

# RESPIRATORY PHYSIOLOGY ..... Proff.Amjad Fawzi

### Respiratory System Functions

1. Gas exchanger
2. Regulation of blood pH
3. Voice production
4. Olfaction
5. Protection

### Respiration includes 2 processes:

6. External respiration: uptake of O<sub>2</sub> and removal of CO<sub>2</sub> between lungs and environment.
7. Internal respiration: uptake of O<sub>2</sub> and removal of CO<sub>2</sub> between cells and their fluid medium.

The respiratory system is made up of a gas exchanging organ(the lungs) and a pump that ventilate the lungs. This pump is made up of:

1. Chest wall muscles which increase and decrease the size of thoracic cavity.
2. least resistance to air flow is in the very small bronchioles and terminal bronchioles because of their large cross-sectional area. Alveoli are lined mostly by thin layer of squamous epithelium.
3. Brain centers which control the respiratory muscles.
4. Nerves which connect the brain with respiratory muscles.

### Respiratory Airways:

1. Anatomical classification: nose, pharynx (*upper respiratory tract*), larynx, trachea, bronchi, bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (*lower respiratory tract*).
2. Physiological classification: nose, pharynx, larynx, trachea, bronchi, bronchioles, terminal bronchioles (*conducting zone-divided 16 times*), respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli (*respiratory zone-divided 7 times*). These 23 divisions greatly increase the total cross sectional area thus much reducing air flow through small airways.

To keep the trachea from collapsing multiple cartilage rings extend about five sixth of the way around the trachea which become less and less extensive and then they are completely gone in the bronchioles which by now are not prevented from collapsing by any rigidity of their walls. Instead, they are expanded by the same transpulmonary pressures that expand the alveoli. In all areas of the trachea and bronchi not occupied by cartilage plates, the walls are composed mainly of smooth muscles. *The walls of the bronchioles are almost entirely smooth muscles*, with the exception of the respiratory bronchioles that has only a few smooth muscle fibers. The chief site of airway resistance in the airway passages is at the medium-sized segmental bronchi, where the radius of the individual bronchi is decreased. The type I alveolar cells and few thick (type II) surfactant secreting cells in addition to the alveolar macrophages which engulf small particles reaching the alveoli. Mast cells also present which contains histamine responsible for allergic reactions (bronchial asthma).

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### Respiratory functions of the nose:

[1] **Warming** the air by the extensive surfaces of the conchae and septum.

[2] The air is almost completely **humidified**.

[3] The air is **filtered**.

When a person breathes air through a tube directly into the trachea (as through a tracheostomy), the cooling and especially the drying effect in the lower lung can lead to serious lung crusting and infection. The nasal filtration of air for removing particles from air is so effective that almost no particles larger than 4 to 6 microns in diameter enter the lung through the nose. Of the remaining particles, many of smaller size settle out in the smaller bronchioles as a result of gravitational precipitation. Some of the particles smaller than 1 micron in diameter diffuse against the walls of the alveoli and adhere to the alveolar fluid. But many particles smaller than 0.5 micron in diameter remain suspended in the alveolar air and are later expelled by expiration. For instance, the particles of cigarette smoke have a particle size of about 0.3 micron. Almost none of these are precipitated in the respiratory passageways before they reach the alveoli. However, up to one third of them do precipitate in the alveoli by the diffusion process, and the remaining suspended and expelled in the expired air. Particles that become entrapped in the alveoli are removed mainly by alveolar macrophages. An excess of particles causes growth of fibrous tissue in the alveolar septa, leading to permanent debility.

All the respiratory passages are kept moist by a layer of mucus that coats the entire surface which is secreted by goblet cells in the epithelial lining of the passages and by small submucous glands. The mucus also traps small particles out of the inspired air and keeps most of these from ever reaching the alveoli. Then the mucus itself is removed from the passages by the continual beating of the cilia, which cover the entire surface of the respiratory passages. The cilia in the lower respiratory passages beat upward while those in the nose beat downward. This continual beating causes the coat of mucus to flow slowly toward the pharynx. Then the mucus and its entrapped particles are either swallowed or coughed to the exterior.

**[A] Nervous control of the bronchioles:** The only important nervous control to the bronchioles is by way of parasympathetic vagus nerve fibers. These nerves secrete acetylcholine and when activated cause *mild to moderate constriction of the bronchioles*. Irritants entering the airways, such as smoke, dust, sulfur dioxide, and some of the acidic elements in smog, can all initiate local reactions that cause obstructive constriction of the bronchioles mediated through a parasympathetic reflex.

**[B] Humoral control of the bronchioles:** several different humoral substances are often quite active in causing bronchiolar constriction. Two of the most important of these are *histamine* and the substance called slow reactive substance of anaphylaxis (*SRA*). Both of these are released in the lung tissues by mast cells during allergic reactions. Therefore, they play key roles in causing the airway obstruction that occurs

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in allergic asthma. In addition, the airway smooth muscle is highly responsive to  $\text{CO}_2$ , *high blood  $\text{CO}_2$  producing bronchodilation and low  $\text{CO}_2$  bronchoconstriction*. In contrast to the humoral substances that constrict the bronchioles, two other hormones, *epinephrine and norepinephrine*, both of which are secreted by the adrenal glands in response to sympathetic stimulation relax the bronchioles (by activation of  $\beta_2$  receptors). Therefore, activation of the sympathetic nervous system is often valuable in relaxing the airways and preventing obstruction.

Factor	Effect
Parasympathetic stimulation	Bronchoconstriction
Histamine and SRA	Bronchoconstriction
Low blood $\text{PCO}_2$	Bronchoconstriction
High blood $\text{PCO}_2$	Bronchodilatation
Sympathetic stimulation to the adrenal glands (epinephrine and norepinephrine)	Bronchodilatation

### The process of respiration can be divided into four major events:

- [1] Pulmonary ventilation which means the inflow and outflow of air between the atmosphere and the lung alveoli.
- [2] Pulmonary diffusion (gas exchange in the lung).
- [3] Transport of oxygen and carbon dioxide in the blood and body fluids to and from the cells.
- [4] Regulation of ventilation.

#### (I) **Pulmonary Ventilation:** Which includes *inspiration* and *expiration*.

[A]**Inspiration:** Normal inspiration is an active process. The lungs can expand in two ways:

[1] By downward and upward movement of the muscles of diaphragm (supplied by phrenic nerves). The downward movement of diaphragm accounts for 75% of the change in intrathoracic volume during quiet inspiration. In inspiration, contraction of the diaphragm pulls the lower surfaces of the lungs downward.

[2] By raising the rib cage. In natural resting position, the ribs are extended forward and downward, thus allowing the sternum to fall backward toward the spinal column. But when the rib cage is elevated, the ribs project directly forward so that the sternum now also moves forward away from the spine, making the anteroposterior thickness of the chest greater during maximum inspiration. The forward movement of sternum accounts for 25% of the change in intrathoracic volume during quiet inspiration. The muscles for raising the rib cage (muscle of inspiration) are *external intercostals, sternocleidomastoid, and scalene*. At rest,

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adequate ventilation can be maintained by diaphragm or external intercostals muscle alone.

**[B]Expiration:** Normal expiration is a passive process. The lungs can be shrunk or contracted by two

ways:

**[1]**Relaxation of diaphragm and the inspiratory muscles which cause compression on the lungs. In contrast, during heavy breathing, however, the compression forces are not powerful enough to cause the necessary rapid expiration, so that abdominal muscles (*abdominal recti*) and the muscles that pull the rib cage downward (*internal intercostals*), i.e. muscles of expiration are contracted and added to the force needed for rapid expiration.

**[2]**Elastic recoil tendency of the lung.

Maximal expiratory pressure is achieved by fully contracting the expiratory muscles with the lungs fully inflated and the glottis- or airway closed. Forced expiration against a closed airway is termed a *Valsalva maneuver* and is commonly performed when lifting heavy objects or when defecating. Normally, the maximal expiratory pressure that can be achieved is 100-150 cm H<sub>2</sub>O greater than atmospheric pressure. As lung volume decreases, the maximal achievable expiratory pressure decreases as well.

**Elastic recoil tendency of the lungs:** The lungs have a continual elastic tendency to collapse and therefore to pull away from the chest wall. This is called the elastic recoil tendency of the lungs and it is caused by two different factors:

**[A]The presence of elastic fibers** throughout the lungs which are stretched by lung inflation and therefore attempt to shorten. They account for about *one third of the recoil tendency*.

**[B]The surface tension of the fluid lining the alveoli** which is more important, accounts for about *two third of the recoil tendency*, and causes a continual elastic tendency for the alveoli to collapse. The surface tension is caused by intermolecular attraction between the surface molecules of the alveolar fluid that is each molecule pulls on the next one.

**Intrapleural (intrathoracic) pressure:** The negative (subatmospheric) pleural pressure in the pleural space required to prevent collapse of the lungs is called the pleural pressure (or intrathoracic pressure) which is about -2.5 mm Hg at the end of expiration and -12 to -18 mm Hg at the end of inspiration.

**Pressure changes during inspiration and expiration:** A thin layer of fluid normally present between visceral and parietal pleurae. This fluid helps the lung to slide easily on the chest wall (lubricant) but resist being pulled away from it (sealant) in the same way that 2 moist pieces of glass slide on each other but resist separation.

The lungs are stretched when expanded at birth. At end of quiet expiration, their tendency to recoil from the chest wall is just balanced by the tendency of the chest wall to recoil in the opposite direction (neutral point). If the chest wall is opened, the lungs collapse (pleural pressure becomes atmospheric) and if the lungs lose their

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elasticity the chest expands and becomes barrel- shaped(eg: emphysema).Inspiration is an active process.The contraction of the inspiratory muscles increases the intrathoracic volume.During quiet breathing, the intrapleural pressure ,which is about -2.5 mmHg (relative to atmospheric)at the start of inspiration, decreases to about -6mmHg and lungs become more expanded. The pressure in the airway becomes slightly negative, and air flows into the lungs. At the end of inspiration, the lung recoil pulls the chest back to the expiratory position, where the recoil pressure of the lungs and chest wall balance. The pressure in the airway becomes slightly positive, and air flows out of the lungs. Expiration during quiet breathing is passive since it does not involve expiratory muscle contraction(depends on lung recoil).Strong inspiratory effort during exercise reduces pleural pressure to as low as -30 mmHg and correspondingly greater lung expansion. Adequate deflation is achieved by contraction of expiratory muscles(expiration here is active).

**The role of surfactant:** A substance known as surfactant, which is a lipoprotein secreted from type II alveolar epithelial cells and has many important functions:

[1]**It reduces the surface tension** of the fluid lining the alveoli by decreasing the forces between the surface molecules of the alveolar fluid, and therefore, allowing the lungs to expand. In the absence of surfactant, -20 to -30 mm Hg intrapleural pressure required to overcome the collapse tendency of the alveoli as it occur in some premature babies who do not secrete adequate quantities of surfactant a condition known as *hyaline membrane disease or respiratory distress syndrome*.

[2]Surfactant also plays an important role in **stabilizing the sizes of the alveoli**. When the alveolus becomes smaller and the surfactant becomes more concentrated at the surface of the alveolar lining fluid, the surface tension becomes progressively more reduced. On the other hand, as an alveolus becomes larger and the surfactant becomes less concentrated at the surface of the alveolar lining fluid, the surface tension becomes much greater. Thus, this special characteristic of surfactant helps to stabilize the sizes of the alveoli, causing the larger alveoli to contract more and the smaller ones to contract less. This effect helps to ensure that the alveoli in any one area of the lung all remain approximately the same size.

[3]Surfactant is also playing a role in **preventing accumulation of edema fluid in the alveoli**. This can be explained as follow; the surface tension of the fluid in the alveoli not only tends to cause collapse of the alveoli, but it also tends to pull fluid into the alveoli from the alveolar wall. In the normal lung, when there is adequate amounts of surfactant, still the surface tension can pull fluid from the wall with an average pressure of -3 mm Hg into the alveoli which can reabsorb to interstitium with an average pressure of -9 mm Hg. This is what keeps the alveoli dry. On the other hand, in the absence of surfactant, the average surface tension force may becomes as great as -10 to -20 mm Hg which tends to pull fluid into the alveoli causing massive filtration of fluid out of the capillaries wall into the alveoli, thus filling the alveoli with fluid causing severe pulmonary edema.

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**Expansibility of the lungs and thorax( Compliance):**defined as *the volume increase in the lungs for each unit increase in alveolar pressure*.It indicates how easily a structure can be stretched or inflated. **Compliance** =  $[V_2 - V_1] / [P_2 - P_1]$ .

The compliance and elasticity (elastance) are inversely related,i.e., *Compliance = 1/elastance*.

The Compliance of the normal lungs and thorax combined (total pulmonary Compliance) is 120-130 ml / cm H<sub>2</sub>O. That is, every time the alveolar pressure is increased or intrapleural pressure decreased by 1 cm of water, the lungs expand 130 ml.Any condition that restrict expansion of the lungs (*restrictive lung diseases*) causes abnormal low compliance such as:

[1]fibrotic or edematouslung.

[2] Any abnormality that reduces the expansibility of the thoracic cage like neuromuscular or musculoskeletal diseases such as deformities of the chest cage (as kyphosis, sever scoliosis).

Increased compliance is produced by the pathological processes that occur in emphysema and also result of the aging process. In both condition, there is a decrease in the retractive force in the lungs with consequent increase in compliance.

**The Work Of Breathing:**During normal quiet respiration, respiratory muscle contraction occurs only during inspiration, whereas expiration is entirely a passive process caused by elastic recoil of the lung and chest cage structures. Thus, the respiratory muscles normally perform work only to cause inspiration and not at all to cause expiration. During normal quiet breathing most of the work performed by the respiratory muscles is used to expand the lungs against its elastic forces (**compliance work**). A small amount of only few per cent of the total work is used to overcome tissue resistance (**tissue resistance work**) which is due to the viscosity of the lungs and chest wall structures and somewhat more is used to overcome airway resistance (**airway resistance work**).

The work required to expand the lungs is greater in adults than in children because greater volumes of gas have to be shifted in adults than in children.

Compliance work and tissue resistance works are especially increased by diseases that cause fibrosis of the lungs. On the other hand, airway resistance work is increased in heavy breathing and in obstructive airway diseases in which air must flow through the respiratory passageways at a very high velocity and greater proportion of the work is then used to overcome airway resistance. During normal quiet respiration (at a basal level of total energy production by the body) or even during heavy exercise (at a high level of total energy production by the body), only 2-3% of the total energy (total O<sub>2</sub>consumption) expended by the body is required to energize the pulmonary ventilatory process. On the other hand, pulmonary diseases that decrease the pulmonary compliance, or that increases airway resistance, or that increase the viscosity of the lung or chest wall can at times increase the work of breathing up to

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30% or more of the total energy expended by the body is for respiration alone which may in certain circumstances lead to death.

**The dead space:** *It is the space in which the gas exchange is not taking place.*

Some of the air that a person breathes never reaches the gas exchange areas but instead goes to fill the respiratory passages. The respiratory passages where no gas exchange takes place is called the **anatomical dead space** (which consist of nose, pharynx, larynx, trachea, bronchi, bronchioles). The normal anatomical dead space air in the young adult is about **150 ml**. This increases slightly with age. It also increases by more than half during a maximal inspiration because the trachea and bronchi expand markedly as the lungs expand. There is another type of dead space and is called **physiological dead space**. This is due to some alveoli are not functional or are only partially functional because of absent or poor blood flow through adjacent pulmonary capillaries. Therefore, from a functional point of view, these alveoli must also be considered to be dead space. In the normal person, all the alveoli are functional in the normal lung. Therefore, the volume of physiological dead space is equal to zero.

Total dead space = anatomical D.S. + physiological D.S.

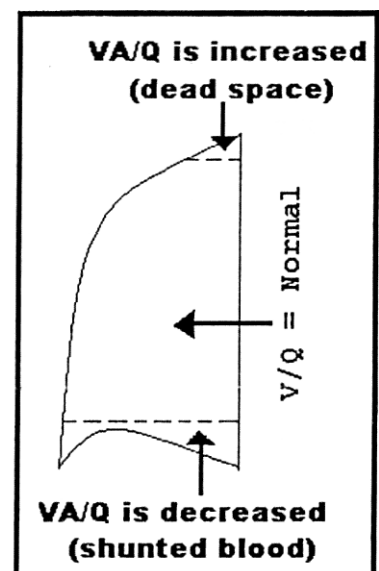
= 150 + 0 = 150 ml. i.e. equal to anatomical dead space.

In person with partially functional or nonfunctional alveoli in some part of lungs, the physiologic dead space is sometimes as much as ten times the anatomical dead space. If the tidal volume is 500 ml, a normal dead space of 150 ml, and a respiratory rate of 12 times per minute, **alveolar ventilation** equals  $12 \times (500 - 150) = 4200 \text{ ml / min.}$

### Ventilation — Perfusion Ratio (VA/Q):

[1] If some areas of the lungs are well ventilated but have no or almost no blood flow,  $VA/Q = \text{infinity}$ . Therefore, the alveolar air has the same composition and concentration of the humidified inspired air ( $pO_2 = 149 \text{ mm Hg}$ ,  $PCO_2 = 0.3 \text{ mm Hg}$ ). In normal person in the upright position, both blood flow and alveolar ventilation are considerably less in the upper part of the lung than in the lower part. However, blood flow is decreased considerably more than ventilation because the low-pressure pulmonary capillaries at the lung apices are compressed by the higher-pressure lung alveoli. Therefore, at the top of the lung,  $VA/Q$  is as much as three times as great as the ideal value, which causes a moderate degree of **physiologic dead space** in this area of the lung.  $VA/Q$  equal to infinity does not occur in the normal lung

but instead occurs only in abnormal conditions such as in some lung diseases, a fall in arterial pressure (following haemorrhage) or breathing against a high pressure as occurs when a person is blowing on a musical instrument. Breathing against a high pressure causes a compression of the pulmonary capillaries by the high alveolar



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pressure. In some chronic obstructive lung diseases such as emphysema, some areas of the lungs exhibit very serious physiologic shunt and other areas very serious physiologic dead space. Both of these tremendously decrease the effectiveness of the lungs as gas exchange organ.

[2] If some areas of the lung have excellent blood flow but little or no ventilation,  $VA/Q = \text{zero}$ . Therefore, the alveolar air comes to equilibrium with the venous blood gases ( $PO_2 = 40$  mm Hg,  $PCO_2 = 45$  mm Hg) without further gases exchange because there is no new gas coming from the exterior air to the alveoli. Whenever  $VA/Q$  is below normal (i.e. low ventilation and normal perfusion), the ventilation is not enough to provide the  $O_2$  needed to oxygenate the blood flowing through the alveolar capillaries and consequently leads to hypoxemia. Therefore, a certain fraction of the venous blood passing through the pulmonary capillaries does not become oxygenated. This fraction is called *shunted blood* as it occurs normally in the bottom of the lung with  $VA/Q$  as low as 0.6 times the ideal value. Also, some additional blood flows through the bronchial vessels rather than through the alveolar capillaries, normally about 2% of the cardiac output, this too is unoxygenated, i.e. shunted blood. The total quantitative amount of shunted blood per minute is called the **physiologic shunt**

At a ratio of either zero (shunt) or infinity (dead space), there will be no proper exchange of gases through the respiratory membranes of the affected alveoli. When alveolar ventilation is normal for a given alveolus and blood flow is also normal for the same alveolus, the  $VA/Q$  is also said to be normal (0.8). Therefore,  $PCO_2$  (40 mm Hg) and  $PO_2$  (104 mm Hg) in the alveoli lie somewhere between that of the inspired air and that of venous blood.

## Compensatory Mechanisms For Matching The Ventilation And Perfusion:

For proper blood oxygenation, the right proportion of air and capillary blood should be available to each alveolus, *local changes in the tone of smooth muscles of bronchioles and pulmonary vessels help to maintain this equilibrium through two mechanisms:*

[1] **Local blood  $PCO_2$ :** if an alveolus is receiving too much air for its blood supply, the blood  $CO_2$  will be washed out and the concentration of  $CO_2$  in the blood and in the surrounding tissue will be low. Consequently the airways supplying the alveolus are exposed to this low tissue  $CO_2$  concentration and become constricted and vice versa. By this local mechanism, ventilation can be matched to blood supply.

[2] **Local blood  $PO_2$ :** if an alveolus is receiving too little air for its blood supply, the blood and tissue  $O_2$  will be decreased. A decreased  $O_2$  concentration in the pulmonary vessel causes a constriction to these vessels and vice versa (the opposite effect that exerted on systemic arteries). By this local mechanism, perfusion can match ventilation.

## (II) Pulmonary Diffusion (Gas Exchange in the Lungs):



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After the alveoli are ventilated with fresh air, the next step is diffusion of oxygen from the alveoli into the pulmonary blood and diffusion of CO<sub>2</sub> in the opposite direction, from the pulmonary blood into the alveoli. At rest, during each minute, body cells consume about 200ml of oxygen and produce about the same amount of CO<sub>2</sub>. The relative amounts of these two gases depend primarily upon what nutrients are being used for energy; e.g., when glucose is utilized, one molecule of CO<sub>2</sub> is produced for every molecule of oxygen consumed. The ratio of CO<sub>2</sub> produced / O<sub>2</sub> consumed is known as the *respiratory quotient (RQ)*; accordingly for glucose RQ = 1. When fat is utilized, only 7 molecules of CO<sub>2</sub> are produced for every 10 molecules of O<sub>2</sub> consumed, and RQ = 0.7. On mixed diet, the RQ is between these values.

**Composition of alveolar air:** Alveolar air does not have the same concentrations of gases as atmospheric air and there are several reasons for this difference:

[1] The alveolar air is only partially replaced by atmospheric air with each breath. This is because that the amount of alveolar air replaced by new atmospheric air with each breath (tidal volume - dead space) is only one several of functional residual capacity. So that many breaths are required to exchange most of the alveolar air. This slow replacement of alveolar air is of particular importance in preventing sudden changes in gaseous concentrations in the blood. This makes the respiratory control mechanism much more stable and helps to prevent excessive increases and decreases in tissue oxygenation, tissue CO<sub>2</sub> concentration, and tissue pH when respiration is temporarily interrupted.

[2] O<sub>2</sub> is constantly being absorbed from the alveolar air into the blood of the lungs, and new O<sub>2</sub> is continually entering the alveoli from the atmosphere. Therefore, O<sub>2</sub> concentration in the alveoli, and therefore, its partial pressure as well, is controlled by: [a]- the rate of absorption of O<sub>2</sub> into the blood, [b]- the rate of entry of new O<sub>2</sub> into the lungs by ventilatory process.

[3] CO<sub>2</sub> is constantly diffusing from the pulmonary blood into the alveoli. The two factors that determine alveolar concentration of CO<sub>2</sub> and also its partial pressure are (a) the rate of excretion of CO<sub>2</sub> from the blood into the alveoli and (b) the rate at which CO<sub>2</sub> are removed from the alveoli out by alveolar ventilation.

[4] Dry atmospheric air that enters the respiratory passage is humidified even before it reaches the alveoli. This water vapor simply dilutes all the other gases in the inspired air as shown in the table.

Composition	Atmospheric air (mm Hg)	Humidified air (mm Hg)	Alveolar air (mm Hg)	Expired air (mm Hg)
N <sub>2</sub>	567	563.7	569	566
O <sub>2</sub>	<b>159</b>	<b>149</b>	<b>104</b>	<b>120</b>
CO <sub>2</sub>	<b>0.3</b>	<b>0.3</b>	<b>40</b>	<b>27</b>
H <sub>2</sub> O	37	47	47	47
Total	760	760	760	760

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**The Respiratory Unit:** It is composed of a respiratory bronchiole, alveolar ducts, alveolar sacs, and alveoli (about 300 million in the two lungs). Each alveolus having an average diameter of about 0.2 mm. the alveolar gases are in close proximity to the blood of the capillaries. The gaseous exchange between the alveolar air and the pulmonary blood occurs through the membrane of all the terminal portions of the lungs. These membranes are collectively called the *respiratory membrane (pulmonary membrane)* which consist of the following layers:

- [1] A layer of fluid lining the alveolus and containing surfactant.
- [2] The alveolar epithelium.
- [3] The epithelial basement membrane.
- [4] A very thin interstitial space.
- [5] A capillary basement membrane that in many places fuses with the epithelial basement membrane and obliterating the interstitial space.
- [6] The capillary endothelial membrane.

The average thickness of these layers is about 0.63 micron. The total surface area of the respiratory membrane is estimated to be about 160 square meters, over which a quantity of blood of about 60-140 ml only (the quantity of blood in the capillaries if the lung at any given instant) is spread, which explain the rapidity of respiratory exchange of gases. In addition, the diameter of the pulmonary capillaries is about 8 microns which is about the same diameter of RBC, therefore, RBC as it pass through these capillaries are in fact in close contact with the endothelial membrane. This also help in making the gas exchange rapid because the gases can pass directly from RBC to the alveoli without passing through significant plasma.

### Factors That Affect Rate Of Gas Diffusion Through The Respiratory Membrane:

[1] **The thickness of the membrane:** any factor that increases the thickness to more than two or three times the normal can decrease significantly the rate of gases diffusion. This can occur in edema of the interstitial space of the membrane, and in some fibrotic diseases of the lung.

[2] **The surface area of respiratory membrane:** when the total surface area is decreased to about one third to one fourth normal, exchange of gases through the membrane is impeded to a significant degree even under resting conditions. This can occur in emphysema of the lung in which many alveoli coalesce with dissolution of many alveolar walls.

[3] **The diffusion coefficient:** depends proportionally on the solubility of the gas in the membrane and inversely on the square root of its molecular weight. Therefore, for a given pressure difference, CO<sub>2</sub> diffuse through the membrane about 20 times as rapidly as O<sub>2</sub>. Oxygen in turn diffuses about two times as rapidly as nitrogen.

[4] **The pressure difference** between the two sides of the membrane, which tends to move the gas from area of higher partial pressure to an area of low partial pressure.

### (III) **Transport of oxygen and carbon dioxide in the blood and body fluids:**

Blood transports O<sub>2</sub> and CO<sub>2</sub> between the lungs and other body tissues. Gases are transported in different forms:

1. Dissolved in plasma
2. Chemical combination with Hb
3. Converted into different molecule.

It is important to understand the difference between the partial pressure of a gas and the gas content of a liquid. The *partial pressure* of the gas represents the pressure it would exert in the gas phase. The *gas content* represents the volume of the gas per unit volume of liquid that is present. Liquids must be exposed to a gas tension for a finite time for the gases to dissolve in the liquid phase. If the exposure time is long enough, the gas tension in the liquid will become equal to that of the gas phase and an equilibrium will exist between the gases and the liquid phases. Gases can move from one point to another by diffusion, which is driven by the pressure difference between the two points. Thus, O<sub>2</sub> diffuses from the alveoli (PO<sub>2</sub> = 104 mm Hg) into the pulmonary capillary blood (PO<sub>2</sub> = 40 mm Hg) where it combines with Hb. Then from the systemic capillaries (PO<sub>2</sub> = 95 mm Hg) O<sub>2</sub> diffuses to and equilibrate with interstitial fluid of 40 mm Hg and then diffuses to the cells (PO<sub>2</sub> = 23 mm Hg). Therefore, PO<sub>2</sub> of the blood leaving the tissues capillaries and entering the veins is about 40 mm Hg. Conversely, when O<sub>2</sub> is metabolized in the cells, the PCO<sub>2</sub> rises to a high value (PCO<sub>2</sub> = 46 mm Hg), which causes CO<sub>2</sub> to diffuse into the interstitial fluid with PCO<sub>2</sub> of 45 mm Hg and then it diffuses to and equilibrate with CO<sub>2</sub> of blood in tissue capillaries (PCO<sub>2</sub> = 40 mm Hg) and combines with chemical substances in the blood that increase CO<sub>2</sub> transport. Therefore, PCO<sub>2</sub> of the blood leaving the tissue capillaries and entering the veins is about 45 mm Hg. Similarly, it diffuses out of the blood into the alveoli because the PCO<sub>2</sub> in the alveoli (40 mm Hg) is lower than that in the pulmonary capillary blood (45 mm Hg).

About 98% of the blood that enters the left atrium from the lungs passes through the alveolar capillaries and becomes fully oxygenated (PO<sub>2</sub> = 104 mm Hg) and 2% passes through the bronchial circulation (dead space), which represents the shunted blood by passing the gas exchange areas and has a PO<sub>2</sub> about the same of the normal venous blood (PO<sub>2</sub> = 40 mm Hg). This blood combines in the pulmonary veins with the oxygenated blood from the alveolar capillaries. This mixing of the blood is called *venous admixture* of blood, and it causes the PO<sub>2</sub> of the blood pumped by the left heart into the aorta to fall to about 95 mm Hg.

**The PO<sub>2</sub> in the interstitial fluids is affected by:**

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1- The blood flow: As the blood flow increases, the  $O_2$  delivery to the tissues increases.

2- Tissue metabolism; if the cells utilize more  $O_2$  for metabolism than normally, this tends to reduce the interstitial fluid  $PO_2$ .

3- Hb concentration; because about 97% of the  $O_2$  transported in the blood is carried by Hb, a decrease in Hb concentration reduces the  $O_2$  delivery to the interstitial fluid causing a reduction in  $PO_2$  in the interstitial fluid.

Since only 3 mm Hg of  $O_2$  pressure is normally required for full support of the metabolic processes of the cell, one can see that even this low cellular  $PO_2$ , 23 mm Hg, is more than adequate and actually provides a considerable safety factor.

**The  $PCO_2$  in the interstitial fluid can be affected by:**

1- the decrease in blood flow which causes an increase in the  $PCO_2$ .

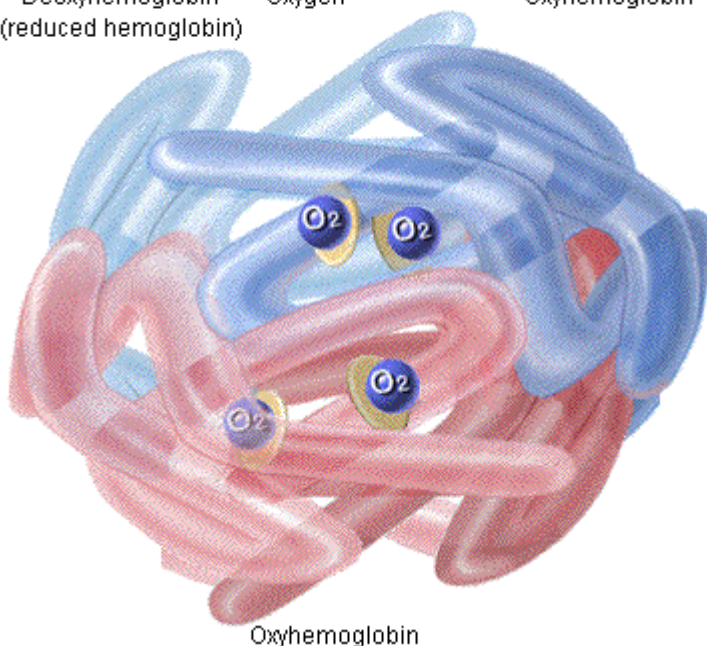
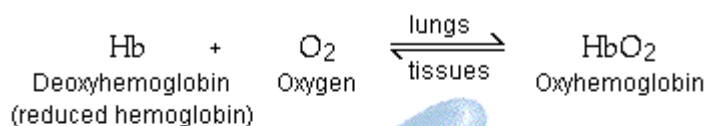
2- increase in metabolic rate greatly elevates the  $PCO_2$  at all levels of blood flow.

## Oxygen Transport

Each RBC molecule contains about 250 million Hb molecules. Each Hb molecule consists of:

1. globin portion (4 polypeptide chains)
2. Four iron containing pigments (heme groups)

Each iron atom binds one oxygen molecule thus Hb molecule can bind up to 4 oxygen molecules (100% saturated) or fewer  $O_2$  molecules (partially saturated).



## RESPIRATORY SYSTEM

**Oxygen binding occurs in response to the high PO<sub>2</sub> in the lungs forming oxyhemoglobin.**

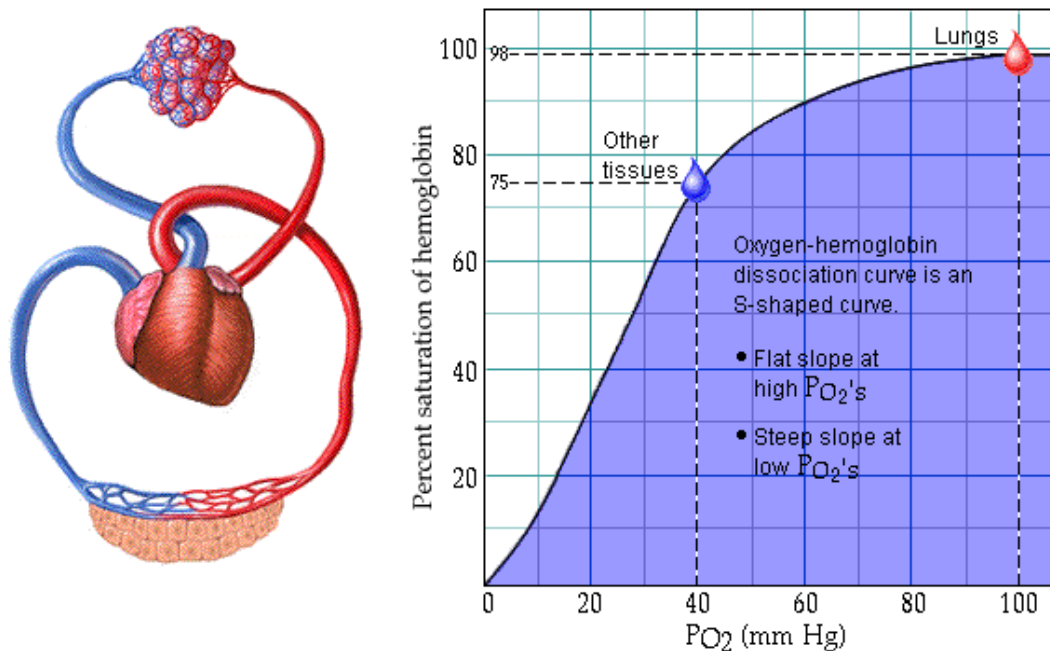
Once O<sub>2</sub> binds to Hb, other molecules bind more readily because Hb affinity for O<sub>2</sub> increases as its saturation increases (*co-operative binding*).

The formation of oxyHb is the reversible reaction ( $\text{Hb} + \text{O}_2 = \text{HbO}_2$ ) depending on concentration of reactants and products of reaction.

In the lungs, when PO<sub>2</sub> is high the reaction proceeds to the right forming HbO<sub>2</sub> (O<sub>2</sub> loading).

In the tissues, when PO<sub>2</sub> is high the reaction proceeds to the left; oxyHb is dissociated releasing O<sub>2</sub> (O<sub>2</sub> unloading).

### OXYGEN-HEMOGLOBIN DISSOCIATION CURVE



This is a curve which correlates between partial pressure of oxygen and hemoglobin saturation with oxygen.

The degree of Hb saturation depends on PO<sub>2</sub>. In the lungs, the PO<sub>2</sub> is about 100 mmHg, Hb has high affinity for O<sub>2</sub> and it is 98% saturated with O<sub>2</sub>. In the tissues, PO<sub>2</sub> is 40 mmHg, Hb has lower affinity for O<sub>2</sub> and it is 75% saturated with O<sub>2</sub> when leaving the tissues.

The curve is "S" shaped with flat slope at higher PO<sub>2</sub>s (80-100 mmHg) and steep slope at lower PO<sub>2</sub> (10-60 mmHg).

At sea level, PO<sub>2</sub> in the lungs = 100 mmHg and Hb is 98% saturated.

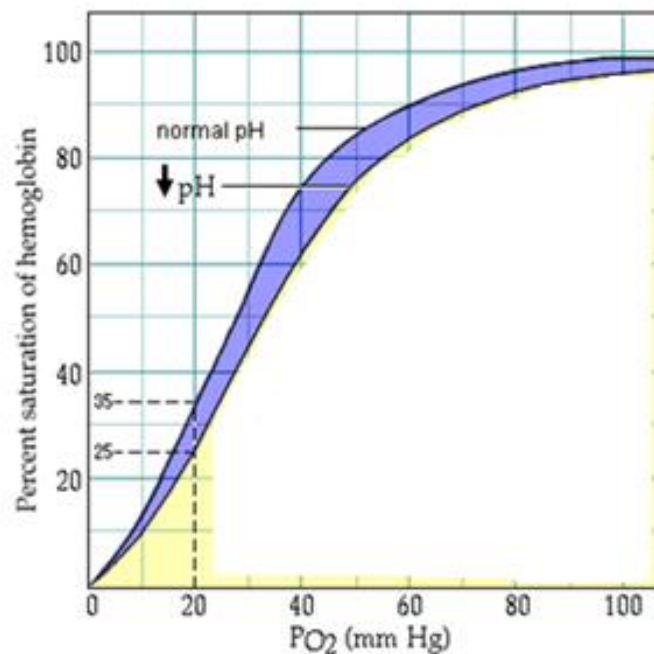
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At higher altitude or cardiopulmonary diseases  $PO_2$  decreases by 20% ( $PO_2=80\%$ ) but Hb is still highly saturated(95%).

In the tissues where  $PO_2=40$  mmHg, Hb has a lower affinity for  $O_2$  and it is only 75% saturated. During vigorous exercise,  $PO_2$  decreases (20 mmHg) because muscles use more  $O_2$  and Hb is 35% saturated. As  $PO_2$  decreases, Hb releases much more  $O_2$  to the tissues. This allows the body to match closely between  $O_2$  delivery by Hb and the  $O_2$  utilization by tissues.

In addition to  $PO_2$ , Hb saturation is altered by four other factors:

### FACTORS ALTERING HEMOGLOBIN SATURATION



1. pH
2. temperature
3.  $PCO_2$
4. BPG(Biphosphoglycerate)

Any of these factors or all of them together play a role during exercise.

During vigorous exercise, contracting muscle produce more metabolic acids like lactic acid which lowers pH, more temperature and more

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CO<sub>2</sub>. In addition, high temp and lower PO<sub>2</sub> increase BPG production by RBC which decreases Hb affinity for O<sub>2</sub> thus releasing more O<sub>2</sub> to active cells. When pH decreases, the curve shifts to right (increased O<sub>2</sub> unloading). A similar shift occurs in response to high temp, high POC<sub>2</sub>, high BPG.

At decreased temperatures, the Hb affinity for O<sub>2</sub> is higher (less O<sub>2</sub> is released); the curve shifts to left. Similar shift occurs in response to high pH, low PCO<sub>2</sub>, low BPG.

**The role of 2,3 — PPG:** It is highly charged anion that binds to the B chains of deoxygenated Hb but not to those of oxyHb as follow:  $\text{HbO}_2 + 2,3\text{-DPG} \rightarrow \text{Hb-2,3-DPG} + \text{O}_2$ . In this equilibrium, an increase in the concentration of 2,3-DPG shifts the reaction to the right, causing more O<sub>2</sub> to be liberated.

The normal 2,3-DPG in the RBC keeps the O<sub>2</sub>-Hb dissociation curve shifted slightly to the right all the time. In hypoxic conditions that last longer than a few hours, the quantity of 2,3-DPG in the RBC increases considerably, thus shifting the curve even farther to the right. This mechanism might be important for adaptation to hypoxia. However, the presence of the excess 2,3-DPG also makes it difficult for the Hb to combine with O<sub>2</sub> in the lungs when the alveolar PO<sub>2</sub> is reduced, thereby often creating as much harm as good. Thyroid hormones, growth hormone, and androgens increase the concentration of 2,3-DPG in the RBC and hence P<sub>50</sub>. 2,3-DPG is very plentiful in RBC.

**The role of Hb-F:** The greater affinity of Hb-F than Hb-A for O<sub>2</sub> facilitates the movement of O<sub>2</sub> from the mother to the fetus. The cause of this greater affinity is the poor binding of 2,3-DPG by the  $\gamma$  polypeptide chains that replace B chains in Hb-F.

**Transport of O<sub>2</sub> in the dissolved state:** 0.17 ml of O<sub>2</sub> is normally transported in the dissolved state to the tissues by each 100 ml of blood (3% of the total transported O<sub>2</sub>). If a person breathes O<sub>2</sub> in high concentration (very high alveolar PO<sub>2</sub>), the amount then transported in the dissolved state can become very high.

**Myoglobin:** It is an iron-containing pigment found in skeletal muscle. It resembles Hb but binds one rather 4 mol of O<sub>2</sub> per mol. Its dissociation curve is a rectangular rather than a sigmoid curve. Because its curve is to the left of the Hb curve, it takes up O<sub>2</sub> from Hb in the blood. It releases O<sub>2</sub> only at low PO<sub>2</sub> values, but the PO<sub>2</sub> in exercising muscle is close to zero. The muscle blood supply is compressed during contractions, and myoglobin may provide O<sub>2</sub> when blood flow is cut off.

**Combination of Hb with CO:** CO has affinity of 230 times to combine with Hb than O<sub>2</sub> do and form *carboxyHb*. A patient poisoned with CO can be treated by

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administration pure  $O_2$ , for  $O_2$  at high alveolar pressure displaces CO from its combination with Hb far more rapidly than can  $O_2$  at the low pressure of atmospheric  $O_2$ . The patient can also be benefited by simultaneous administration of a few per cent  $CO_2$  because this strongly stimulates the respiratory center. This increases alveolar ventilation and reduces the alveolar CO concentration, which allows increased CO release from the blood.

### CO<sub>2</sub> Transport:

7% dissolved in plasma and 93% carried by RBC(23% combined with Hb forming carbamino-Hb, 70% converted into bicarbonate ions).

**Carbamino-Hb:**  $CO_2$  combines reversibly with the globin portion of Hb forming carbamino-Hb.

- a. In the tissues where  $PCO_2$  is high, Hb- $CO_2$  is formed.
- b. In the lungs where  $PCO_2$  is low, Hb- $CO_2$  is dissociated and  $CO_2$  is exhaled.

**Bicarbonate ions:** 70% of  $CO_2$  is converted into bicarbonate ions (faster than  $CO_2$ ) within the RBC in a sequence of reversible reactions then transported in plasma:

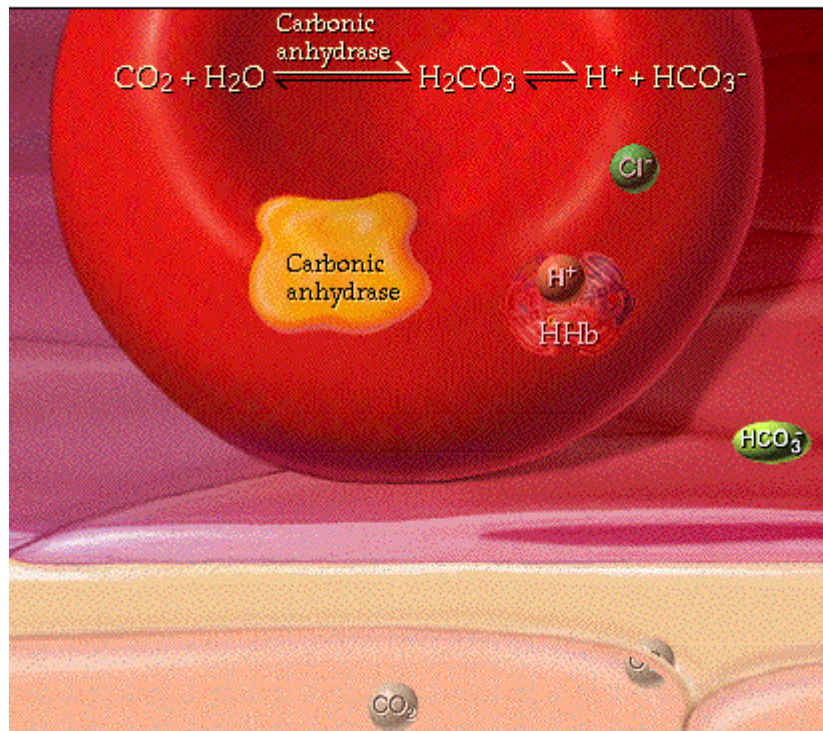
- a. **In the tissues**( regions with high  $PCO_2$ )  $CO_2$  enters RBC combines with water to form carbonic acid. This reaction is catalyzed by carbonic anhydrase enzyme. Similar reaction occurs in plasma but without enzyme it is very slow. Carbonic acid dissociates into  $H^+$  and bicarbonate. Hydrogen ions is buffered by Hb forming(H-HB). To maintain electrical neutrality, bicarbonate ions diffuse out of RBC in exchange with chloride ions(chloride



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shift). Within the plasma, bicarbonate ions act as pH buffer. .

### CO<sub>2</sub> TRANSPORT: BICARBONATE IONS (TISSUES)



- b. **In the lungs**, CO<sub>2</sub> diffuses out of the plasma into the alveoli. This lowers PCO<sub>2</sub> in the blood causing the chemical reactions to reverse. Bicarbonate ions diffuse back into RBC and chloride ions diffuse out (chloride shift). Hydrogen ions combine with bicarbonate ions to form carbonic acid. Carbonic acid breaks down into CO<sub>2</sub> and H<sub>2</sub>O. This reverse reaction is also

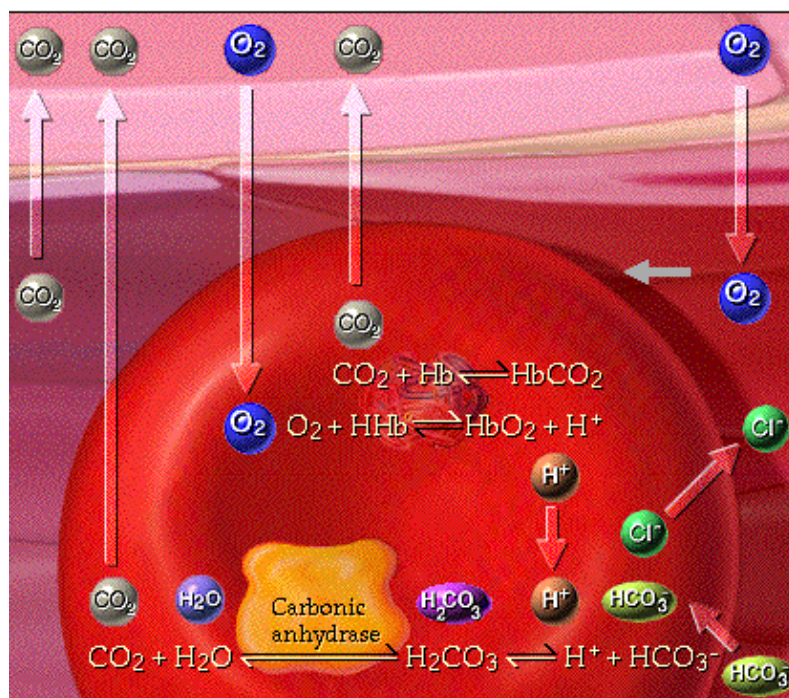
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catalyzed by carbonic anhydrase enzyme.

### CO<sub>2</sub> TRANSPORT: BICARBONATE IONS (LUNGS)



### SUMMARY: O<sub>2</sub> LOADING AND CO<sub>2</sub> UNLOADING (LUNGS)



During external respiration, small amounts of O<sub>2</sub> remain dissolved in plasma with the majority in combination with Hb forming oxy-hemoglobin (Hb-O<sub>2</sub>). When Hb is saturated with O<sub>2</sub>, its affinity for CO<sub>2</sub> decreases. Any CO<sub>2</sub> combined with Hb

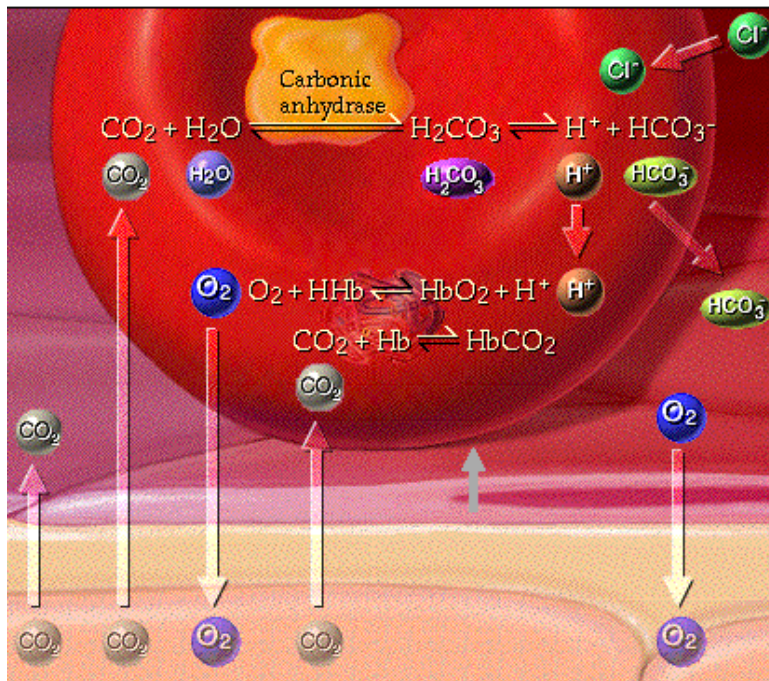


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,dissociates and diffuses out of RBC through plasma and then to alveoli. The  $H^+$  ions released from Hb are combined with bicarbonate ions which diffuse into RBC from plasma in exchange for chloride (chloride shift). Then reaction between  $H^+$  and bicarbonate to form carbonic acid which breaks down into  $CO_2$  and  $H_2O$ . This  $CO_2$  plus small amounts transported in the dissolved form diffuse into alveoli.

In other words,  $O_2$  loading facilitates  $CO_2$  unloading from Hb. This is called **Haldane effect**.

### SUMMARY: $O_2$ UNLOADING AND $CO_2$ LOADING (TISSUES)



During internal respiration, small amounts of  $CO_2$  remain dissolved in plasma with the majority within RBC reacting with water to form carbonic acid which dissociates into  $H^+$  and Bicarbonate ions. Within RBC,  $H^+$  ions are buffered by Hb forming H-Hb. When Hb is bound to  $H^+$  it has lower affinity for  $O_2$  thus  $O_2$  dissociates from Hb and diffuses out of RBC to the tissue. The interaction between  $H^+$  binding and Hb affinity for  $O_2$  is called **Bohr effect**. By forming  $H^+$  ions,  $CO_2$  loading facilitates  $O_2$  unloading. Small amounts of  $O_2$  transported in dissolved state also diffuse out into tissue cells. DeoxyHb has high affinity to  $CO_2$ .

### The Response of Respiratory System to Exercise and Stress:

During exercise or other stressful conditions, the body may require as much as 20 times of the normal amount of  $O_2$ . The increased cardiac output causes blood to stay half normal time in the pulmonary capillary. Yet, the blood is still almost completely saturated with  $O_2$  when it leaves the pulmonary capillaries due to an increase in the diffusing capacity of the respiratory membrane for  $O_2$  about threefolds during exercise, the reasons for this are:

[A] The average RBC spends approximately 0.75 sec in the pulmonary capillary. If  $O_2$  equilibration occurs in 0.25 sec, then there is normally no increase in the  $O_2$  content for the last 0.50 sec of transit through the pulmonary capillary. This time provides a *safety margin* that ensures an adequate  $O_2$  uptake during periods of stress.

[B] The opening up a number of previously dormant pulmonary capillaries, and dilatation of already functioning pulmonary capillaries thereby increases the surface area of blood into which the oxygen can diffuse.

[C] Increased alveolar ventilation.

[D] More ideal ventilation-perfusion ratio in the upper part of the lungs.

[E] During exercise, there is a considerable shift of the Hb- $O_2$  dissociation curve to the right (i.e. decrease in the affinity of Hb to combine with  $O_2$ ) in the muscle capillary blood due to the release of large amounts of  $CO_2$ , acids, and phosphate compounds, in addition to high temperature of the muscles. Then in the lungs, the events are reversed, thus, the shift occurs in the opposite direction (i.e. to the left, which means an increase in the affinity of Hb to combine with  $O_2$ ), thus allowing pickup of extra amounts of  $O_2$  from the alveoli.

## (IV) Regulation of Respiration

**The respiratory centre:** The respiratory cycle (inspiration and expiration) is regulated by the respiratory center in the brain which is composed of three major groups of neurons located bilaterally in the medulla oblongata and pons and these are:

[1] **The dorsal group of neurons:** This group of neurons is located in the medulla within the *nucleus of the tractus solitarius* which is also the sensory termination of both the *vagal and glossopharyngeal nerves* transmitting sensory signals into the respiratory center from the peripheral chemoreceptors, baroreceptors and several different types of receptors in the lung. They are responsible for the basic rhythm of respiration by autonomous repetitive bursts of inspiratory action potentials. The nerve signal that is transmitted to the inspiratory muscles (through contralateral phrenic and intercostal motoneurons and to the ventral respiratory group) begins very weakly at first and increase steadily in a ramp fashion for about 2-sec. Then it abruptly ceases for approximately the next 3 sec, and then begins again for still another cycle, and again

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and again. The advantage of this is that it causes a steady increase in the volume of the lungs during inspiration, rather than inspiratory gasps.

**[2] The pneumotaxic group:** This group of neurons is located within the pons in the *nucleus parabrachialis* and they transmit impulses continuously to the dorsal respiratory group of neurons. The primary effect of these is to control the switch off point of the inspiratory ramp, thus controlling the duration of the filling phase of the lung cycle.

**[3] The ventral group:** These neurons are located in the *nucleus ambiguus* and *nucleus retroambiguus* and is comprised of the upper motor neurons of the vagus and the nerves to accessory muscles of respiration. These neurons contribute to both inspiration and expiration, however, they are especially important in providing the powerful expiratory forces during expiration. Thus, this area operates more or less as an overdrive mechanism when high levels of pulmonary ventilation are required.

**Control Of Respiration:** The respiratory centers and consequently the ventilation can be controlled by the following chemical and neural factors:

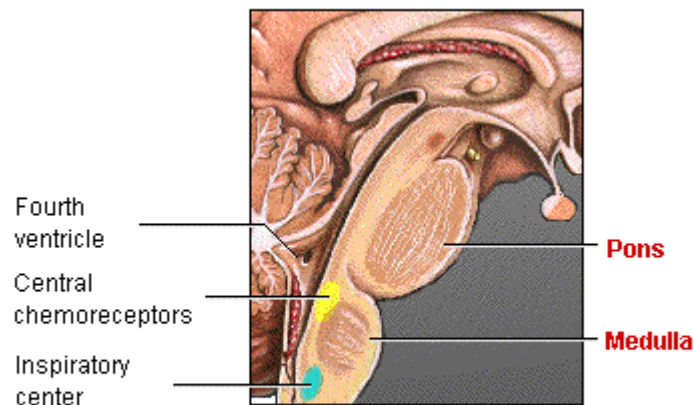
1. Chemical control: mediated through changes in  $\text{PCO}_2$ ,  $[\text{H}^+]$ , and  $\text{PO}_2$ .
2. Neural control:
  - a. Higher brain centers and peripheral proprioceptors control of respiration.
  - b. Motor cortex control of respiration.
  - c. Vasomotor center control of respiration.
  - d. Body temperature control of respiration.

### 1. Chemical control of respiration:

**A: Central chemoreceptors:** Surplus of  $\text{CO}_2$  or  $\text{H}^+$  affected respiration mainly by excitatory effects on the respiratory center itself, causing greatly increased strength of both the inspiratory and expiratory signals to the respiratory muscles. The resulting increase in ventilation (4-fold increase caused by decreasing the blood pH or 11-fold increase caused by increasing  $\text{PCO}_2$ ) increases the elimination of  $\text{CO}_2$  from the blood, this also removes  $\text{H}^+$  from the blood because decreased  $\text{CO}_2$  also decreases the blood carbonic acid. It is believed that the blood  $\text{CO}_2$  and  $\text{H}^+$  do not affect the respiratory centers directly. Instead, a chemosensitive area located bilaterally only a few microns beneath the surface of the medulla ventral to the entry of the glossopharyngeal and vagal nerves into the medulla, this area is *highly sensitive to changes in  $\text{H}^+$  ion concentration*, and it in turn excites the other portions of the respiratory center. It has especially potent effects on increasing the degree of activity of the inspiratory center, increasing both the rate of rise of the inspiratory ramp signals and also the intensity of the signal. However,  $\text{H}^+$  do not easily cross either the blood-brain barrier or the blood-cerebrospinal fluid barrier. For this reason, changes in  $\text{H}^+$  concentration in the blood actually have considerably less effect in stimulating the chemosensitive neurons than do changes in  $\text{CO}_2$ . This is because  $\text{CO}_2$  passes through blood-brain barrier and blood-cerebrospinal fluid barrier very easily. Consequently, whenever the blood  $\text{CO}_2$  concentration increases, the  $\text{PCO}_2$  in both the interstitial fluid of the medulla and in the

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cerebrospinal fluid also increase. In both of these fluids the  $\text{CO}_2$  immediately reacts with the water to form carbonic acid which dissociates into  $\text{H}^+$  and bicarbonates. Thus, paradoxically, more  $\text{H}^+$  are released into the respiratory chemosensitive sensory area when the blood  $\text{CO}_2$  concentration increases than when the blood  $\text{H}^+$  concentration increases. For this reason, respiratory center activity is affected considerably more by changes in blood  $\text{CO}_2$  than by changes in blood  $\text{H}^+$ .



The stimulatory effect of increased  $\text{CO}_2$  on respiration reaches its peak within a few minutes after an increase in blood  $\text{PCO}_2$ . Thereafter, the stimulation gradually declines for the next one to two days to as little as one-fifth the initial effect due to *adaptation of the receptors*. Therefore, A change in blood  $\text{CO}_2$  concentration has a very potent acute effect on controlling respiration but only a weak chronic effect after a few days' adaptation.

**$\text{PO}_2$ :** Arterial  $\text{PO}_2$  does not have a significant direct effect on the respiratory center of the brain in controlling respiration. Instead, it acts almost entirely on peripheral chemoreceptors located in the carotid and aortic bodies, and these in turn transmit appropriate nervous signals to the respiratory center for control of respiration.

**B: Peripheral chemoreceptors(carotid and aortic bodies):**Carotid bodiesare located bilaterally in the bifurcations of the common carotid arteries, and their afferent never fibers pass to the glossopharyngeal nerves and thence to the dorsal respiratory area of the medulla. Aortic bodies are located along the arch of the aorta, and their afferent fibers pass through the vagito the dorsal respiratory area.

The blood flow through the carotid and aortic bodies is extremely high. Because of this, arteriovenousoxygen difference is very small, which means that the venous blood leaving these bodies still has a  $\text{PO}_2$  nearly equal to that of the arterial blood. It also means that  $\text{PO}_2$  of the tissues in these bodies remains at all

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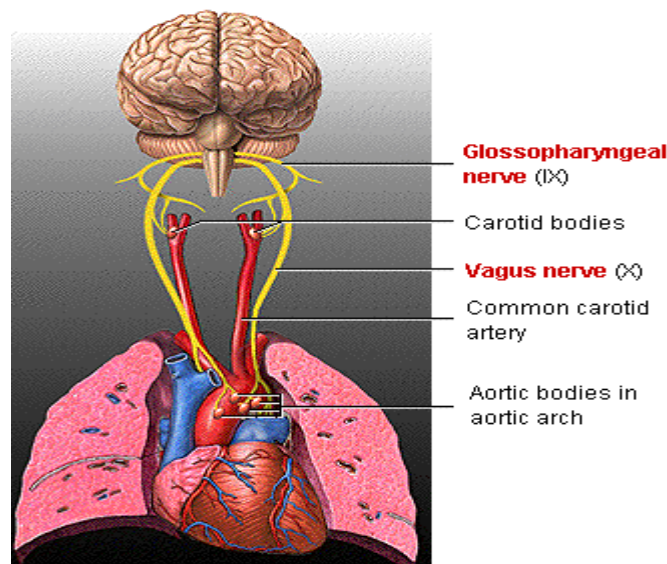
times almost equal to that of the arterial blood. These bodies are more influenced by :

**(a)arterial  $PO_2$** , which is determined by the amount of dissolved  $O_2$  rather than by arterial oxygen content. Hence, they are not influenced by a low Hb level. When the arterial  $PO_2$  falls below normal (especially  $PO_2$  in the range between 60 and 30 mm Hg), or when the blood pressure sufficiently low causing a low blood flow (even though constituents of blood do not change), the chemoreceptors become strongly stimulated.

**(b)increase in  $CO_2$  or  $H^+$  concentration:** also excites the chemoreceptors and in this way indirectly increases respiratory activity. However, the direct effects of both these factors in the respiratory center itself are so much powerful.

The cause of the poor effect of low  $PO_2$  on respiratory control in comparison to those of  $CO_2$  and  $H^+$  concentration can be explained as follows: The increase in ventilation that does occur when the  $PO_2$  falls blows off the respiratory stimulants ( $CO_2$  and consequently  $H^+$ ). However, over several days, the respiratory center gradually becomes adapted to the diminished  $CO_2$  and alveolar ventilation then rises to as high as five to seven times normal. This is part of the acclimatization that occurs as a person slowly ascends a mountain. Yet, under some abnormal conditions, as occurs in pneumonia, emphysema in which gas exchange is impaired, the  $PCO_2$  and  $H^+$  concentrations increase at the same time that the arterial  $PO_2$  decrease. Under these conditions, all three of the feedback mechanisms work together, and the  $PO_2$  mechanism then exerts its full share of respiratory stimulation, sometimes becoming even more potent as a controller of respiration than the  $PCO_2$  and  $H^+$  mechanisms.

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## 2. Neural control:

### A: Peripheral receptors:

- **Stretch receptors:** in the wall of the bronchi and bronchiole transmit signals through the vagi into the dorsal respiratory group of neurons when the lungs become overstretched (the tidal volume increases to greater than approximately 1.5 liters). Therefore, when the lungs become overly inflated, the stretch receptors activate an appropriate feedback response that switches off the inspiratory ramp and thus limits further inspiration. This is called the *Hering-Breuer inflation reflex*, this reflex appears to be mainly a protective mechanism for preventing excess lung inflation rather than important ingredient in the normal control of ventilation.
- **J receptors:** These receptors are located in the pulmonary interstitium at the level of the pulmonary capillaries and are stimulated by distension of the pulmonary vessels (e.g., as caused by left ventricular failure, pulmonary embolization, and certain chemicals or drugs). These receptors initiate reflexes causing rapid, shallow breathing (tachypnea).
- **Chest wall receptors:** which can detect the force generated by the respiratory muscle during breathing. If the force required to distend the lungs becomes excessive (either as a result of high airway resistance or low compliance), the information from these receptors gives rise to the sensation of dyspnea (difficulty in breathing).
- **Irritant receptors:** located in the large airways and are stimulated by smoke, noxious gases, and particulates in the inspired air. These receptors initiate reflexes that cause coughing, bronchoconstriction, mucus secretion, and breath holding (i.e., apnea).
- **Joint proprioceptors** During exercise, the body movements, especially of the limbs, are believed to increase pulmonary ventilation by exciting that then transmit excitatory impulses to the respiratory center.



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**B.Motor cortex:** Respiration can be controlled voluntarily, and that one can hyperventilated or hyporventilated to such an extent that serious derangements in  $\text{PCO}_2$ , pH and  $\text{PO}_2$  can occur in the blood. This is mediated by the nervous pathway for voluntary control passes directly from the motor cortex and other higher centers downward through the corticospinal tract to the spinal neurons that drive the respiratory muscles.

**C.Vasomotor center:** The vasomotor center that control peripheral vasoconstriction and heart activity is closely related to respiratory center in the medulla. A moderate degree of spillover of nerve signals occurs between the two centers. Therefore, almost any factor that increase the activity of the vasomotor center also has at least a moderate effect on increasing respiration.

**D.Body temperature:** An increase in body temperature increases the rate of respiration directly by increasing respiratory center activity and indirectly by increasing the cellular metabolism and eventually enhances the chemical stimuli for increased respiration.

*In strenuous exercise*,  $\text{O}_2$  utilization and  $\text{CO}_2$  formation can increase as much as twentyfold associated with increase in alveolar ventilation. This increase in alveolar ventilation is not mainly due to change in blood  $\text{PO}_2$ ,  $\text{PCO}_2$ , and  $\text{H}^+$  concentration which all remain almost exactly normal, There are at least two different effects seem to be predominantly concerned :

[A] The brain, on transmitting impulses to the contracting muscles, is believed to transmit collateral impulses into the brain stem to excite the respiratory center .But, occasionally, the nervous signals are either too strong or too weak in their stimulation of the respiratory center, then the chemical factors play a very significant role in bringing about the final adjustment in respiration required to keep the  $\text{CO}_2$  and  $\text{H}^+$  concentrations of the body fluids as nearly normal as possible.

[B] Joint proprioceptors transmit excitatory impulses to the respiratory center.

**Pulmonary Blood Flow:** The pulmonary circulation is basically *low-pressure, low-resistance, highly compliant system*. Pressure in the pulmonary artery is about 25 mmHg systolic and 8 mmHg diastolic (a mean of about 14 mmHg). Pressure in the left atrium is about 5 mmHg, resulting in pressure drop across the pulmonary circulation of about 9 mmHg. Pulmonary vascular resistance is 1.8 mmHg/L/min which is about 10% of the systemic vascular resistance (18 mmHg/L/min).

### Abnormalities Of Respiratory Control:

**1.Respiratory center depression:** the activity of respiratory center may be depressed or even totally inactivated by cerebrovascular disease, acute brain edema, anesthesia and overdose of narcotics.

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**2.Periodic breathing:**The most common type of periodic breathing is called *cheyne-stokes breathing* which is characterized by slowly waxing and waning respiration separated by periods of apnea and can be seen in heart failure or brain stem lesions.

**3.Kussmaul's respiration**which is a rapid, deep breathing often seen in patients suffering from *diabetic ketoacidosis*. It occurs as the body tries to compensate for metabolic acidosis by increasing the rate of CO<sub>2</sub> excretion.

**Hypoxia:**Hypoxia is cellular deficiency of O<sub>2</sub>. Traditionally hypoxia has been divided into 4 types:

- [1] **Hypoxic hypoxia:** In which the PO<sub>2</sub> of the arterial blood is reduced due to low atmospheric O<sub>2</sub>, inadequate ventilation of the alveoli or insufficient diffusion of O<sub>2</sub> through the respiratory membrane.
- [2] **Anaemic hypoxia:** In which the arterial PO<sub>2</sub> is normal but the amount of Hb available to carry O<sub>2</sub> is reduced.
- [3] **Ischaemic hypoxia:** In which the blood flow to a tissue is so low that adequate O<sub>2</sub> is not delivered to it despite a normal PO<sub>2</sub> and Hb concentration.
- [4] **Histotoxic hypoxia:** because of the action of certain toxic agents, the tissue cells cannot make use of the O<sub>2</sub> supplied to them such as in cyanide poisoning, in which the action of cytochrome oxidase (respiratory chain enzyme in the mitochondria) is completely blocked. Also, deficiency of oxidative enzymes such as vitamin B deficiency (Beriberi).

**Cyanosis:**It is a dusky bluish discoloration of the tissues and appears when the reduced Hb concentration of the blood in the capillaries is more than 5 gm/dl. Cyanosis is easily seen in mucous membrane and thin skin areas like lips, fingers, ear lobes, also nail bed. In polycythaemia, cyanosis is very common because of the large amount of Hb in the blood whereas in anaemia, cyanosis is rare because it is difficult for there to be enough deoxygenated Hb to produce the cyanotic color. Cyanosis is divided into 2 types:

- [1] **Central cyanosis:** In which there is *Hb-undersaturation* or an abnormal Hb derivative, and the mucous membranes and skin are both affected.
- [2] **Peripheral cyanosis:** Which is due to a slowing of blood flow to an area and abnormally *great extraction of O<sub>2</sub>* from normally saturated arterial blood. It results from vasoconstriction and diminished peripheral blood flow, such as occurs in moderate cold exposure, shock, heart failure, and peripheral vascular disease. Often, in these conditions, the mucous membranes of the oral cavity may be

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spared. In very cold weather cyanosis does not develop, because the drop in skin temperature inhibits the dissociation of oxy Hb and the  $O_2$  consumption of the cold tissues is decreased. Cyanosis does not occur in anaemic or histotoxic hypoxia. In CO poisoning, the color of reduced Hb is obscured by the cherry red color of carboxyHb. A discoloration of the skin and mucous membranes similar to cyanosis is produced by high circulating levels of met Hb.

**Hypercapnia:** It means excess  $CO_2$  in the body fluids. Hypercapnia is associated with hypoxia when hypoxia is caused by hypoventilation or by circulatory deficiency. Hypoxia resulting from poor diffusion through pulmonary membrane, serious hypercapnia usually does not occur because  $CO_2$  diffuses 20 times as rapidly as  $O_2$ .

**$O_2$  Therapy:** In hypoxia,  $O_2$  therapy is of great value, especially in certain types of hypoxia (such as low atmospheric  $O_2$ , hypoventilation hypoxia, diffusional hypoxia) and of slight value in hypoxia due to other causes. In chronic hypoxia,  $O_2$  lack becomes a far more powerful stimulus to respiration than usual, sometimes increasing the ventilation as much 5-7 times. Therefore, during  $O_2$  therapy, relief of the hypoxia occasionally causes the level of pulmonary ventilation to decrease so low that lethal levels of hypercapnia develop. For this reason,  $O_2$  therapy in hypoxia is sometimes contraindicated.

**$O_2$  Toxicity:** Administration of 100%  $O_2$  has been demonstrated to exert toxic effects. The toxicity seems to be due to the production of the superoxide anion ( $O_2^-$ ) and  $H_2O_2$ . When 80-100%  $O_2$  administered for periods of 8 hours or more the respiratory passages become irritated, causing substernal distress, nasal congestion, sore throat and coughing. Exposure for 24-48 hours causes lung damage as well. The reason  $O_2$  produces the irritation is probably due to inhibition of the ability of lung macrophages to kill bacteria, and surfactant production is reduced.

### Lung Volumes And Capacities

Pulmonary ventilation can be recorded by using the *spirometer* and the process called *spirometry* by which volume of air that is moved in and out of the lung can be recorded. The volumes and capacities of lungs are:

[1] **The tidal volume (TV):** Is the volume of air inspired or expired with each normal breath and it is about **500 ml** in average young adult man.

[2] **The inspiratory reserve volume (IRV):** Is the extra volume of air that can be inspired over and beyond tidal volume and it is about **3000 ml**.

[3] **The expiratory reserve volume (ERV):** Is the amount of air that can be expired after the normal tidal expiration, which is about **1100 ml**.

[4] **The residual volume (RV):** Is the volume of air still remaining in the lungs after the most forceful expiration, which is about **1200 ml**. This is important because it provides air in the alveoli to aerate the blood even between breaths which otherwise the concentration of oxygen and carbon dioxide in the blood would rise and fall markedly with each respiration, which would certainly be disadvantageous to the respiratory process.

This volume cannot be measured directly by spirometer. Therefore, an indirect method must be used usually the *helium dilution method*. Once the functional residual capacity (FRC) has been determined, the residual volume can then be determined by subtracting the expiratory reserve volume from the functional residual capacity, i.e.  $RV = FRC - ERV$ .

The other way for determination of lung RV is by using body plethysmograph.

[5] **The inspiratory capacity (IC)** =  $TV + IRV = 500 + 3000 = 3500 \text{ ml}$ . This is the amount of air that a person can breathe beginning at the normal expiratory level and distending the lungs to the maximum amount.

[6] **The functional residual capacity (FRC)** =  $ERV + RV = 1100 + 1200 = 2300 \text{ ml}$ . This is the amount of air remaining in the lungs at the end of normal expiration.

[7] **The vital capacity (VC)** =  $IRV + TV + ERV = 3000 + 500 + 1100 = 4600 \text{ ml}$ . This is the maximum amount of air that a person can expel from the lungs after filling the lungs first to their maximum extent, and then expiring to the maximum extent.

Vital capacity can be decreased markedly in restrictive lung diseases (paralysis of the respiratory muscles, tuberculosis, lung cancer, fibrotic pleurisy, pulmonary vascular congestion and edema as in left sided heart failure) and may be normal in obstructive lung diseases (asthma, chronic bronchitis, emphysema). When the vital capacity is reduced to about 40% of normal, the patient can no longer perform even the simplest movements without becoming breathless.

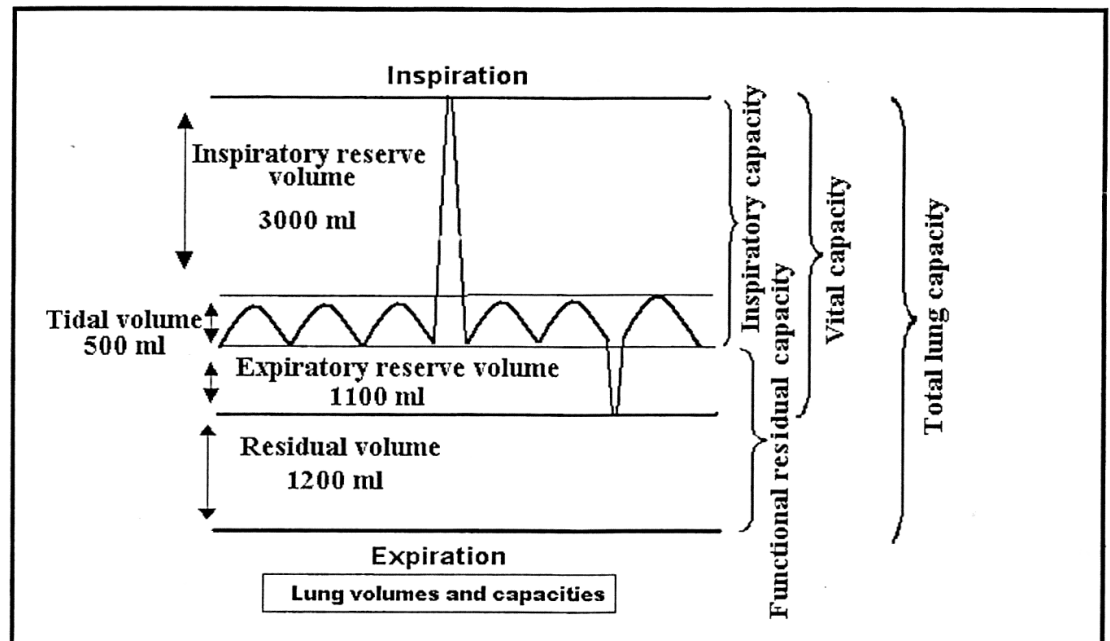
[8] **The total lung capacity (TLC)** =  $VC + RV = 4600 + 1200 = 5800 \text{ ml}$ . This is the maximum volume to which the lungs can be expanded with the greatest possible inspiratory effort.

All pulmonary volumes and capacities are about 20-25% less in women than men, and they are greater in large athletic persons than in small and asthenic persons. Pulmonary volumes and capacities change with the position of the body, most of them decreasing when the person lies down and increasing on standing, this change with position is caused by two factors:

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[A] - a tendency for the abdominal contents to press upward against the diaphragm in the lying position.

[B]-an increases in the pulmonary blood volume in the lying position, which correspondingly decreases the space available for pulmonary air.



## Lung Function Tests

**1.Forced vital capacity (FVC):** It is the maximum volume of air expired forcefully following maximum inspiration, a normal subject this is accomplished in 3-4 sec.

**2.Timed vital capacity (forced expiratory volume-1 sec, FEV1):** It is the volume of air expired during the first second of forceful expiration.

**3.Percent vital capacity (FEV1%):**  $[FEV1/VC] \times 100$ . In normal subject, the FEV1% is at least 80%. However, in obstructive lung diseases like asthma, FEV1% is markedly reduced while normal in restrictive lung diseases.

**4. Peak expiratory flow (PEF):** It is the maximum airflow obtained during maximum expiratory effort after maximum inspiration. When a person expires with great force through *Wright peak flow meter*, the expiratory airflow reaches a maximum flow beyond which the flow cannot be increased even with greatly increased additional force. This is because the pressure that force the air outside also tends to collapse the bronchioles at the same time, thus greatly increasing the airway resistance and opposing the movement of the air to the exterior. The maximum expiratory flow is much greater when the lungs are filled with a large volume of air than when they are almost empty. The curve recorded for maximum expiratory flow was achieved by asking the subject first to inhale as much air as possible and then expires with maximum expiratory effort until he can expire no more. A normal subject can quickly reach a maximum expiratory airflow over **400 liters/min.** Maximum expiratory flow is reduced in cases of restrictive (constrictive) lung diseases like fibrotic diseases of lungs, kyphosis, scoliosis, fibrotic pleurisy, and in obstructive lung diseases like asthma, and emphysema. In restrictive lung diseases there is a reduction in the compliance of the lungs and consequently there is a reduction in total lung capacity. Therefore, the maximal expiratory flow cannot rise to equal that of the normal curve.

In obstructive lung diseases, there is much more difficulty in expiration than on inspiration, because the closing tendency of the airways is greatly increased by positive pressure in the chest during expiration, while negative pleural pressure of inspiration actually pulls the airway open at the same time that it expands the alveoli. Therefore, because of the obstruction of the airways and its tendency to collapse easily during expiration, the maximum expiratory flow is greatly reduced.

**5. The Forced Expiratory Flow<sub>25%-75%</sub> (FEF<sub>25%-75%</sub>):** The FEF<sub>25%-75%</sub> is the average flow rate that occurs during the middle 50 percent

of an FVC measurement. This average measurement reflects the condition of medium- to small-sized airways. The average  $FEF_{25\%-75\%}$  for normal healthy men aged 20 to 30 years is about 4.5 L/sec (270 L/min), and for women of the same age, about 3.5 L/sec (210 L/min). The  $FEF_{25\%-75\%}$  decreases with age and in obstructive lung disease. In obstructive lung disease, flow rates as low as 0.3 L/sec (18 L/min) have been reported. The  $FEF_{25\%-75\%}$  is also decreased in patients with restrictive lung disorders, primarily because of the low vital capacity associated with restrictive lung disorders. Although the  $FEF_{25\%-75\%}$  has no value in distinguishing between obstructive and restrictive disease, it is helpful in further confirming—or ruling out—an obstructive pulmonary disease in patients with borderline low FEV<sub>1</sub>.

**6.The minute respiratory volume (the minute ventilation):**The minute respiratory volume *is the total amount of new air moved into the respiratory passages each minute* and this is equal to TV (500 ml) x respiratory rate (about 12 breaths / min) = **6000 ml**. Respiratory rate is between 14-34 breaths / min between 2-4 years of age, 20-25 breaths/min between 5-14 years of life, and 10-18 breaths/min in adult subject.

**7.Test For Lung Diffusing Capacity:** The ability of the respiratory membrane to exchange a gas between the alveoli and the pulmonary blood can be expressed in quantitative terms by its *diffusing capacity*, which defined as the *volume of a gas that diffuses through the membrane each minute for a pressure difference of 1 mm Hg*.

Gas dilution method ( Helium and CO mixture in low concentrations) is used to test lung diffusing capacity(**DLCO-single breath test**). In average young male adult, the diffusing capacity for oxygen under resting conditions average **21-25 ml/min/mm Hg**. Since the diffusion coefficient of CO<sub>2</sub> is **20** times that of O<sub>2</sub>, one would expect a diffusing capacity for CO<sub>2</sub> under resting conditions of about **400-450 ml/min/mm Hg** and during

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exercise of about 1200-1300 ml/min/mm Hg. The importance of this high diffusing capacity for CO<sub>2</sub> is that: *when the respiratory membrane becomes progressively damaged, its capacity for transmitting O<sub>2</sub> into the blood is often impaired enough to cause death of the person while CO<sub>2</sub> diffusion can still occur in adequate amounts.* However, the patient's life can be maintained by intensive O<sub>2</sub> therapy that overcomes the reduction in O<sub>2</sub> diffusing capacity.