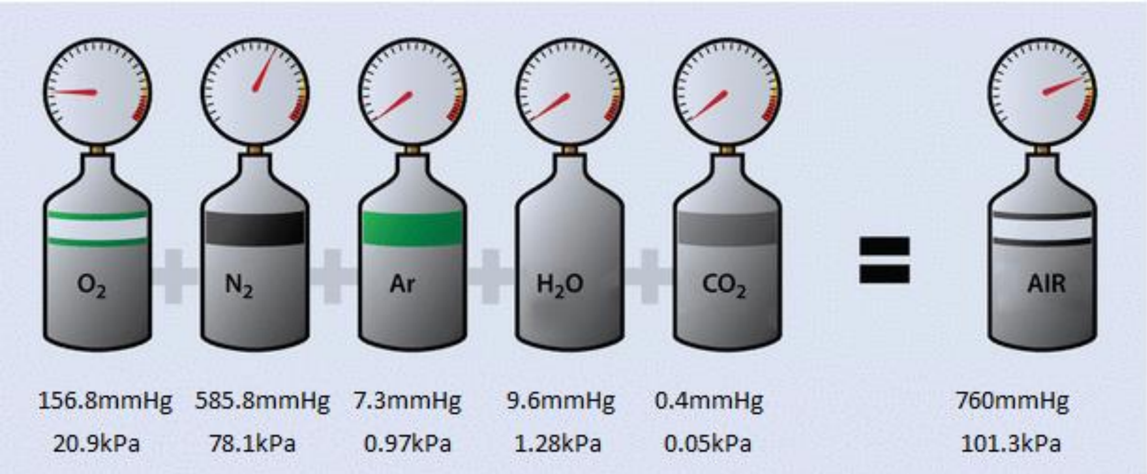
The base camp for Mount Everest is about 5000 meters above sea level, and the atmospheric pressure there is only about 400 mmHg. As the concentration of oxygen is still 21%, the partial pressure of oxygen is only 84 mmHg, or 400 mmHg x 0.21. So you see, at base camp, only 84 mmHg of pressure pushes the oxygen into our blood, compared with 160 mmHg at sea level. It is the partial pressure of a gas that drives diffusion not the concentration.

How do partial pressures work and what is Dalton's Law?

The partial pressures of gas in the atmosphere are governed by Dalton's Law.

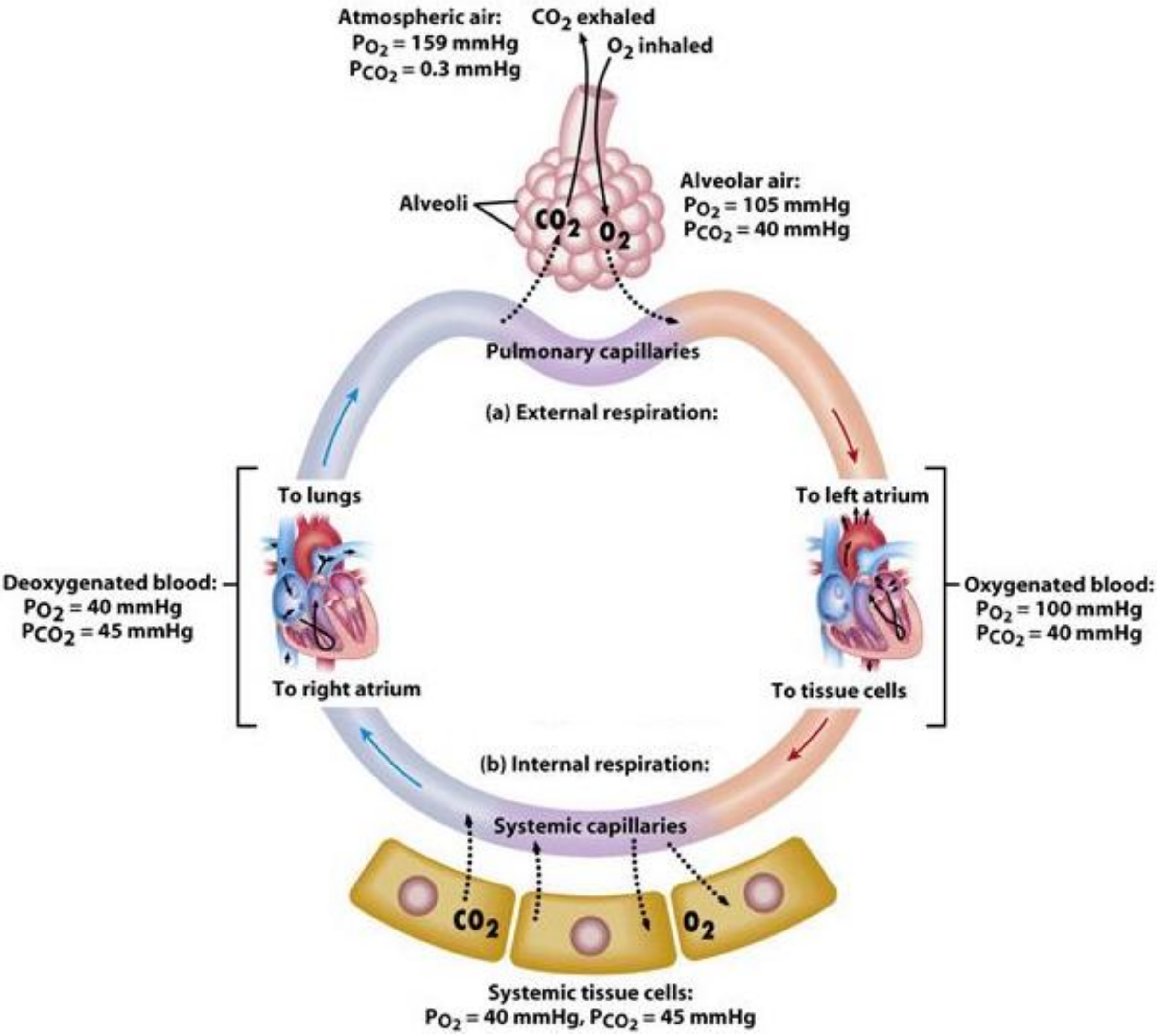
According to this law each gas in a mixture of gases exerts its own pressure as if all the other gases were not present. The pressure of a specific gas in a mixture is called its **partial pressure** and is denoted as p. Adding all the partial pressures of the gases within a mixture gives you the total pressure of the mixture.

Atmospheric air (see below) is a mixture of several gases, the main ones being oxygen, nitrogen, carbon dioxide and water vapour. So pressure of atmospheric air is the sum of the pressure of all of these gases.



Dalton's Law

What are the partial pressures in the respiratory system?



Why is the partial pressure of alveolar air less than atmospheric air?

The composition of air in the atmosphere and in the alveoli differs. In both cases, the relative concentration of gases is nitrogen > oxygen > water vapor > carbon dioxide. The amount of water vapor present in alveolar air is greater than that in atmospheric air. This is because the respiratory system works to humidify incoming air, thereby causing the air present in the alveoli to have a greater amount of water vapor than atmospheric air. In addition, alveolar air contains a greater amount of carbon dioxide and less oxygen than atmospheric air. This is no surprise, as gas exchange removes oxygen from and adds carbon dioxide to alveolar air and there is some mixing of the gases.

A lot of this book is based on:

https://openstax.org/books/anatomy-and-physiology/pages/1-introduction

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