RESPIRATORY SYSTEM PHYSIOLOGY

Objectives after studying this chapter, you should be able to . . .

1. Explain the anatomical and physiological classification of the respiratory system.
2. Describe the functions of pleura.
3. Expound the processes of inspiration and expiration.
4. Define the general classification of lung disorders.
5. Identify the role of surfactant in respiratory physiology.
6. Explain the compliance of the lung and the work of breathing.
7. Describe the pulmonary volumes and capacities and their measurement.
8. Identify the dead space.
9. Expound the respiratory passageways resistance.
10. Explain nervous and humeral control over the airway smooth muscles.
11. Describe the respiratory unit, respiratory membrane, and the factors that affect rate of gas diffusion through the respiratory membrane.
12. Identify ventilation – perfusion ratio of the lungs and its regulation.
13. Describe the transport of oxygen and carbon dioxide in the blood and body fluids.
14. Expound O_2-Hb dissociation curve and its importance in loading and unloading of oxygen by the blood.
15. Explain the brainstem respiratory center control over respiration.
16. Describe the factors that regulate respiration through modulation of the activity of respiratory center.
17. Expound the pulmonary blood flow.
18. Define hypoxia and its types.
19. Define hypercapnia.
20. Describe specific ventilatory patterns.

The functions of the respiratory system are:
- **Gas exchange**
- **Acid-base balance**
- **Phonation**
- **Pulmonary defense and metabolism**
- **Handling of bioactive materials**

Anatomically the respiratory system consists of:
1. **Upper respiratory tract** which consists of **nose** and **pharynx**.
2. **Lower respiratory tract** which consists of **larynx**, **trachea**, **bronchi** (decrease in diameter and length with each successive branching but the sum of their cross-sectional areas actually increases), **bronchioles** (about 1 mm in diameter), **terminal bronchioles** (about 0.5 mm in diameter), **respiratory bronchioles**, **alveolar ducts**, **alveolar sacs**, and **alveoli** (figure 6.1).

The epithelium of the bronchial tree is ciliated except in the distal ends of the respiratory bronchioles and beyond. The ciliated epithelium functions as a mucociliary escalator. That is, the mucus traps inhaled debris and then the ciliary beating drives the mucus up to the pharynx, where it is swallowed or coughed to the exterior.

The wall of alveoli composed of three types of cells and these are **[1] type I cell,** are the major sites of alveolar gas exchange, **[2] type II cell**, are the primary source of pulmonary surfactant and **[3] macrophages**. A mucous layer, commonly referred to as the mucous blanket, covers the epithelial lining of the tracheobronchial tree. The mucus is produced by **(1) the goblet cells**, and **(2) the submucosal or bronchial glands**.
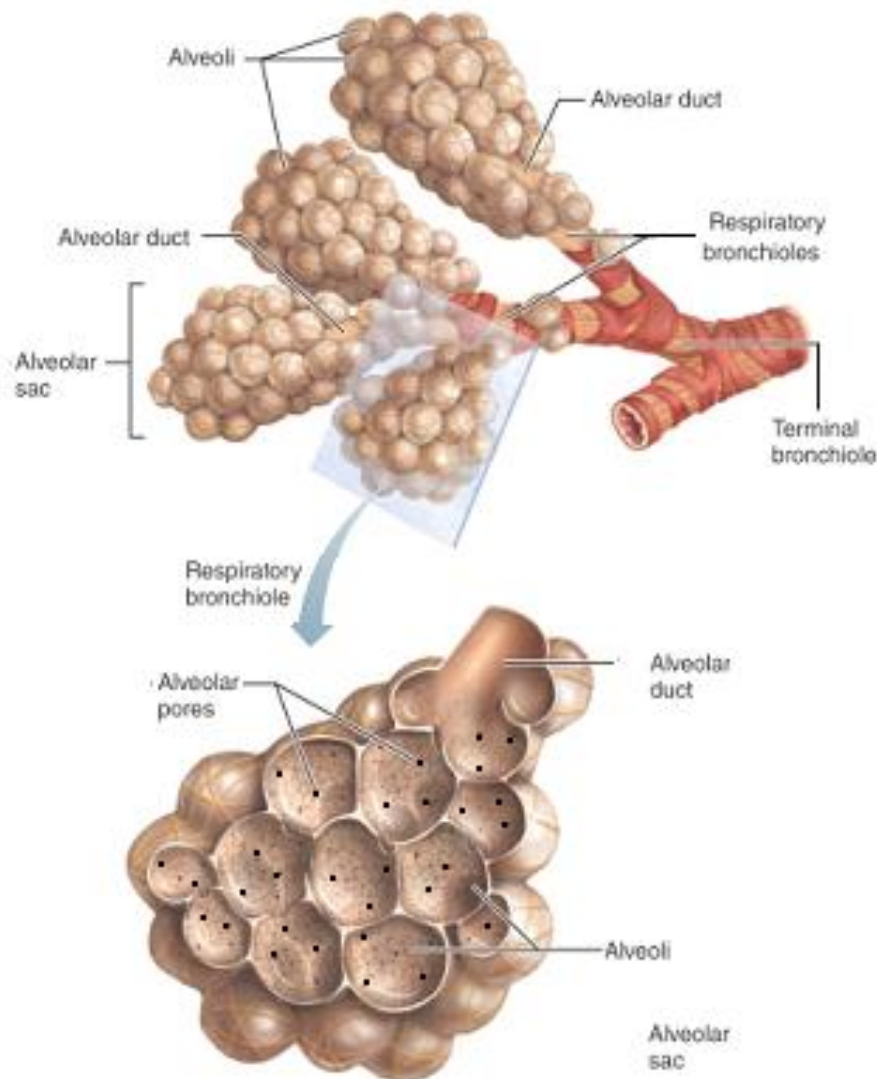

Figure 6.1: Respiratory zone of the airway passages.

- Sympathetic discharge through adrenal glands (no direct sympathetic innervation) causes **pulmonary vasoconstriction, bronchodilation,** and **decreases glandular secretions**.
- Parasympathetic discharge causes **pulmonary vasodilation**, **bronchoconstriction**, and **increase glandular secretion**.

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.

Physiologically, the respiratory system can be divided into:
1. Conducting zone: Starts from the nasal cavity and ends with terminal bronchioles (16 generations).
2. Respiratory zone: Starts with respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli (7 generations).

Figure 6.2: The pleurae of the lung.

The Pleura: The lungs are surrounded by , a serous membrane which folds back upon itself to form a two-layered, membrane structure. The thin space between the two pleural layers is known as the **pleural space**; it normally contains a small amount of **pleural fluid** (a few milliliters) (figure 6.2). The outer pleura (parietal pleura) is attached to the chest wall. The inner pleura (visceral pleura) covers the lungs and adjoining structures, i.e. blood vessels, bronchi and nerves. The visceral and parietal pleurae normally slide against each other, so that the lungs are stuck to the chest wall in the same manner as two wet pieces of glass sticking to each other. The parietal pleura is highly sensitive to pain; the visceral pleura is not, due to its lack of sensory innervation. The functions of the pleura are:

1. Lubrication: The pleurae are coated with lubricating pleural fluid which allows the pleurae to slide effortlessly against each other during ventilation.
2. Holding the lungs and rib cage together: Surface tension of the pleural fluid and the negative intrapleural pressure lead to close opposition of the lung surfaces with the chest wall. Therefore, movements of the chest wall are coupled to movements of the lungs.
3. Prevents lung collapse (creation of pressure gradient): This is achieved by the

Figure 6.3: Intrapulmonary and intraplural pressure relationships.

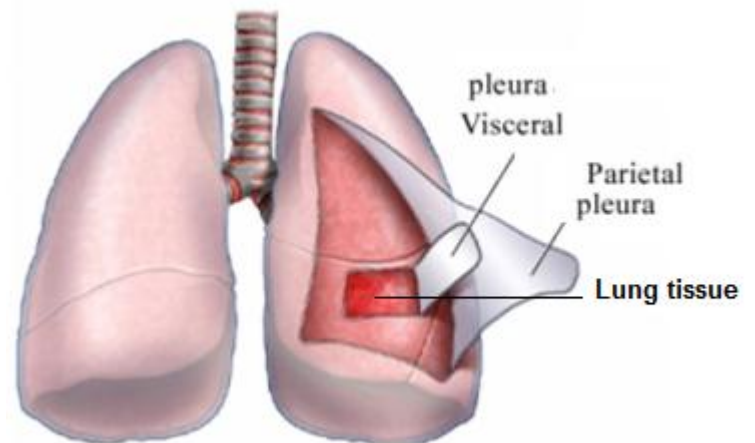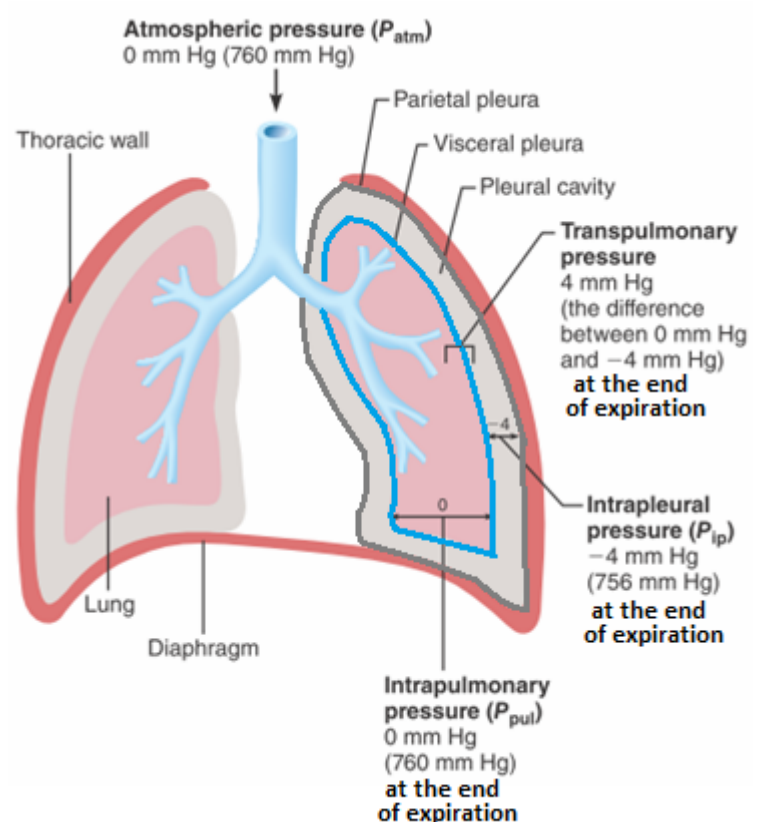negative pleural pressure created by tendency of lung to collapse (the elastic recoil of the lung is inward)

and chest wall to expand (the elastic recoil of the chest wall is outward). Intrapleural pressure (or intrathoracic pressure) (figure 6.3) is always slightly below atmospheric pressure **(– 4 mm** Hg, i.e. about 756 mmHg), at the **end of expiration** and **– 6 mm Hg** at the **end of inspiration**. The difference between pleural pressure and alveolar pressure is the **transpulmonary pressure** (figure 6.3) <u>which is the driving pressure for lung expansion</u>**.** The difference between the alveolar pressure and the body surface pressure is called **transthoracic pressure.** The difference between the mouth pressure and the alveolar pressure is called **transairway pressure.**

Pneumothorax is the presence of air in the pleural space, which causes collapse of the lung on that side (atelectasis) away from the chest wall (figure 6.4). The pleural space is only a potential space because the serous fluid keeps the pleural membranes adhering to one another, and the intrapleural pressure is always slightly below atmospheric pressure. Should air at atmospheric pressure enter the pleural cavity, the suddenly higher pressure outside the lung will contribute to its collapse (the other factor is the normal elasticity of the lungs). When air is introduced into the pleural space, the pleural pressure becomes equal to atmospheric pressure—the chest wall springs outward and the lungs collapse. A spontaneous pneumothorax, without apparent trauma, may result from rupture of weakened alveoli on the lung surface. Pulmonary diseases such as emphysema may weaken alveoli. Puncture wounds of the chest wall also allow air into the pleural space, with resulting collapse of a lung. In severe cases, large amounts of air push the heart, great vessels, trachea, and esophagus toward the opposite side (mediastinal shift),

Figure 6.4: Pneumothorax of the lung.

putting pressure on the other lung and making breathing difficult. This is called tension pneumothorax, and requires rapid medical intervention to remove the trapped air.
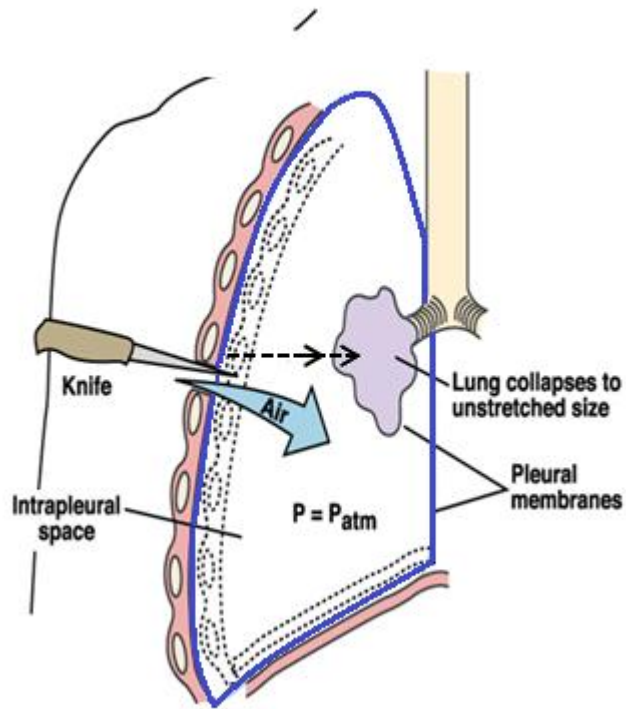
4. Compartmentalization: The pleurae, mediastinum, and pericardium compartmentalize the thoracic organs and prevent infections of one organ from spreading easily to neighboring organs.

When the pleural membrane becomes inflamed in a condition called **pleurisy**, a sticky discharge roughens the pleura, causing painful irritation. An accompanying bacterial infection means that pus accumulates in the pleural cavity in a condition known as **empyema**.

Thoracic cage: Its functions are:
- Respiratory pump.
- Protects lungs.
- Prevents collapse of lungs.

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 breaths 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 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. Smaller size particles settle out in the lower respiratory tract as a result of gravitational precipitation and adhere to the fluid lining the lower respiratory tract or diffuse to the wall of the respiratory tract and some of them remain suspended in the alveolar air and are later expelled by expiration (for instance, the nicotine particles size is about 0.3 micron). 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.

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] Gas exchange between alveoli and blood (external respiration) and between blood and tissues (internal respiration).

[3] Transport of oxygen and carbon dioxide in the blood and body fluids to and from the cells.

[4] Regulation of ventilation.

Pulmonary ventilation: This includes inspiration and expiration.

[A] Inspiration: It is an **active process** due to increase in the chest cage volume causing the lungs to be expanded. Chest cage volume is increased by:

[1] Downward movement of the diaphragm (supplied by phrenic nerves, originating from C4, with small contributions from C3 and C5) which 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] 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. When the rib cage is elevated due to contraction of **external intercostal muscles**, the ribs are now projected directly forward so that the sternum now also moves forward away from the spine, making the anterioposterior thickness of the chest greater during maximum inspiration. The foreword movement of sternum accounts for **25%** of the change in intrathoracic volume during quiet inspiration. The other **accessory inspiratory muscles** for raising the rib cage are **sternocleidomastoid**, **anterior serrati**, and **scalenis**. These muscles are not used for respiration during normal quiet breathing but are used during heavy breathing and exercise.

Pressure changes during respiration: At the beginning of inspiration, the alveolar pressure is equal to atmospheric pressure. As the chest cage volume increases at the beginning of inspiration, it pulls the parietal pleura away from visceral pleura causing a further decrease in the intrapleural pressure (figure 6.5). The decrease

a Changes in intrapulmonary pressure during a single respiratory cycle

b Changes in intrapleural pressure during a single respiratory cycle

c A plot of tidal volume, the amount of air moving into and out of the lungs during a single respiratory cycle

Figure 6.5: Intra-alveolar and intraplural pressure changes during respiratory cycle.

in the intrapleural pressure in turn pulls the visceral pleura that cover the lung and consequently the alveoli to expand. As the alveoli are expanded, alveolar pressure decreases to less than atmospheric pressure (i.e. becomes negative) (figure 6.5). The pressure gradient between the atmosphere and the alveoli now causes air to flow into the lungs, and airflow will continue until the pressure gradient dissipates. Because lung pressures are expressed relative to atmospheric pressure, alveolar pressure is said to be zero (i.e., equal to atmospheric pressure) at the beginning of inspiration (i.e., at the end of expiration). During expiration, the alveolar pressure becomes greater than atmospheric pressure
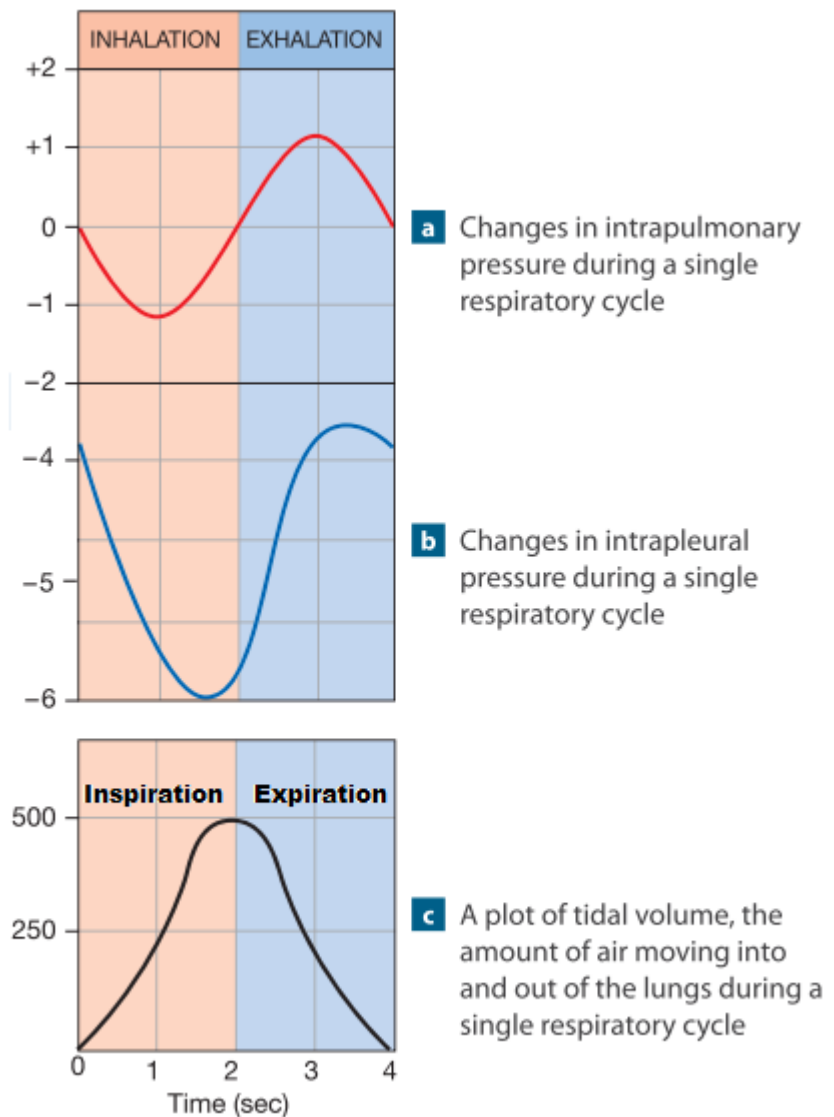
(i.e., becomes positive) because alveolar gas is compressed by diaphragm, rib cage, and the elastic forces of the lung. Thus, alveolar pressure is now higher than atmospheric pressure, and the pressure gradient is reversed, and air flows out of the lungs.

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

   [1] Relaxation of diaphragm and the inspiratory muscles which cause compression on the lungs.

   In contrast, during heavy breathing such as in exercise or when there is airway obstructive disease like **asthma**, however, the compression forces are not powerful enough to cause the necessary rapid expiration, so that other **accessory expiratory muscles** such as abdominal muscles (**abdominal recti,** and **transverse abdominus**) and **internal intercostal muscles** are contracted and added to the force needed for rapid expiration.

   [2] Elastic recoil tendency of the lung. The lungs have a continual elastic tendency to collapse and therefore to pull away from the chest wall. It is caused by two different factors:

[A]. The presence of elastic fibers (elastin) 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 thirds 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.

   The intrapleural pressure may become positive during forced expiration. Maximal intrapleural pressure (i.e. 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, or coughing. Normally, the maximal expiratory pressure that can be achieved is 75-110 mm Hg greater than atmospheric pressure. As lung volume decreases, the maximal achievable expiratory pressure decreases as well.

The Heimlich maneuver has received much well deserved publicity, and indeed it is a life-saving technique. If a person is choking on a foreign object (such as food) lodged in the pharynx or larynx, the air in the lungs may be utilized to remove the object. The physiology of this technique is illustrated in the accompanying figure 6.6. The person performing the maneuver stands behind the choking victim and puts both arms around the victim's waist. One hand forms a fist that is placed between the victim's navel and rib cage (below the diaphragm), and the other hand covers the fist. It is important to place hands correctly, in order to avoid breaking the victim's ribs. With both hands, a quick, forceful upward thrust is made and repeated if necessary. This forces the diaphragm upward to compress the lungs and force air out. The forcefully expelled air is often sufficient to dislodge the foreign object.
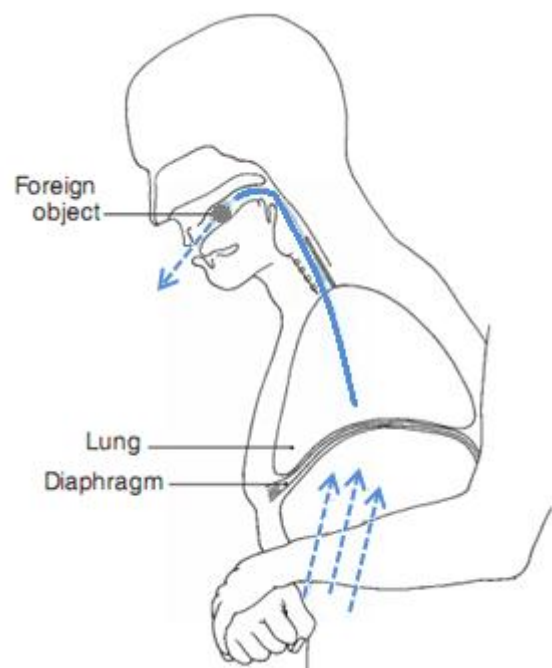
Figure 6.6: The Heimlich maneuver.

If the trachea becomes occluded through inflammation, excessive secretion, trauma, or aspiration of a foreign object, it may be necessary to create an emergency opening into this tube so that ventilation can still occur. A **tracheotomy** is the procedure of surgically opening the trachea, and a **tracheostomy** involves the insertion of a tube into the trachea to permit breathing and to keep the passageway open. A tracheotomy should be performed only by a competent physician because of the great risk of cutting a recurrent laryngeal nerve or the common carotid artery.

Types of Breathing:
[A]. **Diaphragmatic Breathing** (abdominal Breathing): Involves using the diaphragm mostly. It is deep and slow breathing seen mostly during sleep or deep relaxation.
[B]. **Costal Breathing**: Involves using the intercostal muscles mostly. It is shallow and fast breathing seen mostly after running or while "panting".

We typically use diaphragmatic breathing at minimal levels of activity. As we need increased volumes of air, our inspiratory movements become larger and the contribution of rib movement increases. Even when we are at rest, costal breathing can predominate when abdominal pressures, fluids, or masses restrict diaphragmatic movements. For example, pregnant women rely more and more on costal breathing as the enlarging uterus pushes the abdominal organs against the diaphragm.

General classification of lung disorders: Lung disease is any disease or disorder where lung function is impaired. There are three major physiologic categories of lung diseases:
1. **Obstructive lung diseases:** Difficulty to exhale all the air in the lungs. A decrease in the exhaled air flow caused by a narrowing or blockage of the airways, such as with **asthma** , **emphysema** , and **chronic bronchitis**.
2. **Restrictive lung diseases:** Difficult to get air in to the lungs. A decrease in the total volume of air that the lungs are able to hold. Often, this is due to a decrease in the elasticity of the lungs themselves or caused by a skeletal or neural problems related to the expansion of the chest wall during inhalation such as:
   - **Pulmonary fibrosis** (as in asbestosis, silicosis, and tuberculosis),
   - **Neuromuscular diseases** (as in paralysis of respiratory muscles).
   - **Skeletal abnormalities** (such as Kyphosis, Scoliosis).
3. **Gas diffusion diseases:** A defect in the ability of the tissue of the alveoli to move oxygen into a person's blood through the respiratory membrane.

The role of surfactant: A lipoprotein substance which is present in the fluid lining the alveoli, and is secreted from type II alveolar epithelium. Surfactant may be present as early as 24th week of gestation and is almost always present by gestational week 35. A lecithin / sphingomyelin ratio greater than 2:1 in amniotic fluid reflects mature levels of surfactant. It 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**. Surface tension refers to the tendency of water molecules to pull toward each other and to collapse a sphere. In the absence of surfactant, about –20 to –30 mm Hg intrapleural pressure is required to overcome the collapse tendency of the alveoli due to high surface tension force.

Hyaline membrane disease (respiratory distress syndrome): Occurs in some premature babies who do not secrete adequate quantities of surfactant. The transpulmonary (transmural) pressure which is the difference between the intrapulmonary pressure and the intrapleural pressure required for the first breath of life is fifteen to twenty times that required for subsequent breaths, and an infant with respiratory distress syndrome must duplicate this effort with every breath. Fortunately, many babies with this condition can be saved by mechanical ventilators and by exogenous synthetic surfactant

delivered to the baby's lungs by means of an endotracheal tube. The mechanical ventilator and exogenous surfactant help to keep the baby alive long enough for its lungs to mature, so that it can manufacture sufficient surfactant on its own.

[2] It stabilizes the sizes of the alveoli: Surfactant plays an important role in stabilizing the sizes of the alveoli ensure that the **alveoli in any one area of the lung all remain approximately the same size**. 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.

[3] It prevents accumulation of edema fluid in the alveoli: 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 an adequate amount 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 sever pulmonary edema.

There are many causes of pulmonary surfactant deficiency like hypoxia, acidosis, pulmonary congestion, pulmonary edema, pneumonia, adult respiratory distress syndrome (ARDS) and many others.

Expansibility of the lungs and thorax: Compliance: It is a measure of the ease with which the lung inflates. This is expressed as the **volume** increase in the lungs for each unit increase in alveolar **pressure** or for each unit decrease in pleural pressure (figure 6.7 A).

Compliance = [V2-V1] / [P2-P1]. The compliance and elasticity (elastance) are inversely related, i.e., **Compliance = 1/ elastance**. Inflation of the lung (inspiration) follows a different curve than deflation of the lung (expiration), i.e. during expiration; the compliance of the lung is greater which means that the volume is greater for a given pressure. This difference is called **hysteresis** (figure 6.7 B). Hysteresis is primarily attributable to the interaction of surface tension and surfactant.

The Compliance of the normal lungs and thorax combined (total pulmonary Compliance) is about 200 ml / cm H_2O. That is, every time the alveolar pressure is

Figure 6.7: Lung-chest wall pressure-volume curve.

increased or intrapleural pressure is decreased by 1 cm of water, the lungs expand 200 ml. The lungs alone, when removed from the chest, are almost twice as distensible as the lungs and thorax together, because the thoracic cage itself must also be stretched when the lungs are expanded in situ.
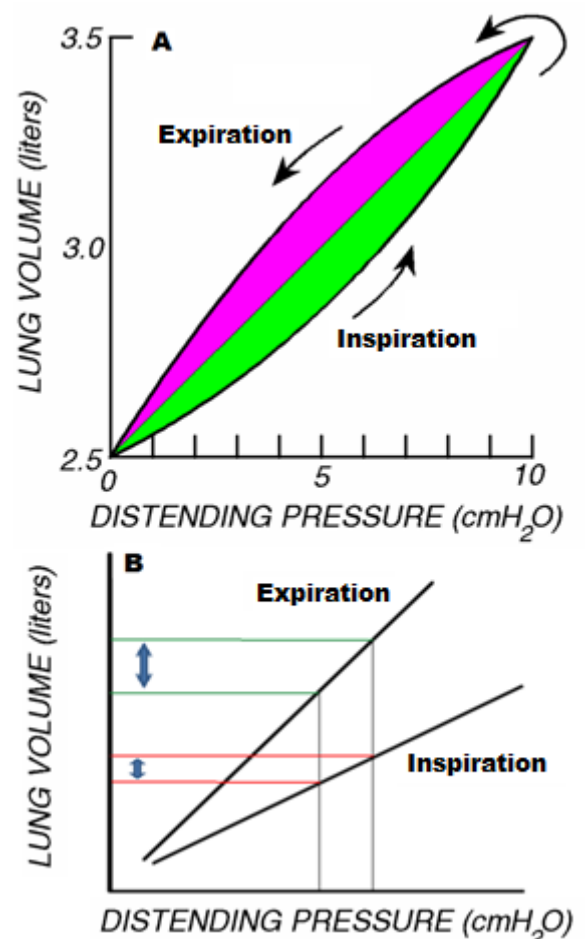
Furthermore, **the larger is the lung volumes**, the less is the compliance of it. <u>This means that the lungs are stiffer at high lung volumes</u>.

Any conditions that restrict expansion of the lungs (**restrictive lung diseases**) cause abnormal low compliance such as:

[1] Lack of surfactant.

[2] Pulmonary fibrosis, pulmonary edema.

[3] Pleural fibrosis.

[4] Decrease in the amount of ventilated lung tissue, such as removal of one lung (pneumonectomy).

[5] Diseases of the thoracic cage muscles such as paralyzed and fibrotic muscles.

[6] Diseases that reduces the expansibility of the thoracic cage such as deformities of the chest cage (as kyphosis, sever scoliosis).

Increased compliance is produced by the pathological processes that occur in **emphysema** (due to decrease of elastic fibers) 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.

Emphysema, a form of chronic obstructive pulmonary disease (COPD), is a degenerative disease in which the alveoli lose their interalveolar septum and their elasticity and cannot recoil (figure 6.8). In patients with emphysema, alveolar walls degenerate and small alveoli combine to form larger alveoli. The result is fewer alveoli, but alveoli with an increased volume and decreased surface area. Although the enlarged alveoli are still ventilated, surface area is inadequate for complete gas exchange, and the physiological dead space increases. Inhaled irritants damage the alveolar walls and the elastic connective tissue surrounding the alveoli. Macrophages migrate to the damaged areas and seem to produce an enzyme that also enhances the destruction of the protein elastin. As the alveoli break down, larger air cavities are created that are not efficient in gas exchange. In progressive emphysema, damaged lung tissues replaced by fibrous connective tissue (scar tissue), which further limits the diffusion of gases. In progressive emphysema, blood oxygen level is decreased and blood carbon dioxide level is increased. Accumulating carbon dioxide decreases the pH of body fluids; this is a respiratory acidosis. One of the most characteristic signs of emphysema is that the affected person must make an effort to exhale. The loss of lung elasticity (due to damaged elastin) makes normal exhalation an active process, rather than the passive process it usually is. The person must expend energy to exhale in order to make room in the lungs for inhaled air. This extra "work" required for exhalation may be exhausting for the person and contribute to the debilitating nature of emphysema.

Atelectasis of lung: Atelectasis means partial or complete collapse of the lung. With atelectasis of one lung, a collapse of the lung tissue occurs, which <u>increases the resistance to blood flow</u>. In addition, the <u>hypoxia in the collapsed lung</u> causes an <u>additional vasoconstriction</u>. The net effect is to <u>shift blood to the opposite, ventilated lung</u>, resulting in the majority of flow in the ventilated lung. A slight compromise in V/Q ratio will occur. With minimal changes in the V/Q ratio, there will be minimal changes in PO_2 and PCO_2. Thus there should be a slight decrease in arterial PO_2 and a slight decrease in saturation and content.

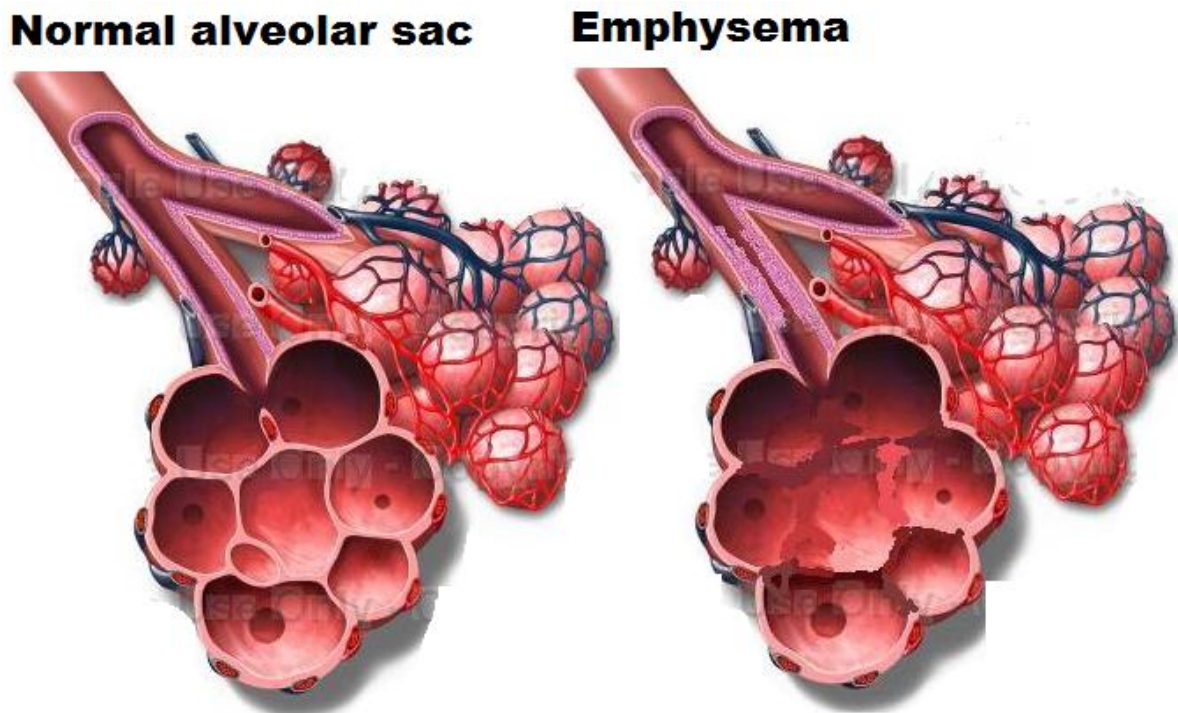**Normal alveolar sac**   **Emphysema**

Figure 6.8: Appearance of normal and emphysematous alveolar sac.

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_2 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 30% or more of the total energy expended by the body is for respiration alone which may in certain circumstances lead to death.

Efficiency of sketal muscles is defined as the ratio of mechanical work done to move air to the amount of metabolic energy used by the respiratory muscles. The respiratory system uses less than 3% of the body's total oxygen consumption at rest.

The pulmonary 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 (figure 6.9):
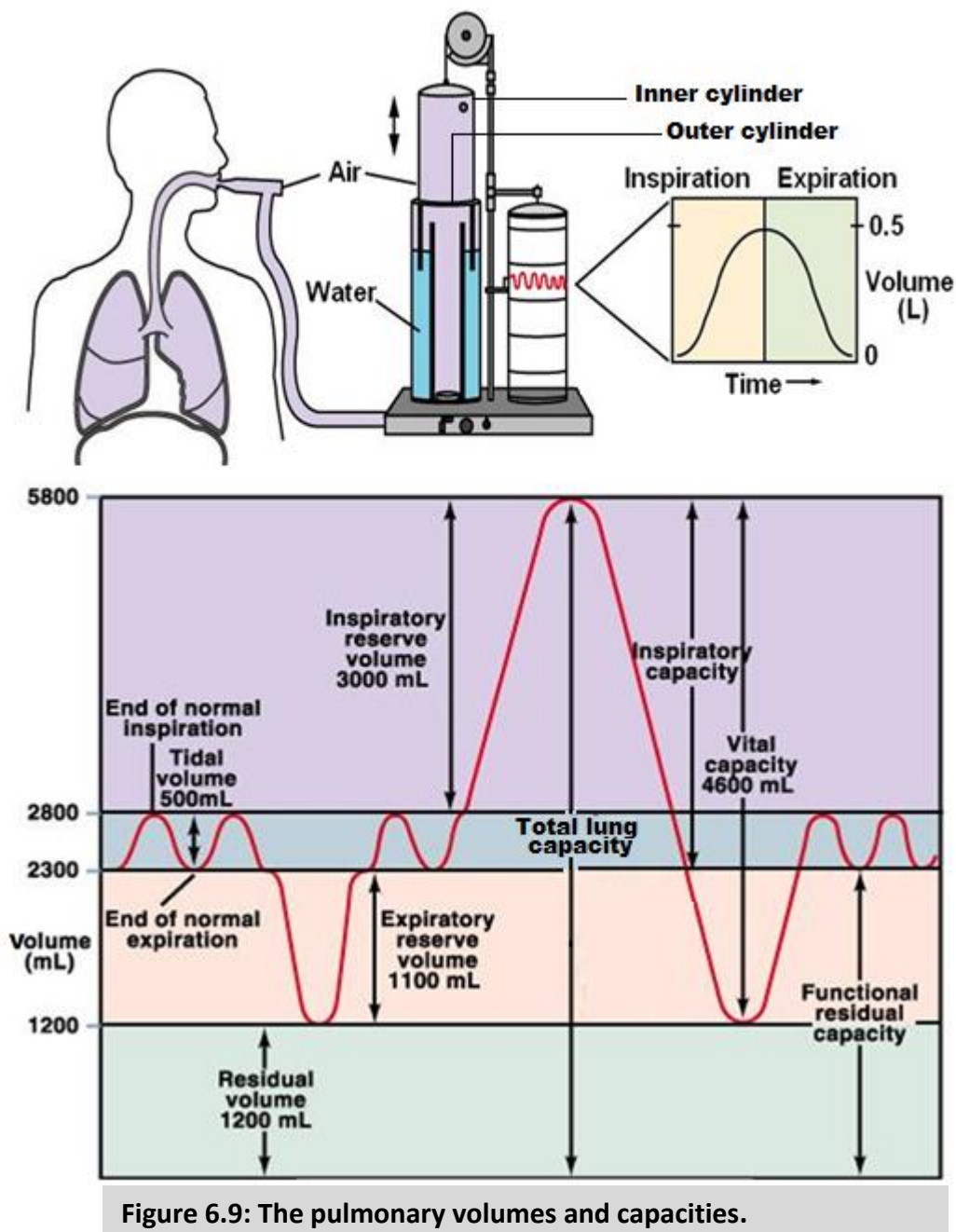

Figure 6.9: The pulmonary volumes and capacities.

[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 extra volume 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, indirect methods must be used as will be described later.

[5] The inspiratory capacity (IC) = TV +IRV = 500 +3000 = **3500 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 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 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 (similar to lung compliance) can be decrease 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, and 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 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 that 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:

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

[B]. An increase in the pulmonary blood volume in the lying position, which correspondingly decreases the space available for pulmonary air.

Figure 6.10 shows the changes in respiratory volumes and capacities in restrictive and obstructive lung diseases. In **restrictive lung diseases, TLC is reduced mainly due to reduction in VC**. While in **obstructive lung diseases**, **TLC is increased mainly to increase in RV**.
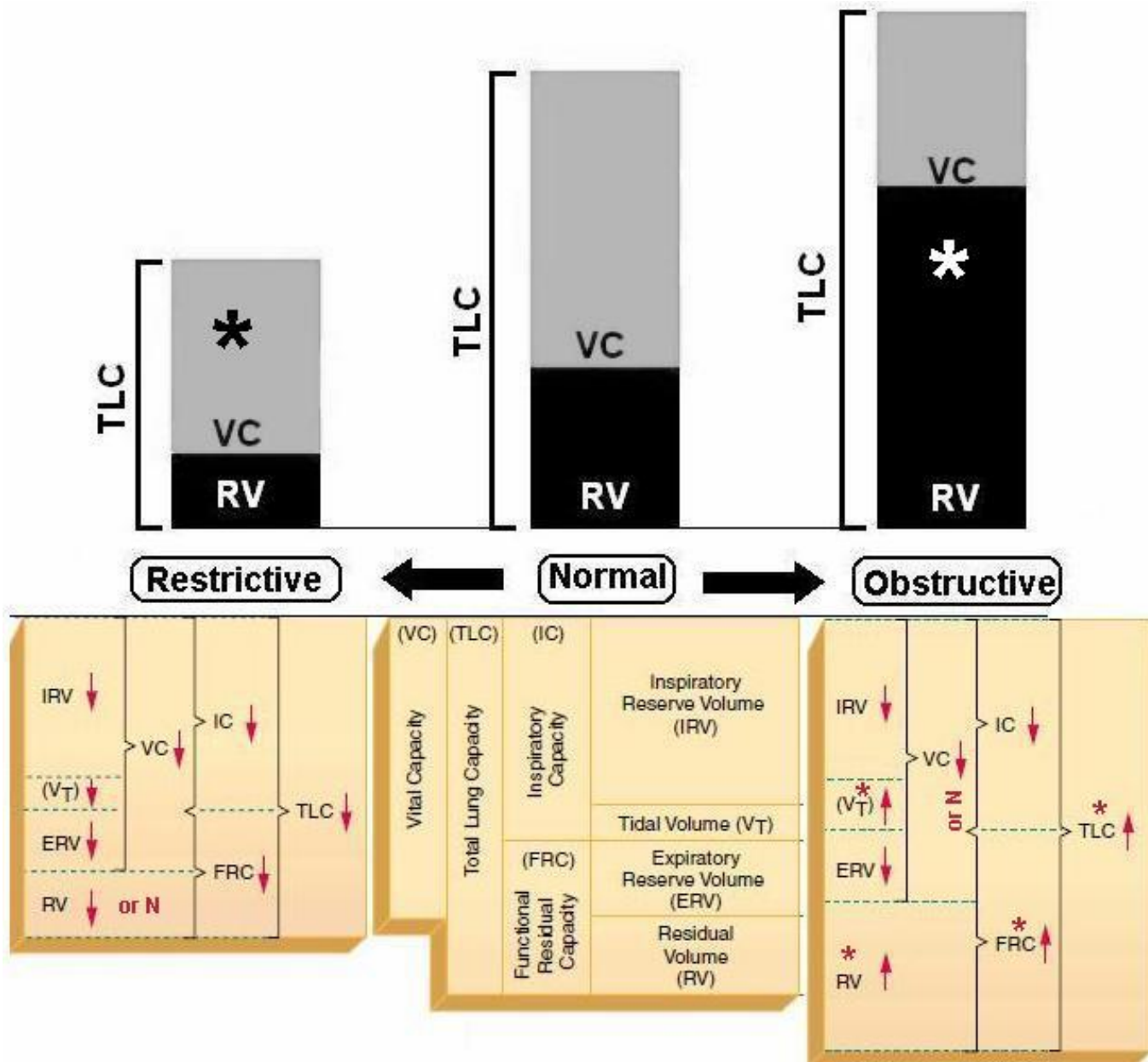
Figure 6.10: The pulmonary volumes and capacities in restrictive and obstructive lung diseases.

Residual volume measurement: This volume **cannot be measured directly by spirometer**. Therefore, indirect methods must be used. Among these methods is t**he closed circuit helium dilution technique.** A spirometer of known volume is filled with air mixed with helium at a known concentration. Before breathing from the spirometer, the person expires normally. At the end of **this expiration** the remaining volume of gases in the lungs is **exactly equal to the functional residual capacity (FRC)**. At this point the subject immediately begins to breathe from the spirometer, and the gases of the spirometer begin to mix the gases of the lungs, as a result, the helium becomes diluted by the functional residual capacity gases, and the volume of the functional residual capacity can then be calculated from the degree of dilution of the helium (figure 6.11), using the following formula;

V1 x C1 = V2 x C2

V1 = the initial volume of spirometer cylinder.

C1 = the initial concentration of helium in the spirometer cylinder.

C2 = the new volume (V1 + FRC).

V2 = the new concentration of helium in the spirometer cylinder.

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.

Other methods for the measurement of RV are the open circuit nitrogen washout technique and Body plethysmography method.
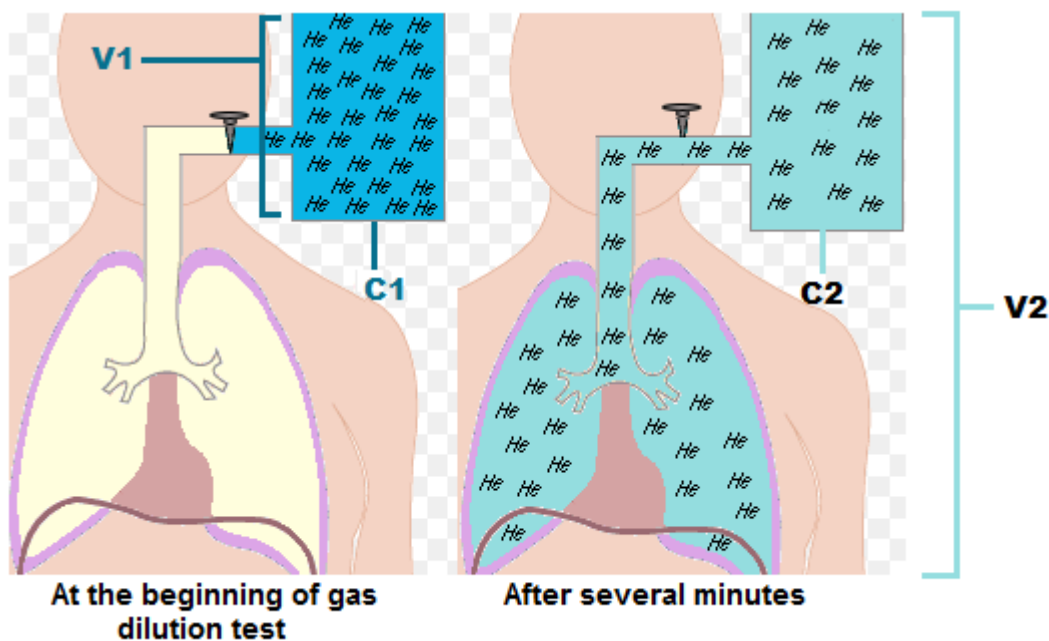

Figure 6.11: The basis of the closed circuit helium dilution technique

Peak expiratory flow (PEF): It is the maximum airflow obtained during maximum expiratory effort after maximum inspiration; the results may be recorded on a peak flow chart. 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 (figure 6.12). The descending portion of the curve is sometimes referred to as the "**effort-independent**" portion of the curve because the patient cannot increase expiratory flow rate to a higher level even when a greater expiratory effort is expended. This is because the pressure that forces 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.
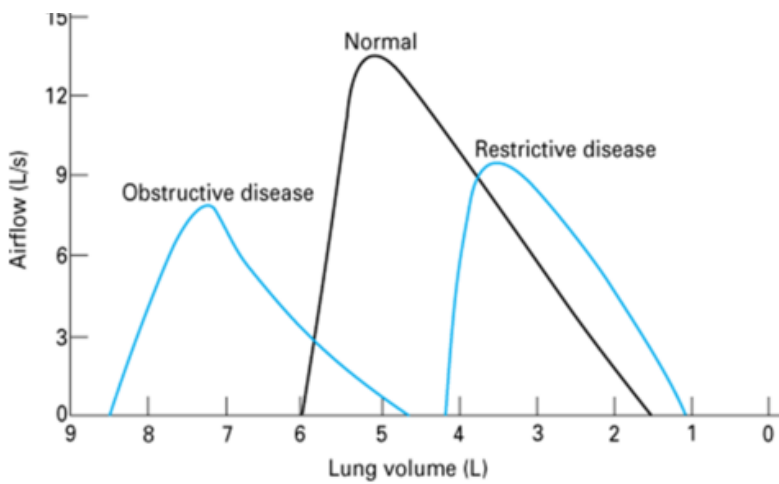

Figure 6.12: Peak expiratory flow in obstructive and restrictive lung diseases.

The maximum expiratory flow is much greater when the lungs are filled with a large volume of air than when they are almost empty. A normal subject can quickly reach a maximum expiratory airflow over **400-600 liters/min**. PEF is affected by age, gender, and by height of the subject (figure 6.13).
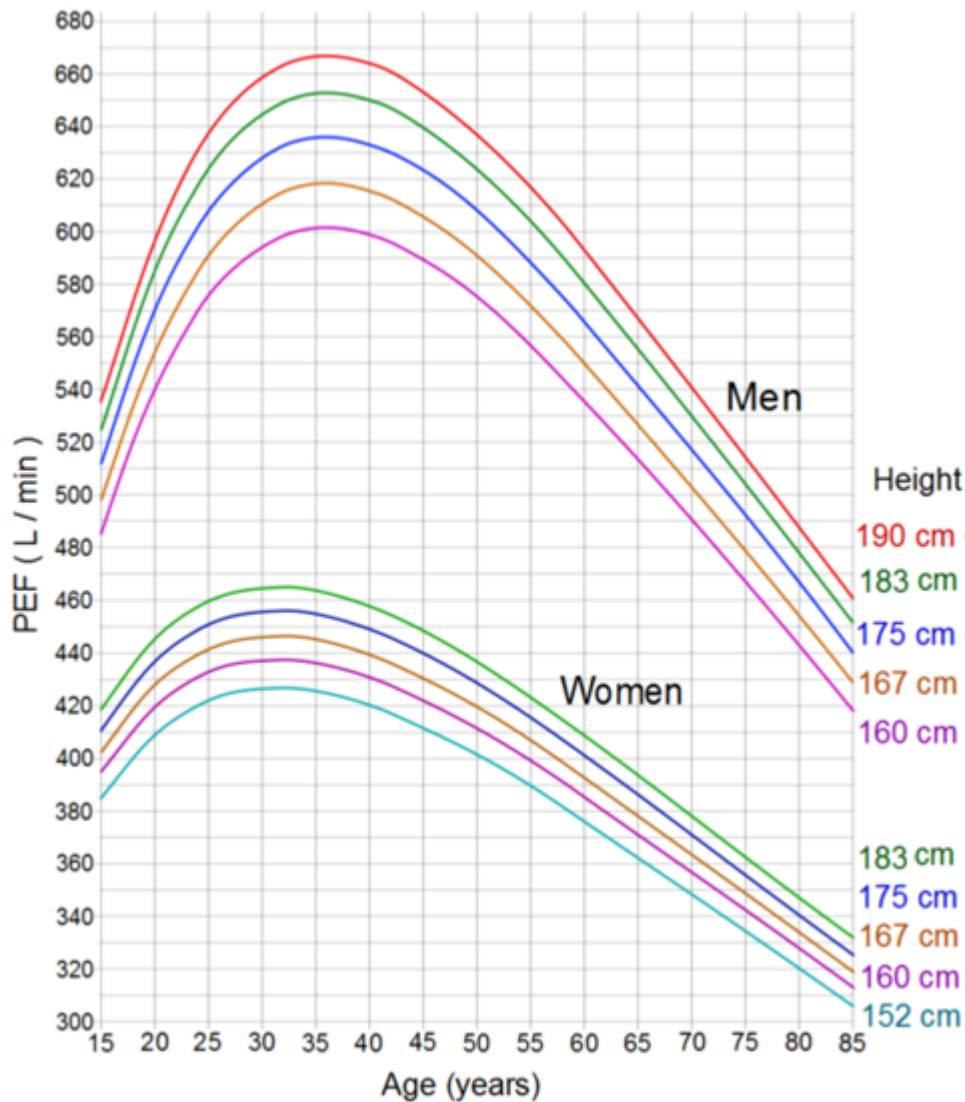
Figure 6.13: Normal values for peak expiratory flow (PEF).

Maximum expiratory flow is reduced in cases of restrictive 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.

Forced expiratory volume (FEV) measures how much air a person can exhale during a forced breath. The amount of air exhaled may be measured during the first (FEV1), second (FEV2), and/or third seconds (FEV3) of the forced breath. FEV1 is the volume of air expired during the first second of forced vital capacity. Normally it is about 80% of the total FVC (figure 6.14).

Forced vital capacity (FVC), is the maximum volume of air expired **forcefully** following maximum inspiration. In normal subject, the FVC is the person's vital capacity (VC). However, in obstructive lung diseases, FVC is lower than VC because of small airway collapse and air trapping.

Percent vital capacity (FEV$_1$%): It is equal to [FEV$_1$/VC] x 100. In normal subject, the FEV1% is at least 80%. However, in obstructive lung diseases like asthma, FEV$_1$% is markedly reduced while normal in restrictive lung diseases (figure 6.16).
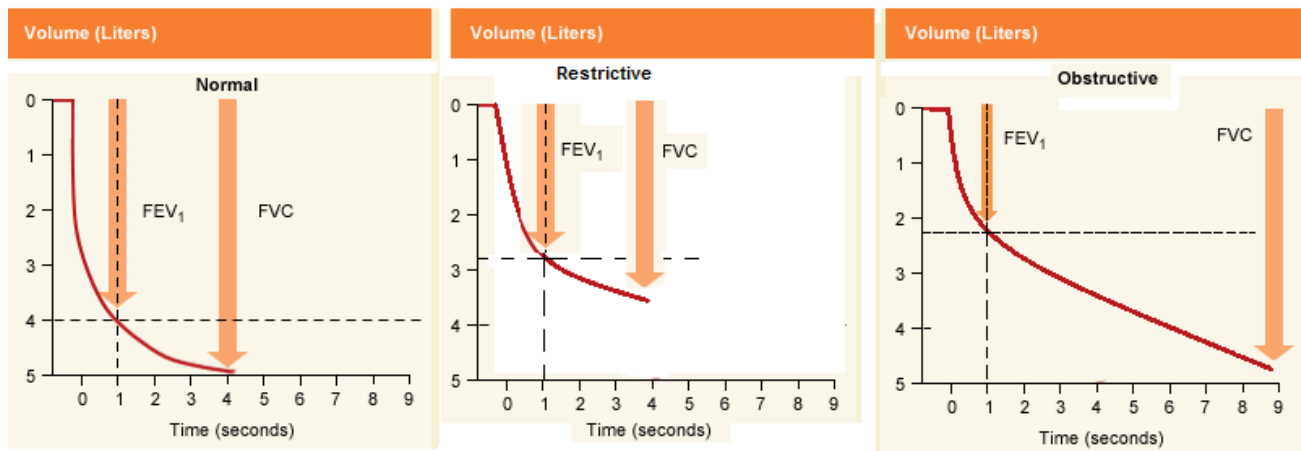

Figure 6.14: Timed vital capacity (timed forced expiratory volume per first sec, FEV$_1$) and FEV$_1$%.

Table 6.1 shows the changes in PEF, VC, FEV$_1$, and FEV$_1$% in restrictive and obstructive lung diseases.

Table 6.1: PEF, VC, FEV$_1$, and FEV$_1$% in restrictive and obstructive lung diseases.				
Condition	**Peak expiratory flow**	**Vital capacity**	**FEV$_1$**	**[FEV$_1$/VC] x 100**
Restrictive lung diseases	Decrease	Decrease	Decrease	Normal
Obstructive lung diseases	Decrease	May be normal	Decrease	Decrease

Forced Expiratory Flow $_{25\%-75\%}$ (FEF $_{25\%-75\%}$): The FEF $_{25\%-75\%}$ is the **average flow rate that occurs during the middle 50 percent of an FVC measurement** (figure 6.15). This can be measured by flow volume loops technique. The FEF 25%–75% 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 and for women of the same age, about 3.5 L/sec. 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 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$_1$%.
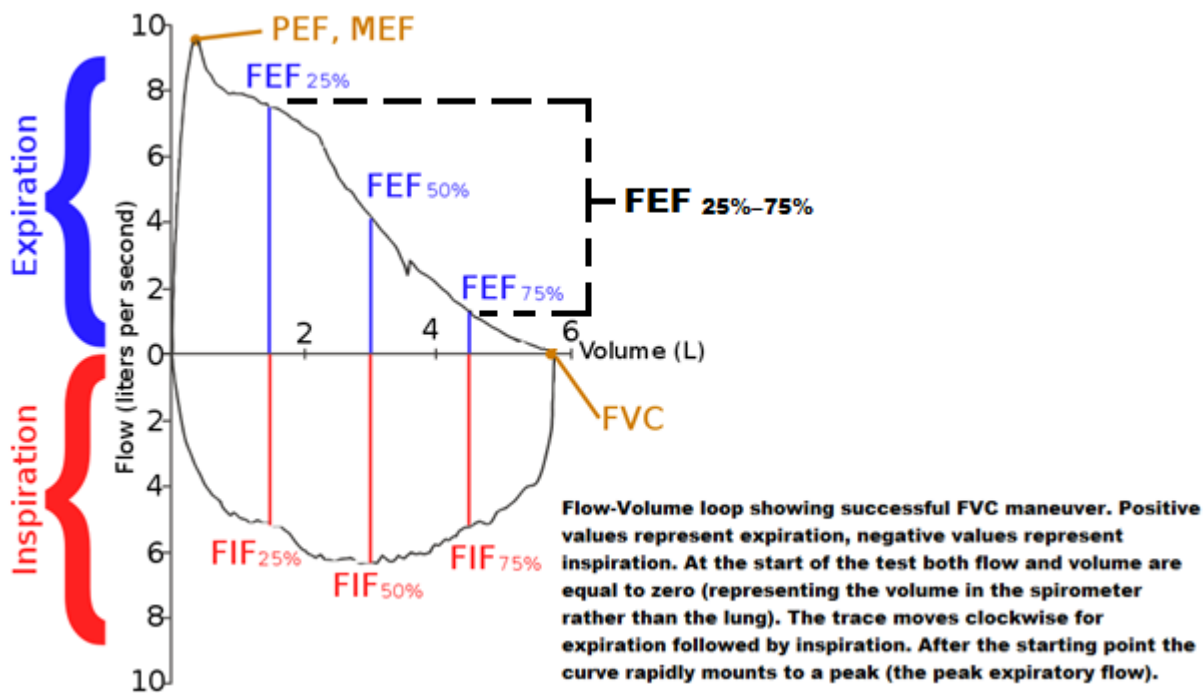
Flow-Volume loop showing successful FVC maneuver. Positive values represent expiration, negative values represent inspiration. At the start of the test both flow and volume are equal to zero (representing the volume in the spirometer rather than the lung). The trace moves clockwise for expiration followed by inspiration. After the starting point the curve rapidly mounts to a peak (the peak expiratory flow).

Figure 6.15: Flow-Volume loop using digital spirometer showing Forced Expiratory Flow 25%–75%.

The minute respiratory (pulmonary) volume (or Total 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.

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 are called the **anatomical dead spaces** (which consist of nose, pharynx, larynx, trachea, bronchi, and bronchioles). The normal anatomical dead space air in the young adult is about **150 ml**. This increases slightly with age. It also increases during a maximal inspiration because the trachea and bronchi expand 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. 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, **minute alveolar ventilation** equals 12 x (500 – 150) = **4200 ml/min**. **The minute alveolar ventilation** is the volume of new air that reaches the alveoli and is available for gas exchange with the blood. Alveolar ventilation is a more accurate measure of the level of ventilation since it takes into account only the volume of gas that

interfaces with the respiratory epithelium. It can be seen that if a subject takes rapid, shallow breaths, they will become hypoxaemic despite numerically adequate minute ventilation.

The factors that affect resistance to air flow:
1. Airway diameter is the **main component of airway resistance**. Resistance to air flow is inversely proportional to air way diameter (or cross sectional area of the air way passages). According to airway diameter, resistance to air flow is of three types:

[A] Fixed resistance (cannot change the diameter as in nose, pharynx, larynx, and trachea). The upper airway offers high fixed resistance, which then declines rapidly from the fifth generation of airway division. Because the collective cross-sectional area of lung acini is enormous, the respiratory zone of the lung has very low resistance.

[B] Variable resistance (can change the diameter due to the presence of smooth muscles as in bronchi and bronchioles). Parasympathetic nerves release acetylcholine and cause bronchoconstriction. Catecholamines relax bronchial smooth muscle through β_2 receptors.

Selective β_2-receptor agonists are used to induce bronchodilation and reduce air-way resistance in patients with asthma. Asthma is a classic, obstructive lung disease whose key differentiating feature demonstrated on spirometry is reversible bronchoconstriction following treatment with a β_2 agonist such as albuterol. Asthma is characterized by inflammatory hyperreactive airways, and triggers can include allergens (most common), infections (often viral), exercise, cold air, and drugs such as aspirin. When attempting to diagnose airway hyperreactivity, methacholine (a parasympathomimetic agent) can be given during pulmonary function testing to provoke bronchospasm. In asthmatic subjects, bronchospasm is induced by smaller doses (methacholine challenge test).

[C] Dynamic resistance (also called dynamic airway compression: (change in diameter in airway passages that are not supported by cartilages in response to transpulmonary pressures as in bronchioles and distal to them). Airway resistance increases during forced expiration because intrapleural pressure becomes positive and the airways are compressed (reduction in diameter) and vice versa. This does not affect the larger airways, which have cartilaginous support to resist collapse. The distal bronchioles do not have cartilaginous support to resist dynamic compression and, therefore, are at risk of collapsing. Instead, they are expanded by the same transpulmonary pressures (also called transmural pressure which is equal to alveolar pressure minus intrapleural pressure) that expand the alveoli. Normal airways are compressed in forced expiration and airway resistance rises.

Dynamic airway compression is a particular problem in patients with emphysema, where destruction of the lung architecture weakens the radial traction forces. Airway collapse occurs upon forced expiration, dramatically increasing airway resistance and trapping gas in the alveoli.

2. Lung volume is an important determinant of airway resistance because the overall cross-sectional area of airways varies with lung volume, causing global changes in airway radius. **At low lung volume, the cross-sectional area is reduced and airway resistance increases, and vice versa**. For example, patients with pulmonary fibrosis have low lung compliance and low resting lung volume; high airway resistance contributes to their increased work of breathing.

3. Turbulent gas flow: As the turbulent of the gas flow is increased the resistance to air flow is increased. Turbulent flow occurs in the larger central airways (trachea and larger bronchi), where flow velocity is high, and at branch points of the conducting airways (middle of the bronchial tree), and become laminar flow near the end of the bronchial tree, and in reduction in the airway diameter which results in an increase in the velocity of flow. Disorganization of the gas stream requires more pressure to drive flow and effectively increases resistance.

Bronchoconstriction reduces the airway diameter and increases the velocity of flow. High velocity causes turbulent flow, which generates a wheezing sound (e.g., in asthma).

Respiratory passageways resistance: Considering the whole respiratory system, **approximately one-half of the resistance to airflow occurs in the upper respiratory tract (nose** and **pharynx) when breathing through the nose.** This is significantly reduced when mouth breathing. In exercise, the airway resistance may increase significantly due to high air flows inducing turbulence when breathing is through the nose. Therefore, it is normal under these conditions to switch to mouth breathing to reduce airway resistance. **The other one-half of the resistance lies within the lower respiratory tract** (figure 6.16)**. The chief site of airway resistance in the airway passages is at the medium-sized bronchi**, where the radius of the individual bronchi is decreased. The least resistance to air flow is in the very small bronchioles and terminal bronchioles because of their large cross-sectional area.
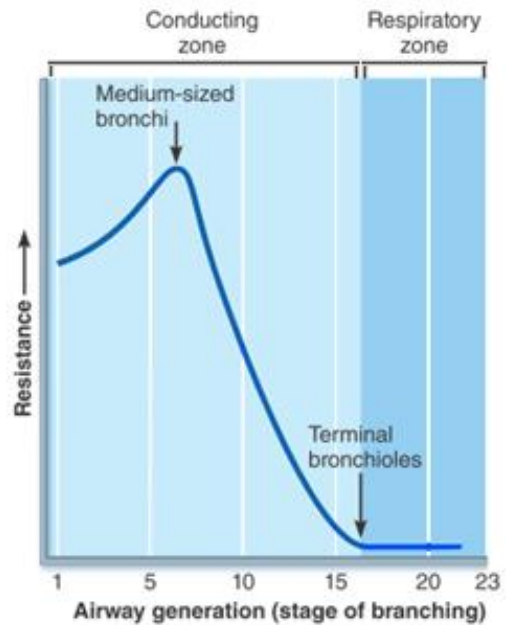

Figure 6.16 Resistance in respiratory passageways.

The smooth muscles of the bronchioles are under nervous and humoral control:
[A] Nervous control of the bronchioles: The only important nervous control to the bronchioles is by way of parasympathetic vagus nerves fibers. These nerves secrete acetylcholine and when activated cause **mild to moderate constriction of the bronchioles** (table 6.2). 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, leukotrienes** and the substance called **slow reactive substance of anaphylaxis (SRA)** (table 6.4)**.** 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 in allergic asthma. In addition, the airway smooth muscle is highly responsive to **CO_2 (high blood CO_2 producing bronchodilataion** and **low 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 β_2 receptors). Therefore, activation of the sympathetic nervous system is often valuable in relaxing the airways and preventing obstruction.

Table 6.2: Nervous and humoral control of bronchiole smooth muscle contractions.	
Factor	Effect
Parasympathetic stimulation	Bronchoconstriction
Histamine, leukotrienes, platelet activating factor and SRA	Bronchoconstriction
Low blood PCO_2	Bronchoconstriction
High blood PCO_2	Bronchodilatation
Sympathetic stimulation to the adrenal glands (epinephrine and norepinephrine), NO, VIP (vasoactive intestinal polypeptide)	Bronchodilatation

Inactivity of either the sympathetic or the parasympathetic nervous system allows the action of the other to dominate the bronchial smooth muscle response. For example, if a β_2-blocking agent such as propranolol is administered to a patient, the parasympathetic nervous system becomes dominant and bronchial constriction ensues. In contrast, if a patient receives a parasympathetic blocking agent such as atropine, the sympathetic nervous system becomes dominant and bronchial relaxation occurs.

Artificial Respiration:
Mouth-to-mouth resuscitation: Is an emergency measure performed when someone stops breathing. The patient is placed flat on the back. While pinching the patient's nostrils shut, the aid-giver places his or her mouth on the patient's mouth and blows forcefully into the patient's lungs. This raises the alveolar pressure in the patient's lungs relative to the atmospheric pressure outside the chest and causes the lungs and chest to expand (inspiration). The rescuer then removes his or her mouth to allow the patient to exhale. Expulsion of the air blown into the lungs (expiration) occurs due to the intrinsic elastic recoil of the lungs and chest. This process can be accelerated by pressing down on the chest. The rescuer should ventilate the patient at a rate of about 16/min. The expiratory O_2 fraction of the rescuer is high enough to adequately oxygenate the patient's blood. The color change in the patient's skin from blue (cyanosis) to pink indicates that a resuscitation attempt was successful.

Mechanical ventilation: Mechanical **intermittent positive pressure ventilation (IPPV)** works on the same principle. This technique is used when the respiratory muscles are paralyzed due to disease, anesthesia, etc. The pump of the respirator drives air into the patient's lung during inspiration. The external inspiratory and expiratory pathways are separated by a valve (close to the patient's mouth as possible) to prevent enlargement of dead space. Ventilation frequency, tidal volume, inspiratory flow, as well as duration of inspiration and expiration can be preselected at the respirator. The drawback of this type of ventilation is that venous return to the heart is impaired to some extent. Today, the standard technique of mechanical respiration is **continuous positive pressure ventilation (CPPV)**. In contrast to IPPV, the end-expiratory pressure is kept positive in CPPV. In any case, all ventilated patients should be continuously monitored (expiratory gas fraction; blood gas composition, etc.).

The cough reflex: The trachea, bronchi, respiratory bronchioles, and alveoli are very sensitive to irritation and touch. Afferent impulses pass from the respiratory passages mainly through the **vagus nerves** to the medulla. There, an automatic sequence of events is triggered by the neuronal circuits of the **medulla** causing the following effects:

[1] About 2.5 liters of air is inspired.

[2] The epiglottis closes, and the vocal cords shut tightly to entrap the air within the lungs.

[3] The abdominal muscles contract forcefully, pushing against the diaphragm while other expiratory muscles also contract forcefully. Consequently the pressure in the lungs raises to as high as 100 mm Hg or more.

[4] The vocal cords and the epiglottis suddenly open widely so that air under pressure in the lungs explodes outward. The rapidly moving air (75-100 miles / hour) usually carries with it any foreign matter that is present in the bronchi or trachea.

The sneeze reflex: The sneeze reflex is very much similar to cough reflex except that it applies to the nasal passageways instead of to the lower respiratory passages. The initiating stimulus of the sneeze reflex is irritation in the nasal passageways, the afferent impulses passing in the **5th cranial nerve (trigeminal nerves)** to the medulla where the reflex is triggered. A series of reactions similar to those for the cough reflex takes place, however, the uvula is depressed so that large amounts of air pass rapidly through the nose, as well as though the mouth, thus helping clear the nasal passages of foreign matter.

Exchange of gases between alveoli and tissues: After the alveoli are ventilated with fresh air, the next step in the respiratory process is diffusion of oxygen from the alveoli into the pulmonary blood and transported by the blood to the tissue capillaries and then leaves the tissue capillaries and cross cell membrane to gain entry into cells. Diffusion of CO_2 is in the opposite direction, from the pulmonary blood into the alveoli.

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 (table 6.3):

[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. Therefore, 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_2 concentration, and tissue pH when respiration is temporarily interrupted.

[2] Oxygen is constantly being absorbed from the alveolar air into the blood of the lungs, and new O_2 is continually entering the alveoli from the atmosphere. Therefore, O_2 concentration in the alveoli, and therefore, its partial pressure as well, is controlled by: [a]- the rate of absorption of O_2 into the blood, [b]- the rate of entry of new O_2 into the lungs by ventilatory process.

[3] Carbon dioxide is constantly diffusing from the pulmonary blood into the alveoli. The two factors that determine alveolar concentration of CO_2 and also its partial pressure are [a] the rate of excretion of CO_2 from the blood into the alveoli and [b] the rate at which CO_2 are removed from the alveoli by alveolar ventilation.

[4] Dry atmospheric air that enters the respiratory passage is humidified even before it reaches the alveoli. The partial pressure of water vapor in the alveolar air at normal body temperature is 47 mm Hg. Since the total pressure in the alveoli cannot rise to more than the atmospheric pressure, this water vapor simply dilutes all the other gases in the inspired air as shown in the table 6.3.

Table 6.3: Composition of inspired, alveolar, and expired air.				
	Atmospheric air (mm Hg)	Inspired air Humidified air (mm Hg)	Alveolar air Alveolar air (mm Hg)	Expired air Expired air (mm Hg)
N_2	597	563.7	569	566
O_2	159	149	104	120
CO_2	0.3 (≈ 0)	0.3 (≈ 0)	40	27
H_2O	37	47	47	47
Total	760	760	760	760

The respiratory unit: The part of the respiratory system at which gas exchange between the pulmonary blood and the alveolar air is taking place through its membrane. It is composed of a respiratory bronchiole, alveolar ducts, alveolar sacs, and alveoli (about 300 million in the two lungs). Each alveolus has 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. This membrane is called the **respiratory membrane** which consists of the following layers (figure 6.17):

Figure 6.17: The layers of alveolar-capillary membrane (respiratory membrane).

[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 0.6 micron. The total surface area of the respiratory membrane is estimated to be about **100 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, creating a film 10 μ (or approximately one red cell diameter which explain the rapidity of respiratory exchange of gases). In addition, the diameter of the pulmonary capillaries is about 8 microns which is
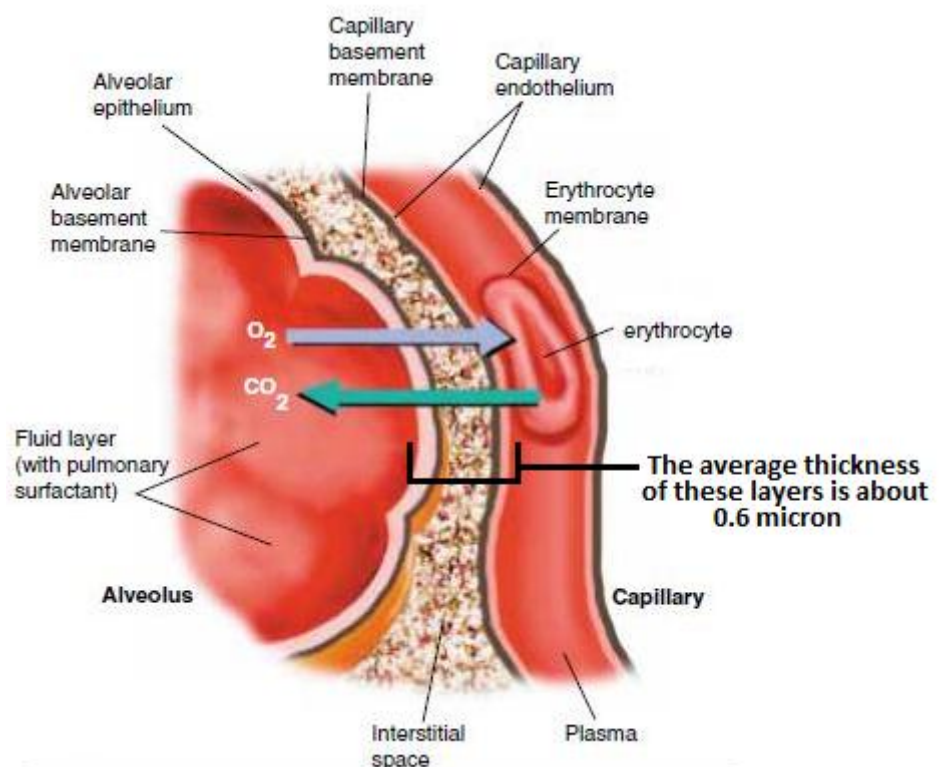
about the same diameter of RBC, therefore, RBC as it pass through these capillaries are in fact in close contact with the endothelial membrane. This also help in making the gas exchange rapid because the gases can pass directly from RBC to the alveoli without passing through significant plasma.

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 of the gas in the substance of the membrane, which is the water of the membrane: This depends <u>proportionally on the solubility of the gas in the membrane</u> and <u>inversely on the square root of its molecular weight</u>. Therefore, for a given pressure difference, CO_2 diffuse through the membrane about 20 times as rapidly as O_2. 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. Therefore, at an altitude of 14000 meters, consciousness is lost despite administration of 100% oxygen. This is because the barometric pressure at this altitude is far too low to permit adequate diffusion of oxygenation to arterial blood.

> **Mathematically, these factors can be summarized by Fick's law of diffusion** states that: **Diffusion = (Pressure gradient × Surface area × Solubility) / (Distance × $MW^{\frac{1}{2}}$).**

Lung diffusing capacity: The ability of the respiratory membrane to exchange a gas between the alveoli and the pulmonary blood can be expressed quantitatively 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**. 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_2 is 20 times that of O_2, one would expect a diffusing capacity for CO_2 under resting conditions of about **400-450 ml/min/mm Hg** and during exercise of about 1200-1300 ml/min/mm Hg. The importance of this high diffusing capacity for CO_2 is this: when the respiratory membrane becomes progressively damaged, its capacity for transmitting O_2 into the blood is often impaired enough to cause death of the person while CO_2 diffusion can still occur in reasonable amounts. However, the patient's life can be maintained by intensive O_2 therapy that overcomes the reduction in O_2 diffusing capacity.

The diffusing capacity (also called **D**iffusion **L**imited, **DL**) of the respiratory membrane for oxygen (DL_{O2}) can be measured directly, but this is technically extremely difficult. Measuring the diffusing capacity of carbon monoxide (DL_{CO}) is much easier and provides a valid reflection of the diffusion of oxygen.

The DL_{CO} test measures the amount of CO that moves across the alveolar-capillary membrane into the blood in a given time. In essence, this test measures the physiologic effectiveness of the alveolar-capillary membrane. The normal diffusion capacity of CO is 25 mL/min/mm Hg.

Ventilation of the lungs: The lower zones of the lung ventilate better than the upper zones, and the middle zones have intermediate ventilation. These differences in regional ventilation can be explained by regional differences in pleural pressure. The pleural pressure is typically about −10 cm H2O in the upper regions and about −2.5 cm H2O in the lower regions. A less negative pleural pressure in the lower regions of the chest cavity causes less expansion of the lower zones of the lung during resting conditions. Therefore, the bottom of the lung is relatively compressed during rest but expands better during inspiration compared with the apex.

Ventilation – perfusion ratio (V/Q): It is the ratio of ventilation of a given alveolus to its blood perfusion. If some alveoli are well ventilated but have no or almost no blood flow, V/Q = infinity. Therefore, the alveolar air has the same composition and concentration of the humidified inspired air (PO_2 = 149 mm Hg, PCO_2 = 0 mm Hg). If some alveoli have little or no ventilation but excellent blood flow, V/Q = 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. At a ratio of either zero or infinity, 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 V/Q is also said to be normal (V/Q = 1.0) with 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. The mean V/Q for the entire lung is **0.93** (range 0.8-1).

- 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
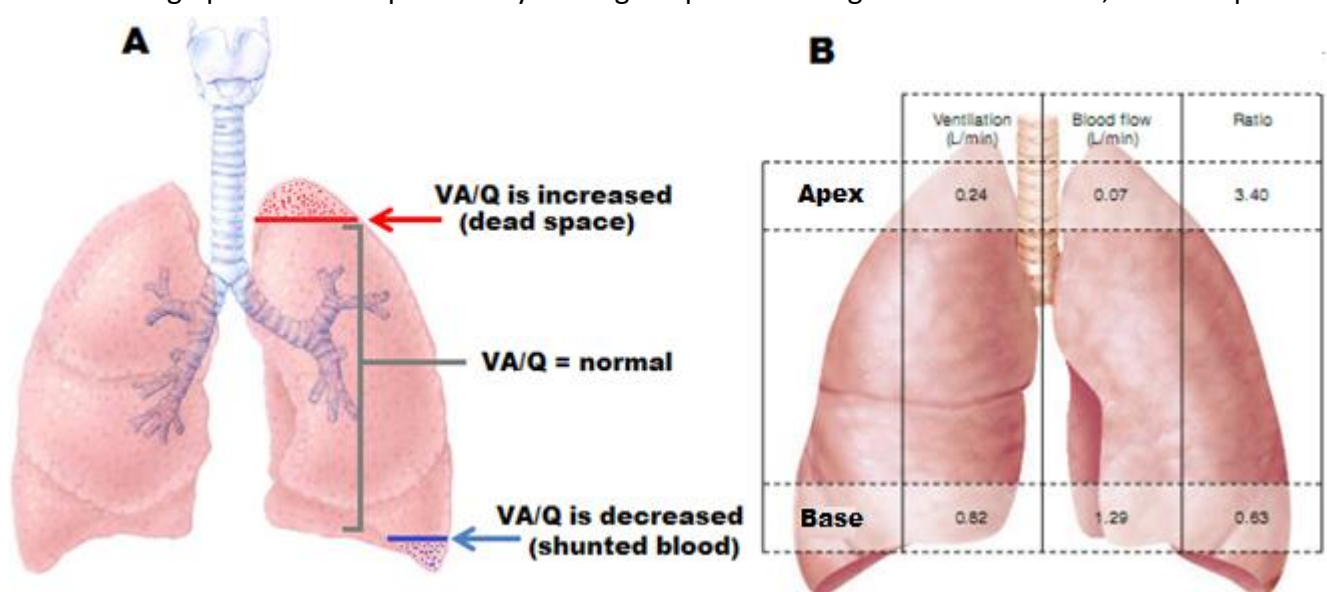

Figure 6.18: Ventilation – perfusion ratio (V/Q) at different regions of the lung.

lung, V/Q is higher (>1.0) than the ideal value, which causes a moderate degree of **physiologic dead space** in this area of the lung (figure 6.18 A & B). With an increase physiological dead space, ventilation became **wasted ventilation** leading to severe **muscular fatigue.**

An increase in V/Q causes a **high alveolar PO_2** and **low alveolar PCO_2, in association** with **high arterial PO_2 and low arterial PCO_2**. V/Q equal to infinity does not occur in the normal lung but instead occurs only in abnormal conditions such as in some lung diseases (pulmonary embolism), a fall in arterial pressure (following hemorrhage) 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 pressure. The alveoli at the apex of the lung are larger than those at the base so their compliance is less. Because the compliance is reduced, less inspired gas goes to the apex than to the base. Also, because the apex is above the heart, less blood flows through the apex than through the base. However, the reduction in airflow is less than the reduction in blood flow, so that the V/Q ratio at the top of the lung is greater than it is at the bottom. The increased V/Q ratio at the apex makes PCO_2 lower and PO_2 higher at the apex than they are at the base.

- Whenever V/Q is below normal (i.e. low ventilation and normal perfusion) as in the base of the lung, the ventilation is not enough to provide the O_2 needed to oxygenate the blood flowing through the alveolar capillaries and consequently leads to **low alveolar PO_2** and **high alveolar, PCO_2**, this leads to **low arterial PO_2 (hypoxemia)** and **high arterial PCO_2**. In addition, low V/Q ratio causes arterial oxygen levels (PO_2) to decrease, with consequent decrease in O_2 dissolved in plasma and saturation of Hb. Certain fraction of the venous blood passing through the pulmonary capillaries does not become oxygenated (**wasted perfusion**). This fraction of blood is called **physiological shunted blood** (venous blood that passes to the systemic circulation without first being oxygenated in the lungs) as it occurs normally in the bottom of the lung with V/Q < 0.8 times the ideal value (figure 6.18 A & B). However, the low V/Q and its consequences on the arterial PO_2, the low PO_2 will stimulate the peripheral chemoreceptors, which, in turn, will increase alveolar ventilation and decrease PCO_2. The decreased PCO_2 will cause a respiratory alkalosis (increasing pH). Hypoxemia will also cause lactate levels to rise.
- 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. **anatomical shunted blood**. The total quantitative amount of shunted blood is called the **physiological-anatomical shunt.**
- Because the lungs are essentially "hanging" in the chest, the force of gravity on the lungs causes the intrapleural pressure to be more negative at the top of the lung. This also causes the alveoli at the apex (top) of the lung to be larger than those at the base (bottom) of the lung. Larger alveoli are already more inflated and are less compliant than smaller alveoli. During inspiration, when all alveoli are subjected to essentially the same alveolar pressure, more air will go to the more compliant alveoli. Because of the effect of gravity on blood, more blood flow will go to the base of the lung. This does not appreciably affect lung compliance. Ventilation is about three times greater at the base of the lung, but flow is about 10 times greater at the base than at the apex of the lung. Therefore, the V/Q ratio is lower at the base than at the apex in a normal lung.

Any condition that decreases gas exchange between the alveoli and the blood can increase the amount of shunted blood. For example, obstruction of the bronchioles in conditions such as asthma can decrease ventilation beyond the obstructed areas. The result is a large increase in shunted blood because the blood flowing through the pulmonary capillaries in the obstructed area remains unoxygenated. In pneumonia or pulmonary edema, a buildup of fluid in the alveoli results in poor gas diffusion and less oxygenated blood.

Compensatory mechanisms (autoregulation) for matching the ventilation and blood flow (perfusion) in alveoli:

For proper V/Q (to be equal to 1), i.e., 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 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 (figure 6.19 A).

[2] 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 (figure 6.19 B).
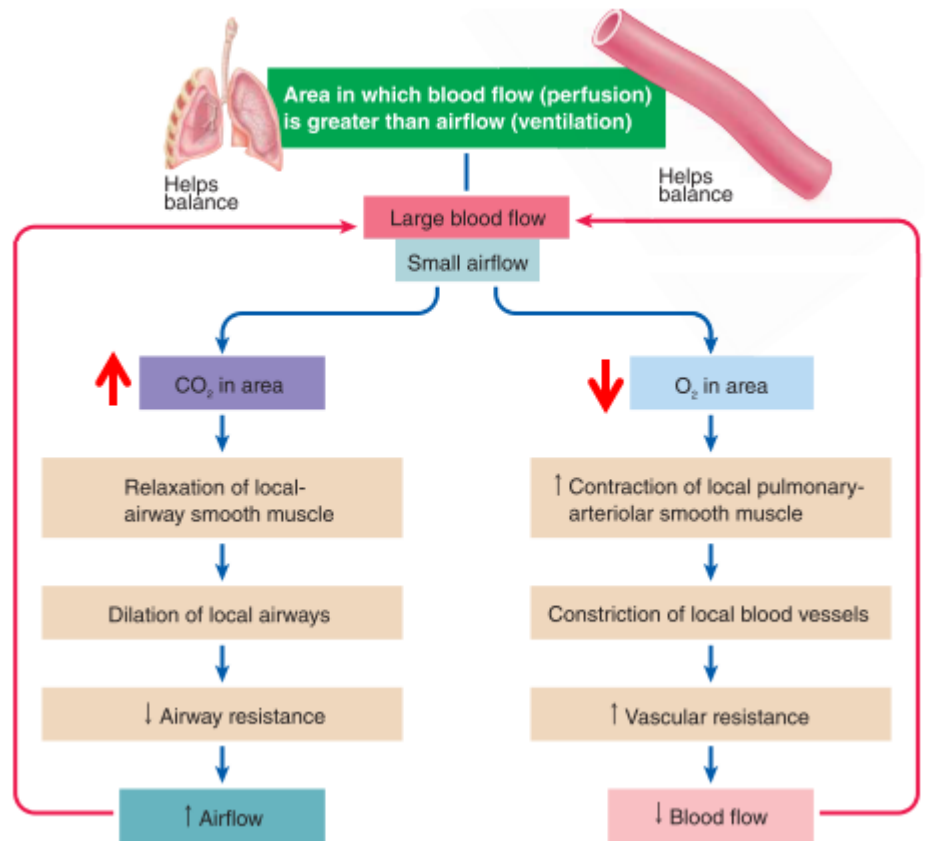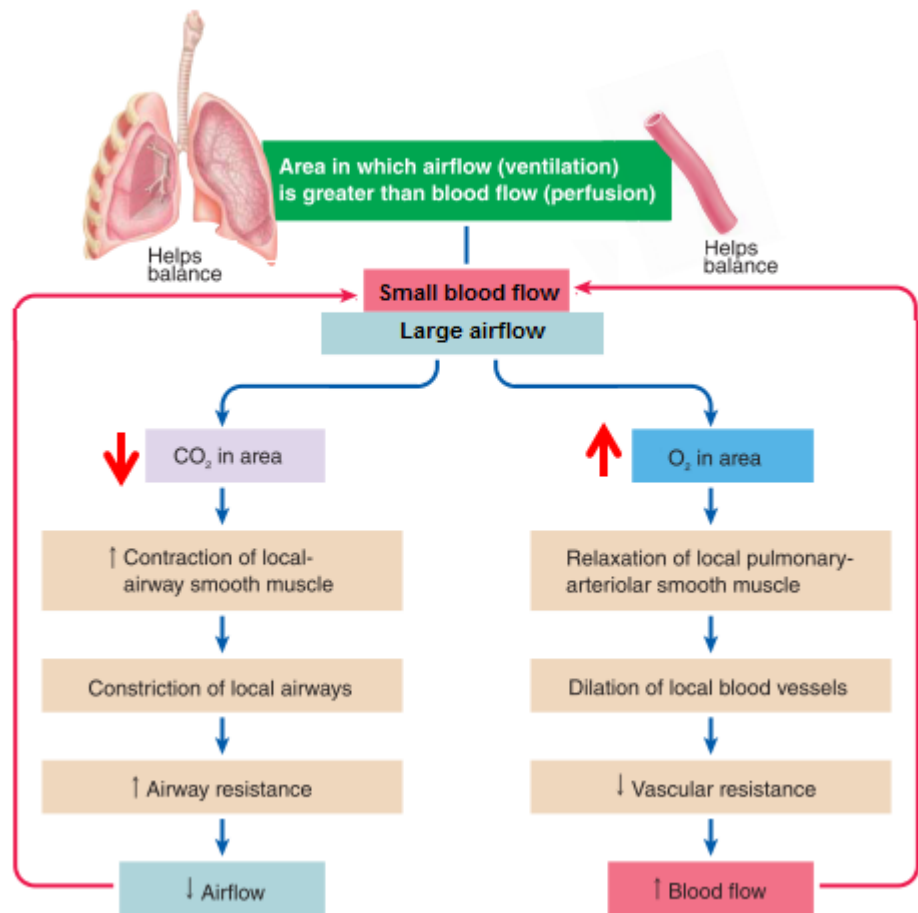

Figure 6.19 A: Adjustment of V/Q when the alveolar blood flow is high and the airflow is low.

A rapid ascent to a high altitude, where atmospheric PO_2 is low, causes pulmonary vasoconstriction and may cause pulmonary hypertension. This mechanism is the opposite response to most systemic vascular beds, which vasodilate in response to hypoxia. Hypoxic pulmonary vasoconstriction has two important physiologic roles:

1. In fetal life, the lungs are not necessary for gas exchange. Before a breath is taken, hypoxic pulmonary vasoconstriction shunts blood away from the lungs. Immediately after birth, when the first inspiration occurs, the pulmonary arterioles dilate, pulmonary vascular resistance decreases, and normal lung perfusion is established.
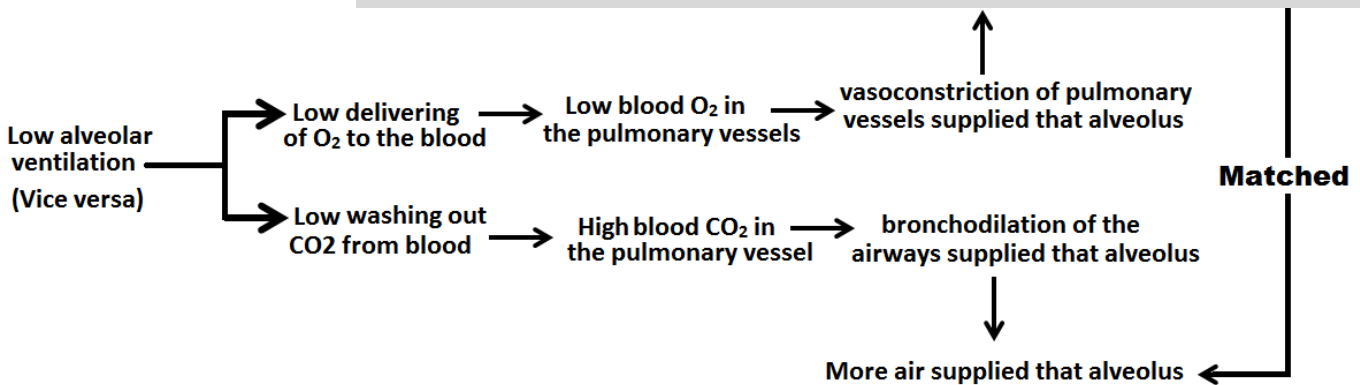
2. After birth, hypoxic pulmonary vasoconstriction shunts blood away from poorly ventilated regions of the lung, thereby improving ventilation-to-perfusion matching.

Figure 6.19 B: Adjustment of V/Q when the alveolar blood flow is small and the airflow is large.

In summary

Transport of oxygen and carbon dioxide in the blood and body fluids: 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 limited 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 equilibrium will exist between the gas 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_2 diffuses from the alveoli (PO_2 = 104 mm Hg) into the pulmonary capillary blood (PO_2 = 40 mm Hg) where it combines with Hb (figure 6.20). Then from the systemic capillaries (PO_2 = 95 mm Hg) O_2 diffuses to and equilibrate with interstitial fluid O_2 of 40 mm Hg and then diffuses to the cells (PO_2 = 23 mm Hg). Therefore, PO_2 of the blood leaving the tissues capillaries and entering the veins is about 40 mm Hg. Conversely, when O_2 is metabolized in the cells, the PCO_2 rises to a high value (PCO_2 = 46 mm Hg), which causes CO_2 to diffuse into the interstitial fluid with PCO_2 of 45 mm Hg and then it diffuses to and equilibrate with CO_2 of blood in tissue capillaries (PCO_2 = 40 mm Hg) and combines with chemical substances in the blood that increase CO_2 transport. Therefore, PCO_2 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_2 in the alveoli (40 mm Hg) is lower than that in the pulmonary capillary blood (45 mm Hg).

- In pulmonary circulation, the diffusion of oxygen and carbondioxide will continue until equilibrium is reached; this is usually accomplished in about **0.25** second. Under normal resting conditions, the total transit time for blood to move through the alveolar-capillary system is about **0.75** second. Thus, the diffusion of oxygen and carbondioxide is completed in about one-third of the time available. In exercise, however, blood passes through the alveolar-capillary system at a much faster rate and, therefore, the time for gas diffusion decreases (i.e., the time available for gas diffusion is < 0.75 second). In the healthy lung, oxygen equilibrium usually occurs in the alveolar-capillary system during exercise in spite of the shortened transit time. In the presence of certain pulmonary diseases, however, the time available to achieve oxygen equilibrium in the alveolar-capillary system may not be adequate. Such diseases include alveolar fibrosis, alveolar consolidation, and pulmonary edema.
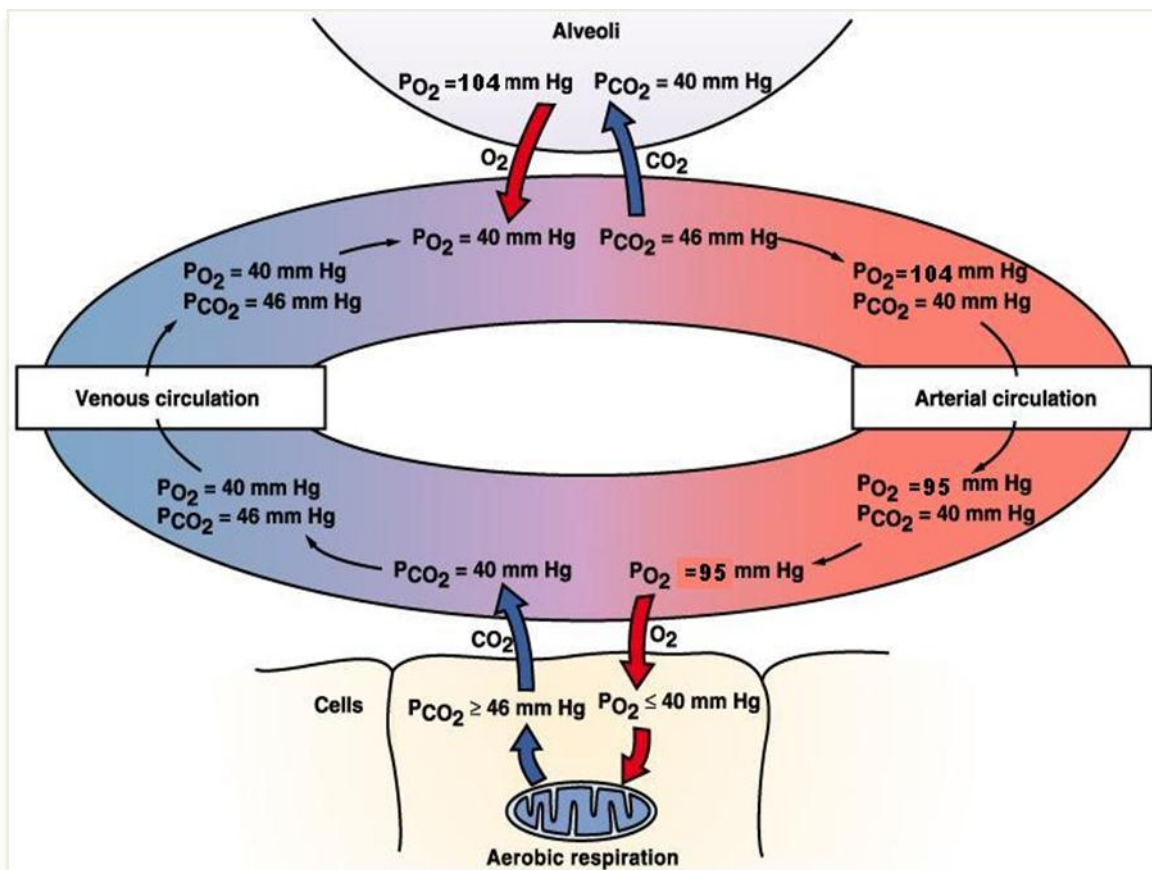
Figure 6.20: Partial pressure of oxygen and carbon dioxide in the blood and body fluids.

About 98% of the blood that enters the left atrium from the lungs passes through the alveolar capillaries and becomes fully oxygenated (PO_2 = 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_2 about the same of the normal venous blood (PO_2 = 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_2 of the blood pumped by the left heart into the aorta to fall to about 95 mm Hg.

The PO_2 in the interstitial fluids is affected by:
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 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.

PCO_2 in the interstitial fluid can be affected by:
1. The blood flow: The decrease in blood flow which causes an increase in the PCO_2.
2. Tissue metabolism; increase in metabolic rate greatly elevates the PCO_2 at all levels of blood flow.

Transport of O_2 in the blood: Normally about 97% of O_2 transported from the lungs to the tissues is carried in chemical combination with Hb in RBC and the remaining 3% is carried in the dissolved state in the water of the plasma and blood cells. O2 solubility in plasma = 0.003 ml O2/100 ml plasma/ mm Hg PO_2.The percent of the Hb that is bound with O_2 (percent saturation of the Hb) increases as the PO_2 increase, plotting the per cent saturation of Hb against the PO_2 will produce **O_2– Hb dissociation curve**.

O_2-Hb dissociation curve: The oxygen-Hb dissociation curve **is** a graph that shows the relationship between the percent saturation of hemoglobin and partial pressures of oxygen.
It is an S – shaped curve with a steep slope between 10 and 60 mm Hg PO_2 and a flat portion between 70 and 100 mm Hg PO_2 (figure 6.21 A). At a **PO_2 of 60 mm Hg, 90% of the total Hb is combined with O_2**. From this point on, a further increase in PO_2 produces only a small increase in O_2 binding. Since the blood in the arteries usually has a PO_2 of about 95 mm Hg, one can see from the dissociation curve that the usual O_2 saturation of arterial blood is about 97% (i.e. 19.4 ml of O_2 / 100 ml of blood). This means that the **Carrying Capacity** of Hb with 97-100% saturation is **1.34 ml O_2/gm Hb.** Assuming that the normal average Hb concentration is 15 gm/dl, then the total O2 carrying capacity of blood is 1.34 ml O_2/gm Hb x 15 gm/dl = 20 ml O_2/dl of blood. On the other hand, in normal venous blood returning from the tissues the PO_2 is about 40 mm Hg and the saturation of Hb is about 75% (i.e. 14.4 ml of O_2 / 100 ml of blood). Thus, under normal conditions about 5 ml of O_2 is transported to the tissues by each 100 ml of blood. During strenuous exercise, the muscle cells utilize O_2 at a rapid rate causing a fall in PO_2 in the interstitial fluid to as low as 15 mm Hg. At this pressure 15 ml of O_2 is transported to the tissues by each 100 ml of blood. This in combination with an increase in cardiac output to about 6 - 7 times, lead to an increase in O_2 transport about 20-fold. Under basal conditions, the amount of oxygen consumed per minute is about 250 ml and 200 ml of CO_2 is produced.
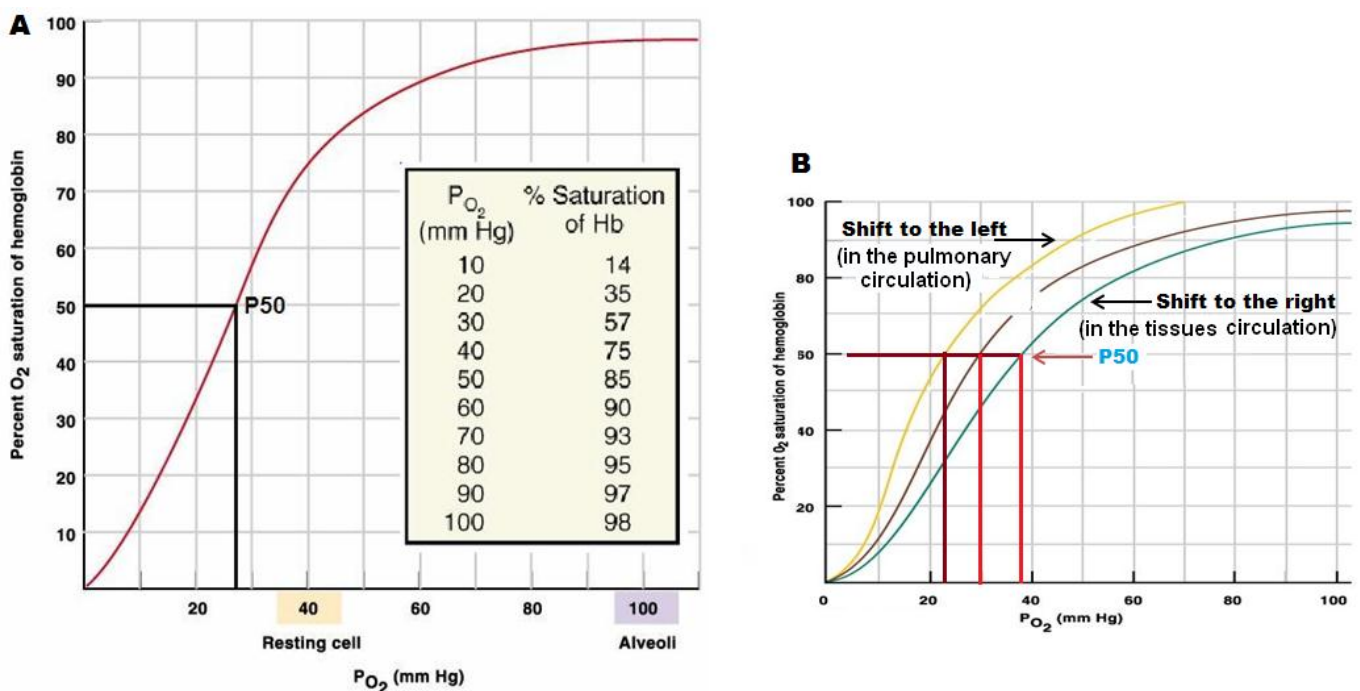
Figure 6.21: O_2-Hb dissociation curve.

Factors that cause shifting of the O_2-Hb dissociation curve: There are several factors which can displace the dissociation curve in one direction or the other. A convenient expression of such shifts is **P_{50}**, which can be defined by the **PO_2 at which the Hb is half saturated with O_2** (figure 6.21 B). This mean that the higher the P_{50}, the lower the affinity of Hb for O_2, and vice versa. The normal value of P_{50} on the oxyhemoglobin dissociation curve in an adult is **26 mm Hg.**

The factors that displace the curve to the right, which means that at any given PO$_2$, Hb has less affinity for O$_2$ (higher P$_{50}$), are (figure 6.22):
[1] Increased [H$^+$] with pH decreasing from 7.4 to 7.2.
[2] Increased CO$_2$ concentration.
[3] Increased 2,3-diphosphoglycerate (2,3-DPG) which is a phosphate compound normally present in the blood but in differing concentrations under different conditions.
[4] Increased blood temperature.

The factors that shift the curve to the left, which means that at any given PO$_2$, Hb has more affinity for O$_2$, are (figure 6.22):
[1] Decrease in [H$^+$] with an increase in pH from 7.4 to 7.6.
[2] Decreased CO$_2$ concentration.
[3] Decreased 2,3-diphosphoglycerate (2,3-DPG) as in stored blood under blood bank conditions.
[4] Decreased blood temperature.
[5] The presence of large amount of Hb-F.
[6] Carbon monoxide poisoning.

Shift of the O$_2$-Hb dissociation curve by changes in the blood CO$_2$ and [H$^+$] is important to enhance oxygenation of the blood in the lungs and also to enhance release of oxygen from the blood in the tissues. This is called **Bohr Effect which** can be defined as **the effect of CO$_2$ concentration and [H$^+$] on the affinity of Hb to O$_2$.**

As the blood passes through the lungs, CO$_2$ diffuses from the blood into the alveoli. This reduces the blood PCO$_2$ and also decreases the [H$^+$] because of the resulting decrease in blood

Figure 6.22: Factors that cause shifting of the O$_2$-Hb dissociation curve to the right.

carbonic acid. Both these effects shift the O$_2$-Hb dissociation curve to the left and upward, i.e. Hb now has a higher affinity to combine with O$_2$. Therefore the quantity of O$_2$ that binds with the Hb at any given alveolar PO$_2$ becomes considerably increased, thus allowing greater O$_2$ transport to the tissues. Then when the blood reaches the tissue capillaries exactly the opposite effect occurs. CO$_2$ entering the blood from the tissue will shift the curve rightward and displaces O$_2$ from Hb, therefore delivers O$_2$ to the tissue at a higher PO$_2$ than would otherwise occur.

The **Fick principle** has been applied to the measurement of cardiac output. Its underlying principles may also be applied in a variety of clinical situations.
CO = VO$_2$/(C$_a$ − C$_v$). Where CO = Cardiac Output, C$_a$ = Oxygen concentration of arterial blood and C$_v$ = Oxygen concentration of mixed venous blood, VO2 = oxygen (O2) consumption .

The role of 2,3 – DPG: It is highly charged anion that binds to the β chains of deoxygenated Hb but not to those of oxyHb as follow: HbO$_2$ + 2,3-DPG ➜ Hb-2,3-DPG + O$_2$. In this equilibrium, an increase in the concentration of 2,3-DPG shifts the reaction to the right, causing more O$_2$ to be liberated.

The normal 2,3-DPG in the RBC keeps the O_2-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 causes O_2 to be released to the tissue as much as 10 mm Hg O_2 pressure than would be the case without this increased 2,3-DPG. 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_2 in the lungs when the alveolar PO_2 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_{50}. 2,3-DPG is very plentiful in RBC.

The role of Hb-F: The greater affinity of Hb-F than Hb-A for O_2 facilitates the movement of O_2 from the mother to the fetus. The cause of this greater affinity is the poor binding of 2,3-DPG by the γ polypeptide chains that replace β chains in Hb-F.

Transport of O_2 in the dissolved state: About 0.17 ml of O_2 is normally transported in the dissolved state to the tissues by each 100 ml of blood (3% of the total transported O_2). If a person breathes O_2 at very high alveolar PO_2, 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 four molecules of O_2 per molecule. Its dissociation curve is a rectangular hyperbola rather than a sigmoid curve. Because its curve is to the left of the Hb curve, it takes up O_2 from Hb in the blood. It releases O_2 only at low PO_2 values, but the PO_2 in exercising muscle is close to zero. The muscle blood supply is compressed during contractions, and myoglobin may provide O_2 when blood flow is cut off.

Combination of Hb with CO: CO has affinity of 230 times to combine with Hb than O_2 do and form **carboxyHb**.. After the carbon monoxide has selectively bound to hemoglobin the oxygen-hemoglobin dissociation curve of the remaining oxyhaemoglobin shifts to the left, reducing oxygen release to the tissues, associated with normal PO_2 in the alveolar air and in the blood (PO_2 of the blood is a measure of dissolved PO_2; therefore, the PO_2 will be normal) and a low O_2 content (because CO binds to the Hb, displacing the O_2 bound to Hb, leading to a decrease in content). A patient poisoned with CO can be treated by 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. In addition, the patient can 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.

Transport of CO_2 in the blood: Under normal resting conditions an average of 4 ml of CO_2 is transported from the tissues to the lungs in each 100 ml of blood. CO_2 diffuse out of the tissue cells in the gaseous form. On entering the tissue capillaries, the CO_2 in the venous blood (figure 6.23) will be carried to the lung in the following ways:
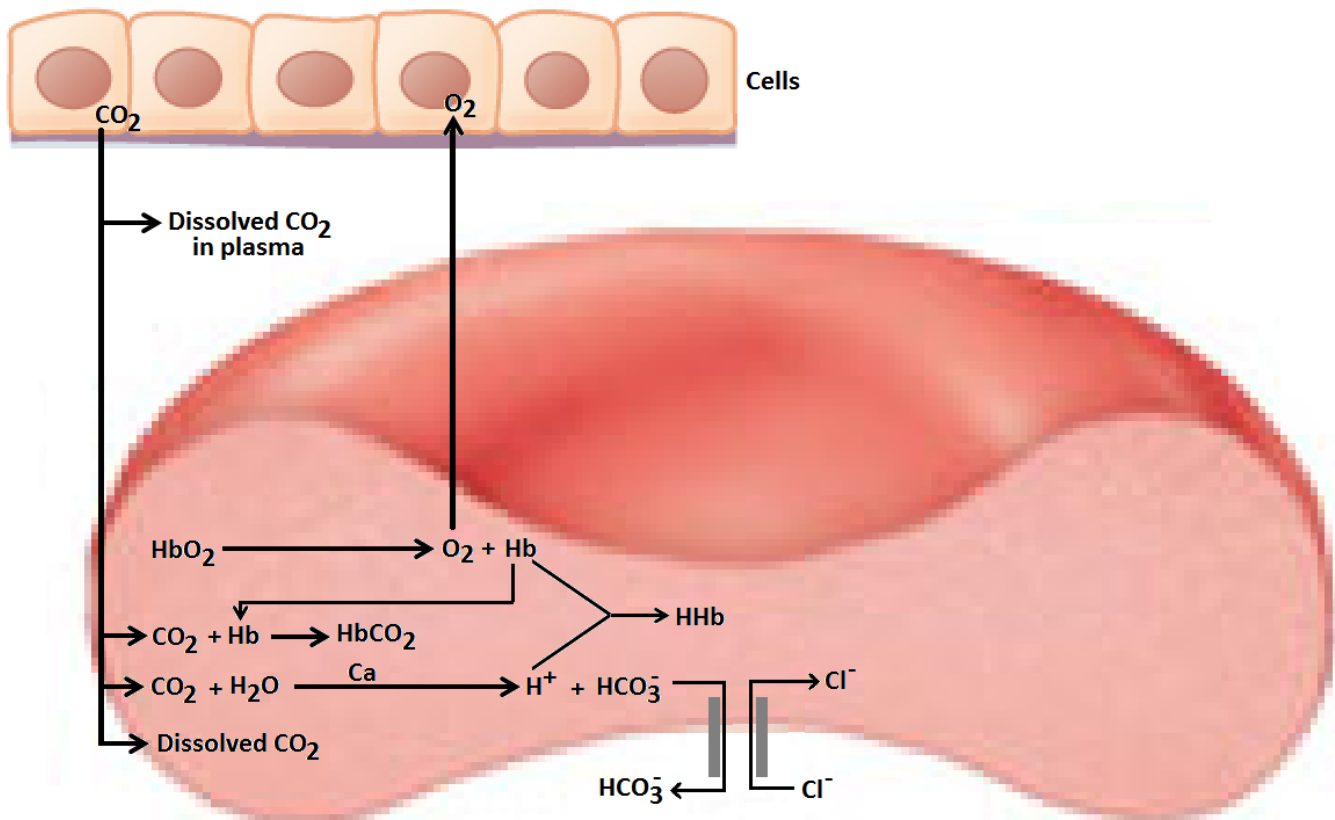
Ca = Carbonic anhydrase

All reactions and arrows are reversed at pulmonary circulation adjacent to alveoli

Figure 6.23: Transport of CO_2 in the blood.

[1] About **7%** of all CO_2 transported to the lungs is in a **dissolved** state in the blood (plasma and RBCs).

[2] About **70%** of CO_2 react with water inside the RBC to form **carbonic acid**, a reaction catalyzed by the enzyme in RBC called carbonic anhydrase which accelerates this reaction about 5000-fold. This allows tremendous amounts of CO_2 to react in a small fraction of a second with RBC water even before the blood leaves the tissue capillaries. In another small fraction of a second the carbonic acid formed in the RBC dissociates into hydrogen and bicarbonate ions. Most of the hydrogen ions (the H^+ generated cannot escape due to cell membrane impermeability) then combine with the deoxyHb (mainly the imidazole groups of the globin polypeptide chain) in the RBC because deoxyHb is a powerful acid-base buffer. In turn, many of the bicarbonate ions diffuse into the plasma while chloride ions diffuse into the RBC to take their place through bicarbonate–chloride carrier protein in the RBC cell membrane. Thus, the chloride content of the venous RBC is greater than that of arterial cells, a phenomenon called the **chloride shift**. All of the bicarbonate and Cl^- generated following CO_2 carriage by the red cell increases the intracellular osmotic pressure. This causes the cell to swell with extra H_2O that diffuses through the cell membrane. This is why the haematocrit (Hct) of venous blood is some 3% higher than in arterial blood.

[3] The remaining **23%** of CO_2 are transported to the lungs by combination with plasma proteins and with Hb in form of **carbaminohaemoglobin (HbCO$_2$)** (and very little H_2CO_3 is formed in the plasma because of absence of carbonic anhydrase in plasma). This combination of CO_2 with Hb is a reversible reaction that occurs with a very loose bond, so that the CO_2 is easily released into the alveoli where the PCO_2 is lower than in the tissue capillaries.

Carbon dioxide's ability to bind to hemoglobin is affected by the amount of oxygen bound to hemoglobin. The smaller the amount of oxygen bound to hemoglobin, the greater the amount of carbon dioxide that can bind to it, and vice versa. This relationship is called the **Haldane effect**. In the lungs, binding of oxygen with Hb tends to displace CO_2 from the blood. Haldane effect, therefore, can be defined as **the effect of O_2 concentration (PO_2) on the affinity of Hb to CO_2**. This effect can be explained as follow:

1. Binding of oxygen to Hemoglobin appears to directly reduce the affinity of the protein for carbon dioxide in the form of carbaminohemoglobin. Consequently, binding of oxygen to hemoglobin displaces hemoglobin-bound carbon dioxide, facilitating elimination of carbon dioxide in the lungs.

2. Binding of oxygen renders Hemoglobin a more acidic molecule thus resulting in the release of free hydrogen ions (H^+). The higher concentration of free hydrogen ions following oxygen binding pushes the reversible equilibrium between bicarbonate and carbon dioxide in the direction of carbon dioxide. Consequently, binding of oxygen to hemoglobin facilitates conversion of bicarbonate to carbon dioxide in the pulmonary circulation and in turn enhances carbon dioxide elimination.

The respiratory exchange ratio (R) & **respiratory quotient (RQ):** RQ is the ratio of CO_2 produced to O_2 consumed while food is being metabolized. It can be measured by <u>invasive technique</u> <u>directly</u> at the tissues. If the ratio of CO_2 produced to O_2 consumed measured <u>non-invasively</u> at mouth to assess these two parameters <u>indirectly</u> we called this ratio **respiratory exchange ratio**. A value of 0.8 therefore means that the amount of **CO_2 produced** by the tissues (<u>4 ml</u>) is 80% of the amount of **O_2 used by the tissues** (<u>5 ml</u>), which also means that the amount of CO_2 transported from the tissues to the lungs in each 100 milliliters of blood is 80% of the amount of O_2 transported from the lungs to the tissues in each 100 milliliters of blood. Although R changes under different metabolic conditions, accordingly for glucose RQ = 1. When fat is utilized, only 7 molecules of CO_2 are produced for every 10 molecules of O_2 consumed, and RQ = 0.7. On mixed diet, the RQ is between these values.

At rest, during each minute, body cells consume about 200 ml of oxygen and produce about the same amount of CO_2, when a person diet is exclusively carbohydrates.

Dangerous Raptures of the Deep

As divers descend to greater and greater depths underwater, the pressure on their bodies rises proportionately [1] atmosphere (760 mm Hg) of pressure for each 10 m (33 ft) of descent] because of the increasing weight of the water. Scuba gear (self-contained underwater breathing apparatus) has freed divers from air lines to the surface and heavy pressurized suits because it permits continual equalization of the air pressure (provided by the mixture of compressed air in the tank) with the water pressure; that is, air enters the lungs at a higher-than-normal pressure. Thus descent is not usually a problem, unless divers descend below 100 feet and remain there for an extended time.

Although nitrogen ordinarily has little effect on body functioning, hyperbaric conditions for an extended time force so much nitrogen into solution in the blood that it provokes a narcotic effect called nitrogen narcosis. Nitrogen is far more soluble in lipids than in water, so it tends to concentrate in lipid-rich tissues such as the central nervous system, bone marrow, and fat deposits. Divers become dizzy, giddy, and appear to be intoxicated, which is why this condition is sometimes called "rapture of the deep".

Assuming divers take care to avoid these narcotizing effects, and ascend to the surface gradually, dissolved nitrogen gas can be driven out of the tissues and eliminated by the lungs without problems. But if the ascent is rapid, the PN_2 decreases abruptly and the poorly soluble nitrogen gas appears to "boil" from the tissues and out of solution in the body fluids. Gas bubbles in blood represent potentially lethal emboli, and those formed within joints, bones, and muscles can cause excruciating musculoskeletal pain, commonly called the "bends."

If divers ascend suddenly and without exhaling, the alveoli are likely to rupture. This situation usually occurs when they panic after aspirating seawater or encountering other hazards, such as equipment failure, strong currents, or rough waters. Under such conditions, connections occur between the alveoli and the pulmonary bloodstream, and life-threatening gas emboli develop. Since divers typically ascend head-up, the emboli usually invade the cerebral circulation. Seizures, localized motor and sensory deficits, and unconsciousness are all possibilities. Indeed, many scuba-related drownings appear to follow loss of consciousness due to arterial gas embolism .

The usual and most effective treatment for decompression sickness is hyperbaric therapy: reinstituting compression and then redoing decompression.

The control and regulation of respiration: The respiration is **controlled by the respiratory center** and is **regulated by various factors.**

Respiratory center is located in the brain which is composed of three major groups of neurons located bilaterally **within the reticular formation** of the **medulla oblongata** and **pons** and these are (figure 6.24):

[1] The dorsal respiratory group (DRG) of neurons: This group of neurons is located in the **medulla** within the **nucleus of the tractus solitorius** which is also the sensory termination of both the **vagal** (X cranial nerve) and **glossopharyngeal nerves** (IX) transmitting sensory signals into the respiratory center from the peripheral chemoreceptors, mechanoreceptors, baroreceptors and several different types of receptors in the lung. **DRG is responsible for the basic rhythm of respiration by autonomous repetitive bursts of inspiratory action potentials.** The nerve signal from DRG is transmitted to:

- The inspiratory muscles (through contralateral phrenic).
- To external intercostal muscles through spinal motoneurons.
- To the ventral respiratory group.

The nerve signal from DRG begins very weakly at first and increase steadily in a **ramp** fashion for about 2 sec (figure 6.25 B). Then it abruptly ceases for approximately the next 3 sec, and then begins again for still another cycle, and again 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 ventral respiratory group (VRG): These neurons are located in the medulla and innervate mainly **inspiratory and expiratory accessory muscles**. VRG remains almost totally inactive during normal quiet respiration. When the respiratory drive for increased pulmonary ventilation becomes greater than normal (such as during exercise), respiratory signals from DRG spell over into the VRG. As a consequence, the VRG contributes to the respiratory drive as well.

Figure 6.24: Brain respiratory center.

[3] The pneumotaxic group: This group of neurons is located within the upper **pons** 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.** When the pneumotaxic signals are strong, inspiration become shallow and short (might last for as little as 0.5 sec), and increase the rate of breathing, but when the pneumotaxic signals are weak, the inspiratory ramp might continue to rise for perhaps as long as 5-10 sec and prolong and fills the lungs with a great air leading to a deep and long inspiration with a decrease in the rate of breathing. Therefore the respiratory rate is decreased.
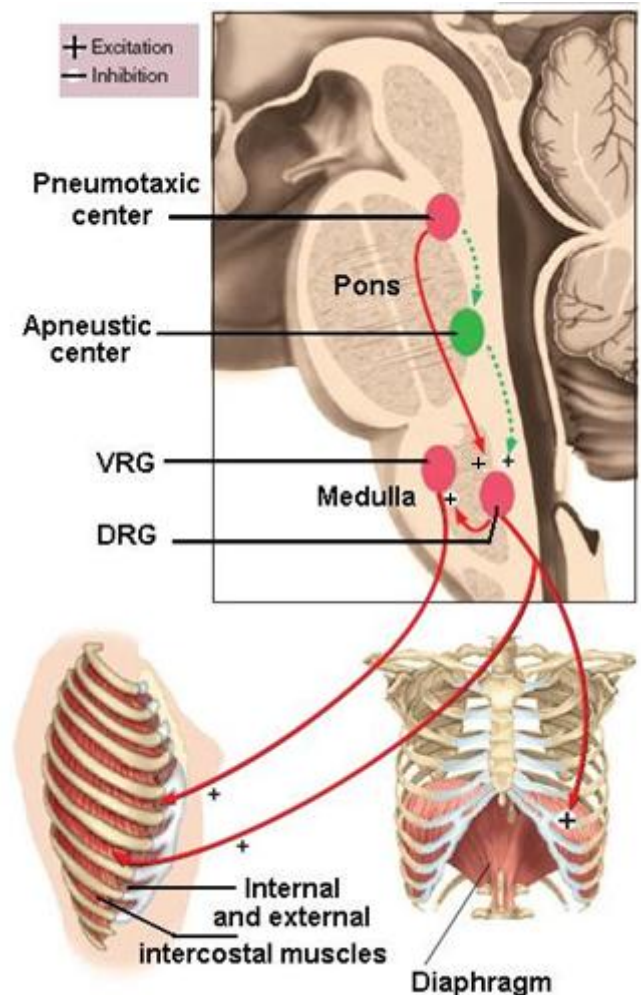
[4] Apneustic center: This is located in the lower pons. The apneustic center of pons sends signals to the dorsal respiratory center in the medulla to delay the 'switch off' signal of the inspiratory ramp provided by the pneumotaxic center of pons. It is **inhibited** by pneumotaxic center and by vagus nerves (through pulmonary stretch receptors). Lesions of pneumotaxic center and vagotomy lead to **apneusis** (figure 25 A). Apneusis is an abnormal respiratory pattern consisting of a pause at full inspiration; a prolonged inspiratory ramp. It controls the intensity of breathing. During forced breathing, the

Normal breathing pattern

Apneustic respiration (apneusis)

- *sustained periods of inspiration, followed by brief periods of exhalation*
- *loss of input from vagal nerve and pneumotaxic center*
- *brain damage, intoxication*

Figure 6.25 A: Normal and apneustic pattern of respiration.

apneustic centers adjust the degree of stimulation in response to sensory information from the vagus nerve concerning the amount of lung inflation.
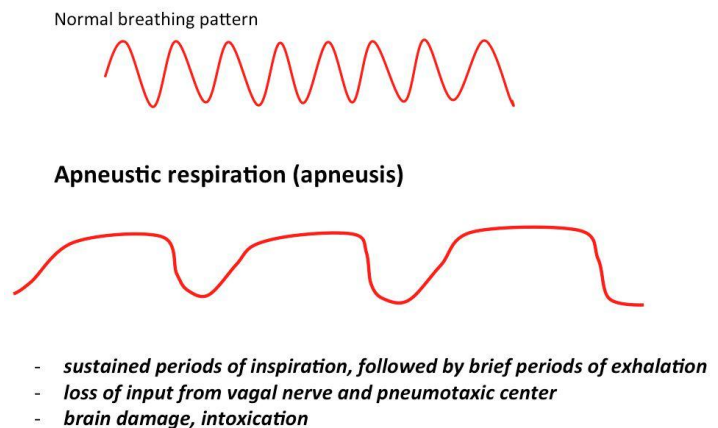
Regulation of respiratory center activity: The respiratory centers and consequently the ventilation can
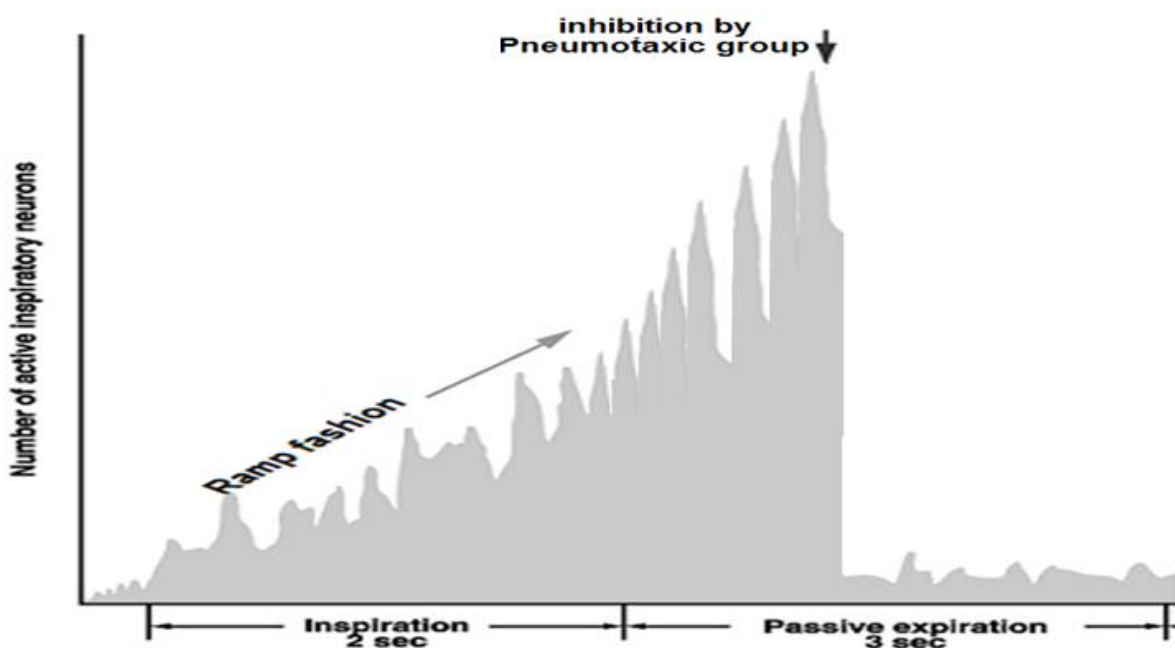
Figure 6.25 B: Ramp fashion of inspiratory action potentials of the dorsal respiratory group of neurons.

be regulated by the following factors:
[1] Chemical regulation of respiration mediated through changes in PCO_2, $[H^+]$, and PO_2.
[2] Peripheral receptors and proprioceptors regulation of respiration.
[3] Brain centers regulation of respiration.
[4] Motor cortex regulation of respiration.
[5] Vasomotor center regulation of respiration.
[6] Body temperature regulation of respiration.

1. Chemical regulation of respiration:
[A] [CO₂] and [H⁺]: Surplus of CO_2 or H^+ stimulate respiratory center **indirectly** through **central chemoreceptors** (located bilaterally in the medulla close to the exit of cranial nerves IX and X) which is

highly sensitive to changes in H^+ concentration, and it in turn excites the other portions of the respiratory center causing greatly increased strength of both the inspiratory and expiratory signals to the respiratory muscles. The resulting increase in ventilation increases the elimination of CO_2 from the blood; this also removes H^+ from the blood because decreased CO_2 also decreases the blood carbonic acid. About **80% of the drive for ventilation is a result of stimulation of the central chemoreceptors**. However, H^+ does not easily cross either the blood-brain barrier or the blood–cerebrospinal fluid barrier. For this reason, changes in H^+ concentration in the blood actually have considerably less effect in stimulating the chemosensitive neurons than do changes in CO_2. This is because CO_2 passes through blood–brain barrier and blood-cerebrospinal fluid barrier very easily (figure 6.26). Consequently, whenever the blood CO_2 concentration increases, the PCO_2 in both the interstitial fluid of the medulla and in the cerebrospinal fluid also increase. In both of these fluids the CO_2 immediately reacts with the water to form carbonic acid which dissociates into H^+ and bicarbonates. Thus, paradoxically, more H^+ are released into the respiratory chemosensitive sensory area when the blood CO_2 concentration increases than when the blood H^+ concentration increases. For this reason, respiratory center activity is affected considerably more by changes in blood CO_2 than by changes in blood H^+.

The stimulatory effect of increased CO_2 on respiration reaches its peak within a few minutes after an increase in blood 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 CO_2 concentration has a **very potent acute effect** on controlling respiration but **only a weak chronic effect after a few days' adaptation**.

Figure 6.26: Chemical regulation of respiration, effect of [CO_2].
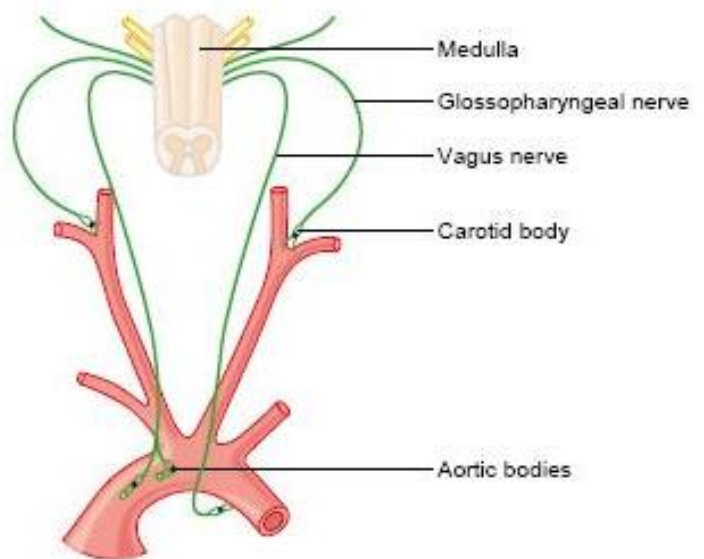
Figure 6.27: Respiratory control by peripheral chemoreceptors in the carotid and aortic bodies.

[B] PO₂: Arterial PO_2 does not have a significant direct effect on the respiratory center of the brain in controlling respiration. Instead, it acts either entirely or 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 (figure 6.27).
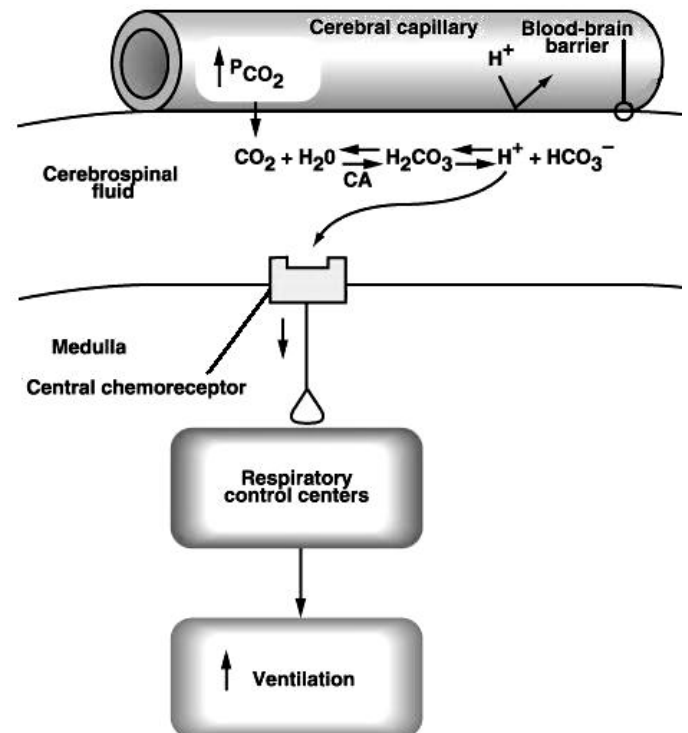
Peripheral chemoreceptors are stimulated when:
- $\downarrow PO_2$
- $\uparrow PCO_2$ (less effective)
- $\uparrow [H^+]$
- $\downarrow$ Blood flow
- $\uparrow$ Temperature

The carotid bodies are supplied by the autonomic nervous system, which appears to alter their sensitivity to hypoxia by regulating blood flow to the chemoreceptor:
- Sympathetic action vasoconstricts, increasing sensitivity to hypoxia
- Parasympathetic action vasodilates, reducing sensitivity to hypoxia.

Carotid bodies are 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 nerve fibers pass through the **vagi** to the dorsal respiratory area.

The blood flow through the carotid and aortic bodies is extremely high. Because of this, arterio-venous oxygen difference is very small, which means that the venous blood leaving these bodies still has a PO_2 nearly equal to that of the arterial blood. It also means that PO_2 of the tissues in these bodies remain at all times almost equal to that of the arterial blood. **These bodies are more influenced by arterial PO_2 and not by arterial oxygen content**. Hence, they are not influenced by a low Hb level, methaemoglobinaemia, or CO poisoning because **the O_2 tension is determined by the amount of dissolved O_2 which remains normal.**

When the arterial PO_2 falls below normal level of 100 mm Hg, or when the blood pressure sufficiently low causing a low blood flow (even though constituents of blood do not change), the chemoreceptors will be stimulated, and become strongly stimulated when arterial $PO_2 < 60$ mm Hg causing the alveolar ventilation to increase only **1.5 to 1.7 fold.** An increase in either 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 than their effects mediated through the chemoreceptors.

The cause of the poor effect of PO_2 changes on respiratory control in comparison to those of CO_2 and H^+ concentration can be explained as follow: The increase in ventilation that does occur when the PO_2 falls blows off CO_2 from the blood and therefore decreases the PCO_2, at the same time it also decreases the H^+ concentration. Therefore, the two powerful respiratory stimulants were decreased and therefore exert inhibitory effects that oppose the excitatory effect of the diminished O_2. As a result, they keep the decreased O_2 from causing a marked increase in ventilation until the fall to 20-40 mm Hg, a range that is incompatible with life for more than a few minutes.

When the concentration of CO_2 and H^+ are prevented from changing, the decreased blood PO_2 will increase the ventilation 8 to 10 times as great as when the CO_2 and H^+ concentration do change and oppose the PO_2 effect. **Thus, under normal conditions, the PO_2 mechanism plays only small role in control of respiration.**

When a person first ascends to high altitudes, the diminished O_2 in the air stimulates the O_2 lack control system of respiration (table 6.4). The respiration at first increases to a maximum of only about two-thirds above normal. The cause of this slight increase is the powerful opposition effects of the CO_2 and H^+ control mechanisms on the O_2 lack mechanism. However, over several days, the respiratory center gradually becomes adapted to the diminished CO_2 so that its opposition effect to the O_2 control is gradually lost, 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.

Table 6.4: Summary of adaptation to high altitude.	
Parameter	**Response**
Alveolar PO_2	Decrease
Arterial PO_2	Decrease (hypoxaemia)
Ventilation rate	Increase (hyperventilation)
Arterial PCO_2	Decrease
Arterial pH	Increase (respiratory alkalosis), compensated later by the kidney
Hb concentration	Increase (polycythaemia)
2,3-DPG concentration	Increase
Hb-O_2 curve	Shift to right, decrease affinity
Pulmonary vascular resistance	Increase

Yet, under some abnormal conditions 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 support each other, 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.

2. Peripheral receptors and proprioceptors regulation of respiration (figure 6.28)**:**
[A] Stretch receptors:
- **Bronchial C stretch receptors:** Located in the wall of the bronchi and bronchiole that transmit signals through the vagi into the dorsal respiratory group of neurons when the lungs become overstretched. These signals affect inspiration in much the same way as signals from the pneumotaxic center, that is, they limit the duration of inspiration. 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**. In human beings, this reflex probably is not activated until the tidal volume increases to greater than approximately 1.5 liters. Therefore, 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 (juxtacapillary) receptors:** These receptors are located in the alveolar walls, close to the 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:** This can detect the force generated by the respiratory muscle during breathing. If the force required distending 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).

[B] Irritant receptors: Those are located between the epithelial cells of 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 breathe holding (i.e., apnea).
[C] Joint proprioceptors: Those are located in the joint capsules and transmit excitatory impulses to the respiratory center.
[D] Touch, thermal, and pain receptors: Can also stimulate the respiratory center. For example, irritants in the nasal cavity can initiate a sneeze reflex. In addition, through these receptors one can observe the respiratory response when cold water is splashed onto a person, and also the common practice of spanked a newborn baby on the buttocks.

3. Brain centers regulation of respiration:

[A] **Reticular Activating System (RAS):** Located in the reticular system of the brain stem; its activity is associated with the "awake" or "conscious" state. When active, it simulates respiratory ventilation. When RAS activity is reduced, as during sleep, ventilation is reduced and PCO_2 increases by a few mmHg.

A condition is called sleep apnea seen in some individuals, in which ventilation ceases temporarily (10 seconds) during sleep. Sleep apnea can be of many types: [i] Central apnea: reduced CNS respiratory drive. [ii] Obstructive apnea: increased upper airway resistance (laryngospasm and/or bronchospasm) (snoring). [iii] Complex or mixed sleep apnea.

In infants, sleep apnea can lead to SIDS (Sudden Infant Death Syndrome).

[B] **Limbic System:** Respiratory changes in emotion.

[C] **Motor cortex regulation of respiration:** Respiration can be controlled **voluntarily**, and that one can hyperventilate or hypoventilate to such an extent that serious derangements in PCO_2, pH and 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. **Strenuous exercise does not significantly change the mean arterial PO_2, PCO_2, or pH,** it is unlikely that these play an important role in stimulating the immense increase in ventilation. Although the mean venous PO_2 decreases during exercise, the venous vasculature does not contain chemoreceptors that can sense PO_2. The brain, upon transmitting motor impulses to the contracting muscles, is believed to transmit collateral impulses to the brainstem to excite the respiratory center. Also, the movement of body parts during exercise is believed to excite joint and muscle proprioceptors that then transmit excitatory impulses to the respiratory center.

[D] Vasomotor center regulation of respiration: 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 increases the activity of the vasomotor center also has at least a moderate effect on increasing respiration.

[E] Body temperature regulation of respiration: 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.
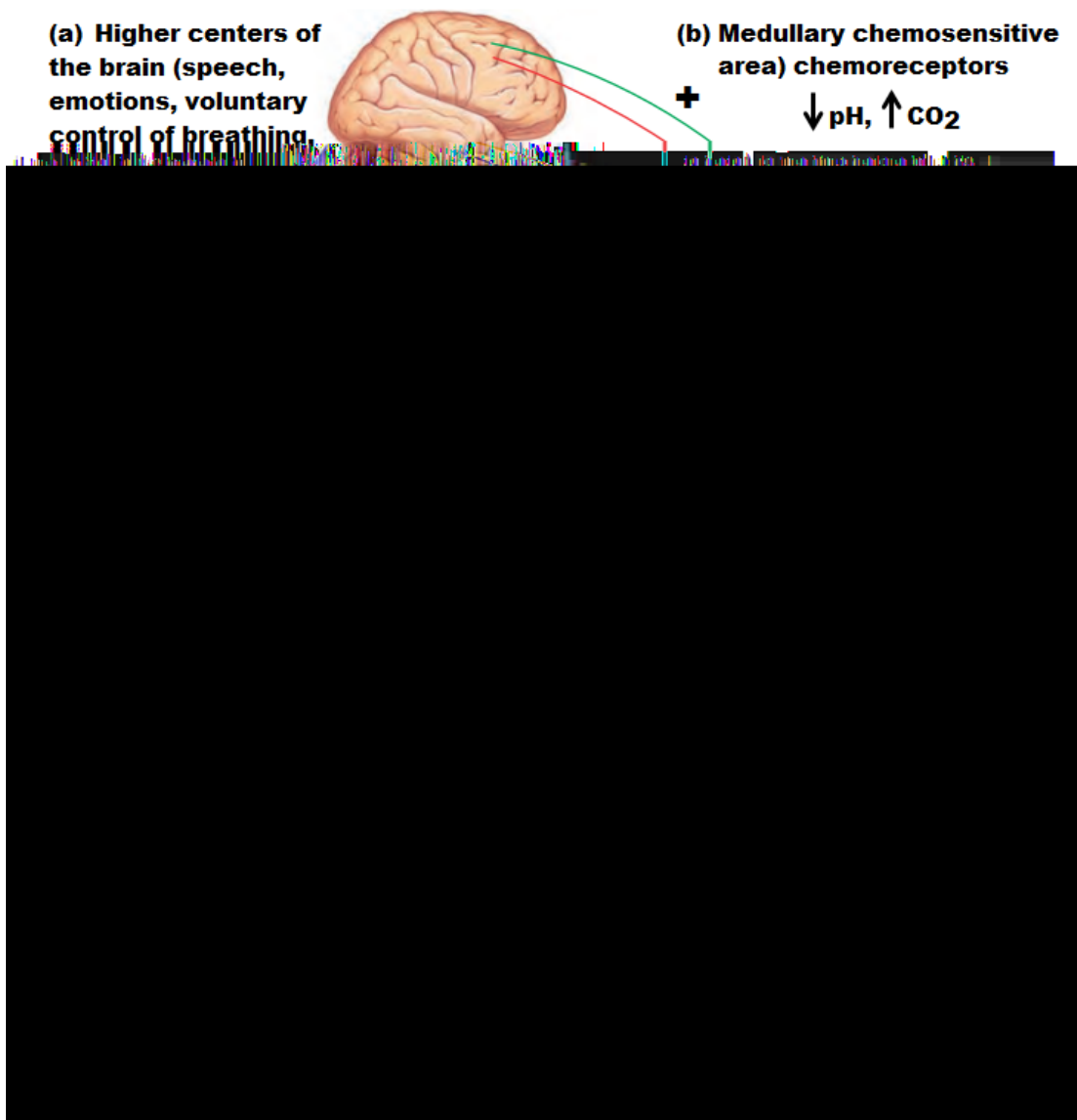
Figure 6.28: Central, peripheral receptors and proprioceptors regulation of respiration.

The response of the respiratory system to exercise and stress: In exercise or other stressful conditions, O_2 utilization and CO_2 formation can increase as much as twenty fold associated with increase in alveolar ventilation and cardiac output (table 6.5). However, the blood is still almost completely saturated with O_2 when it leaves the pulmonary capillaries due to:

[A] An increase in the diffusing capacity of the respiratory membrane for O_2 about threefold during exercise, the reasons for this is due to 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.

[B] Increased alveolar ventilation, this is due to

- Reflexes originating from body movements (proprioceptors). The body movements, especially of the limbs, are believed to increase pulmonary ventilation by exciting joint proprioceptors that then transmit excitatory impulses to the respiratory center.
- Increase in body temperature.
- Epinephrine release (during exercise).
- Impulses from the cerebral cortex to the contracting muscles, is believed to transmit collateral impulses into the brain stem to excite the respiratory center.

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

[D] 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.

Table 6.5: Summary of respiratory responses to exercise.	
Parameter	**Response**
O_2 consumption	Increase
CO_2 production	Increase
Ventilation rate	Increase
Arterial PO_2 and PCO_2	No change
Arterial pH	No change in moderate exercise, decrease in strenuous exercise (lactic acidosis)
Venous PCO_2	Increase
Pulmonary blood flow (cardiac output)	Increase
V/Q ratio	More evenly distributed in lung

Pulmonary blood flow: The pulmonary circulation is basically **low-pressure**, **low-resistance**, **highly compliant system**. In addition, the **interstitial fluid pressure is more negative** in the pulmonary circulation than in the systemic circulation. The **pulmonary capillaries are more permeable to proteins** than the skeletal muscle capillaries, and, therefore, **the interstitial concentration of protein is greater** in the pulmonary circulation. 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 mm Hg/L/min).

The pulmonary circulation is composed principally of two types of vessels: **extra alveolar** (larger arteries and veins) which are located outside the alveoli and are tethered to the elastic tissue of the lung and are exposed to the intrapleural pressure. The **intra alveolar** vessels (pulmonary capillaries) those are located between the alveoli.

At lower lung volumes, the intra alveolar vessels are near maximally open, and therefore, their resistance to blood flow is minimal. However, with increasing lung volume, these intra alveolar vessels are compressed by the distended alveoli, and this progressively increases their resistance to blood flow.

Conversely, at low lung volumes, the caliber of the extra alveolar vessels is small because the transmural pressure gradient across the walls of these vessels is reduced due to the lesser subatmospheric pressure in the intrapleural space. Consequently, vascular resistance in the extra

alveolar vessels is high at low lung volume. With increasing lung volume, the intrapleural pressure becomes more subatmospheric elevating the transmural pressure gradient across the extra alveolar vessels coupled with the added radial traction on the extra alveolar vessels imposed by the surrounding lung tissue as it expand, cause these vessels to distend and thereby decrease their vascular resistance.

Pulmonary vascular resistance is mainly determined by intra alveolar vessels because the greatest cross-sectional area exists in the millions of intra alveolar vessels. Thus the total pulmonary vascular resistance is heightened at higher lung volumes when vascular resistance in the intra alveolar vessels is high. Total pulmonary vascular resistance is lowest at the functional residual capacity when there is sufficient lung inflation to open the extra alveolar vessels with minimal closing of the intra alveolar vessels.

The pulmonary circulation is remarkably compliant. The pulmonary vascular resistance declines as the pressure in the pulmonary circulation rises. At a normal pressure, approximately half the pulmonary capillaries are closed. With increasing pulmonary arterial pressures (for example as a consequence of increase of left atrial pressure), these **previously closed capillaries open** (recruitment) and **distended**. The net effect is an increase in the total cross-sectional area of the pulmonary capillaries, resulting in decreased pulmonary vascular resistance.

In addition, sympathetic stimulation constricts the pulmonary blood vessels, whereas parasympathetic stimulation causes vasodilation. There are a varity of vasoactive compounds that affect pulmonary vascular resistance. The vasoconstricting agents include arachidonic acid, leukotrienes, thromboxane A_2, prostaglandin F_2, angiotensin-II, serotonin, epinephrine, and norepinephrine. The vasodilating compounds are Ach, bradykinin, and prostacyclin.

Pulmonary blood flow and pressure decreases from the bottom to the top of the lung in upright individuals. This occurs because gravity creates a gradient of vascular pressures from the top to the bottom of the lung such that the pressure is lower at the apex than at the base of the lung. The gradient in pulmonary blood flow from the top to the bottom of the lung is also caused by the higher lung (alveolar) volumes at the top of the lung (relative to the base) which tend to compress the capillaries and increase resistance in the apical region. When an individual is supine, the pressure differences between the apex and base of the lung are abolished and consequently, pulmonary blood flow is more homogeneous throughout the supine lung than throughout the upright lung.

Effects of aging on the respiratory system: Most aspects of the respiratory system are affected by aging. Even though vital capacity, maximum ventilation rates, and gas exchange decrease with age, the elderly can engage in light to moderate exercise because the respiratory system has a large reserve capacity.

Vital capacity decreases with age because of a decreased ability to fill the lungs (**decreased inspiratory reserve volume**) and a decreased ability to empty the lungs (**decreased expiratory reserve volume**). As a result, **maximum minute ventilation rates decrease**, which in turn decreases the ability to perform intense exercise.

These changes are related to the **weakening of respiratory muscles** and to **decreased compliance of the thoracic cage** caused by the stiffening of cartilage and ribs. **Lung compliance actually increases** with age, but this effect is offset by the decreased thoracic cage compliance. Lung compliance increases because parts of the alveolar walls are lost, which reduces lung recoil. There are no significant age-related changes in lung elastic fibers or surfactant. **Residual volume increases** with age as the alveolar ducts and many of the larger bronchioles increase in diameter. This **increases the dead space**, which decreases the amount of air available for gas exchange (alveolar ventilation). In addition, **gas exchange across the respiratory membrane is reduced** because parts of the alveolar walls are lost, which decreases the surface area available for gas exchange, and the remaining walls thicken, which decreases the diffusion of gases. A gradual **increase in resting tidal volume** with age

compensates for these changes. With age, mucus accumulates within the respiratory passage ways. The **mucus–cilia escalator is less able to move the mucus** because it becomes more viscous and because the number of cilia and their rate of movement decrease. As a consequence, the elderly are more susceptible to respiratory infections and bronchitis.

Hypoxia (cellular deficiency of O_2): Brain is the most sensitive tissue to hypoxia; complete lack of oxygen can cause unconsciousness in 15 sec and irreversible damage within 2 minute. Traditionally; hypoxia has been divided into 4 types (table 6.6):

      [1] Hypoxic hypoxia: In which the PO_2 of the arterial blood is reduced due to insufficient O_2 gets to the alveoli or inadequate ventilation of the alveoli or insufficient diffusion of O_2 through the respiratory membrane.

      [2] Anaemic hypoxia: In which the arterial PO_2 is normal but the amount of Hb available to carry O_2 is reduced.

      [3] Stagnant or ischaemic hypoxia: In which the blood flow to a tissue is so low that adequate O_2 is not delivered to it despite a normal PO_2 and Hb concentration.

      [4] Histotoxic hypoxia: In which the amount of O_2 delivered to a tissue is adequate because of the action of a toxic agent, the tissue cells cannot make use of the O_2 supplied to them such as in cyanide poisoning, in which the action of cytochrome oxidase is completely blocked and therefore, the tissues cannot utilize the O_2. Also, deficiency of oxidative enzymes or other elements in the tissue oxidative system can lead to this type of hypoxia such as vitamin B deficiency (Beriberi).

Table 6.6: Types of hypoxia.

Type of Hypoxia	O_2 Uptake in Lungs	Hemoglobin	Circulation	Tissue O_2 Utilization
Hypoxic	**Low**	Normal	Normal	Normal
Anemic	Normal	**Low**	Normal	Normal
Ischemic	Normal	Normal	**Low**	Normal
Histotoxic	Normal	Normal	Normal	**Low**

Severe hypoxia:
A. leads to accumulation of lactate ions in tissues
B. stimulates the sympathetic nervous system
C. decreases cerebral vascular resistance
D. induces erythropoietin secretion
E. increases synthesis of 2,3-BPG
F. increases P50 of Hb

Cyanosis: It is a darkness or blueness of the skin and mucous membrane and appears when the reduced Hb concentration of the blood in the capillaries is more than 5 gm/dl. 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 arterial blood undersaturation or an abnormal Hb derivative, and the mucous membranes and skin are both affected.

[2] Peripheral cyanosis: This is due to a slowing of blood flow to an area and abnormally great extraction of O_2 from normally saturated arterial blood. It result 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 spared. In very cold weather cyanosis does not developed, 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 does not occur in association with hypoxia except only when hypoxia is caused by hypoventilation or by circulatory deficiency.** Obviously, hypoxia caused by too little O_2 in the air, by too little Hb, or by poisoning of the oxidative enzymes has to do with the availability of O_2 or use of O_2 by the tissues. Therefore, it is ready understandable that hypercapnia is not a concomitant of these types of hypoxia. Also, in 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. Also, if hypercapnia does begin to occur this immediately stimulates pulmonary ventilation which corrects the hypercapnia but not necessarily the hypoxia. However, in hypoxia caused by hypoventilation, CO_2 transfer between the alveoli and the atmosphere is affected as much as is O_2 transfer. Therefore, hypercapnia may result along with the hypoxia. In circulatory deficiency, diminished flow of blood decreases the removal of CO_2 from the tissues, resulting in tissue hypercapnia. However, the transport capacity of the blood for CO_2 is about three times that for O_2, So that even here the tissue hypercapnia is much less than the tissue hypoxia.

Danger of hypercapnia during O_2 therapy: In hypoxia, O_2 therapy is of great value, especially in certain types of hypoxia (such as atmospheric hypoxia, hypoventilation hypoxia, diffusional hypoxia) and of slight value in hypoxia caused by anaemia or other abnormality of Hb transport, and ischaemic hypoxia, but of almost no value at all in histotoxic hypoxia. Many patients require only a supplementary level of oxygen in the room air they are breathing, rather than pure or near pure oxygen, and this can be delivered through a number of devices dependent on the situation, flow required and in some instances patient preference. A nasal cannula and face masks options, often used at between 5 and 8 liters per minute of oxygen delivery with a final concentration of oxygen to the patient of between 28% and 50%.

On the other hand, 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, particularly in conditions that otherwise tend to cause hypercapnia, such as depressed respiratory center activity or airway obstruction.

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 is 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 produce the irritation is probably due to **inhibition the ability of lung macrophages** to kill bacteria, and **surfactant production is reduced**. Administration of 100% O_2 at increased pressure

accelerates the onset of O_2 toxicity and produces central nervous system symptoms. O_2 toxicity **decreases GABA content of the brain**, in addition to **decrease in ATP content of the liver and kidney**.

Furthermore, hyperbaric O_2 administration causes the tissue PO_2 to increase leading to an increase in the production of the oxidizing free radicals which can not be removed by the available enzyme and now they do have serious destruction and even lethal effects on the cells. Hyperbaric O_2 and the high PO_2 in the tissue causes **severe arteriolar constriction** and the local tissues blood flow sometimes decreases to less than 50% of the normal. Under these conditions, it is possible that the delivery of various cellular nutrients may become too low maintain normal cellular functions. Yet hyperbaric O_2 is of useful in treatment of gas gangrene, leprosy, CO poisoning, and probably cyanide poisoning. However, O_2 toxicity limits exposure to less than 5 hours and pressure to 3 atmospheres or less.

Nonrespiratory lung functions: The lungs have metabolic, immunologic, and filtration functions. They filter out small blood clots (small pulmonary emboli), preventing the serious complications of systemic embolization. Bronchial secretions contain secretory immunoglobulins (IgA) and other substances that serve to resist infection. Pulmonary alveolar macrophages are actively phagocytic and remove bacteria and small particles inhaled by the lungs as well as performing the other functions of macrophages. The metabolic and endocrine functions of the lung include:

- Production of factor VIII and surfactant.
- Conversion of angiotensin I to angiotensin II by converting enzyme.
- Synthesis of prostaglandins, histamine, and kallikerin in addition to a number of other substances.
- The lungs contain a fibrinolytic system that lyses clots in the pulmonary veins.

Figure 6.29: Biot`s respiration.

Overview of specific ventilatory patterns:

The following are ventilatory patterns frequently seen by the respiratory care practitioner in the clinical setting.

Eupnea: Normal, spontaneous breathing.

Apnea: Complete absence of spontaneous ventilation. This causes the arterial PO_2 and alveolar PO_2 to rapidly decrease and the arterial PCO_2 and alveolar PCO_2 to increase. Death will ensue in minutes.

Biot's respiration: Short episodes of rapid, uniformly deep inspirations, followed by 10 to 30 seconds of apnea (figure 6.29). This pattern was first described in patients suffering from meningitis. Biot's respiration is caused by damage to the medulla oblongata due to strokes or trauma or by pressure on the medulla due to uncal or
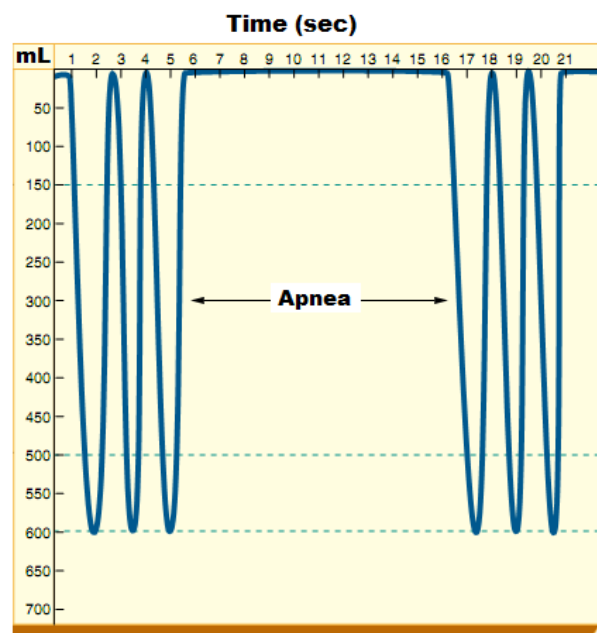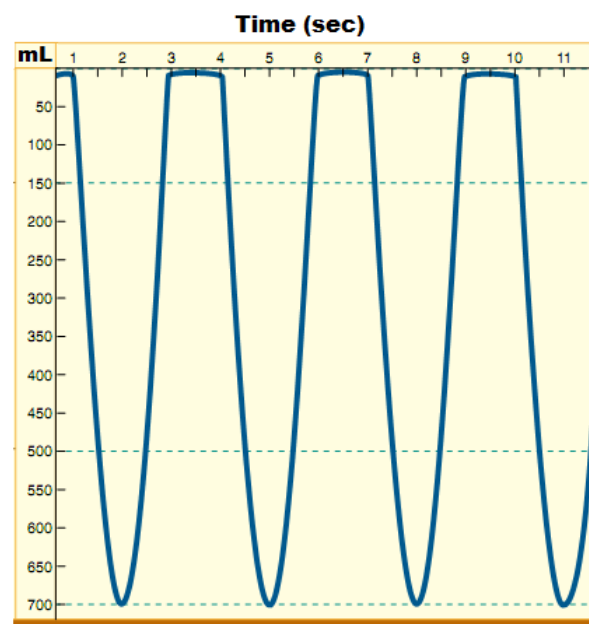

Figure 6.30: hyperpnoea.

tentorial herniation. It can be caused by opioid use. It generally indicates a poor prognosis.

Hyperpnoea: Increased depth (volume) of breathing with or without an **increased frequency** when **required and desirable to meet metabolic demand of body tissues**, such as during or **following exercise**, or when the **body lacks oxygen (hypoxia)**, for instance in high altitude or as a result of anemia (figure 6.30).

In contrast, **hyperventilation** (increase rate and/or depth of breathing), **the rate of ventilation is inappropriate for the body's needs. The result is a decrease in arterial PCO_2.**

Hyperpnoea associated with diabetic ketoacidosis is called **Kussmaul's Respiration.** It causes the alveolar and arterial PCO_2 to decline and the alveolar and arterial PO_2 to increase. It also can be seen in uremia, sepsis, and salicylate and methanol over dosage.

Hyperpnoea is deep rapid breaths and it differs from that of **tachypnea** in which the breathing is **shallow** and **rapid**.

In adult humans at rest, any rate between 12-20 breaths per minute is normal and tachypnea is indicated by a ventilatory rate greater than 20 breaths per minute. Tachypnea may have physiological (such as exercise and labor during pregnancy) or pathological causes.

Hypoventilation: It is also known as **respiratory depression**. A decrease in alveolar ventilation, produced by any ventilatory pattern that causes a decrease in either the ventilatory rate (figure 3.31 A) or the depth of breathing (figure 6.31 B), that **causes** the alveolar PCO_2 and, therefore, the arterial PCO_2 to increase. It can be caused by medical conditions, such as **stroke** affecting the brainstem, by breathholding, or by drugs, typically when taken in overdose.
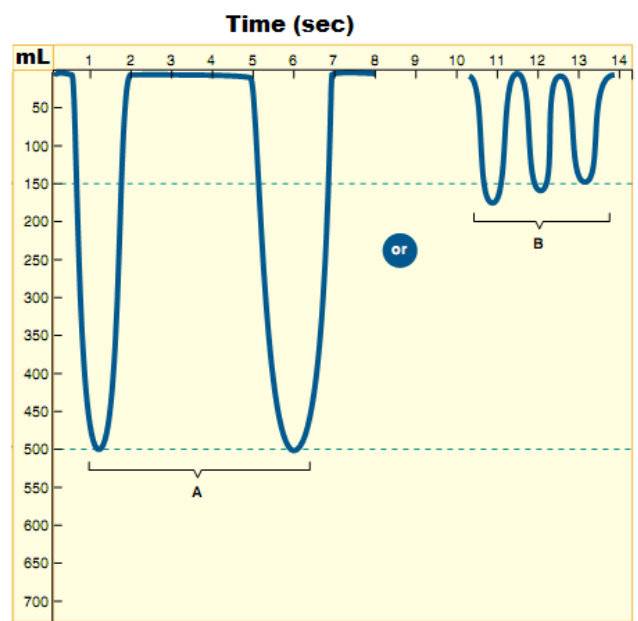

Figure 6.31: Hypoventilation.

Cheyne-Stokes respiration: 10 to 30 seconds of apnea, followed by a gradual increase in the volume and frequency of breathing, followed by a gradual decrease in the volume of breathing until another period of apnea occurs (figure 6.32). As the depth of breathing increases, the alveolar and arterial PCO_2 fall and the alveolar and arterial PO_2 rise. It can be seen in **heart failure** or **brain stem lesions**.

Orthopnea (dyspnea when lying flat): A condition in which an individual is able to breathe most comfortably only in the upright position.

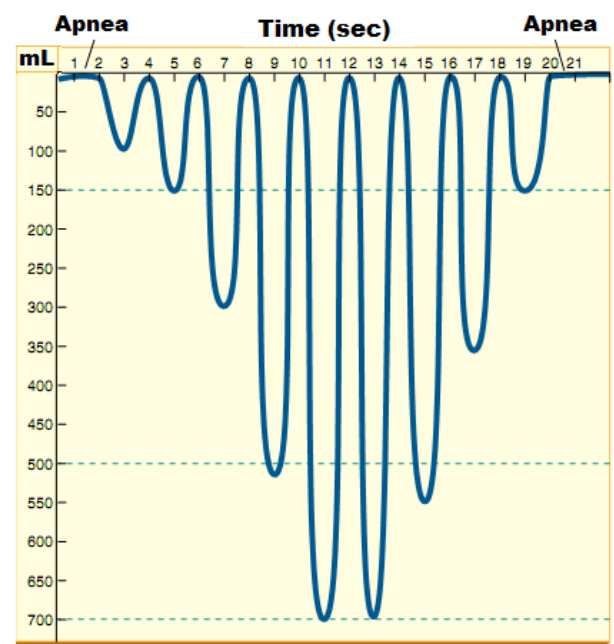**Dyspnea:** Difficulty in breathing, of which the individual is aware.

Figure 6.32: Cheyne-Stokes respiration.

Summary of Nerves and Muscles Physiology
Anatomically the respiratory system consists of:
[1] Upper respiratory tract which consists of nose and pharynx.
[2] Lower respiratory tract which consists of larynx, trachea, bronchi (decrease in diameter and length with each successive branching but the sum of their cross-sectional areas actually increases), bronchioles (about 1 mm in diameter), terminal bronchioles (about 0.5 mm in diameter), respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli.

Physiologically, the respiratory system can be divided into:
1. Conducting zone: Starts from the nasal cavity and ends with terminal bronchioles.
2. Respiratory zone: Starts with respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli.

- Sympathetic discharge causes pulmonary vasoconstriction, bronchodilation, and decreases glandular secretions.
- Parasympathetic discharge causes pulmonary vasodilation, bronchoconstriction, and increase glandular secretion.

The functions of the pleura are:
1. Lubrication: The pleurae are coated with lubricating pleural fluid which allows the pleurae to slide effortlessly against each other during ventilation.
2. Holding the lungs and rib cage together: Surface tension of the pleural fluid and the negative intrapleural pressure lead to close opposition of the lung surfaces with the chest wall. Therefore, movements of the chest wall are coupled to movements of the lungs.
3. Prevents lung collapse (creation of pressure gradient): This is achieved by the the negative pleural pressure created by tendency of lung to collapse and chest wall to expand). Intrapleural pressure (or intrathoracic pressure) (figure 6.3) is always slightly below atmospheric pressure (– 4 mm Hg, i.e. about 756 mmHg), at the end of expiration and – 6 mm Hg at the end of inspiration. The difference between pleural pressure and alveolar pressure is the transpulmonary pressure.
4. Compartmentalization: The pleurae, mediastinum, and pericardium compartmentalize the thoracic organs and prevent infections of one organ from spreading easily to neighboring organs.

Thoracic cage: Its functions are:
- Respiratory pump.
- Protects lungs.
- Prevents collapse of lungs.

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.

Pulmonary ventilation: This includes inspiration and expiration.
[A] Inspiration: It is an active process due to increase in the chest cage volume causing the lungs to be expanded. Chest cage volume is increased by:
[1] Downward movement of the diaphragm which 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] Contraction of external intercostal muscles raises the rib cage with consequent movement of sternum forward away from the spine, making the anterioposterior thickness of the chest greater (by 25%) during maximum inspiration.

- When extra drive for respiration is needed or in restrictive airway diseases, the other accessory inspiratory muscles for raising the rib cage came into action such as sternocleidomastoid, anterior serrati, and scalenis.

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

[1] Relaxation of diaphragm and the inspiratory muscles which cause compression on the lungs.

- When extra drive for respiration is needed or in obstructive airway diseases, the other accessory expiratory muscles are contracted and added to the force needed for rapid expiration such as abdominal recti and internal intercostal muscles.

[2] Elastic recoil tendency of the lung. The lungs have a continual elastic tendency to collapse and therefore to pull away from the chest wall. It is caused by two different factors:

[A]. The presence of elastic fibers (elastin) 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 thirds 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.

General classification of lung disorders: Lung disease is any disease or disorder where lung function is impaired. There are three major physiologic categories of lung diseases:

1. **Obstructive lung diseases:** Difficulty to exhale all the air in the lungs, such as asthma , emphysema , and chronic bronchitis.
2. **Restrictive lung diseases:** Difficult to get air in to the lungs, such as pulmonary fibrosis, neuromuscular disease, and kyphosis).
3. **Gas diffusion diseases:** A defect in the ability of the tissue of the alveoli to move oxygen into a person's blood through the respiratory membrane.

The role of surfactant: It has many important functions:

[1] It reduces the surface tension of the fluid lining the alveoli and therefore, allowing the lungs to expand.

[2] It stabilizes the sizes of the alveoli: Surfactant plays an important role in stabilizing the sizes of the alveoli ensure that the alveoli in any one area of the lung all remain approximately the same size.

[3] It prevents accumulation of edema fluid in the alveoli: By decreasing the surface tension of the fluid in the alveoli which tends to pull fluid into the alveoli from the alveolar wall.

Expansibility of the lungs and thorax: Compliance: It is a measure of the ease with which the lung inflates. This is expressed as the volume increase in the lungs for each unit increase in alveolar pressure or for each unit decrease in pleural pressure. Compliance = [V2-V1] / [P2-P1]. The Compliance of the normal lungs and thorax combined (total pulmonary Compliance) is 120-130 ml / cm H_2O. Any conditions that restrict expansion of the lungs (restrictive lung diseases) cause abnormal low compliance. Increased compliance is produced by the pathological processes that occur in emphysema (due to decrease of elastic fibers) and also result of the aging process.

The work of breathing: 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). 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.

The pulmonary volumes and capacities: Pulmonary ventilation can be recorded by using the **spirometer.**
[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 extra volume 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, indirect methods must be used.
 [5] The inspiratory capacity (IC) = TV +IRV = 500 +3000 = 3500 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 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 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.
[8] The total lung capacity (TLC) = VC + RV = 4600 + 1200 = 5800 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 that 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:
[A]. A tendency for the abdominal contents to press upward against the diaphragm in the lying position.
[B]. An increase in the pulmonary blood volume in the lying position, which correspondingly decreases the space available for pulmonary air.

Figure 6.10 (must be reviewed) shows the changes in respiratory volumes and capacities in restrictive and in obstructive lung diseases.
- In restrictive lung diseases, TLC is reduced mainly due to reduction in VC. While in obstructive lung diseases, TLC is increased mainly to increase in RV.

Peak expiratory flow (PEF): It is the maximum airflow obtained during maximum expiratory effort after maximum inspiration (400-600 liters/min). The maximum expiratory flow is much greater when the lungs are filled with a large volume of air than when they are almost empty. Consequently, PEF is

affected by age, gender, and by height of the subject. Maximum expiratory flow is reduced in cases of restrictive lung diseases and in obstructive lung diseases.

Forced vital capacity (FVC): It is the maximum volume of air expired _forcefully_ following maximum inspiration. In normal subject, the FVC is the person's vital capacity (VC). However, in obstructive lung diseases, FVC is lower than VC because of small airway collapse and air trapping.

Timed forced vital capacity (or **timed forced expiratory volume per first sec, FEV$_1$):** It is the volume of air expired during the first second of forced vital capacity. Normally it is about 80% of the total FVC.

Percent vital capacity (FEV$_1$%): It is equal to [FEV$_1$/VC] x 100. In normal subject, the FEV1% is at least 80%. However, in obstructive lung diseases like asthma, FEV$_1$% is markedly reduced while normal in restrictive lung diseases.

The minute respiratory volume (the minute pulmonary 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.

The dead space: It is the space in which the gas exchange is not taking place. The respiratory passages where no gas exchange takes place are called the _anatomical dead spaces_ (which consist of nose, pharynx, larynx, trachea, bronchi, and bronchioles). The normal anatomical dead space air in the young adult is about _150 ml_. This increases slightly with age. It also increases during a maximal inspiration because the trachea and bronchi expand 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.

The minute alveolar ventilation is the volume of new air that reaches the alveoli and is available for gas exchange with the blood equals to = respiratory rate x (tidal volume-dead space), 12 x (500 − 150) = _4200 ml/min_.

The factors that affect resistance to air flow:
- **1. Air way diameter:** Is the main component of airway resistance.
- Resistance to air flow is inversely proportional to air way diameter (or cross sectional area of the air way passages).
- According to airway diameter, resistance to air flow is of three types:
   [A] Fixed resistance (cannot change the diameter as in nose, pharynx, larynx, and trachea).
   [B] Variable resistance (can change the diameter due to the presence of smooth muscles as in bronchi and bronchioles)
   [C] Dynamic resistance (change in diameter in airway passages that are not supported by cartilages in response to transpulmonary pressures as in bronchioles and distal to them).
2. **Lung volume:** At low lung volume, the cross-sectional area is reduced and airway resistance increases, and vice versa.
3. **Turbulent gas flow**: As the turbulent of the gas flow is increased the resistance to air flow is increased. Turbulent flow occurs where gas flow velocity is high as in:
- In the larger central airways (small total cross sectional area),
- At branch points along the conducting airways,
- Reduction in air way diameter as in bronchoconstriction as a result of reduction in the airway diameter and increases the velocity of flow.

Respiratory passageways resistance:
- Approximately one-half of the resistance to airflow occurs in the upper respiratory tract (nose and pharynx, fixed resistance) when breathing through the nose (small cross sectional area). This is significantly reduced when mouth breathing.
- The other one-half of the resistance lies within the lower respiratory tract (variable resistance). This includes bronchi, bronchioles, and terminal bronchioles. This is because they contain smooth muscle in their walls. The chief site of airway resistance in the airway passages is at the medium-sized bronchi, where the radius of the individual bronchi is decreased (i.e. small cross sectional area).
- The least resistance to air flow is in the very small bronchioles and terminal bronchioles because of their large cross-sectional area. However, they are liable to dynamic airway compression because they are not prevented from collapsing by any rigidity (cartilage rings) of their walls.

The smooth muscles of the bronchioles are under nervous and humoral control:

Table 6.2: Nervous and humoral control of bronchiole smooth muscle contractions.	
Factor	**Effect**
Parasympathetic stimulation	Bronchoconstriction
Histamine, leukotrienes and SRA	Bronchoconstriction
Low blood PCO_2	Bronchoconstriction
High blood PCO_2	Bronchodilatation
Sympathetic stimulation to the adrenal glands (epinephrine and norepinephrine)	Bronchodilatation, by activation of β_2 receptors

COUGH REFLEX: Stimulated by irritation of lower respiratory mucosa (protective) ➜ Afferent (vagus) ➜ Medulla oblongata ➜ Set of responses.

SNEEZE REFLEX: Stimulated by irritation of upper respiratory mucosa ➜ 5th cranial nerve (trigeminal nerves) ➜ Medulla oblongata ➜ Set of responses.

There, an automatic sequence of events is triggered by the neuronal circuits of the medulla causing the following effects:

[1] About 2.5 liters of air is inspired.

[2] The epiglottis closes, and the vocal cords shut tightly to entrap the air within the lungs.

[3] The abdominal muscles contract forcefully, pushing against the diaphragm while other expiratory muscles also contract forcefully. Consequently the pressure in the lungs raises to as high as 100 mm Hg or more.

[4] The vocal cords and the epiglottis suddenly open widely (in case of cough reflex and the uvula, in addition, is depressed in case of sneeze reflex) so that air under pressure in the lungs explodes outward. The rapidly moving air (75-100 miles / hour) usually carries with it any foreign matter that is present in the bronchi or trachea or the nasal passages.

The respiratory unit (respiratory membrane): The part of the respiratory system at which gas exchange between the pulmonary blood and the alveolar air is taking place through its membrane. It consists 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.

Factors that affect rate of gas diffusion through the respiratory membrane:
[1] The thickness of the membrane: Any factor that increases the thickness can decrease the rate of gases diffusion (as occurs in in edema of the lung and in some fibrotic diseases of the lung).
[2] The surface area of respiratory membrane: When the total surface area is decreased the exchange of gases through the membrane is decreased (as occurs in emphysema of the lung).
[3] The diffusion coefficient of the gas in the substance of the membrane, which is the water of the membrane: This 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_2 diffuse through the membrane about 20 times as rapidly as O_2. 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.

Lung diffusing capacity: It is the volume of a gas that diffuses through the membrane each minute for a pressure difference of 1 mm Hg. In average young male adult, the diffusing capacity for oxygen under resting conditions average 21-25 ml/min/mm H, and for CO_2 of about 400-450 ml/min/mm Hg.

Ventilation – perfusion ratio (V/Q): It is the ratio of ventilation of a given alveolus to its blood perfusion which is 0.93 (range 0.8-1) and at which proper gas exchange between the blood of alveolar capillaries and alveolar blood is taking place.
   • At the top of the lung, V/Q is higher (>1.0) (i.e. normal ventilation and low perfusion) than the ideal value, which causes a moderate degree of **physiologic dead space ➔ wasted ventilation ➔** severe **muscular fatigue** and **high alveolar PO₂** and **low alveolar PCO2** (as occurs in pulmonary embolism, a fall in arterial pressure following hemorrhage or breathing against a high pressure as occurs when a person is blowing on a musical instrument).
   • At the base of the lung, V/Q is low (<0.8) (i.e. low ventilation and normal perfusion) than ideal value as in the base of the lung, which causes a moderate degree **of physiological shunted blood ➔ wasted perfusion ➔ low blood PO₂ (hypoxemia)** and **high blood PCO₂ (hypercapnia)**. 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. anatomical shunted blood. The total quantitative amount of shunted blood is called the physiological-anatomical shunt.

Compensatory mechanisms (autoregulation) for matching the ventilation and blood flow (perfusion) in alveoli:
[1] Local blood PO₂: Low alveolar ventilation ➔ Low delivering of O_2 to the blood ➔ Low blood O_2 in the pulmonary vessel ➔ vasoconstriction of pulmonary vessels supplied that alveolus and vice versa.
[2] Local blood PCO₂: High alveolar ventilation ➔ High washing out CO2 from blood ➔ Low blood CO_2 in the pulmonary vessel ➔ bronchoconstriction of the airways supplied that alveolus and vice versa.
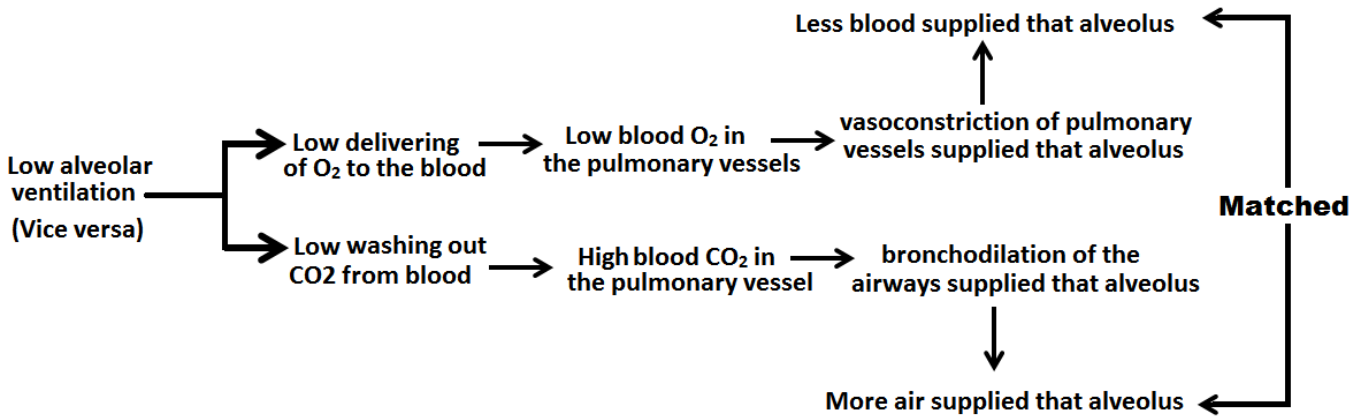
Transport of oxygen and carbon dioxide in the blood and body fluids:

	Alveolar air	Arterial blood	Cellular gases	Venous blood
PO$_2$ (mm Hg)	104	95	<40	40
PCO$_2$ (mm Hg)	40	40	>46	46

Transport of O$_2$ in the blood:
- 97% of O$_2$ transported in by the blood in chemical combination with Hb in RBC.
- 3% of O$_2$ transported in by the blood in a dissolved state in the water of the plasma and blood cells.

O2-Hb dissociation curve: Is a graph that shows the relationship between the percent saturation of hemoglobin and partial pressures of oxygen. It is an S – shaped curve.
- A change (whether an increase or a decrease) in PO$_2$ between 10 and 60 mm Hg is associated with similar steep proportional change in the percent saturation of hemoglobin with O$_2$. At a PO$_2$ of 60 mm Hg, 90% of the total Hb is combined with O$_2$.
- From 60 mm Hg PO$_2$ and above, a further increase in PO$_2$ produces only a much small increase in O$_2$ binding.
- Arteries blood has a PO$_2$ of about 95 mm Hg ➔ Hb saturation with O$_2$ is 97% (from O2-Hb dissociation curve) ➔ 19.4 ml of O$_2$ / 100 ml of blood.
- Venous blood has a PO$_2$ of about 40 mm Hg ➔ Hb saturation with O$_2$ is 75% (from O2-Hb dissociation curve) ➔ 14.4 ml of O$_2$ / 100 ml of blood.
- Therefore, under normal conditions about 5 ml of O$_2$ is transported to the tissues by each 100 ml of blood.
- **P$_{50}$**, is PO$_2$ at which the Hb is half saturated with O$_2$.
- The O2-Hb dissociation curve is not fixed in position; but it can be shift to the left or right.
- The factors that displace the curve to the right, which means that at any given PO$_2$, Hb has less affinity for O$_2$ (higher P$_{50}$), are:
    - [1] Increased [H$^+$] with pH decreasing from 7.4 to 7.2.
    - [2] Increased CO$_2$ concentration.
    - [3] Increased 2,3-diphosphoglycerate (2,3-DPG).
    - [4] Increased blood temperature.
- The factors that shift the curve to the left, which means that at any given PO$_2$, Hb has more affinity for O$_2$, are:
    - [1] Decrease in [H$^+$] with an increase in pH from 7.4 to 7.6.
    - [2] Decreased CO$_2$ concentration.

[3] Decreased 2,3-diphosphoglycerate (2,3-DPG) as in stored blood under blood bank conditions.

[4] Decreased blood temperature.

[5] The presence of large amount of Hb-F.

- **Bohr Effect** is the effect of CO_2 concentration and $[H^+]$ on the <u>affinity</u> of Hb to O_2.

[1] In pulmonary circulation ➔ Excess washout of CO_2 from blood to alveoli ➔ Decrease in $[CO_2]$ and $[H^+]$ in the blood of pulmonary circulation ➔ Hb has more affinity for O_2 (lower P_{50}) ➔ Blood pick up more O_2 from alveoli (loading with O_2).

[2] In tissue circulation ➔ Excess picking up of CO_2 from cells to the blood ➔ Increase in $[CO_2]$ and $[H^+]$ in the blood of tissue circulation ➔ Hb has less affinity for O_2 (higher P_{50}) ➔ Blood release more O_2 from blood to cells (unloading with O_2).
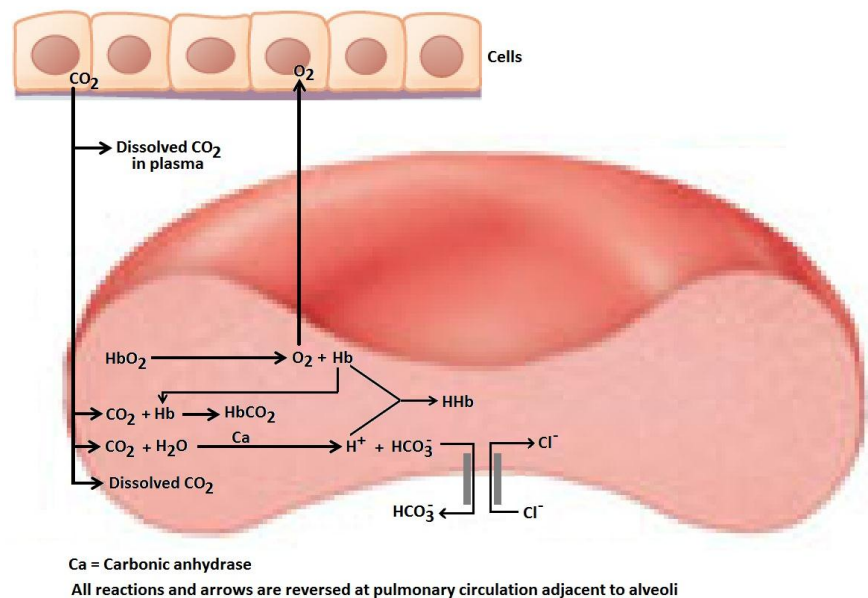
Transport of CO_2 in the blood: Under normal resting conditions an average of 4 ml of CO_2 is transported from the tissues to the lungs in each 100 ml of blood. The CO_2 in the venous blood is carried to the lung in the following ways:

[1] About 7% of all CO_2 transported to the lungs is in a dissolved state in the blood (plasma and blood cells).

[2] About 70% of CO_2 react with water inside the RBC to form carbonic acid, a reaction catalyzed by the enzyme in RBC called carbonic anhydrase.

[3] The remaining <u>23%</u> of CO_2 are transported to the lungs by combination with plasma proteins and with Hb in form of <u>carbaminohaemoglobin (HbCO2).</u>

- **Haldane effect:** Is the effect of O_2 concentration on the <u>affinity</u> of Hb to CO_2 ($HbCO_2$). The smaller the amount of oxygen bound to hemoglobin, the greater the amount of carbon dioxide that can bind to it, and vice versa.

Ca = Carbonic anhydrase
All reactions and arrows are reversed at pulmonary circulation adjacent to alveoli

The control of respiration: This is achieved by respiratory center is located in the brain which is composed of three major groups of neurons located bilaterally within the reticular formation of the medulla oblongata and pons.

[1] The dorsal respiratory group (DRG) of neurons: DRG is responsible for the basic rhythm of respiration by autonomous repetitive bursts of inspiratory action potentials. The nerve signal from DRG is transmitted to:

- The diaphragmatic muscles (through contralateral phrenic).
- To external intercostal muscles through spinal motoneurons.
- To the ventral respiratory group.

[2] The ventral respiratory group (VRG): These neurons are located in the medulla and innervate mainly inspiratory and expiratory accessory muscles. VRG is inactive during during normal quiet respiration. When the respiratory drive for increased pulmonary ventilation becomes greater than normal (such as

during exercise), respiratory signals from DRG spell over into the VRG. As a consequence, the VRG contributes to the respiratory drive as well.

[3] The pneumotaxic group: This group of neurons is located within the upper pons and they transmit impulses continuously to the dorsal respiratory group of neurons. The primary effect of these is to control the the duration of the filling phase of the lung cycle (duration of inspiration).

Regulation of respiratory center activity:

1. Chemical regulation of respiration:

    [A] PCO$_2$ and [H$^+$]: An increase in blood [CO$_2$] ➔ causes an increase in brain interstitial fluid [H+] ➔ Stimulate <u>central chemoreceptors</u> ➔ Stimulate respiratory center ➔ causing greatly increased strength of both the inspiratory and expiratory signals to the respiratory muscles.

- <u>80%</u> of the drive for ventilation is a result of stimulation of the central chemoreceptors.
- Central chemoreceptors are adaptable type of receptors (within 1-2 days). They have a very potent acute effect on controlling respiration but only a weak chronic effect after a few days' adaptation.

    [B]. PO$_2$: A decrease in blood PO2 ➔ stimulates <u>peripheral chemoreceptors</u> (in the carotid and aortic bodies) ➔ send signals through glossopharyngeal and vagus nerves ➔ DRG ➔ causing increased strength of both the inspiratory and expiratory signals to the respiratory muscles.

- Peripheral chemoreceptors are also sensitive to PCO$_2$, pH, blood flow, and to temperature.
- Sympathetic discharge ➔ vasoconstriction ➔ increasing the sensitivity to hypoxia.
- Parasympathetic discharge ➔ vasodilation ➔ decreasing sensitivity to hypoxia.
- Arterio-venous oxygen difference in peripheral chemoreceptors is very small.
- Under normal conditions, the PO2 mechanism in regulation of respiration plays only small role.

2. Peripheral receptors:

[A] Stretch receptors:

- Bronchial stretch receptors are located in the wall of the bronchi and bronchiole that transmit inhibitory signals through the vagi into the dorsal respiratory group of neurons when the lungs become overstretched (Hering-Breuer inflation reflex).
- j (juxtacapillary) receptors are located in the alveolar walls, close to the capillaries and are stimulated by distension of the pulmonary vessels.
- Chest wall receptors are located within the respiratory muscles. This can detect the force generated by the respiratory muscle during breathing. If the force required distending 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).

[B] Irritant receptors: Those are located between the epithelial cells of 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 breathe holding (i.e., apnea).

[C] Joint proprioceptors: Those are located in the joint capsules and transmit excitatory impulses to the respiratory center.

[D] Touch, thermal, and pain receptors: Can also stimulate the respiratory center. For example, irritants in the nasal cavity can initiate a sneeze reflex. In addition, through these receptors one can observe the respiratory response when cold water is splashed onto a person, and also the common practice of spanked a newborn baby on the buttocks.

3. Brain centers regulation of respiration:

- Reticular Activating System (RAS): Located in the reticular system of the brain stem; its activity is associated with the "awake" or "conscious" state. When active, it simulates respiratory ventilation. When RAS activity is reduced, as during sleep, ventilation is reduced and PCO$_2$ increases by a few mmHg.
- Limbic System: Respiratory changes in emotion.

- Motor cortex regulation of respiration (respiration can be controlled voluntarily).
- Vasomotor center regulation of respiration: Almost any factor that increases the activity of the vasomotor center also has at least a moderate effect on increasing respiration.
- Body temperature regulation of respiration.

The response of the respiratory system to exercise and stress:

[A] An increase in the diffusing capacity of the respiratory membrane for O_2, due to 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.

[B] Increased alveolar ventilation, this is due to
- Reflexes originating from body movements (proprioceptors).
- Increase in body temperature.
- Epinephrine release (during exercise).
- Impulses from the cerebral cortex to the contracting muscles, is believed to transmit collateral impulses into the brain stem to excite the respiratory center.

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

[D] 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.

[E] The pulmonary blood flow can increase severalfold without causing an excessive increase in pulmonary artery pressure for the following two reasons: previously closed vessels <u>open up (recruitment),</u> and the <u>vessels enlarge (distension).</u> Recruitment and distension of the pulmonary blood vessels both serve to lower the pulmonary vascular resistance (and thus to maintain low pulmonary blood pressures) when the cardiac output has increased.

Hypoxia (cellular deficiency of O_2): Brain is the most sensitive tissue to hypoxia; complete lack of oxygen can cause unconsciousness in 15 sec and irreversible damage within 2 minute. Traditionally; hypoxia has been divided into 4 types (see also table 6.6):

[1] Hypoxic hypoxia: In which the PO_2 of the arterial blood is reduced due to insufficient O_2 gets to the alveoli or inadequate ventilation of the alveoli or insufficient diffusion of O_2 through the respiratory membrane.

[2] Anaemic hypoxia: In which the arterial PO_2 is normal but the amount of Hb available to carry O_2 is reduced.

[3] Stagnant or ischaemic hypoxia: In which the blood flow to a tissue is so low that adequate O_2 is not delivered to it despite a normal PO_2 and Hb concentration.

[4] Histotoxic hypoxia: In which the amount of O_2 delivered to a tissue is adequate because of the action of a toxic agent, the tissue cells cannot make use of the O_2 supplied to them such as in cyanide poisoning, in which the action of cytochrome oxidase is completely blocked and therefore, the tissues cannot utilize the O_2. Also, deficiency of oxidative enzymes or other elements in the tissue oxidative system can lead to this type of hypoxia such as vitamin B deficiency (Beriberi).

Cyanosis: It is a darkness or blueness of the skin and mucous membrane and appears when the reduced Hb concentration of the blood in the capillaries is more than 5 gm/dl.

Hypercapnia: It means excess CO_2 in the body fluids.