

# Respiratory System

## The Respiratory Tract

Air enters the **nostrils**, passes through the **nasopharynx** and the **oral pharynx** into the **trachea** and the right and left **bronchi**, which branches and rebranches into **bronchioles**, each of which terminates in a cluster of **alveoli**.

Only in the alveoli does actual gas exchange takes place. There are some 300 million alveoli in two adult lungs.

The **trachea** or **windpipe** commences at the larynx and bifurcates into the bronchi allowing the passage of air to the lungs.

15 – 20 incomplete C-shaped cartilaginous rings reinforce the anterior and lateral sides of the trachea and prevent it from collapsing. The oesophagus lies posterior to the trachea.

The trachea divides into two main **bronchi**, the left and the right.

The right main bronchus subdivides into three segmental bronchi while the left main bronchus divides into two.

The segmental bronchi divide into **bronchioles**, which further divide into alveolar ducts which terminate in alveolar sacs.

The wall of most of the respiratory tract is lined with ciliated columnar epithelium cells interspersed with goblet cells which produce mucus.

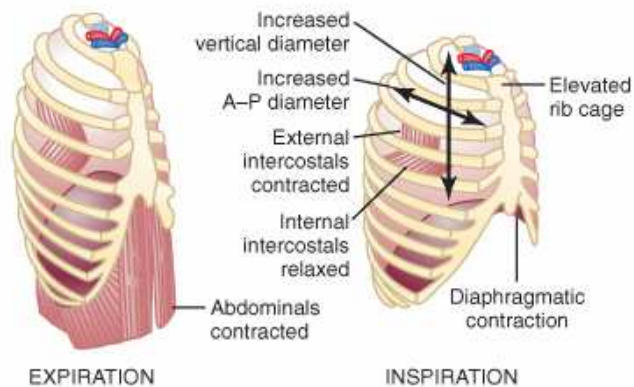
The lungs can be expanded and contracted in two ways:

- (1) by downward and upward movement of the diaphragm to lengthen or shorten the chest cavity
- (2) by elevation and depression of ribs to increase and decrease the anteroposterior diameter of the chest cavity.

Normal quiet breathing is accomplished almost entirely by movement of diaphragm. During inspiration, contraction of the diaphragm forces abdominal contents downward and the ribs outward.

During expiration, the diaphragm relaxes, and the elastic recoil of the lungs, chest wall, and abdominal structures compresses the lungs and expels the air.

During heavy breathing, however, the elastic forces are not powerful enough to cause the necessary rapid expiration, so that extra force is achieved mainly by contraction of the abdominal muscles, which pushes the abdominal contents upward against the bottom of the diaphragm, thereby compressing the lungs.



The second method for expanding the lungs is to raise the rib cage. This expands the lungs.

All the muscles that elevate the rib cage are classified as muscles of inspiration, most important among which are the external intercostals; other muscles eg. the sternocleidomastoid contract only in active inspiration.

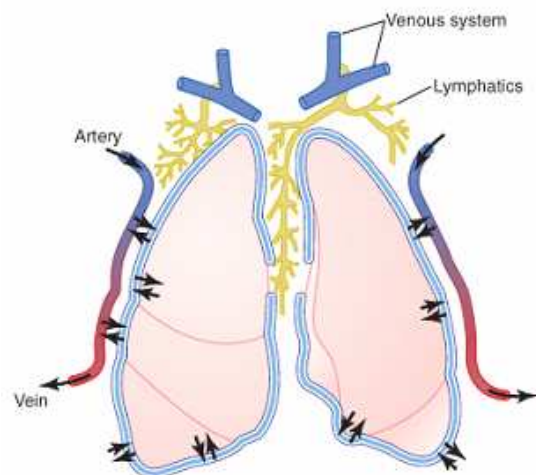
Muscles that depress the chest cage are classified as muscles of expiration – these include the internal intercostals and the abdominal recti which contract only in active expiration.

When the lungs expand and contract during normal breathing, they slide back and forth within the pleural cavity. To facilitate this, a thin layer of mucoid fluid lies between the parietal and visceral pleurae.

The total amount of fluid in each pleural cavity is only a few ml. Whenever the quantity becomes more than barely enough to begin flowing in the pleural cavity, the excess fluid is pumped away by lymphatic vessels.

A negative force is required on the outside of the lungs to keep the lungs expanded; this is provided by negative pressure in pleural space.

The normal collapse tendency of the lungs is about -4 mm Hg. The pleural fluid pressure must always be at least as negative as -4 mm Hg (usually it is around -7 mm Hg) to keep the lungs expanded.



**Lungs and the pleural cavity**

The expanding lung is broadly subdivided into  
the root zone (non expandable – bronchii, pulmonary vessels, lymphatics)  
the intermediate zone (varying elasticity – vascular and bronchial branches radiating outward)  
the subpleural zone (outermost zone of maximum distensibility– the alveolar zone)

The extent to which the lungs will expand for each unit increase in transpulmonary pressure is called the **lung compliance**. Compliance is given by

$$C = \Delta V / \Delta P$$

The total compliance of both lungs together in a normal adult averages about 200 ml of air per cm of water transpulmonary pressure.

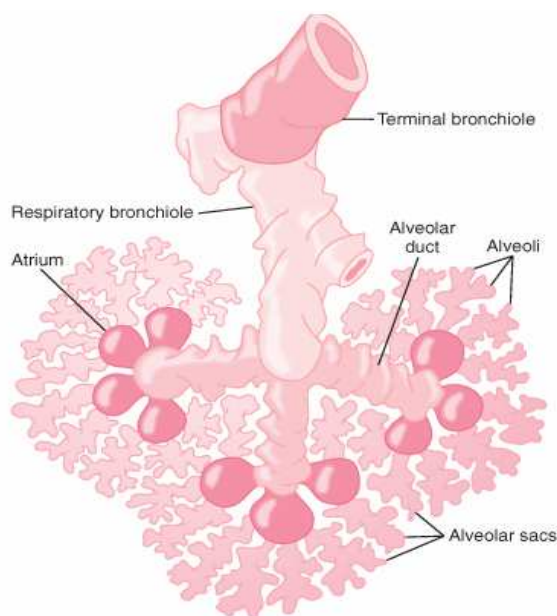
## The Alveoli

The respiratory unit (also called "respiratory lobule") is composed of a respiratory bronchiole, alveolar ducts, and alveoli.

There are over 700 million alveoli present in the human lungs giving a total area of 70 - 90 m<sup>2</sup>.

The wall of each alveolus is about 0.1 µm thick. On the outside is a dense network of blood capillaries which originate from the pulmonary artery and rejoin to form the pulmonary vein.

The alveoli are lined principally by moist squamous epithelium (type I cells) and the larger more sparsely distributed type II cells which secrete pulmonary surfactant.



The respiratory lobule

The principal pulmonary surfactant is dipalmitoyl phosphatidyl choline (DPPC). Pulmonary surfactants increase compliance by decreasing the surface tension of the fluid layer lining the alveolus. This reduces the effort required to breathe in and inflate the lungs during inspiration and prevents the alveoli from collapsing during expiration.

Infant respiratory distress syndrome (IRDS), also called "respiratory distress syndrome" is caused in premature infants by deficiency of surfactant; as a result the alveoli collapse after each expiration and much greater effort is required to inflate them.

## Lung volumes

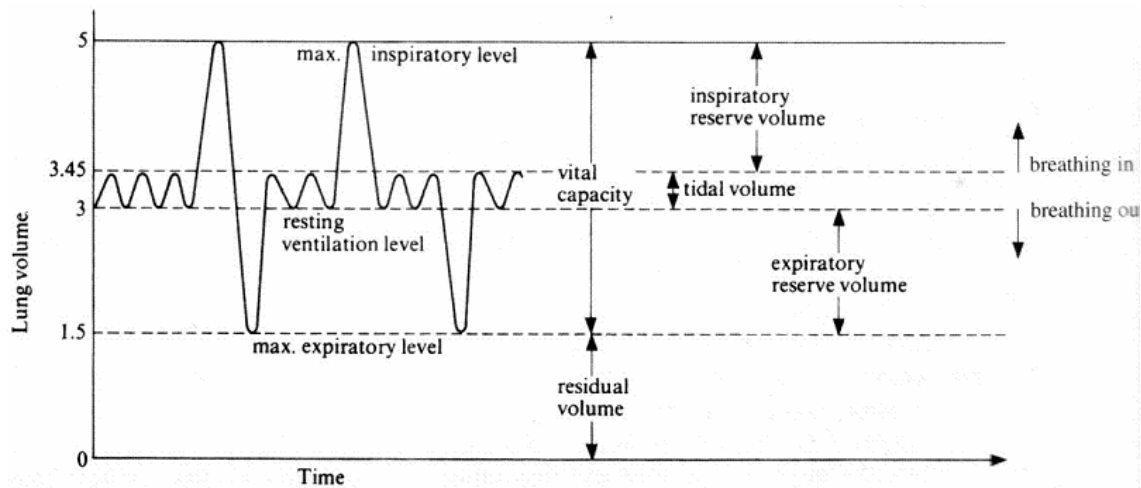
The volume of gas exchanged during normal respiration during one breath in or out is called the **tidal volume (TV)**. During normal breathing it is about 450 – 500 cm<sup>3</sup>.

The amount of additional air that can be inhaled after a normal tidal breath in is termed the **inspiratory reserve volume (IRV)** – it is about 1500 - 2500 cm<sup>3</sup> in a normal adult.

The amount of additional air that can be exhaled after a normal tidal breath out is termed the **expiratory reserve volume (ERV)** – it is about 1500 cm<sup>3</sup> in a normal adult.

**Vital capacity (VC)** is the maximum amount of air that a person can expel from the lungs after first filling the lungs to their maximum extent. It is equivalent to the inspiratory reserve volume (IRV) plus the tidal volume (TV) plus the expiratory reserve volume (ERV) ie.  $VC = IRV + TV + ERV$ .

The amount of air left in the lungs after a maximal exhalation is termed the **residual volume (RV)**. This cannot be expelled and is about 1500 cm<sup>3</sup>.



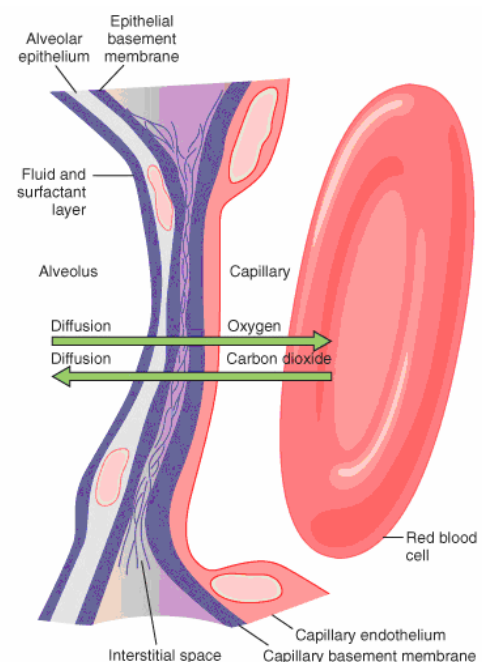
**Dead space** air is air that is inhaled by the body in breathing which does not partake in gaseous exchange. This includes anatomical dead space (air remaining in the conducting airways – about 150 cm<sup>3</sup>) and physiological dead space air (air remaining in the alveoli which does not participate in gaseous exchange). Expired air is a combination of dead space air and alveolar air.

## Gaseous Exchange in the Lungs

Gaseous exchange occurs in the respiratory zone comprising the respiratory bronchioles, the alveolar ducts and the alveoli but primarily in the alveoli.

Oxygen diffuses across the alveolar epithelium and basement membrane, a thin interstitial space and the capillary endothelial membrane. It passes first into the blood plasma and then combines with haemoglobin in the blood cells to form oxyhaemoglobin.

Carbon dioxide diffuses in the reverse direction from the blood to the alveoli from which it can be exhaled.



Net diffusion is determined by the diffusion coefficient of the gas through the membrane and difference between partial pressures.

For oxygen, the partial pressure is greater in the gas phase in the alveoli so more molecules will diffuse into the blood than in the other direction.

For carbon dioxide, the partial pressure is greater in the dissolved state in the blood, thus net diffusion will occur toward the gas phase in the alveoli.

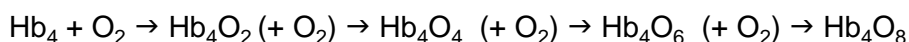
	Atmospheric Air (mm Hg)		Alveolar Air (mm Hg)		Expired Air (mm Hg)	
N <sub>2</sub>	597.0	(78.62%)	569.0	(74.9%)	566.0	(74.5%)
O <sub>2</sub>	159.0	(20.84%)	104.0	(13.6%)	120.0	(15.7%)
CO <sub>2</sub>	0.3	(0.04%)	40.0	(5.3%)	27.0	(3.6%)
H <sub>2</sub> O	3.7	(0.50%)	47.0	(6.2%)	47.0	(6.2%)
TOTAL	760.0	(100.0%)	760.0	(100.0%)	760.0	(100.0%)

## Oxygen and Carbon Dioxide Transport in Blood

### Formation and dissociation of oxyhaemoglobin

In adults, haemoglobin (HbA) is a heterotetramer consisting of two  $\alpha$  chains and two  $\beta$  chains. Each haemoglobin chain has a haeme prosthetic group (containing a central bivalent atom of iron) attached to a polypeptide globin chain.

There are 4 such chains in each haemoglobin molecule and each can bind with 2 atoms of oxygen. Thus 8 oxygen atoms can be transported by each haemoglobin molecule.



Measurement of the dissociation constants of each of the states shows that binding of oxygen to haemoglobin is co-operative and once Hb<sub>4</sub>O<sub>6</sub> has been formed, chances of formation of Hb<sub>4</sub>O<sub>8</sub> is nearly 250 times higher than formation of any other molecule.

Haemoglobin can exist in two conformational states:

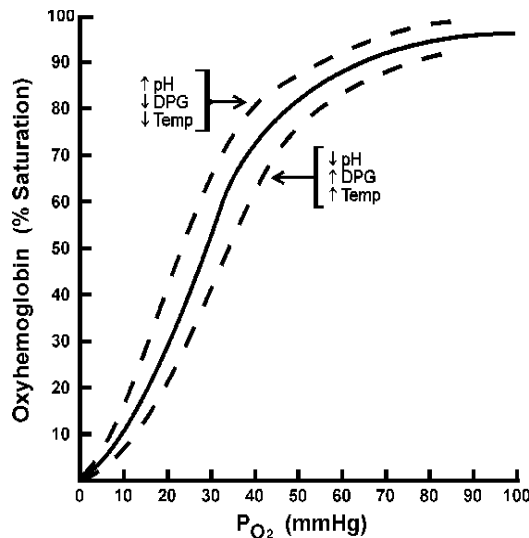
Relaxed (R) state - this corresponds to the quaternary structure of oxyhaemoglobin and favours oxygen binding

Tense (T) state - this corresponds to the quaternary structure of deoxyhaemoglobin and has a lower binding affinity for oxygen.

Binding of oxygen causes a change in the conformational state of the haemoglobin molecule bringing about a change in the position of the haem groups. When oxygen is taken up the 2  $\beta$  chains move closer; when oxygen is released the chains move apart.

When  $O_2$  binds to the haeme iron (oxygenation of Hb) and when  $O_2$  is released (deoxygenation), the oxidation stage of the iron does not change as  $O_2$  does not bind to the positive bonds of Fe –it binds with coordination bonds of the Fe atom.

### Oxygen Dissociation Curve



The partial pressure of oxygen in the blood at which the haemoglobin is 50% saturated, typically about 26.6 mm Hg for a healthy person, is known as the  $P_{50}$ .

**Oxygen dissociation curve.**  
Changes in temperature, pH and organic phosphates like DPG directly effect the dissociation of oxygen.

### Shift to the right

A rightward shift indicates that haemoglobin has a decreased affinity for  $O_2$ . This makes it more difficult for haemoglobin to bind oxygen (requiring a higher  $pO_2$  to achieve the same oxygen saturation) but makes it easier for haemoglobin to release bound oxygen.

- 1) **An increase in  $H^+$ :** When  $H^+$  concentration increases the pH of blood decreases. A decrease in pH shifts the standard curve to the right as the Hb changes from its normal R form to its T form, lowering its affinity for oxygen.
- 2) **An increase in  $pCO_2$ :** An increase in  $pCO_2$  causes the standard curve to shift to the right.  $CO_2$  also causes a decrease in intracellular pH shifting the curve to the right.
- 3) **An increase in 2,3-DPG:** 2,3-Diphosphoglycerate (2,3 DPG/ 2,3 BPG) formed in erythrocytes during glycolysis is a competitive inhibitor of  $O_2$ , binds to the same binding site on Hb. An increase in 2,3 DPG shifts the curve to the right.

### Shift to the left

A leftward shift indicates that haemoglobin has an increased affinity for oxygen so that haemoglobin binds oxygen more easily, but unloads it more reluctantly.

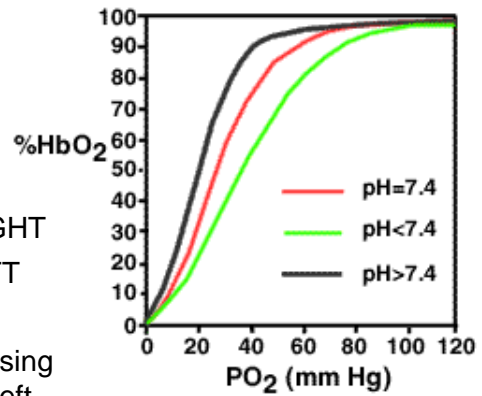
- 1) **A decrease in  $H^+$**
- 2) **A decrease in  $pCO_2$**
- 3) **A decrease in 2,3-DPG**



The decrease in the oxygen affinity of haemoglobin in response to decreased blood pH especially resulting from increased carbon dioxide concentration in the blood is called the Bohr effect.

Higher  $\text{PCO}_2$  = Higher  $[\text{H}^+]$  = Lower pH = Shift to the RIGHT  
 Lower  $\text{PCO}_2$  = Lower  $[\text{H}^+]$  = Higher pH = Shift to the LEFT

Increased temperature shifts the curve to the right releasing oxygen. Decreased temperature shifts the curve to the left, enhancing oxygen uptake.



Oxygen dissociation curve

## Carbon Dioxide Transport

There are 3 ways in which carbon dioxide is transported in the blood:

### 1. As dissolved $\text{CO}_2$

As  $\text{CO}_2$  is much more soluble in blood than  $\text{O}_2$ , about 5 % of  $\text{CO}_2$  is transported dissolved in the plasma

### 2. Bound to haemoglobin and plasma proteins

$\text{CO}_2$  combines reversibly with haemoglobin to form carbaminohaemoglobin.  $\text{CO}_2$  does not bind to iron but to amino groups on the polypeptide chains of haemoglobin.

$\text{CO}_2$  also binds to amino groups on the polypeptide chains of plasma proteins. About 10 % of  $\text{CO}_2$  is transported this way.

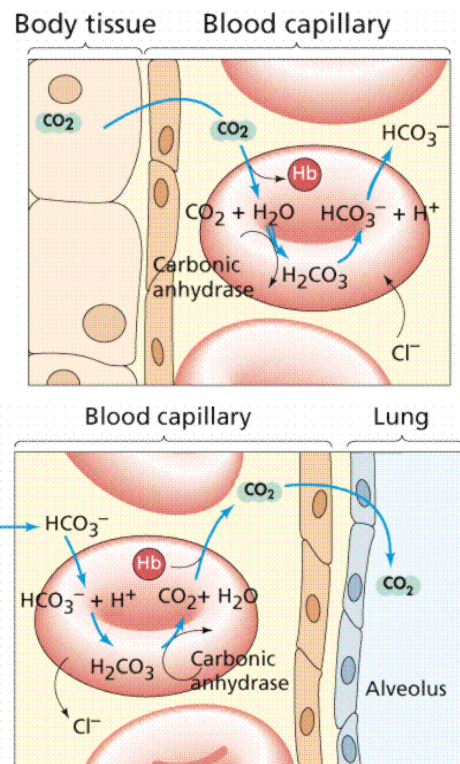
### 3. As bicarbonate ions ( $\text{HCO}_3^-$ )

Around 85 % of  $\text{CO}_2$  is transported this way.  $\text{CO}_2$  enters red blood cells in tissue capillaries where it combines with water to form carbonic acid ( $\text{H}_2\text{CO}_3$ ). This reaction is catalyzed by the enzyme carbonic anhydrase in the RBCs. Carbonic acid dissociates to form bicarbonate ions ( $\text{HCO}_3^-$ ) and hydrogen ions ( $\text{H}^+$ ).

This reaction also occurs in the plasma, but is much slower due to the lack of carbonic anhydrase.  $\text{H}^+$  ions thus formed combine with the haemoglobin in the red blood cell.

Bicarbonate ions diffuse out of the red blood cell into the plasma while chloride ions ( $\text{Cl}^-$ ) diffuse in to take their place.

This is known as the **chloride shift**.



Carbon Dioxide Transport

At the lungs a reversal of the reactions occur and carbon dioxide diffuses out into the alveoli.

# Control of Respiration

Breathing is an involuntary process and like many involuntary processes is controlled by the medulla. The region of the medulla that controls breathing is called the respiratory centre.

The **inspiratory centre (IC)** (also called the dorsal respiratory group or DRG) is located in the dorsomedial region of the medulla.

The inspiratory centre is involved in the generation of respiratory rhythm and is primarily responsible for the generation of inspiration. It transmits regular nerve impulses via the phrenic and intercostal nerves to the diaphragm and intercostal muscles to cause inhalation.

Intrinsic firing and rhythm of the inspiratory centre produces a respiratory rate of 12-16 breaths per minute in humans.

The **apneustic centre** in the pons enhances inspiration and stimulates the inspiratory centres to convert normal respiration into a series of deep inspirations or gasps.

The **pneumotaxic centre** also located in the pons is antagonistic to the apneustic centre and terminates inspiration and prevents gasping under normal circumstances.

The **expiratory centre (EC)** (also called the ventral respiratory group or VRG) is located in the ventral region of the medulla. It is normally silent, has no intrinsic rhythm and functions under conditions of stress when forced expiration is necessary.

## Feedback Control

**Central chemoreceptors** of the central nervous system, located on the floor of the 4<sup>th</sup> cerebral ventricle are sensitive to changes in pH of the cerebral spinal fluid.

An increase in  $p\text{CO}_2$  of the arteries will indirectly cause blood to become more acidic. The cerebral spinal fluid pH is closely comparable to plasma pH as  $\text{CO}_2$  easily diffuses across the blood-brain barrier. Stimulation of these receptors leads to hyperventilation.

**Peripheral chemoreceptors** include the

1) **carotid body**: a small cluster of chemoreceptors located near the bifurcation of the carotid artery. The carotid body is made up of glomus cells which release a variety of neurotransmitters including acetylcholine and supporting type II cells.

The carotid body responds primarily to a decrease in  $p\text{O}_2$  detected by the glomus cells. It also senses increases in  $p\text{CO}_2$  and decreases in arterial pH but to a lesser degree than for  $\text{O}_2$ .

2) **aortic body**: a small cluster of chemoreceptors and supporting cells located along the aortic arch. It responds to a decrease in  $p\text{O}_2$  and an increase in  $p\text{CO}_2$  but not to a change in pH; these are detected by the glomus cells.

The carotid sinus and aortic arch chemoreceptors send their afferent input to the respiratory centres by the glossopharyngeal nerve and the vagus nerve respectively.

**Stretch receptors** in the alveoli and bronchioles detect inhalation and send inhibitory signals to the respiratory centre to cause exhalation. This negative feedback system is continuous and prevents damage to the lungs.