Respiratory System :

Structure & Functions of Respiratory System

Introduction

Why do we respire? Living organisms need a constant supply of energy because of the continuous expenditure of energy by the body. Energy is obtained by oxidation of food substances and energy is stored in the form of high-energy phosphate compounds like ATP, creatine phosphate etc. The products of oxidation are CO_2 and H_2O. CO_2 is eliminated through lungs.

The body can store only about 1500 mL of O_2 at a time. This can maintain life only for 5 minutes. Myocardium and brain are very much dependent on O_2 for their functioning. Cessation of blood flow to cerebral cortex results in loss of function within 5 seconds, loss of consciousness in 10-20 seconds and irreversible changes in 3-5 minutes. Once the neurons are damaged they cannot regenerate.

Definition

The collective process of absorption of O_2 from the environment and oxidation of food materials in the cells with the release of water, CO_2 and energy and elimination of CO_2 into the environment is called respiration.

Respiration occurs by simple diffusion in unicellular organisms, through skin in frogs, through gills in aquatic animals, through air tubes in insects and through lungs in higher animals.

Respiration includes:

- External respiration: the absorption of O_2 and removal of CO_2 from the body as a whole.
- Internal respiration: the utilization of O_2 and production of CO_2 by cells and gaseous exchanges between the cells and their fluid medium.

Properties of gases: (partial pressure)

- The pressure exerted by any one gas in a mixture of gases (its partial pressure) is equal to the total pressure times the fraction of the total amount of gas it represent.
- The composition of dry air is 20.98% O_2, 0.04% CO_2, 78.06% N_2, and 92% other inert gases such as argon and helium. The barometric pressure at sea level is 760mmHg (1 atmosphere). The partial pressure of O_2 (P_{O2}) in dry air = 0.21×760 = 10mmHg. P_{N2} and other inert gases = 0.79×760 = 600mmHg and PCO2 = $.0004\times760$ = 0.3 mmHg
- The water vapor in the air in most climates reduces these percentages, and therefore the partial pressure, to a slight degree.
- Air equilibrated with water is saturated with water vapor, and inspired air is saturated by time it reaches the lungs. The P_{H2O} at body

temperature (37◦C) is 47mmHg.

- ❖ Gas diffuse from area of high pressure to area of low pressure, with rate of diffusion depending on the concentration gradient and the nature of the barrier between the two areas.
- ❖ The partial pressure of gases in a liquid is the pressure that, in the gaseous phase in equilibrium with the liquid, would produce the concentration of gas molecules found in the liquid.

Functions of the Respiratory Tract

Nasal Cavity

1) Air conditionings function of nose (warming, humidification, and filtration of inhaled air). Due to large cross-sectional area, the nose has the capacity to modify temperature and water vapor content of inspired air. The nasal cavity also removes some of the pollutants present in air which are > 5 μm size are filtered by the hair and cilia present in the nasal cavity and are expelled out by sneezing reflex.
2) Olfactory function – olfactory stimuli are received by the olfactory epithelium of the nasal cavity
3) Large hollow resonating chambers of the nose called paranasal sinuses modify speech sounds.

Pharynx

1) Nasopharynx carries air from nose to pharynx. Oropharynx is the common passage for food and air.
2) Pharynx houses the tonsils and thus plays role immunity.
3) Provides a resonating chamber for speech sounds.
4) Opening of the eustachian tube into nasopharynx helps in the equalization of pressure between middle ear and pharynx.

Larynx:

1) Production of sound with the help of vocal cords.
2) Closure of glottis by approximation of vocal cords during swallowing, vomiting etc., help to prevent entry of food into trachea. This is also brought about by horizontal deflection of epiglottis.

Respiratory function of the airways: Airways conduct atmospheric air to alveoli and help in gas exchange so as to maintain normal CO_2 and O_2 levels in the body. Lungs synthesize surfactant, collagen and elastin necessary for proper expansion of lungs. Collagen and elastin form the structural framework of the lung.

Before reaching the alveoli, inhaled air is warmed by blood in the capillaries of the respiratory tract. This is significant because cold air increases air flow resistance and also causes bronchospasm. This is of great importance in patients suffering from bronchial asthma. Inhaled air is humidified, i.e., saturated with water vapor, by mucus secreted by the goblet cells lining **the** respiratory tract and vapor pressure becomes 47 mm Hg at a body

temperature of 37◦ C.

Non respiratory functions of lungs

1) Protective function:
    a) Particles <5 μm in size enter the lung and adhere to the lining mucus. This will be expelled out by cough reflex and also by the escalator action of cilia. The cilia beat towards the pharynx and the action is not influenced by nervous mechanism. Ciliary activity moves the superficial liquid lining layer continually towards the larynx from deep within the lung. Kartagener's syndrome (congenital disease) the motility of the cilia is defective → collection of secretions in the lung → infection → bronchiectasis. A similar condition is produced by cigarette smoke which contains ciliotoxins that damage the cilia.
    b) The neutrophils, lymphocytes and alveolar macrophages present in the alveoli defend against bacteria and viruses.
    c) Lungs synthesize immunoglobulins like IgA for its own defence and are present in bronchial mucus.
2) Acid-base balance: Lungs play an important role in maintaining the body pH by regulating the CO_2 content of blood.
3) Anticoagulant function and filtration of blood: Lungs contain mast cells which contain heparin which is an anticoagulant. Small emboli present in blood are removed from the circulation before they reach the brain and other vital organs.
4) Regulation of blood pressure: The endothelial cells of the pulmonary capillaries secrete an enzyme called angiotensin converting enzyme (ACE) which converts angiotensin I to active angiotensin II (potent vasoconstrictor) → increase blood pressure.
5) Temperature regulation: Some amount of heat is lost from the body during expiration.
6) Regulation of blood volume: Lungs act as a storage organ for blood since pulmonary circulation is a low-pressure system and the vessels are highly distensible. About 300 mL of blood can be diverted to the systemic circulation in times of need.
7) Endocrine function: Lungs synthesize hormones like prostaglandins, serotonin, histamine etc., with the help of APUD (Amine precursor uptake and decarboxylation) cells present in the lung. PGE2 helps to constrict the patent ductus arteriosus in the postnatal period. In asthma or anaphylaxis, lungs release substances like histamine, bradykinin, prostaglandin, slow reacting substance etc., into circulation, which are responsible for the reactions of anaphylaxis.
8) Degradation of substances: Bradykinin, norepinephrine, serotonin, PGE1, PGE2, and PGF2, are degraded and removed by the lungs.

FUNCTIONAL ANATOMY OF THE RESPIRATORY SYSTEM

The respiratory system is made up of a gas exchanging organs (lungs) and a pump that ventilates the lungs. The pump consists of:

1. The chest wall.
2. The respiratory muscles (increase and decrease the size of the thoracic cavity).
3. Areas in the brain than control the muscles.
4. Tracts and nerves that connect the brain to muscles.

Respiratory tract:

1) Upper respiratory tract – from nasal opening to vocal cords which includes nose and pharynx
2) Lower respiratory tract-from vocal cord to alveoli and this includes larynx, trachea, bronchi and lung.

Lining epithelium of respiratory tract:

- Nose: lined by ciliated columnar epithelium with goblet cells containing scattered goblet cells.
- Pharynx: is lined by ciliated columnar epithelium with goblet cells. Oropharynx is lined by stratified ciliated epithelium.
- Larynx: upper part of larynx and vocal cords are lined stratified ciliated epithelium. Lower part is lined by ciliated columnar epithelium.
- Trachea and bronchi: Lined by pseudo-stratified columnar epithelium which contains mucous and serous glands (Ciliary action helps to remove particles)
- Bronchioles: Lined by nonciliated cuboidal epithelium that is devoid of glands. Smooth muscles are absent from respiratory bronchiole onwards and only a single layer of lining cells is seen.

Trachea-bronchial Tree: The air that is inspired is distributed to the alveoli by way of trachea, bronchi and bronchioles.

- ✓ Trachea: Trachea is a hollow tubular structure 11 cm in length and 1.5 in diameter, placed anterior to the esophagus. It is kept permanently open by C-shaped cartilages on its wall, which are deficient posteriorly. In between the cartilages, there are fibroelastic tissue and smooth muscle fibers. Mucus secreted by mucous glands in the mucous membrane moistens the surface and facilitates ciliary action.
- ✓ Trachea divides into two main bronchi or primary bronchi.
- ✓ Each main bronchus divides into secondary or lobar bronchi, 3 on the right and 2 on the left side.
- ✓ Lobar bronchi divide into tertiary or segmental bronchi, 10 on the right and 8 on the left.

- ✓ Bronchioles (<1mmin diameter)→terminal bronchioles →several respiratory bronchioles→2-11 alveolar ducts→5 or 6 alveolar sacs→ alveoli

	Cartilage	Glands	Cilia	Smooth muscle
Trachea	**Ring**	+	+	+
1° Bronchi	**Ring**	+	+	+
2° Bronchi	**Plate**	+	+	+
3° Bronchi	**Plate**	+	+	+
Bronchioles	**No**	-	+	++
Terminal bronchioles	**No**	-	+	+++
Respiratory bronchioles	**No**	-	+	++

Alveoli

- Total number of alveoli in both lungs (300 million).
- Diameter of a single alveolus (0.3 mm). Apical alveoli are larger than basal alveoli in the erect posture.
- Total surface area of alveoli of both lungs (70 m^2).
- Alveolar epithelium is of simple squamous type. Alveoli are lined mainly by two types of epithelial cells:
  1) Type I cells (95%): are flat cells with numerous cytoplasmic extensions. Gas exchange takes place across these cells.
  2) Type II cells (5%): or granular pneumocytes: Are large secretary cells containing lamellated inclusion bodies which produce and store surfactant. These cells are seen between type I cells. They secrete surfactant whose function is to decrease surface tension in the alveoli. In addition to the above cells, alveoli also contain:
     - ✓ Pulmonary alveolar macrophages (PAMS): Pulmonary alveolar macrophages are derived from monocytes of blood. When these cells engulf carbon and dust particles they are called dust cells. When they engulf red blood cells in congestive cardiac failure (CCF) they are called heart failure cells, which produce brick red sputum. They are eliminated by coughing.
     - ✓ Mast cells Mat cells contain histamine, heparin, lipids and proteases they participate in allergic reactions and produce bronchospasm.
     - ✓ Neutrophils, lymphocytes, and plasma cells: Neutrophils phagocytose bacteria and produce inflammatory change Lymphocytes act against both bacteria and viruses.
     - ✓ Fibroblasts

- ✓ APUD cells

Between the trachea and the alveolar sacs, the airways divide 23times.

- Conducting zone: The 1st 16 generations of passages
  - ✓ Made up of bronchi, bronchioles, terminal bronchioles
  - ✓ Transport gas from and to the exterior
- Respiratory zone: The remaining 7 generations of passages
  - ✓ Gas exchange occurs
  - ✓ Made up of respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli

Theses multiple divisions increases the total cross sectional area of the airways, from 2.5 cm^2 in the trachea to 11800 cm^2 in the alveoli ⇨ ↓the velocity of air flow in the small airways

Pleura

The lung is covered by a double-layered serous membrane called pleura. The layer which is closely covering the lung is visceral pleura and the layer that is reflected back the root of the lungs on to the surface of diaphragm and thoracic cage is the parietal pleura. There is a potential space between the two pleural layers called pleural cavity, which contains about 15-25mL of mucoid pleural fluid. Pleural fluid is secreted by the parietal pleura. Excess pleural fluid is pumped away or absorbed by capillaries of visceral pleura and by lymphatics.

Functions of pleural Fluid

1) Pleural fluid keeps the two pleural layers together.
2) Acts as a lubricant and helps in the sliding moves between the two layers.

Bronchial tone:

❖ Nervous control

1. Bronchi and bronchioles innervated by autonomic nervous system:
   a. Parasympathetic NS: Muscurinic receptor: cholinergic discharge →bronchoconstriction
   b. Sympathetic NS:
      - β1 and β2 adrenergic receptors in epithelium, smooth muscle, and mast cells many non innervated, some located on cholinergic nerve ending and ganglia (inhibits Ach release).
      - β2 receptors predominate.
      - β agonist (e.g. salbutamol) →bronchodilitation and ↓secretion.
2. Non cholinergic non adrenergic innervation (VIP) →bronchodilitation.
3. Substance P secreted by some nerve ending to lung →bronchoconstriction and mucus secretion.

❖ Homurol control:

- Histamine and slow reacting substance of anaphylaxis released from mast cells ⇨↑bronchiolar tone.

- Leukotrienes (LTC_4, LTD_4, LTE_4) ⇨ bronchoconstriction. Leukotrienes receptors blocker useful in bronchial asthma.

❖ Circadian rhythm: maximum constriction at about $6:00_{AM}$ and maximum dilation at about $6:00_{PM}$.

❖ Irritants and chemicals e.g. sulfur dioxide produces reflex bronchoconstriction that is mediated via cholinergic pathways by stimulation of sensory receptors in the airways.

❖ Cool air causes bronchoconstriction, exercise also causes bronchoconstriction (increased respiration cools the airways).

Pulmonary ventilation

- Pulmonary ventilation or breathing is the exchange of air between the atmosphere and the lungs. As air moves into and out of the lungs, it travels from regions of high air pressure to regions of low air pressure.
- Normal breathing is called eupoeic breathing. Normal respiratory rate is 12-16/min.
- Increase in the rate of respiration is called tachypnea, e.g., exercise, fever, anxiety etc.
- Arrest of respiration is called apnea, e.g-, deglutition apnea, adrenaline apnea, sleep apnea etc.
- Difficulty in breathing or shortness of breath associated with marked awareness of the effort of respiration is called dyspnea, e.g., bronchial asthma.
- Dyspnea in the lying down posture and getting considerable relief in the erect posture is called orthopnea, e.g., mitral stenosis, left-sided heart failure etc.
- Taking in of air is inspiration and giving out of air is expiration.

- <u>Boundaries of the Thoracic Cage:</u> The thoracic cavity is occupied by heart, lungs and great vessels
- Behind and laterally – vertebral column and ribs. In front and laterally – sternum and ribs
- In the lower part – diaphragm
- Upper part – upper ribs and tissues of the neck

Muscles of respiration:

1. Muscles of Inspiration
   - *Normal inspiration* – diaphragm and external intercostal muscles.
   - *In forced inspiration* as in exercise, asthma etc., accessory muscles of inspiration act which are sternocleidomastoid, pectoralis, elevators of scapula, scalene, serratus anterior and alae nasi.
2. Muscles of Expiration

- No muscles are actively involved in normal quite expiration (expiration during quiet breathing is passive). However, there is some contraction of inspiratory muscles in the early part of expiration. This contraction exerts a braking action on the recoil force and slows expiration. The inspiratory muscles that have contracted, relax.
- *In forced expiration,* muscles of the anterior abdominal wall (recti), internal intercostals and latissimus dorsi, contract.

Mechanism of ventilation of lungs:

- The lung and chest wall are elastic structures. When inspiratory muscles contract, the thoracic cage moves and parietal pleura which is closely adherent to the thoracic cage also moves out. This draws along with it visceral pleura which is adherent to the lungs. Due to dragging force exerted by the visceral pleura and also to elastic property of lung, the lungs expand. The inside volume is increased and the alveolar pressure become sub-atmospheric. As a result, air from outside is sucked into the lungs. This is inspiration. The contraction of inspiratory muscles lasts for about 2-3 seconds.
- Then the contracted muscles relax and the lungs retract due to elastic recoil, thereby creating a pressure more than atmospheric pressure in the alveoli and air driven out. This is expiration.
- *In normal quiet breathing, inspiration is an active process and expiration is passive.*

Movements of the thoracic cage:

During inspiration, dimensions of the thoracic cage increase in three ways:

1. Increase in vertical dimension
2. Increase in anteroposterior dimension.
3. Increase in transverse dimension.

Mechanism of increase in vertical dimension

- This is mainly brought about by contraction of the diaphragm which is a dome-shaped musculotendinous sheet which separates thoracic cavity from abdominal cavity. In normal quiet inspiration when diaphragm contracts, it moves downwards like a piston for about 1.5 -3 cm. In forced inspiration, vertical dimension is increased by 7-10cm. *75% of air entry during inspiration is by the activity of diaphragm.* In diaphragmatic paralysis, respiration is seriously impaired. Diaphragm is supplied by phrenic nerve whose root value is C3, 4 and 5.
- Consists of three parts:
    - The costal portion (muscle fibers attached to the ribs around the bottom of the thoracic cage).

    - The crural portion (fibers that are attached to the ligaments along the vertebra –pass on either side of the esophagus and can compress it when they contract.
    - The central tendon into which the costal and crural fibers insert (it is also the inferior part of the pericardium).
- The costal and crural fibers are innervated by different parts of the phrenic nerves and can contract separately e.g. vomiting increase intra-abdominal pressure by contraction of costal fibers but the crural fibers remain relaxed allowing materials to pass from the stomach into the esophagus.
- *Applied aspect:* Transection of the spinal cord above the third cervical segment is fatal without artificial respiration because it causes paralysis of all respiratory muscles. But transaction below the 5^{th} cervical segment leaves the nerves that innervate the diaphragm intact and its activity is adequate to maintain life.

Mechanism of increase in anteroposterior diameter and transverse diameter

- This is by the contraction of external intercostal muscles which originate from the lower border of upper rib and inserted into the upper border of lower rib. The fibers are directed downwards, forwards and medially. Each rib is connected posteriorly to vertebral column and anteriorly to sternum. The posterior joint is hinged, i.e., it is movable. The lower ribs are more obliquely placed than the upper ribs. During inspiration, the external intercostal muscles contract and the upper ribs become more horizontal. Sternum is thrust upwards and forwards, i.e., it moves away from the vertebral column. Thus, the anteroposterior dimension of the thoracic cage is increased. This movement is referred to as pump handle movement.
- The lower ribs (7, 8, 9, and 10) in addition to moving upwards also swing outwards, thereby increasing the anteroposterior and transverse dimension of the thoracic cage. This movement is called bucket handle movement.

Types of Breathing:

If the contribution by the diaphragm is more in inspiration, then the breathing is called abdominal type of breathing. If external intercostal muscle action predominates, it is called thoracic or costal breathing.

- Abdominothoracic in men
- Thoracoabdominal in women
- Abdominal in children and in injury to the chest wall. In infants, the ribs are more horizontal than oblique, so movement of the thorax is less

visible.

- Thoracic type in advanced pregnancy, severe ascites etc.

Pressure changes during respiratory cycle:

Respiratory pressures are:

- Intrathoracic/intrapleural pressure
- Intrapulmonary/intra-alveolar pressure
- Transpulmonary pressure/transmural pressure

Intrapleural Pressure:

Intrapleural pressure is the pressure developed in between the two layers of pleura. In normal breathing, this presure is *always subatmospheric, i.e.,* it is always negative. Atmospheric pressure which is equal to 760 mmHg is taken as zero atmospheres.

Normal intrapleural pressure = -2.5 (at the base of the lung)

Causes of Negative Intrapleural Pressure

1) The natural tendency of lungs is always to recoil inwards because of its elasticity and surface tension in the alveoli. The tendency of thoracic cage is to expand or recoil outwards. These two forces are equal in intensity and act in opposite directions against a closed space so that the pressure in the space becomes subatmospheric.
2) Negative intrapleural pressure is also caused by the more rapid absorption rate of pleural fluid by pulmonary capillaries and also by the lymphatics. The pressure in the capillaries of visceral pleura is low, i.e., about 18 mm Hg because they belong to pulmonary circulatory system.

Measurement of Intrapleural Pressure

1) By introducing a needle into the pleural space and connecting it to a manometer.
2) By introducing a catheter, whose tip contains a thin walled balloon, into the esophagus and connecting it to manometer. The intraoesophageal pressure will be the same as intrapleural pressure because the negativity of intrapleural pressure makes the mediastinal pressure negative, which in turn makes the intraoesophageal pressure *negative*.

Variation in Intrapleural Pressure

a) During different phases of respiration: at the end of expiration the intrapleural pressure is –2.5 mmHg in normal quiet breathing. During inspiration, thoracic cavity expands and intrapleural pressure becomes –6 to –8 mm, Hg. During expiration, muscles are relaxed and intrapleural pressure becomes less negative and towards the end of expiration it becomes –2.5 to -3mm Hg. In forced inspiration intrapleural pressure

becomes –12 to –18 mm Hg and in forced expiration it becomes a positive pressure. In Muller's maneuvre, i.e., forced inspiration with closed glottis as if sucking fluid with a straw, the intrapleural pressure become –40 mm Hg. In Valsalva's maneuvre, i.e., forced expiration with closed glottis as in straining, intrapleural pressure become +40 mm Hg.

b) Regional variation: Regional variation in intrapleural pressure is due to the effect of gravity.

- Near the apex it is more negative –6 mm Hg
- In the middle of the lung it is –2.5 mm Hg
- Near the base it is about –1 mm Hg.

Importance of Negative Intrapleural Pressure

1. It increases venous return. During inspiration the increased negativity in the mediastinum helps to suck blood from periphery towards great veins and to the heart.
2. Maintain alveolar stability.
3. Keep the airways open.
4. Prevent collapse of lung, i.e., keeps lungs in an expanded position. If the chest wall is opened, the negative intrapleural pressure is lost and the lungs collapse.

Effects of Positive Intrapleural Pressure

Positive intrapleural pressure compresses the great vessels in the thoracic cavity and decreases venous return to heart, which in turn decreases cardiac output. This produces cerebral ischemia leading to loss of consciousness.

This is the reason for the syncopcal attacks, following continuous severe bouts of cough especially in old people and in cardiac patients.

Intrapulmonary pressure.

Pressure developed inside the alveoli is intrapulmonary pressure. As alveoli are in connection with the atmosphere, at the end of normal expiration the intrapulmonary pressure is equal to atmospheric pressure, i.e., zero.

During normal breathing in inspiration it becomes negative and at midinspiration becomes –1 mm Hg. As more and more air enters the lungs, the negativity decreases and at the end of inspiration, the intrapulmonary pressure becomes zero or atmospheric.

During quiet expiration it becomes more positive and at mid-expiration become +1 mm Hg and towards the end of expiration again the pressure becomes same as that of atmospheric pressure.

In forced inspiration, i.e., in Muller's maneuvre, it becomes –80 mm Hg and in forced expiration, i.e., Valsalva's maneuvre, it becomes +100 mm Hg.

Transpulmonary/Transmural Pressure:

The pressure difference across the lung, i.e., the pressure difference between the alveolar pressure and pleural pressure, is called transpulmonary pressure.

Transpulmonary pressure = Intrapulmonary pressure - Intrapleural pressure

Importance of Transmural Pressure

1) It is necessary for the expansion of lung.
2) It gives a measure of the elastic recoil of lung.
3) An increase in transpulmonary pressure causes greater stretching of lung and more will be the lung volume, i.e., transpulmonary pressure decides the lung volume.

Transpulmonary pressure is increased during inspiration and decreased during expiration.

The different values of transpulmonary pressures at the end of normal expiration in different parts of the lung are as follows:

- At the apex of the lung: 0 - (-6) = 6 mmHg
- In the middle of the lung: 0- (-2.5) = 2.5 mm Hg
- At the base of the lung: 0 - (-1) = 1 mm Hg

Since the transmural pressure is more at the apex than at the base, during first part of inspiration more of inspired air goes to the apex than to the base of the lung. Since the transmural pressure is less at the base of the lung, the lung is less expanded at the base. This pressure further decreases at the end of forced expiration causing the airways to close at the base.

Elastic behavior of the lungs (reasons for recoil of lung):

- Tissue elasticity
- Surface tension of alveolar fluid

Tissue Elasticity

Lung parenchyma contains large quantity of elastic fibers arranged in a peculiar pattern. The geometric arrangement of elastin fibers in lung can be compared to nylon stock elasticity. This elasticity contributes to 1/3 of elastic recoil tendency of lung.

Surface Tension

Surface tension phenomenon in lungs contributes to 2/3 of recoil tendency of lung. The alveolar wall is lined by epithelial cells which secrete alveolar fluid. Inside the alveolus there is air. The interphase is between air and alveolar fluid and the surface tension exerted between air and alveolar fluid is very high. So, there is a tendency to reduce the size of the alveolus due to intermolecular attraction.

Surfactant:

Introduction:

Surfactant is a surface tension lowering agent present in the alveolus between the alveolar fluid and air. It is secreted by type II alveolar epithelial cells which contain lamellar bodies containing the phospholipid of surfactant.

Composition of surfactant:

Composition of surfactant:

Dipalmitoylphosphatidyl choline	62%
Phosphatidylglycine	5%
Other phospholipids	10%
Neutral lipids	13%
Proteins	8%
carbohydrate	2%

Functions of *Surfactant*

1) Surfactant decreases surface tension 6 times. Distending pressure of each alveolus lined by surfactant is only 3 mm Hg. If the alveolus was lined by water the distending pressure may be as high as 15 mmHg (18 cm of water).
   Surface tension of alveolar fluid= 50 dynes/cm'
   Surface tension of surfactant = 5-30 dynes/cm2
2) It maintains alveolar stability and helps in even distribution of ventilation. Surfactant prevents over distension or collapse (atelectasis) of alveoli. Surface tension in the alveolus is inversely proportional to the number of surfactant molecules per unit area. When there is increase in the diameter of the alveolus as in inspiration, the number of surfactant molecules per unit area decreases and the surface tension increases and this prevents overdistension of lung. When there is decrease in the diameter of alveoli, as in expiration, the surfactant molecules come closer and number of surfactant molecules per unit area increases and surface tension decreases, and this prevents collapse of lung during expiration. Surfactant thus maintains alveolar stability.
3) Surfactant prevents pulmonary edema and keeps the alveoli dry. Collection of fluid in the alveoli is called pulmonary edema. If surfactant was not present in the alveoli, the unopposed surface tension in the alveoli will produce a 20mm Hg force favoring transudation of fluid from the blood into the alveoli leading to pulmonary edema. This is prevented by surfactant by decreasing surface tension.
4) In newborn infants, surfactant prevents hyaline membrane disease or infant respiratory distress syndrome (IRDS). At the time of birth, the alveoli of the fetus are filled with fluid and the lung is completely

collapsed. When the umbilical cord is cut, fetus develops hypoxia and violent inspiratory effort produces very high negativity in the mediastinum and the lungs try to expand. Surfactant should be there for proper expansion of lung.

Due to stretching of capillaries when the lungs expand, there is a sharp fall in the pulmonary capillary pressure and the colloidal osmotic pressure will be more. So, alveolar fluid enters the pulmonary capillaries due to Starling's forces and the fetal alveoli become dry. In the fetus, development of surfactant is completed only by 31-32 weeks of intrauterine life. If birth occurs before this stage of development, the lung maturity is not complete and the lungs fail to expand leading to death of the baby. This is neonatal or infant respiratory distress syndrome (NRDS / IRDS). The condition is treated using synthetic surfactant or bovine surfactant preparation available for use by inhalation. This decreases the severity of IRDS. Steroid is also of much benefit because glucocorticoids increase the synthesis of surfactant.

In adults, deficiency of surfactant is a cause for adult respiratory distress syndrome (ARDS). Causes of surfactant deficiency include chronic cigarette smoking, long-term inhalation of 100% O2, occlusion of a main bronchus or one pulmonary artery etc.

5) Surfactant increases the compliance of the lungs, i.e., distensibility of lung.
6) It reduces the work of breathing by decreasing the elastic recoil of lung.

Factors Affecting Surfactant Production

a) Prematurity
b) Nervous factors: Vagus stimulates type II cells and increases the production of surfactant. Cutting vagal supply to the lungs leads to the development of pulmonary edema.
c) Hormonal factors
   - Thyroid hormone stimulates type II cells. Surfactant production is decreased in hypothyroidism.
   - Glucocorticoid hormones stimulate production and maturation of surfactant. Towards the later stages of pregnancy, glucocorticoid levels are high in the fetus and mother, and the lung of fetus is rich in glucocorticoid receptors.
   - Insulin ⇨ ↓surfactant. Fetal hyperinsulinemia occurs in diabetic mothers ⇨ ↑ incidence of IRDS in infants born to diabetic mothers.
d) Smoking ⇨ ↓surfactant
e) Occlusion of a main bronchus or one pulmonary artery
f) Oxygen toxicity (long term O_2 therapy-100%) ⇨ ↓surfactant

APPLICATION OF LAW OF LAPLACE IN LUNG

Law of Laplace

Laplace's law states that the distending pressure P, in the case of a distensible spherical organ is equal to 2T / R, where, T is the surface tension and R the radius of the organ. P is the pressure required to keep the alveoli inflated. P will be high when T is high or R is less.

In the lung, all the alveoli will have a constant size due to the presence of surfactant. Whenever the diameter of the alveoli changes, surfactant causes appropriate changes in the surface tension so that pressure in the alveoli is maintained constant.

According to law of Laplace:

a) During expiration, the radius of the alveolus is reduced and if surface tension is not simultaneously reduced it will exceed the distending pressure and lead to collapse of lung. But due to the presence of surfactant, surface tension is suitably altered during the phases of respiration and collapse or overdistension is prevented.
b) If there is no surfactant, air flows from smaller alveoli to larger ones so that smaller ones become smaller and larger ones become larger and finally collapse of smaller alveoli occurs.

ALVEOLAR STABILITY

Alveolar stability depends on three important factors:

1. Interdependence As the adjacent alveoli are supported by each other it is difficult for an alveolus to contract on its own with out contraction of other alveoli. This mutual support is interdependence.
2. Negative intrapleural pressure
3. Surfactant

Interdependence

Factors that Keep the Alveoli Dry

a. Surfactant prevents the collection of fluid in the alveoli by decreasing surface tension.
b. The colloidal osmotic pressure of pulmonary capillary blood is more (25 mm Hg) than capillary hydrostatic pressure (10 mm Hg). This is because pulmonary circulation is a low-pressure system. This inward directed pressure gradient of about 15 mmHg favors reabsorption of fluid from the alveoli according to Starling’s hypothesis and thus alveoli are kept dry. When pulmonary capillary hydrostatic pressure becomes more than 25 mmHg, as in left ventricular failure or in mitral stenosis, there is increase in the back pressure and increase in pulmonary capillary pressure leading to collection in the alveoli.

EFFECTS OF CIGARETTE SMOKING

1. Tobacco smoke contains ciliotoxins which destroy the cilia. Inhibition of ciliary activity leads to accumulation of secretions in the lung leading to chronic cronchitis and bronchiectasis. Here, only coughing can move mucus and dust particles from the airways. This is the reason why *smokers often cough.*
2. Carbon monoxide in smoke is injurious and decreases O_2 carrying capacity of blood.
3. Cigarette smoke contains very fine particles, < 0.3 micrometer in size, which reach the alveoli and cause fibrosis of lung.
4. Smoke decrease surfactant secretion.
5. Smoke destroys lung tissue, especially the intralveolar septa, causing a decrease in the surface area for gas exchange. This is due to accumulation of large quantities of elastases released by macrophages in lung which destroy the lung tissue. Normally, these elastases are destroyed by alpha 1 antitrypsin. Cigarrte smoke inactivates alpha1 antitrypsin leading to emphysema. All the above factors impair oxygenation of blood in the lungs.
6. Smoke leads to lung cancer. Carcinogens in cigarrete smoke include tar, polynuclear hydrocarbons, nitrosamines etc.
7. Smoking produces coronary heart disease like angina, coronary thrombosis etc.
8. Cigarette smoke contains high concentration of various free radicals which are extremely reactive, leading to damage of almost all biological macromolecules. For example, it causes damage to cell membrane, polysaccharides depolymerisation and DNA breaks leading to inhibition of protein and enzyme synthesis. All these lead to cell death or mutation and carcinogenesis.
9. Chronic tobacco smoking lead to tobacco amblyopia(scotomas) caused by cyanide in tobacco smoke. It also leads to optic atrophy, psychosis, headache, vertigo etcc.
10. Inhalation of cigarette smoke by pregnant ladies (either active or passive) leads to fetal abnormalities and SIDS (sudden infant death syndrome). It is more common in newborn whose mothers smoked during pregnancy.

Stethography or pneumography:

A corrugated rubber tube covered with canvas, closed at both ends is tied around thoracic cage of the individual at the level of nipple. To the cavity of the stethograph is connected pressure tubing and this tube is connected to a Marcy's tambour which has a cup-shaped structure covered with a thin diaphragm and a tube. The pressure tubing is

connected to the tubular portion. Over the diaphragm of the Marey's tambour is placed a movable lever.

During inspiration, the corrugated rubber tube elongates and pressure is decreased and the thin diaphragm moves downwards and a downstroke is recorded. In expiration, diaphragm moves up and an upstroke is recorded.

Spirometry

- Technique — Spirometry
- Device — Spirometer
- Record — Spirogram

Spirometer was devised by Hutchinson in 1846. Two types of spirometers are:

- Dry type or bellow type
- Wet type or water filled type

Procedure of Wet Type

The subject is asked to breathe normally through a mouth piece connected to the spirometer and the volume of air that is taken in or given out with each normal breath is recorded on the graduated paper provided in the spirometer. The subject is then asked to inhale maximally and then to exhale rapidly and completely into the mouth piece. It should be taken care that the subject's nose is clipped properly so that he breathes only through the mouth piece.

Using spirometer, we can determine the volume of air taken in, given out etc., at various stages of respiration. A graph is recorded on a graph paper with time on the X-axis and volume in mL on the Y-axis. *During inspiration, an upstroke is recorded, and during expiration, a downstroke is recorded.*

Lung volumes and capacities: Lung volume and capacities are divided into

1. Static lung volume and capacities.
2. Dynamic lung volume and capacities

Static lung volume and capacities.

Static lung volumes: Static lung volumes whose values do not change with time.

a) Lung volumes:

- Tidal volume (TV): volume of air inspired or expired during each normal breathing s tidal volume. Normal values: Newborn: 15-20 ml, males: 600ml, females: 450ml.
- Inspiratory reserve volume (IRV): extra volume of air that can be inspired over and above the normal tidal volume is inspiratory reserve volume. Normal value: males: 3.3 L, females: 1.9L.
- Expiratory reserve volume (ERV): extra volume of air that can be expired by forceful expiration after the end of a normal expiration is expiratory reserve volume. Normal value: males: 1L, females: 0.7L.

- Residual volume (RV): the volume of air remaining in the lung even after the most forceful expiration is residual volume. This volume cannot be measured by Spirometry. Normal value: males: 1.2L, females: 1.1L. The residual volume can be removed from the lungs only by surgery or by collapsing the lungs. Minimal volume: opening the thoracic cavity allows the intrapleural pressure to equal the atmospheric pressure forcing out some of the residual volume. The air remaining is called minimal volume. Minimal volume is normally 10% of TLC.

  Functions of residual volume:

  1) It acts as a buffer in between breaths to aerate the pulmonary capillary blood.
  2) Medicolegal importance: to detect whether the baby was stillborn (born dead) or born alive. If the baby has taken the first breath, minimal volume will be there and lungs float in water. If it was stillborn, lungs will be solid because they contain no air and sink down.

b) Lung capacities: Are combination of specific lung volumes.

- Inspiratory capacity (IC): maximum volume of air that can be inspired after a tidal inspiration. IC= TV + IRV
- Functional residual capacity (FRC): volume of air remaining in the lungs after a tidal expiration. This is also called resting volume of lungs. FRC = ERV + RV

  Importance of FRC:

  1) This gas helps in the continuous exchange of gases peen lungs and blood in between two breaths.
  2) It prevents marked rise or fall in concentration of blood O2 and CO2 levels in between breaths.
  3) If FRC is increased, it means that lungs are hyperinflated as in emphysema, partial obstruction to airways, old age etc.
- Total lung capacity (TLC): volume of air in the lungs after a maximum inspiration. TLC = TV + IRV + ERV + RV
- Vital capacity (VC): maximum volume which can be expired after a maximum inspiration. VC = IRV + TV+ ERV

Vital capacity is frequently measured clinically as an index of pulmonary function since it can be measured using simple spirometer.

<u>Factors Affecting Vital Capacity</u>

a) Age: vital capacity is maximal in young adults.
b) Sex: VC is more in males than in females.
c) Build and physical training: VC will be more in well built individuals and in athletes.
d) Height: VC varies with height:
   - In males - height in cm × 25 mL
   - In females - height in cm 20 × Ml

- Athletes - height in cm ×29 mL

e) Body surface area: VC can be calculated from body surface area
   - In males: 2.6 L/square meter body surface area.
   - In females: 2.1 L/sq m body surface area.
   - In athletes - 2.8 L/sq m body surface area.
   - Vital index - Vital capacity related to the body surface area is called vital index. Vital index= Vital capacity/Body surface area

f) Posture: VC is maximal when the person is seated in a slightly reclined posture. VC is decreased in down and standing posture.

g) Other factors affecting VC are:
   - Strength or power of the respiratory muscles.
   - Airway resistance
   - Compliance of lung
   - Elasticity of lungs

Variations in Vital Capacity

a) *Physiological Decrease*: In pregnancy due to inability of diaphragm wove down satisfactorily, there will be a reduction in VC.

b) *Pathological Decrease*:

- Neurological diseases affecting muscles of respiration, like neuritis, poliomyelitis etc
- Diseases of muscles, like myasthenia gravis.
- Deformities of thoracic cage. Like kyphosis, scoliosis etc.
- Diseases of lung, like emphysema. Fibrosis, pneumonia, tuberculosis etc.
- Diseases of pleura, like pleural effusion, pneumothorax etc.
- Diseases of heart, like congestive cardiac failure (CCF), pericardial effusion etc.
- Diseases of abdominal cavity, like ascites large tumor etc

Importance of Vital Capacity:

1) VC has prognostic value during treatment of a respiratory problem. If the vital capacity increases with treatment it means that the patient is responding to the treatment.
2) We can assess the progress of a chronic disease like emphysema. If there is a rapid reduction in vital capacity it means that the disease is rapidly progressing and the mortality is higher.
3) VC is used for assessing physical fitness (sportsmen, health check ups in schools, recruitment in police etc).

TLC, FRC and RV cannot be measured using an ordinary spirometer since RV cannot be expelled out.

Dynamic Lung Volumes and Capacities: Dynamic lung volumes quantify time rate of gas flow along respiratory tree.

Significance

1) Dynamic volumes and capacities have greatest application in conditions with impaired expiratory flow like emphysema, bronchial asthma etc.
2) Helps in clinical evaluation of dyspnea and pulmonary disability.

- *Maximum Ventilatory Volume (MVV) or Maximum Voluntary Ventilation or Maximum Breathing Capacity (MBC):*
  Maximum volume of air that can be moved into and out of the lungs in one minute by maximum voluntary effort is called MVV or the maximum volume of air that can be breathed rapidly and deeply for one minute. Normal value in healthy adult is 125-170 L/min. Drawback of the technique is that it produces giddiness and visual blackout due to washing out of CO_2. MVV is decreased in emphysema and asthma.
- *Forced Expiratory Volume(FEV) or Timed vital capacity:* Timed vital capacity is the fraction of vital capacity that is expired during the first second (FEV1), during the first two seconds (FEV2) and during the first three seconds (FEV3) of forced expiration. For example, FEV1 is the fraction of vital capacity that is expired in the first second of forced expiration. If the amount of air that is expired in the first second of forced expiration after a maximum inspiration is 3.3 L and that expired in the 2nd second is 3.7 L then FEV1, = 3.3 L and FEV2, = 3.7 L respectively. *FEV1%:* TVC_I% is the fraction of vital capacity expelled at the end of first second of forced expiration expressed in percentage. FEV1% =FEV1/FVC ×100. If FEV1 is 3.33 L and the forced vital capacity 4 L then FEV1%= 3.33/4×100=83. It takes about 4 seconds to expel the whole volume of the vital capacity.
  <u>Importance of TVC(FEV)</u>
  - In the early stages of many chronic diseases like emphysema, the vital capacity may remain within normal limits but the timed vital capacity (FEV1) shows abnormality. So, it helps in the early detection of diseases like emphysema.
  - TVC is a very important index to differentiate between obstructive and restrictive diseases. Restrictive diseases are diseases that restrict the movement of either thoracic cage or lungs. Like kyphosis, scoliosis, fibrosis of lung etc. In restrictive diseases, the FVC will be reduced, but FEV1% will be normal.
    Obstructive diseases are due to obstruction of airways, like bronchial asthma. In obstructive diseases, FVC may be reduced or sometimes normal, but FEV1and FEV1% is reduced very much, if FEV1% is reduced to 40%, the person will develop dyspnea.

  - *Peak expiratory flow rate:* It is measured by Wright's Peak expiratory flow meter and electronic spirometer. Normal value= 600 L/min. The value depends on the caliber of the large airways and strength of respiratory muscles.

- *Maximum mid expiratory flow rate* or forced expiratory flow rate (FEF25%-75%)*:* The average rate of airflow during middle two quarters (middle ½) of the volume segment of forced vital capacity (i.e. from 25% to75% of the volume). Normal value=200-400mL/min. Various lung disorders can be diagnosed by comparing the obtained values of lung volumes and capacities with the normal predicted value depending on sex, age, height etc.

Measurement of RV, FRC, and TLC

The methods are:

1. N_2 wash out method.
2. Closed circuit helium dilution method.

In closed circuit helium dilution method, ask the subject to breath 10% He from a spirometer of known volume from the end of maximum expiration for 7-10 minutes. Now the He concentration in the spirometer and lung becomes the same. He is insoluble and inert and so does not enter blood.

Let the initial volume of spirometer be V1

Initial concentration of He in spirometer C1

Amount of He spirometer=C1V1

Initial volume of air in the lungs =V2

Initial concentration of He in the lungs =0

Final concentration of He in lungs or spirometer=C2

Final amount of He in lungs and spirometer=C2 (V1+V2)

Amount of helium before dilution (A1) = Amount of helium after dilution (A2)

C1V1=C2 (V1+V2)

C1√, V√, C2√, V2=RV

Here, V2 is the initial volume of air in the lung which is the residual volume because the subject breathed He from the end of maximum expiration, i.e., only the residual volume is remaining in the lungs at the beginning of the procedure.

We can find out FRC if the experiment is started at the end of normal expiration when the functional residual volume will be present in the lungs.

TLC can be calculated if the experiment is started at the end of maximum inspiration.

Pulmonary ventilation and alveolar ventilation:

Ventilation is divided into two:

- Pulmonary ventilation
- Alveolar ventilation

Pulmonary Ventilation or Respiratory Minute Volume (RMV) or Minute Ventilation

It is the amount of air that is taken in or given out during quiet normal respiration for one minute.

Pulmonary ventilation =Tidal volume × Respiratory rate

$= 500 \times 12 = 6$ L/min

Alveolar Ventilation

It is the volume of fresh air entering the respiratory zone in one minute. The physiologically significant part of pulmonary ventilation is alveolar ventilation because it represents the amount of fresh air available for gas exchange. Though tidal volume is about 500 mL, only 350 mL takes part in gaseous exchange. The rest 150 mL present in the conducting zone or respiratory dead space does not take part in gas exchange.

Alveolar ventilation = (TV - RDS) ×Respiratory rate (RR)

$= (500 - 150 \text{ ml}) \times 12/\text{min}$

$= 350 \times 12 = 4.2$ L/min

So wasted ventilation = RR × Dead space air

$= 12/\text{min} \times 150$ mL $= 1800$ ml/min

RESPIRATORY DEAD SPACE (RDS)

The portion of tidal volume that does not take part in gas exchange is respiratory dead space. It is divided into:

- Anatomical dead space
- Physiological dead space

In normal subjects both are nearly the same. But in patients with lung disease the physiological dead space will be larger due to inequality of blood flow and ventilation in the lungs.

Anatomical Dead Space

It is the volume of air in the respiratory passage from nose to the terminal bronchiole which does not take part in gas exchange.

Physiological Dead Space

It is the volume of air in the respiratory system that is not in equilibrating with blood.

Physiological dead space = Anatomic + Alveolar dead space

Alveolar dead space is the air in the alveoli, i.e., in the non functioning alveoli underperfused or nonperfused alveoli and overventilated alveoli. Nonperfused alveoli do not receive pulmonary capillary blood and the air in these alveoli contributes to alveolar dead space. The volume of air that ventilates alveoli in excess of the volume required to oxygenate the blood in the pulmonary capillaries contributes to overventilation. This air also contributes to alveolar dead space.

Normally alveolar dead space air is about 5-10mL.

Increase in physiological dead space is seen in pulmonary embolism and COPD.

Variations in Dead Space

1. Age: as age advances, there is increase in anatomic dead space (ADS) due to loss of elasticity of respiratory system. In old age, anatomical dead space increases to 200 mL from 150 mL.
2. Sex: in females ADS is less than in male due to decrease in body size. In adult female, ADS is only 100mL.
3. Posture: ADS decreased in lying down posture.
4. Phases of respiration: in inspiration there is increase in dead space, and in expiration there is decrease in ADS volume.
5. Position of neck: Dead space is less when neck is fully flexed and chin depressed than when the neck fully extended.
6. Body weight: ADS in adults in mL is approximately equal to the weight of the subject in pounds.
7. In bronchoconstriction. ADS is decreased
8. Tracheostomy decreases ADS.
9. Emphysema and exercise increase dead space volume.

METHODS OF DETERMINATION OF DEAD SPACE:

Anatomical Dead Space

Single breath method or Fowler's method

Principle

A gas analyzer known as nitrogen meter is used. Flow rate and concentration of N_2 in inspired air and expired air are obtained.

Procedure

At mid inspiration, the subject is asked to take a deep breath of pure O_2 and then to breathe out slowly and evenly into aN_2 meter. The N_2 meter analyzes the volume flow rate.

4 phases are seen in the graph:

- Phase I: The initial gas exhaled is the gas that filled the dead space and contains no N_2.
- Phase II: This part contains a mixture of dead space air and alveolar air.
- Phase III: Pure alveolar air comes out and a plateau phase is seen called alveolar plateau.
- Phase IV: during this phase, the N_2 content of expired air and the graph goes up.

The gas in the upper portion of the lung is richer in N_2 than the gas in the lower dependent portions because the alveoli in the upper portions are more distended at the start of inspiration of O_2, and the N_2 in them is less diluted withO_2.

The dead space volume is found out by drawing a vertical line in phase II of the above graph such that area A is equal to area B. The dead space air is the volume exhaled from peak of inspiration up to the vertical line in phase II. This point is the demarcating point between the gas exchange zone and conducting zone. So the above experiment determines only the anatomical dead space.

Closing Volume

Closing volume is the lung volume above residual volume at which airways in the lower dependent parts of the lung begin to close off because of the lesser transmural pressure in these areas. The intrapleural pressure is more negative at the apex than at the base.

In normal young adults, closing volume is 10% of vital capacity.

In old age it becomes 40% of vital capacity. Closing volume is more in smokers.

Physiological Dead Space

Using Bohr's Equation

Principle

Volume of expired air is equal to the sum of dead space air and alveolar air.

Nitrogen or carbondioxide is taken.

$V_D=V_E\ (Pa_{CO2}-PE_{CO2})-Pa_{CO2}$

V_D= dead space volume

V_E= Volume of expired air which is equal to tidal volume

PE_{CO2}=Partial pressure of CO2 in expired air

Pa_{CO2}= Partial pressure of CO2 in arterial blood

Sample Calculations

1) Calculate alveolar ventilation from the given data:
   Wasted ventilation = 2250 mL
   Respiratory rate =5 /min
   Tidal volume = 450 mL
   Answer
   Dead space volume=2250/15=150Ml
   Alveolar ventilation = (TV – RDS) RR
   =(450–150)15
   =300mL× 15/min = 4500 mL/min
2) Calculate the dead space from the following data:
   Respiratory rate =12 /min
   Pulmonary ventilation = 6 L/min
   $Paco_2$= 40 mm Hg, P_Eco_2 = 28 mm Hg
   Answer:
   TV=600 mL/12=500mL
   VD=500(4-0-28)/40=150mL

COMPLIANCE (PRESSURE—VOLUME RELATIONSHIP)

Definition:

Compliance is defined as the change in lung volume per unit change in airway pressure. Compliance is a measure of the distensibility or the ease with which the lungs and thoracic wall can be expanded.

$$\text{Compliance} = \Delta P/\Delta V$$

Total compliance is the compliance of thorax and lungs together.

Total compliance = 0.13 L/ cm of water, i.e., for every cm of water pressure change, the lungs and thorax expand by 0.13 L.

When the compliance of thorax and lungs are taken separately, the value will be more than total compliance. At FRC, compliance of thorax alone is 0.22 L/cm of water and that of lungs alone is also 0.22 L/cm of water.

Measurement of Compliance

Total Compliance

Procedure

Nose is clipped and after maximum expiration, the subject is asked to inspire 50 mL of air from the spirometer through a mouth piece. Close the valve in the mouth piece in front of the manometer and allow the respiratory muscles to relax. The intrapulmonary pressure is measured. Repeat the procedure for every 50 mL increments.

Plot a graph with volume on the Y-axis and pressure on the X-axis. This is the relaxation pressure curve of the total respiratory system. Compliance is measured in the pressure range where the relaxation pressure curve is steepest.

Relaxation Volume

In the above graph, pressure is zero at a volume corresponds to FRC. This is relaxation volume. Pressure is positive at volumes greater than FRC and pressure is negative at volumes lesser than FRC.

Compliance of Lung Alone

Volume changes are plotted against transpulmonary pressure changes, i.e., intraoesophageal pressure changes are recorded during inspiration and expiration. Lung is an elastic organ. The compliance of lungs varies inversely with volume. At FRC, lungs are normally very compliant

To produce same volume more pressure is required in inspiration than in expiration. For the same pressure, inspiratory compliance curve lags behind expiratory curve and hence a hysteresis loop is obtained.

Compliance of chest wall

1/total compliance= 1/compliance of lung+ 1/compliance of chest wall

1/0.13=1/0.22+1/C

1/C=1/0.13-1/0.22

=0.2L/cm of water

Factors affecting compliance:

1. Lung volume: an individual with only one lung has 1/2 the ΔV for a given

ΔP.

2. Phases of respiration: compliance is slightly greater when measured during deflation than when measured during inflation.

Variations in Lung Compliance

Total compliance is decreased in:

- Restrictive diseases of the thorax like kyphosis, scoliosis etc.
- Fibrosis of respiratory muscles.

Lung compliance is decreased in diseases of lung like:

- Pulmonary edema
- Pleural effusion
- Atelectasis or collapse of lung
- Surfactant deficiency
- Pneumothorax
- Lobectomy of lung

Compliance is increased in conditions due to loss of e as-ticity as in:

- Old age
- Emphysema

Specific Compliance

Since compliance varies with lung volume, specific compliance is usually measured. Specific compliance is compliance per unit volume.

Compliance =Lung volume/pressure

For example, the lung compliance was calculated to be 0.2 L/cm of water in a person. In this case if the person inhaled 1 liter of air, the specific compliance will be 0.2/1 =0.2.

If the compliance of the same person is calculated after removing one lung it will be 0.1 L/cm of water because the volume of air inhaled now will only be 0.5 L. But if the specific compliance is calculated in the same person it will be 0.1/0.5 = 0.2. This shows that the distensibility of the remaining lung is normal as in the initial case and lung volume is not interfering with the value.

WORK OF BREATHING

Work is done only in inspiration and forced expiration. No work is done in normal quiet expiration.

Work = Force × Displacement

= Pressure × Volume

During inspiration, all dimensions of thorax increase and certain amount of work has to be done by the respiratory muscles to overcome 3 factors. Work done is divided into three:

1. Compliance work or elastic work
2. Tissue resistance work
3. Airway resistance work

Compliance Work

This work is done to overcome elastic resistance, i.e., work done in stretching the elastic tissues of chest wall and lungs.

Tissue Resistance Work

This work is done to overcome inelastic tissue resistance or viscous resistance, i.e., in moving inelastic tissues.

Airway Resistance Work

Airway resistance work is done to overcome frictional force of air moving through the respiratory passages. Total work done in quiet breathing = 0.3-0.8 kg-m/m:m

Work done is increased in:

1. Exercise
2. Laboured breathing
3. Obstruction to airflow as in bronchial asthma
4. Pulmonary fibrosis and other lung diseases where compliance is decreased
5. CCF associated with dyspnea and orthopnea.

Pulmonary Circulation

Pulmonary circulation carries deoxygenated blood from right ventricle to the alveoli and returns oxygenated blood from alveoli to left atrium. The pulmonary artery arising from the right ventricle divides into right and left branches. Each branch enters the corresponding lung along with primary bronchus. Inside the lung it divides into small vessels up to capillaries with multiple anastomoses and each alveolus sits in a capillary basket.

❖ Features of Pulmonary Circulation

1) Lung is the only organ receiving the entire cardiac output. Thus the lungs accommodate the amount of blood equal to that accommodated by all the other organs of the body.
2) Distance of pulmonary vessels when compared to systemic circulation from the heart is less and this system is not much affected by gravitational forces.
3) The pulmonary arteries are thin walled (it is 30% as thick as the wall of the aorta) and contain very little smooth muscles and elastic tissue and have larger diameter.
4) Pulmonary capillaries are larger than systemic capillaries and denser with multiple anastomoses so that each alveolus seems to sit in a capillary basket.
5) The pulmonary veins are highly dispensable and act a blood reservoir. The pulmonary blood volume increases by 400 mL as the person lies down and this is the *reason for the reduction in vital capacity in lying down posture and the cause for orthopnea in cardiac failure.*
6) Since the pulmonary circulation is a *low-pressure, low-resistance* system, so all the blood from the right heart can be pumped into this system.
7) Blood vessels of lung consist of two sets originating from two different sources, performing different functions.
    a. From pulmonary artery belonging to pulmonary circulation and contain deoxygenated blood and the function is gas exchange.
    b. From bronchial arteries arising from aorta belonging to systemic circulation and contains oxygenated blood. Function is to supply nutrition to respiratory tree up to terminal bronchiole.
8) Pulmonary blood flow is influenced by intrathoracic pressure.
9) Pulmonary circulation acts as a filter which prevents emboli from reaching the systemic circulation due to the presence of fibrinolytic system in lung.
10) The pulmonary arteries are the only postnatal arteries that carry deoxygenated blood, and pulmonary veins are the only postnatal veins that carry oxygenated blood.

11) Lymphatic channels are abundant in lungs which help to keep alveoli dry and maintain negative intrapleural pressure.
12) Angiotensin converting enzyme (ACE) produced by endothelial cells of pulmonary vasculature helps in the conversion of angiotensin I to angiotensin II which has a major role in maintaining blood pressure.
13) Physiologic shunt — shunt is defined as any mechanism by which blood that has not been oxygenated in the lungs is added to systemic circulation. In the lung there is anastomosis between capillaries of pulmonary vessels and bronchial vessels. So, some bronchial venous blood (impure blood) enters pulmonary veins (pure blood) bypassing the right ventricle and returns to left side of heart. This constitutes 2% of blood in systemic circulation. Pathological shunt in lungs – blood coming from areas of lung with low ventilation-perfusion ratio also contributes to the shunt in abnormal situations, i.e., blood that is drained from non-ventilated gas-exchanging units of lung.

Causes for reduction in arterial PO_2

- Physiological shunt in the lung.
- Some amount of coronary venous blood which is drained from the heart enters the left ventricle **through the thebesian veins. This** constitutes 0.5% of blood in systemic circulation.
- Right-to-left shunts (septa) defects) in patients with cyanotic congenital heart disease contribute to reduction in arterial Po_2. This occurs when there is increase in pressure in the right side as in pulmonary hypertension. Otherwise, the shunt is only from left to right since the pressure in the left side of heart is more.

Reasons

1. *Right ventricular output is a little less than that of left ventricular output.* This is due to two reasons: (a) Part of bronchial blood flow enters pulmonary capillaries and veins bypassing the right ventricle due to anastomosis between the bronchial capillaries and pulmonary vessels; (b) Some amount of venous blood flows from coronary veins to left side of heart through thebesian veins.
2. *The blood in the systemic ystemic arteries has a Po2 about 2 mm Hg less than that of blood that has equilibrated with alveolar air and the saturation of hemoglobin is 0.5% less.*

Reason is physiologic shunt (explain).

PULMONARY BLOOD PRESSURE:

The entire pulmonary vascular system is a distensible low-pressure system. Pulmonary arterial blood pressure is *very low* when compared to systemic arterial blood pressure.

Pulmonary pressure = 24/9 mm Hg

Systemic blood pressure = 120/80 Two, Hg

The pulmonary capillary pressure is about 10 Hg, whereas in the systemic capillary it is 30 mmHg. Pulmonary capillary oncotic pressure is 25 mm Hg. Acording to Starling's hypothesis, the inward directed pressure gradient of about 15 mmHg keeps the alveoli free fluid. When the pulmonary capillary pressure becomes than 25 mm Hg, it leads to pulmonary edema, e.g. mitral stenosis.

Factors that Keep the Alveoli Dry

1. The inward-directed pressure gradient of 15 mmHg in the pulmonary capillaries.
2. Surfactant lining the alveoli decreases the surface tension and prevents fluid collection.
3. Negative pulmonary interstitial fluid pressure sucks fluid that collects in the alveoli. This is drained a by the pulmonary capillaries and the lymphatics.
4. Lung is richly supplied with lymphatic vessels which rapidly drain away excess fluid.

Pulmonary Edema

When there is increase in the pulmonary interstitial fluid pressure to a positive value there will be sudden filling oof pulmonary interstitial spaces and alveoli with large amounts of fluid. This condition is called pulmonary edema.

Causes

a. Left heart failure leads to increase in pulmonary capillary pressure.
b. Damage to capillary membrane as in infections like pneumonia, SO2, Cl2, gas poisoning etc.

Pulmonary Hypertension

Sustained elevation of pulmonary arterial pressure is called pulmonary hypertension. Most important causes are hypoxia and systemic lupus erythematosus (SLE). if the condition is not treated, the increased right ventricular afterload leads to right heart failure and death.

Measurement of Pulmonary blood flow

Since the whole of cardiac output goes through lungs, pulmonary blood flow can be obtained from Fick's principle or indicator dilution technique (refer measurement of cardiac output in cardiovascular system).

Factors influencing pulmonary blood flow or regulation of pulmonary blood flow:

- Cardiac output: since pulmonary blood flow is directly proportional to cardiac output, any factor that alters cardiac out put affects pulmonary perfusion like venous return, force of contraction etc.

- ❖ Pulmonary vascular resisstance: pulmonary perfusion is inversely proportional to pulmonary vascular resistance.
- ❖ Nervous factors:
    - Sympathetic stimulation especially of the cervical sympathetic ganglia reduces pulmonary blood flow by as much as 30% by producing pulmonary vasoconsctiction
    - Parasympathetic stimulation produces vasodilation leading to decrease pulmonary vascular resistance and increased pulmonary perfusion.
- ❖ Chemical factors: hypoxia, hypercapnia, and acidosis produce vasoconstriction and increase pulmonary arterial pressure. In all others areas other than lung, hypoxia produces vasodilation. This is the reason for the development of pulmonary hypertension in patients with COPD. Chronic generalized hypoxia of lung leads to prolonged vasoconstriction and produces histological changes in the pulmonary vasculature leading to increased pulmonary vascular resistance.
- ❖ Effects of gravity: gravity has a remarkable effect on pulmonary circulation. In the erect posture, there is a relatively marked pressure gradient in the pulmonary arteries from top to the bottom of the lungs because of the effect of gravity. This results in a linear increase in pulmonary blood flow from the apex to the base of the lung.
- ❖ Hormonal factors: pulmonary arteriolar vasoconstriction: angiotensin II, epinephrine, norepinephrine, PGF2Aalpha etc.

  Vasodilators:Ach, NO etc.

  Constrictors of pulmonary venules: serotonin, histamine etc.
- ❖ Phases of respiration: in inspiration there is pulmonary vasodilation and increased pulmonary perfusion.

  In expiration there will be vasoconstriction and increased pulmonary vascular resistance leading to decreased perfusion.

Regional variation in distribution of ventilation and perfusion:

Ventilation:

Inhaled air is not distributed equally to all regions of the lung. In erect posture this is due to the effect of gravity on intrapleural pressure. Pleural pressure is more negative at the apex and less negative at the base.

At FRC, more negative intrapleural pressure at the apex causes greater expansion of apical alveoli in the erect posture and has a larger resting volume and less compliance than at the base. At high lung volumes, the lung becomes stiffer, i.e., it becomes less complaint. In contrast, the lower zone of the lung

has a lower resting volume because the alveoli are of small size initially, the compliance is more at low lung volumes and this area expands more readily during inspiration. So, the lower zone of the lung is ventilated better than the apex during inspiration.

Perfusion:

The apex of the lung is well above the level of the heart and the base of lung is below the level of heart. *Gravity plays an important role in perfusion in lung.* In the erect posture there is a linear increase in blood flow from the top to the bottom of the lung. Beside gravity, hypoxic pulmonary vasoconstriction also regulate blood flow. The smooth muscle cells of pulmonary arterioles are very sensitive to alveolar Po_2. As PO2 falls in a particular area, there is arteriolar constriction in that area and redistribution of blood flow to regions of higher alveolar Po2. But if there is generalized alveolar hypoxia it leads to pulmonary hypertension.

Ventilation perfusion ratio:

Is the ratio between alveolar ventilation in one minute and pulmonary perfusion in one minute . for proper O2 and CO2 exchange in the lungs, ventilation and perfusion must be matched. Resting alveolar ventilation is 4 L/min, while pulmonary blood flow which is equal to cardiac output is 5L/min

V/Q=4L/min/ 5L/min=0.8 at the middle of the lung

At the apex of the lung, V/Q=3

At the base of the lung, V/Q=0.6

Ventilation and perfusion are not uniformly distributed throughout the lung Both are preferentially distributed to the dependent regions of the lung at rest.

In the upright posture, ventilation and perfusion are less at the apex and more towards the base. In lying down posture, the posterior part of the lung is well ventilated and perfused than the anterior part. This gravity dependent reduction in flow is more marked with perfusion than with ventilation, or in other words, the gravity dependent reduction in perfusion is more marked at the apex than reduction for ventilation. Hence, the ratio of ventilation to perfusion is highest at the apex and lowest at the base in upright posture.

Clinical Importance

If one lung is not functioning, the patient is advised to lie on the side in which the lung is functioning so that this lung will be well ventilated and perfused.

Pulmonary tuberculosis affects apex of the lung first. Reasons are:

- This is because reduction in perfusion is more than reduction in ventilation at the apex of the lung. So, more O_2 is available at the apex of lung. This provides a favorable environment for the growth of tubercle bacilli which are aerobic bacteria.
- Another reason is poor perfusion at the apex. Antibodies in the blood do not reach the apex satisfactorily. So, apex of the lung is more vulnerable

to bacterial attack.

Importance of Ventilation- Perfusion Ratio

- It is important in determining the gas concentration in alveoli.
- Effectiveness of gas exchange through the alveolocapillary membrane is determined by VA/Q.

MEASUREMENT OF VENTILATION AND PERFUSION IN DIFFERENT PARTS OF THE LUNG

Measurement of Ventilation

The subject inhales a breath of radioactive xenon gas ^{113}Xe. When it enters the lung, it penetrates the chest wall and can be recorded by a radiation camera. In this way the volume of inhaled radioactive xenon going to various regions of the lung can be determined. It is seen that ventilation per unit volume is greater near the base of the lung and progressively lesser towards the top in the erect posture. This difference disappears in the supine position. In the supine position, the posterior part of lung is more ventilated than the anterior part. When the subject lies on his side (lateral position), it is seen that the dependent lung is better ventilated.

Measurement of Distribution of Blood Flow:

Radioactive xenon gas is dissolved in saline and injected into the superior vena cava or any peripheral vein. reaches the pulmonary capillaries, the distribution of radioactivity is measured by a radiation camera mounted behind the chest.

In the upright posture, blood flow seems to decrease linearly from bottom to top of lungs, reaching very low values at the apex. This distribution of radioactivity is affected by change in posture.

Assessment of Ventilation-Perfusion Unifo

- Measurement of dead space. If physiological dead space is increased, V_A/Q will be greater than normal.
- Continuous monitoring of CO2 content of expired air.
- Radioisotope method — a breath of ^{133}Xe is taken. Chest is monitored with a radiation camera. This help to assess ventilation.

Intravenous injection of saline solution of ^{133}Xe into superior vena cava and measuring the distribution of radioactivity helps to assess regional blood flow.

Abnormalities in VJQ

- *Ventilation without perfusion* (alveolar dead space)VA/Q is greater than normal or infinity, e.g., put embolism, pulmonary hypertension.
- *Perfusion without ventilation:* This produces a shunt where impure blood passes to systemic circulation without coming in contact with alveolar air.

  VA/Q will be < normal or zero, e.g., consolidation of the lung, fibrosis,

atelactasis or collapse, pulmonary edema and bronchial obstruction as in COPD.

Pulmonary Gas Exchange

PARTIAL PRESSURE OF GASES

According to Dalton's law, each gas in a mixture of gases exerts its own pressure as if all the other gases were not present. Atmospheric pressure is the sum of the pressures of all the gases present in air like O2, CO2, N2, water vapour and several other gases. In a mixture of gases, the pressure exerted by any one gas is its partial pressure and is equal to the total pressure multiplied by the fraction of the amount of gas which it represents. Total pressure is barometric pressure at that height.

Barometric pressure at sea level is 760 mm Hg. The %of O2 in air is 20.8%.
So. partial pressure of O2 (Po2) in air is calculated

PO2= 20.8 x 760 /100 = 158 mm Hg

The partial pressure of gases is important in the movement of gases, especially O2 and CO2 across the respiratory membrane and between blood and body cells. During diffusion across a permeable membrane, each gas diffuses from an area where its partial pressure is greater to an area where its partial pressure is less.

TECHNIQUES OF COLLECTION OF ALVEOLAR AIR OR SAMPLING OF ALVEOLAR AIR

1) Haldane–Priestly method

- Principle

  Expired gas is a mixture of dead space and alveolar air. The initial portion will be dead space air and latter portion contains alveolar air. The last 10 mL of expired air is collected in a sampling tube and analyzed using a gas analyzer.

- Apparatus

  Haldane's alveolar air tube is used. It is a long tube made of rubber or plastic, about one meter long and 2.5 cm diameter. A mouth piece is connected to one end and close to the mouth piece is a side tube and through it a sampling tube is connected.

- Procedure

  Ask the subject to breathe rapidly and forcefully into the Haldane's tube. Because of the force of expiration, the initial portion of air goes straight, and latter **portion goes to the side sampling tube. The gas is then analyzed.**

2) Two-bag technique

The subject is asked to breathe out through the mouth piece. The initial part of expired air enters bag II because bag I is closed. Then bag I is opened and bag II closed so that latter part of air is collected in bag I.

3) Continuous sampling technique

Mouth piece is connected to devices with automatic inspiratory and expiratory valves. In expiration, 10 nil, of end expiratory air is collected in a side bag.

Methods of Analysis of the Collected Alveolar Gas

1) Haldane's gas analyzer –Alveolar air contains O2 and CO2. The concentration of each gas can be calculated using KOH and pyrogallol. Air is passed through KOH. Let the initial volume of air be X.

   After passing through KOH let the volume be Y

   Concentration of CO2=X-Y×100/X

   Now pass the air having volume Y through pyrogallol which absorbs O2. Let the final volume be Z.

   Concentration of O2 = Y-Z ×100/X
2) Infrared CO2 analyzer: Amount of infrared rays absorbed is proportional to the quantity of CO2 in the alveolar air.
3) Paramagnetic O2 analyzer: Between the poles of two magnets, an evacuated metallic sphere is kept. The quantity of O2 is proportional to the distance through which the sphere is displaced when the alveolar air is passed through the sphere.
4) Other methods are:
   - Polarographic electrodes for CO2 estimation.
   - N2 analyzer
   - Mass spectrometer
   - Gas chromatography

Reasons for the Difference in the Composition of Atmospheric Air and Alveolar Air

1. Partial replacement of alveolar air by atmospheric air with each breath.
2. Constant absorption of O_2 from alveoli to pulmonary capillaries.
3. Diffusion of CO_2 from pulmonary capillaries to alveoli.
4. Humidification of atmospheric air as it passes through the respiratory passages leads to dilution of gases. Water in the respiratory passage is evaporated and the atmospheric air entering the respiratory passage gets saturated with water vapour. Vapour pressure is pressure exerted by water molecules to escape from a surface. At 37°C, vapour pressure is 47 mm Hg.

Mechanisms by which Composition of Air is Kept Constant

1) By proper ventilation and perfusion of lung. O_2 continuously diffuses out

of the alveoli into the blood stream, and CO_2 continuously diffuses into the alveoli from blood. Inspired air mixes with alveolar air, replacing the O_2 and diluting the CO_2.

2) Because of FRC of about 2 L at the end of expiration, 350 mL of inspired air or expired air has little effect on P02 and Pco2 of alveolar air and alveolar gas composition remains constant.
3) Central and peripheral control mechanisms also operates to maintain alveolar gas composition constant.

MECHANISM OF GAS EXCHANGE

Conditions Necessary for Proper Gas Exchange

For proper gas exchange between alveoli and the blood stream, certain conditions must be satisfied.

1. lungs must be sufficiently large. If the surface area of alveoli is reduced as in emphysema or in surgical resection of lung, the surface area of the respiratory membrane is decreased and sufficient gas exchange does not occur.
2. Alveolar ventilation must be adequate to replenish O_2 and wash out CO_2 from the alveoli.
3. Pulmonary circulation must be sufficient in quantity, and ventilation and perfusion must be to the same alveoli. i.e., VA/Q must be normal (0.8).

Structure of Blood-Gas Barrier or Respiratory membrane:

The exchange of respiratory gases between the lungs and blood takes place by diffusion across the alveolar and capillary walls. These layers are collectively called alveolar capillary membrane or respiratory membrane.

Layers of the respiratory membrane
Layer I: Alveolar fluid and surfactant
Layer II: Alveolar epithelium
Layer III: Epithelial basement membrane
Layer IV: Interstitial space
Layer V: Capillary basement membrane
Layer VI: Capillary endothelium

Factors Affecting Diffusion Across the Respiratory Membrane

- Thickness of respiratory membrane
- Surface area of respiratory membrane
- Pressure gradient of gases across the respiratory membrane
- Solubility of the gas
- Molecular weight of the gas
- Diffusion coefficient of gases

Thickness of Respiratory Membrane

Thickness of respiratory membrane = $^{1}/2$ μm
Diameter of pulmonary capillary – 8 μm
Diameter of RBC – 7.2 μm

So, red blood cells are squeezed through pulmonary capillary and so they are in close contact with respiratory membrane. These two factors allow rapid diffusion of gases across the respiratory membrane from alveoli to red blood cells. *Rate of diffusion of gases is inversely proportional to thickness of respiratory membrane.*

E.g., rate of diffusion of gases is decreased in fibrosis of lung, pulmonary edema etc., because the thickness of the membrane is increased.

Surface Area of Respiratory Membrane

Rate of diffusion is directly proportional to the surface area of respiratory membrane. Normal surface area is 70 m^2. Surface area is decreased in emphysema, in chronic smokers and in surgical resection of lung. In emphysema there is destruction of alveolar walls, thereby reducing the total surface area to 1/3rd to $^{1}/4$th normal.

Partial Pressure Difference of Gases

Greater the partial pressure gradient more will be the rate of diffusion.
Alveolar PO_2=100 mm Hg
Pulmonary capillary PO_2= 40 mm Hg
Partial pressure gradient for O_2 across the membrane is 100 – 40 mmHg= 60 mmHg
Alveolar PCO_2= 40 mm Hg
Pulmonary capillary PCO_2=46 mm Hg
Partial pressure gradient for CO_2 across the membrane is 46 – 40 = 6 mmHg

Gases diffuse from a region of higher partial pressure to a region of lower partial pressure across the membrane until the pressure of the gases on the two sides become equal.

Solubility of the Gas

The amount of gas that moves through a membrane is directly proportional to the solubility of the gas in the membrane. Although the partial pressure difference for CO_2 across the respiratory membrane is only 6 mm Hg, it is much more soluble than O_2 and diffuses with ease. Even though the molecular weight of O_2 is less than that of CO_2, CO_2 diffuses 20 times more rapidly than O_2 across the alveolar- capillary membrane. This is because the solubility of CO_2 is 24 times greater than the solubility of O_2 in the membrane.

Molecular Weight of the Gas

Rate of diffusion is inversely proportional to the square root of the molecular weight of the gas.

Diffusion Coefficient of Gases

Diffusion coefficient is the rate of diffusion of a gas through a given area for a given distance for a given pressure gradient.

Or the diffusion coefficient of a gas is the volume of gas in mL which diffuses through 1 cm^2 of a membrane in one minute when there is a pressure difference of 1 mm Hg across the membrane. The diffusion coefficient is directly proportional to the solubility of gas in the membrane and inversely proportional to the square root of molecular weight.

Diffusion coefficient of:

O_2=1
CO_2=20
N_2=0.5
CO=0.8
He=0.9

The diffusion coefficient of CO_2 is 20 times more than that of O_2.

The relation between rate of diffusion of a gas and the factors affecting it can be expressed by the formula

$$D \propto \frac{\Delta P \times A \times S}{d \times \sqrt{MW}}$$

D=Rate of diffusion of the gas
ΔP= Pressure gradient
A:=Surface area
S=Solubility of the gas
D=Thickness of the respiratory membrane
MW= Molecular weight of the gas

Diffusing Capacity of Lungs for O_2 and CO_2.

Diffusing capacity is the volume of gas in mL that is transported across the respiratory membrane in one minute for one mm Hg.

$D_{O2}=A\times dO2/t$

Do2= Diffusing capacity for O_2
A=Total area of respiratory membrane
T=Thickness of the membrane
dO2= Diffusion coefficient

Diffusing capacity for O_2= 20 mL/min/mm Hg
Diffusing capacity for CO_2= 400 mL/min/mm Hg

Diffusing capacity for CO_2 is 20 times that of O_2.even though the pressure gradient for CO_2 across the respiratory membrane is only 6 mmHg, it is adequate for CO_2 transfer because of its high diffusing capacity and diffusion coefficient. It is for the same reason that *diffusion defects causes hypoxemia but not CO_2 retention.*

Variations in Diffusing Capacity

Diffusing capacity is increased in exercise. In sever exercise, diffusion capacity of O2 becomes 65ml/min/mmHg and that of CO, becomes 1400 mL/min/mm Hg. This increase is due to the following reasons:

- Opening up of new capillaries
- Vasodilatation
- Stretching of alveolar membrane decreases the thickness of the respiratory membrane, thereby increasing diffusion rate.

Diffusing capacity is decreased in pulmonary edema, pulmonary fibrosis, sarcoidosis etc.

Measurement of Diffusing Capacity

Diffusion capacity of O_2= O_2 consumption/ /Pulmonary alveolar PO2 - Pulmonary capillars PO_2

Since it is difficult to find out the mean PO2of pulmonary capillary blood, diffusing capacity of carom oxide is estimated.

DC for O2 = DC for CO ×1.23

The subject is asked to inhale a mixture of 0.2% CO in the inspired air to maintain a steady concentration of CO in alveolar air. Hemoglobin has affinity for O2 and CO. when this affinity is compared, affinity of hemoglobin for CO IS about 210 times more than that for O2.

DC for CO= CO consumption/minl alveolar PCO- pulmonary capillary PCO (initially zero)

DC for O2= DC for CO × 1.23

= 17 x 1.23 = 20.9 mUmin/mm Hg

This technique was devised by Bohr in 1909 and later — by Mary Krogh.

Diffusion at Tissue Level

Diffusion of O2

Partial pressure of O_2 in the arterial blood is 95 mmHg and PO2 of tissues is 40 mm Hg because of continuous metabolic activity. A pressure gradient of 55 mm Hg exists between blood and tissues so that O2 can easily diffuse into the tissues.

O_2 content of arterial blood = 19.8 mL/100 mL of blood

O_2 content of venous blood =15 mL/ l 00 mL of blood

Cardiac output=5000 mL

So when 100 mL of blood pass through the tissue 4.5 mL(approximately 5 mL) of O_2 diffuses into the tissues.

Therefore O_2 consumption by the body= 5 ×5000/100=250mL/min

Diffusion of CO_2

Due to continuous metabolic activity CO2 is produced constantly in the tissues and so partial pressure of CO2 in the cells is about 46 nun Hg. Pco2 of arterial blood is 40 mmHg. A pressure gradient of 6 mm Hg is responsible for the diffusion of CO2 from tissues to blood.

CO2 content of arterial blood =48 mL/ 100 mL of blood

CO_2 content of venous blood = 52 mL/100 mL of blood

So the diffusion of CO_2 from tissues to the blood is 4 mL/ 100 mL of blood, i.e., when 100 mL of blood passes through tissues, 4 mL of CO2 enters the blood stream.

CO_2 output/min= 4×5000/100=200mL/min

RESPIRATORY QUOTIENT(RQ) ORRESPIRATORY EXCHANGE RATIO:

Respiratory quotient is the ratio between CO2 output and O2 consumption by the body.

RQ = 200mL/250mL=0.8

It depends on the type of food consumed. RQ of various foods are:

- Carbohydrate =1
- Fat= 0.7
- Protein=0.8

The reason for the difference in RQ is that when carbohydrate is utilized by the body, for every molecule of O_2 consumed one molecule of CO_2 is formed. So, RQ is one. When fat is utilized, O_2 reacts with fat and a large portion of O2 combines with hydrogen ions to form water instead of CO_2. So, CO_2 output is less and RQ is less.

Gas transport between the lungs and tissues:

Objectives:

- ❖ The manner in which O_2 flows downhill from the lungs to the tissues and CO_2 flows downhill from the tissues to the lungs.
- ❖ The reaction of O_2 with hemoglobin and O_2 hemoglobin dissociation curve.
- ❖ The important factors affecting affinity of hemoglobin for O_2 and physiological significance of each.
- ❖ The reactions that increase the amount of CO_2 in the blood, The CO_2 dissociation curve for arterial and venous blood.

The blood transports oxygen and CO_2 between the lungs and other tissues throughout the body. These gases are carried in several different forms: dissolved in plasma, chemically combined with haemoglobin, or converted into a different molecule.

Oxygen Transport:

1. 98.5% combines with hemoglobin
2. 1.5 % dissolved in plasma.

Reaction of hemoglobin and oxygen:

- Hemoglobin is a protein made up of four subunits, each of which contains a heme moiety attached to a polypeptide chain. In normal adults, most of the hemoglobin contains two α and two β chains. Heme is a complex made up of a porphyrin and one atom of ferrous (Fe^{++}) iron. Each of the four iron atoms can bind reversibly one O_2 molecule (the reaction is oxygenation not an oxidation). So each Hb can bind 4 O2s. Heme can also bind carbon monoxide.
- Most O_2 in blood is bound to Hb inside RBCs as *oxyhemoglobin*. Each RBC has about 280 million molecules of Hb, so Hb greatly increases O_2 carrying capacity of blood.
- *Methemoglobin* contains ferric iron (Fe3+), the oxidized form of Hb Lacks electron to bind with O_2. Blood normally contains a small amount of methemoglobin.
- *Carboxyhemoglobin* is heme combined with carbon monoxide (CO). Bond with carbon monoxide is 210 times stronger than bond with oxygen.
- Hemoglobin molecule can transport up to 4 oxygen molecules. When $4O_2$ are bound to Hb, it is 100%saturated, with fewer O2s, it's partially saturated. Oxygen binding occur in response to the high PO_2 in the lungs. Hemoglobin affinity for O_2 increases as its saturation increases. The affinity of HB for O_2 decreases as its saturation decreases.

$$\underset{\text{(Oxyhemoglobin)}}{\mathbf{Hb}} + \underset{\text{Oxygen}}{\mathbf{O_2}} \underset{\text{Tissues}}{\overset{\text{Lungs}}{\rightleftharpoons}} \underset{\text{Oxyhemoglobin}}{\mathbf{HbO_2}}$$

$$\mathbf{Hb_4 + O_2 \leftrightarrows Hb_4O_2}$$
$$\mathbf{Hb_4O_2 + O_2 \leftrightarrows Hb_4O_4}$$
$$\mathbf{Hb_4O_4 + O_2 \leftrightarrows Hb_4O_6}$$
$$\mathbf{Hb_4O_6 + O_2 \leftrightarrows Hb_4O_8}$$

- The reaction is rapid (<0.01 sec). The deoxygenation of $Hb4O_8$ is also very rapid. In deoxygenated Hb, the globin units are tightly bound in a tense (T) state, which reduces the affinity of the molecule for O_2. When O_2 first bound, the bonds holding the globin units are released,

producing a relaxed (R) state, which exposes more O_2 binding sites. The net result is a 500-fold increase in O_2 affinity. In tissues, these reactions are reversed, releasing O_2. The transition from one state to another has been calculated to occur about 10^8 times in the life of a RBC.

- When blood is equilibrated with 100% O_2 (Po_2=760mmHg), the normal Hb becomes 100% saturated. When fully saturated, each gram normal Hb contains 1.39 mL of O_2 → normal blood contains small mount of inactive Hb derivatives → 1.34mL O_2. Normal Hb concentration is 15 gm %(Hb in ♀=14 gm%, Hb in ♂=16 gm% in) →1dL of blood contains 20.1mL (15 × 1.34 mL) of O_2 bound to Hb when the Hb is 100% saturated. The amount of dissolved O2 is a linear function of Po_2 (o.oo3mL/dL blood/mmHg Po_2)
- In vivo, Hb in the blood at the end of the pulmonary capillaries is 97.5% saturated (Po_2 97mmHg). Because of slight admixture with venous blood that bypasses the pulmonary capillaries (physiological shunt) →the Hb in systemic arteries is only 97% saturated (Po_2 95 mmHg) → arterial blood contains 19.8mL of O_2/dL, 0.29 mL dissolved (0.003 × 95), and 19.5 mL combined (20.1×97%). In venous blood at rest Hb is 75%saturted (Po_2 95 mmHg), venous blood contains 15.2mL of O2/dL, 0.12 mL dissolved (0.003 ×40), and 15.1 mL combined (20.1×75). Thus at rest 4.6 mL of O_2 removed by tissues from each dL of blood passing though them (0.17mL in solution and remaining combined) → 250 mL/min.

Gas	ml/dL of blood containing 15 g hemoglobin			
	Arterial blood(Po_2 95 mmHg; Pco_2 40 mmHg; Hb 97% saturated)		Venous blood (Po_2 40 mmHg; Pco_2 46 mmHg; Hb 75 %saturated)	
	Dissolved	Combined	Dissolved	Combined
O_2	0.29	19.5	0.12	15.1
CO_2	2.62	46.4	2.98	49.7
N_2	0.98	0	0.98	0

Oxygen-hemoglobin Dissociation Curve:

- Curve relating percent O_2 saturation of Hb to the Po_2. Haemoglobin saturation is determined by the partial pressure of oxygen.
- O_2-Hb dissociation curve is an S shape curve flat slope at high P_{O2}, steep slope at low P_{O2}.
- The initial flat part of the curve occurs because binding of the first oxygen molecule causes a small structural change to the Hb facilitating the binding of subsequent oxygen molecules. The shape of the curve means that a fall in P_{O2} from normal arterial value will have little effect

on the Hb saturation (and therefore oxygen content) until the steep part of the curve reached, normally around 60mmHg. Once the P_{O2} has reached this level, however, a further decease in P_{O2} will result in a dramatic fall in the Hb saturation.

- Several factors can change the affinity of Hb for oxygen, resulting in the curve moving to the right (acidosis,↑ temperature, ↑2.3-DPG (2.3-diphosphoglycerate) or to the left (foetal Hb, alkalosis, ↓temperature, 2.3-DPG).
- Movement of the curve to the right decreases the affinity of the Hb for oxygen. This is physiologically useful in the tissues, where the slightly acidic environment serves to improve oxygen unloading from the blood (the Bohr effect). A left shift of the curve increases the affinity of HB for oxygen, producing a higher saturation at a given P_{O2}. This act to improve oxygen loading in the pulmonary capillary (slightly alkaline) and is greatly advantageous in the fetus, where the P_{O2} is low.

❖ Haemoglobin saturation at high PO_2s:

- Lungs at sea level: P_{O2} = 100mmHg & Hb 98% saturated.
- Lungs at high elevations: P_{O2} = 80mmHg & Hb 95%saturated. Even though the P_{O2}differs by 20mmHg, there is almost no difference in Hb saturation. When the P_{O2} in the lungs declines below typical sea level values, haemoglobin still has a high affinity for O_2 and remains almost fully saturated.

❖ Haemoglobin saturation at low PO_2s: At a P_{O2} of 40mmHg, haemoglobin has a lower affinity for O_2 and is 75% saturated.

Factors affecting the affinity haemoglobin for oxygen:

1. **pH.**
2. **Temperature.**
3. **2,3-diphosphoglycerate(2,3-DPG).**
    - Arise in temperature or a fall in pH shifts the curve to the right → a higher Po_2 is required for Hb to bind given amount ofO_2.
    - A fall in temperature or a rise in pH shift the curve to the left → a lower P_{O2} is required for Hb to bind given amount ofO_2.
    - P_{50}: the P_{O2} at which Hb is half saturated withO_2. The higher the P_{50} the lower the affinity of Hb for O_2.
    - Bohr Effect: is the decrease in O_2 affinity of Hb when pH of blood falls and is closely related to the fact that deoxygenated haemoglobin (deoxyhemoglobin) binds H^+ more actively than does oxyhemoglobin. The pH of blood falls as its CO_2 content increases → increase in Pco_2→ shifts to the right → P_{50} rises.
    - Red blood cells have no mitochondria; cannot perform aerobic respiration. 2,3-DPG is byproduct of glycolysis in RBCs. Its production is increased by low oxygen levels. Causes Hb to have

lower O_2 affinity, shifting curve to right. 2,3-DPG is very plentiful in red cells. It's formed from 3-phospoglyeraldehude. Its highly charged anions that bind to the β chains of deoxyhemoglobin. HbO_2 + 2,3-DPG ⇆ Hb-2,3-DPG + O_2. ↑2,3-DPG shift the reaction to the right → more O_2 liberated.

Factors affecting concentration of 2,3-DPG in RBC:

1. Acidosis (↓pH) → inhibits glycolysis in RBC → ↓2,3-DPG, Ascent to high altitude→ hypoxia →hyperventilation→ increase in pH →↑ 2,3-DPG →↑ P_{50} (increase of O2 available for tissues). 2,3-DPG levels drop to normal upon return to sea level.
2. Thyroid hormones, growth hormone, and androgens →↑ 2,3-DPG (↑P_{50}).
3. Exercise →↑2,3-DPG within 60 minutes . P_{50} is also increased during exercise (↑ in temperature, ↑ in PCO2, ↓pH in active tissue).
4. Blood banking ⇨↓ 2,3-DPG. In bank blood (stored) → (↓23-DPG) → decrease oxygen release to tissues by this blood (useless in hypoxic individual). Use of citrate –phosphate- dextrose solution (less ↓in 23-DPG in RBC) than use of acid-citrate-dextrose solution.

4. Fetal haemoglobin:

- Greater affinity of fetal Hb (Hb F) than adult Hb (Hb A) for O_2 facilitates the movement of O_2 from the mother to the fetus (poor binding of 2,3-DPG to γ chains that replace β in fetal Hb).
- Abnormal types of haemoglobins in adults (not bind 2,3-DPG) →low P_{50}(high O2 affinity) →tissue hypoxia→ polycythemis.
- Anemia and chronic hypoxia → ↑2,3-DPG → oxygen delivery to tissues.

5. Carbon Monoxide (CO)

- The affinity of Hb for CO is 230 times that for O_2.
  a. CO competitively blocks the combination of O_2 with Hb (CO + Hb ⇨ Hb-CO)
  b. CO also shifts the O_2-Hb dissociation curve to the left (1&2 ⇨ sever tissue hypoxia)
- The CO-Hb dissociation curve is similar to O_2-Hb dissociation curve except⇨ (P_{CO} = 0.4mmHg equal 1/230 alveolar P_{O2}) ⇨ 50% of Hb is Hb –CO
- P_{CO} = 0.7mmHg (0.1% in the air)⇨ lethal
- Treatment of CO poisoning:
  - Pure O_2 (high alveolar P_{O2} displace CO from Hb)
  - Few % of CO_2 (stimulate respiration ⇨ hyperventilation ⇨↓ alveolar CO ⇨↑ CO release from Hb
- A non- smoker living in a rural area (1% CO-Hb)

- Heavy smoker living in urban area (5-8% CO-Hb)

Myoglobin:

- Iron containing pigment in skeletal muscle. Has only 1 globin binds only 1 O2.
- Has higher affinity for O2 than Hb; Hb-O2 dissociation curve is shifted to extreme left → it takes O2 from Hb in the blood.
- It releases O_2 only at low Po_2 (Po_2=zero in exercising muscle). Serves in O2 storage, particularly in heart during systole

Blood substitutes:

The solubility of O2 in plasma is limited. Certain perfluoro compounds dissolve much more O_2 →used to totally replace blood for short period (emergency).

Carbon dioxide transport:

1. 7% dissolved in plasma.
2. 23% combines with Hb.

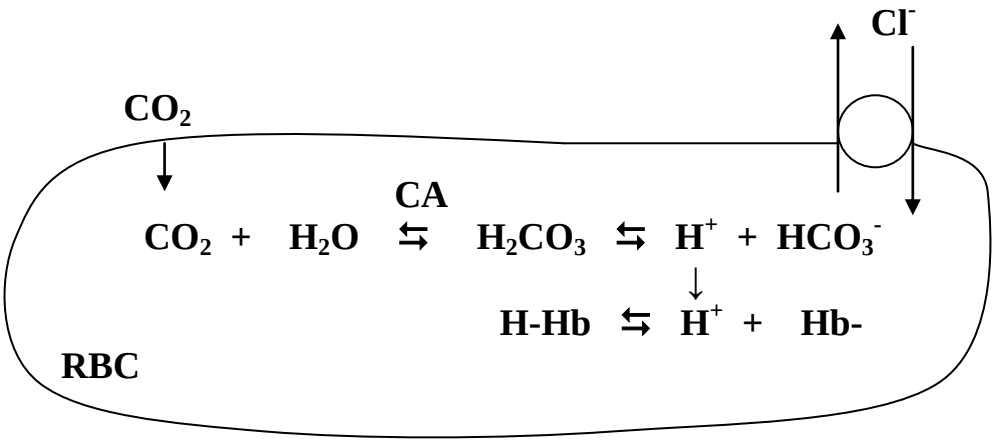
$$Hb + CO_2 \xrightarrow[\text{High } P_{O2}]{} HbCO_2 \text{ (carbaminohemoglobin)}$$

- CO2 binds to the globin portion of the Hb molecule to form carbaminohemoglobin.
- Carbaminohemoglobin forms in regions of high P_{CO2}.
- The formation of carbaminohemoglobin is reversible in the lungs (lower P_{CO2}) CO_2 dissociate from carbaminohemoglobin**.**

3. **70% is converted to bicarbonate ions.**

$$\mathbf{CO_2 + H_2O \overset{CA}{\leftrightarrows} H_2CO_3 \leftrightarrows H^+ + HCO_3^-}$$

- In region with high PCO_2, CO_2 binds with H_2O to form carbonic acid. This reaction is catalysed by the enzyme carbonic anhydrase.
- Carbonic acid dissociate into hydrogen ions and bicarbonate ions.
- Hydrogen ions binds to Hb (H-Hb).
- Chloride shift occurs when bicarbonate ions exchange for chloride ions to maintain electrical neutrality.
- In the plasma, bicarbonate ions act as a buffer to control pH.
- When Hb is saturated with O_2, its affinity for CO_2 decreases. O2 loading facilitates CO_2 unloading from Hb this interaction is called Haldane effect.



Transport of oxygen:

O_2 is transported from lungs to metabolically active tissues by the cardiovascular system. O_2 delivery to a particular tissue depends on the following factors:

- Amount of O_2 entering the lungs
- Adequacy of pulmonary gas exchange
- Btood flow to the tissue
- Capacity of the blood to carry O_2
- Capacity of the tissues to extract O_2 from blood

Blood flow to the tissue depends on:

- Degree of constriction of vascular bed in the tissue
- Cardiac output

Amount of O_2 in the blood depends on:

- Amount of dissolved O_2
- Amount of hemoglobin in blood
- Affinity of hemoglobin for O_2

Forms in which O_2 is Transported in Blood

1) Soluble form: 3% of O_2 is transported in the dissolved form, i.e., 100 ml of pure blood contains 0.3L of O_2 dissolved in plasma. Venous blood contains 0.12 ml of dissolved O_2 in 100 ml. *The volume of dissolved* O_2 *although very less, is of great functional importance for, it is the gas in solution alone that exerts the partial pressure.* It is the Po2 in blood that determines the quantity of O_2 that will combine with hemoglobin.
2) In combination with hemoglobin.

Reaction of Hemoglobin and O_2 or Oxygenation of Hemoglobin

Hemoglobin is a protein made up of 4 heme subunits. Iron is present in the ferrous form in the centre of each heme subunit.

Oxygenationof Hemoglobin

Oxygenation of hemoglobin is the loose and reversible combination of O_2 with ferrous ion in the hemoglobin molecule. *No oxidation reaction takes place,* only oxygenation of iron occurs which is only a physical combination. Even after combination of O_2 with iron, iron remains in the ferrous form, i.e., it is not oxidized to ferric form. That is why the combination of O_2 with hemoglobin is called oxygenation and not oxidation.

Advantages of Oxygenation

- Hemoglobin accepts O_2 readily when partial pressure of O_2 in blood is more to form the loose compound oxyhemoglobin.
- Hemoglobin releases O_2 readily whenever the partial pressure of O_2 in the blood is less, forming deoxygenated hemoglobin or reduced hemoglobin.

Heme-heme Interaction

One molecule of hemoglobin can combine with 4 molecules of O_2. Hemoglobin molecule is represented as Hb_4 and when it reacts with 4 molecules of O_2 it forms Hb_4O_8.

$Hb_4 + O_2 \leftrightarrow Hb_4O_2$

$Hb_4O_2 + O_2 \leftrightarrow Hb_4O_4$

$Hb_4O_4 + O_2 \leftrightarrow Hb_4O_6$

$Hb_4O_6 + O_2 \leftrightarrow Hb_4O_8$

Combination of the first heme in the hemoglobin molecule with one molecule of O_2 increases the affinity of second heme subunit in that hemoglobin molecule for the next molecule of O_2 and so on. This is known as heme-heme interaction. The reaction is rapid and is completed within 0.01 sec.

In the tissues these reactions are reversed releasing O_2. Deoxygenation of Hb_4O_8 is also very rapid.

There are two configuration states for hemoglobin: T or tense state and R or relaxed state. Change from tense state to relaxed state increases the O_2 affinity of hemoglobin 500 fold.

Change from tense to relaxed state is due to the release of bonds holding globin units and it occurs 10^8 times in the life of a red blood cell.

In pure blood, 19.5 mL of O_2 is bound to hemoglobin per 100 mL of blood. In impure blood. 15 mL of O_2 is bound to hemoglobin per 100 mL of blood.

Oxygen Carrying Capacity of Hemoglobin

It is the amount of O_2 contained in 100 mL of blood in combination with hemoglobin when all the hemoglobin is fully saturated with O_2. 97% of O_2 in blood combines with hemoglobin and the presence of hemoglobin increases the

O_2 carrying capacity of blood 70 fold. When fully saturated each gram of hemoglobin can combine with 1.34 mL of O_2. Hemoglobin concentration is 15 g/dL of blood. So, 100 mL of blood contain 15 x 1.34 = 20.1 mL of O_2 bound to hemoglobin when hemoglobin is 100% saturated with O_2

Oxygen Content

Amount of O_2normally present in 100 mL of arterial blood. It is the sum of the amount of O_2 in solution and the amount of O_2 in combination with hemoglobin.

Oxygen content = 0.3 + 19.5 = 19.8 mL/100 mL of blood.

Because of physiological shunt, the hemoglobin in the systemic arterial blood is only 97% saturated. At rest, hemoglobin in the venous blood is 75% saturated and the total O_2 content in venous blood is 15 mL/100 mL of blood. Thus, at rest tissues remove 4.8 mL of O_2 from each 100 mL of blood passing through them. Thus, 250 mL of O_2 is transported to tissues from blood in one minute at rest. This is O_2 consumption.

Percentage Saturation of Hemoglobin

% saturation= O_2 content / O_2 capacity ×100

Oxygen Dissociation Curve of Hemoglobin (ODC)

Principle

Blood samples are exposed to varying O_2 tensions in tonometers and O_2content is determined. Finally, Po2 is so adjusted that hemoglobin is fully saturated with O_2 and O_2 capacity is determined. For each Po2, the % saturation is found out.

Procedure

10 tonometers are filled, each with a known quantity of blood having known hemoglobin concentration. The blood in each tonometer is exposed to O_2 at different partial pressures at a constant temperature. Then the blood in tonometer is analyzed to measure the % saturation of hemoglobin with O_2. The partial pressure of O_2 and % saturation are plotted to get the ODC for hemoglobin. graph is plotted with Po2 on the X-axis and % saturation on the Y-axis.

The CDC of hemoglobin is sigmoid shaped or S shaped because when the partial pressure of O_2 is less, hemoglobin releases O_2. This is due to heme-heme interaction or T-R interconversion. It denotes easy binding of hemoglobin with O_2 when Po2 is high, which occurs at lung level in the body. It also denotes increased dissociation of O_2 from oxyhemoglobin where Po2 is low, i.e., at tissue level in the body.

The graph has three parts or phases

- Flat top

- Steep fall
- Flat bottom

Flat Top

When PO_2 falls from 100 mmHg to 60mmHg, there is not much change in the % saturation of hemoglobin . even at PO_2 of 60mmHg, hemoglobin is 90% saturated and this is sufficient for normal activities. This is a protective measure for a person going to high altitude. Up to 60mmHg, he does not develop hypoxic symptoms.

Steep fall(dissociation phase)

Below PO_2 of 60 mm Hg, there is a marked reduction in % and the curve becomes steep. In this phase there is wide variation in % saturation with minute change in PO_2 and O_2 is released readily from hemoglobin. This is the tissue phase. In the tissues, Po2 is only 40 mm Hg and so oxyhemoglubin releases O2 rapidly and tissues can extract arge quantities of O_2.

Flat bottom

at very low levels of PO_2, dissociation of oxyhemoglobin becomes difficult. For a person with chronic lung disease this is a safety measure. *There will be symptoms of hypoxia at lower Po2 and adequate measures can be taken.*

Factors Affecting ODC

Shift to the Right of ODC

This indicates easy dissociation of O2 from hemoglobin. Here a higher PO2 is required for hemoglobin to bind a given amount of O2, i.e., the affinity of O2 for hemoglobin is decreased.

P50: This is an index used to indicate the affinity of hemoglubin for O_2. P50 is the PO_2 at which hemoglobin is half saturated with O_2.

Normal P50=25mmHg

Higher the P50 lower the affinity of hemoglobin for O_2, i.e., dissociation is favored. In shift to right, P50 is increased. Here, more PO_2 is required to half saturate hemoglobin with O_2.

Factors Causing Shift to Right

- Increase in Pco2
- Increase in H^+ concentration (decrease in pH)
- Increase in temperature
- Increase in 2,3-DPG (diphosphoglycerate)

All the above factors are increased when tissue metabolism is increased as in exercise. 2,3-DPG is seen in plenty in the RBC. It is a product of glycolysis via Embden-Meyerhof pathway. It is a highly charged anion that binds to the a chain of deoxyhemoglobin. An increase in 2,3-DPG causes liberation of more O2 and ODC is shifted to the right.

HbO2 + 2,3-DPG ↔ Hb-2,3-DPG + O2

2,3-DPG is increased in:

1) Exercise
2) Hypoxic conditions as in chronic lung disease, anemia, at high altitude etc. Hypoxic increases glycolysis in RBC.
3) Hormones like thyroid hormones, androgen, growth hormone etc.
4) Alkalosis stimulates glycolysis in RBC, e.g., hyperventilation

Bohr Effect

The decrease in the O_2 affinity of hemoglobin when the pH of blood falls due to increase in PCO_2 is called Bohr effect. There is unloading of 02 from hemoglobin. The O_2 dissociation curve shifts to the right and P50 rises. This is because deoxyhemoglobin binds H+ more actively, than oxyhemoglobin. Greater the CO2 tension in the tissue greater will be the O2 release.

$HbO_2 + H^+ \leftrightarrow HbH^+ + O_2$

All factors that shift ODC to the right influence Bohr effect.

Shift to Left of ODC

Affinity of hemoglobin for O2 is more and P50 is decreased in shift to left. A lower Po2 is required for hemoglobin to bind a given amount of O2.

Factors Causing Shift to Left

- Decrease in PCO_2
- Decrease in H^+ concentration (alkalosis)
- Decrease in temperature
- Decrease in 2,3-DPG
- Fetal hemoglobin

2,3-DPG is decreased in acidosis and in stored blood. In acidosis there is inhibition of red cell glycolysis and 2,3-DPG falls.

Ability of blood stored with acid citrate dextrose (ACD) as anticoagulant, to release O2 to the tissues is less. This decrease is less if blood is stored in citrate-phosphate-dextrose solution rather than ACD. This is a form of preservation injury due to ACD. The 2,3-DPG level falls and ODC shifts to left. *This is the reason why stored blood is not safe to be transfused to a hypoxic patient.*

In fetal hemoglobin (HbF) instead of α chains, there are γ chains. 2,3 DPG cannot combine with γ chains. So, there is a shift to left of ODC, i.e., affinity of hemoglobin for O2 is more and the P50 is reduced.

Significance

- Helps in the movement of O_2 from maternal blood to fetal blood because affinity of fetal hemoglobin for O_2 is more.

- Release of O_2 to the fetal tissues is less since HbF has more affinity for O_2. So, tissues suffer from hypoxia, which in turn stimulates erythropoietin secretion. *This is the reason for the high RBC count in fetus.*

Coefficient of Utilization

Coefficient of utilization= O_2 taken up by the tissues /O_2 content of arterial blood × 100

Normal value = 26%

In severe exercise, the coefficient of utilization in skeletal muscle will be as high as 90%.

Myoglobin

Myoglobin is an iron-containing pigment in muscle, especially skeletal muscle. Only one heme unit is present in myoglobin and so one molecule of myoglobin can combine with only one molecule of O_2. Myoglobin does not show Bohr effect. Myoglobin has a lower P50 than adult hemoglobin. *The ODC for myoglobin is a rectangular hyperbola.* The curve is to the left of hemoglobin curve. So it takes up O_2 from hemoglobin and releases O_2 only at very low PO_2 values, i.e., below 5 mm Hg.

In exercise when there is sustained muscle contraction due to compression of blood vessels, blood flow is cut off and Po2 in the muscle becomes zero or very low and the muscle utilizes O_2 in myoglobin. Thus, myoglobin acts as a temporary storehouse of O_2 in the muscle. A man of average size can store about 1.5 litres of 0, in his myoglobin at rest.

	Hemoglobin	**Myoglobin**
1	**Present in red blood cells**	**Present in muscles especially skeletal muscle**
2	**Contains 4 heme subunits**	**Contains only one heme subunit**
3	**3. Combines with 4 molecules of O2**	**Combines with only one molecule of 02**
4	**Shows Bohr effect**	**Does not show Bohr**
5	**P_{50}=25 mm Hg**	**P50=5 mm Hg**
6	**ODC: sigmoid shaped**	**ODC: rectangular hyperbola**

CARBON DIOXIDE TRANSPORT

Carbon dioxide entering the blood undergoes a series of reversible chemical reactions and forms different compounds. These reactions of CO_2 increase the blood CO_2 content 17 fold. In the blood, CO_2 is transported in 3 forms:

1. Dissolve form = 10%

2. As carbamino compounds = 205
3. In the form of bicarbonate =70%

Dissolved Form

10% of CO_2 in the blood is in the dissolved form., i.e., 2.5mL of CO_2 is dissolved in 100 mL of arterial blood . solubility of CO_2 in blood is 20 times that of O2 and so there is more CO_2 than O_2 in simple solution.

As Carbamino Compounds

20% of CO2 in blood is transported in combination with the amino group of plasma proteins and hemoglobin. CO_2 combines With hemoglobin to form carbaminobemoglobin and with plasma proteins to form carbaminoprotein.

As HCO_3

Changes at the Tissue Level

Since the Pco2 in the tissue is high, CO_2 diffuses from tissues into the plasma. From there it enters the RBC which contains plenty of carbonic anhydrase (CA). In blood, 70% of CO_2 is transported as HCO_3 . in RBC, the following reaction takes place:

$$CO_2 + H_2O \xrightarrow{CA} H2CO3 \leftrightarrow H^+ + HCO_3$$

70% of HCO3 formed in RBC enters the plasma and combines with Na^+ to form $NaHCO_3$. Rest, inside the RBC with K^+ to form KHCO3. H^+ is buffered by hemoglobin, thus maintaining acid-base balance. *Reduced hemoglobin has more affinity for C2 and is a good proton acceptor i.e., it is a strong buffer.* This occurs at tissue level. When HCO3 diffuses from RBC to plasma, in order to maintain electrical neutrality, Cl- ions enter RBC. This is chloride shift or Hamberger phenomenon. Osmotically active substances in the RBC increase and so water enters the RBC. This is water shift. *This is the reason for the larger size of RBCs in venous blood than in arterial blood and also for the increased fragility of red blood cells in venous blood.*

Reasons for the 3% Increase in the Hematocrit Value in Venous Blood

I . Water shift and chloride shift (explain)
2. Small amount of fluid in the arterial blood returns to circulation through the lymphatics rather than through the veins. So, the amount of plasma in venous blood will be less than that in arterial blood.

Changes Occurring at Lung Level

In the lungs, P50 is high and hemoglobin combines with O2 and releases H^+.

$$HHb + O_2 \rightarrow HbO_2 + H^+$$

Oxyhemoglobin is a good proton donor and a poor buffer. H+ combines with HCO_3 to form H2CO3, which dissociates to form H_2O and CO_2. CO_2 diffuses

into the alveoli. HCO3 from plasma enter RBC in exchange for Cl^-.Water also diffuses out of RBC along with Cl^-. This is called reverse Cl^- and water shift.

Carbondioxide Dissociation Curve (CDC)

A graph is plotted with Pco2 on the X-axis and CO2 content on the Y-axis for venous and arterial blood. CO2 dissociation curve will be at a higher level for venous blood than for arterial blood. Point A in the graph denotes that in the arterial blood at a Pco2 of 40 mm Hg, CO2 content is 48 mL/100 mL of blood. Point B denotes that in the venous blood at a Pco2 of 46 mm Hg, CO2 content is 52 mL/ 100 mL of blood. The line joining A and B is called *physiological dissociation curve for CO_2*

Haldane effect or role of O_2- Hb reaction in CO_2 transport:
Deoxygenated hemoglobin binds more CO2 than oxyhemoglobin and forms carbamino hemoglobin and CDC shifts to the left. Whenever hemoglobin is oxygenated, it displaces CO_2 from its combination and CDC shifts to right. This was first detected by Haldane and is known as Haldane effect or CDH effect (Christiansen, Douglas, Haldane efeect)
Causes *of Haldane Effect*

1. Deoxyhemoglobin has more affinity for CO_2 and so there is increased pickup of CO_2 from tissues.
2. Oxyhemoglobin has less affinity for CO_2 and so CO_2 is released from blood to alveoli in the lungs.
3. Reduced hemoglobin is a weaker acid and a strong buffer and binds more H+ at tissue level.
4. Oxyhemoglobin is a stronger acid and releases H+ at lung level. H+ binds with HCO_3 to form H_2CO_3, which in turn splits to form CO_2 ans H_2O, and CO_2 is released from blood to alveoli.

Importance of CDH effect:

- Haldane effect doubles the amount of CO_2 released from blood into the lungs and doubles the pickup of CO_2 from the tissues. If Haldane effect was not there, at the lung level the CO_2 content of blood would have fallen only to 50 volume%. But due to Haldane effect CO_2 content falls to 48 volume%. Thus, 4 ml of CO_2 is removed by lungs when 100 ml of blood passes through the lungs.
- Haldane effect increases the uptake of O_2 by blood in lungs.

<u>Changes Occurring in Exercise</u>

In exercise there is increased metabolism leading to in increased CO_2 production and increased O_2 uptake by the tissues.

1. Pressure gradient for CO_2 at tissue level increases and more CO_2 diffuses into blood.
2. Capillary dilatation in exercise due to metabolites increases capillary

surface area which increases diffusion of gases.

3. O2 uptake in tissues in increased in exercise leading to increase in the oncentration of reduced hemoglobin leading to increased production of carbaminohemoglobin and HHb.
4. Bohr effect — due to decrease in pH and increase in PCO_2, ODC shift to right. Greater the CO_2 tension in the tissue, greater will be the amount of O2 release from hemoglobin. In other words, increased PCO_2 lowers the affinity of hemoglobin for O_2 and more O_2 will be released from oxyhemoglobin.

Regulation of Respiration

The main function of respiratory system is to maintain PCO_2, PO_2, and pH of arterial blood constant by adjusting ventilation. Spontaneous respiration is produced by rhythmic discharges from the brain to the motor neurons that innervate the respiratory muscles. This discharge is regulated by arterial P_{CO2}, P_{O2}, and H^+ concentration. Respiration is regulated by two mechanisms (neural control and chemical control).

Neural control of respiration: (Voluntary, automatic, reflex control)

a) Voluntary Control

- Respiration is a spontaneous (reflex) process. But to some extent it can be controlled voluntarily because most of the muscles concerned with respiration are voluntary muscles. The centre for voluntary control is the motor cortex which sends impulses through the corticospinal tract to the respiratory motor neurons.
- Voluntary hyperventilation and voluntary apnea are possible. The point at which breathing can no longer be voluntarily inhibited is called breaking point. Normally it is 40 seconds. This is because during apnea there is increase in PCO_2, PO_2decrease in PO_2 and increase in H^+ concentration.
- In conditions like bulbar poliomyelitis, tumors of brain stem etc., automatic control will be lost and voluntary control alone will be present. This is because impulses arising from brainstem control automatic respiration?. This condition is known as Ondine's curse.

b) Automatic Control

- The automatic system for control of respiration is located in the pons and medulla. The respiratory centers are located bilaterally. The nerve fibres mediating inspiration converge on phrenic motor neurons (C3, 4, 5) and external intercostal neurons in spinal cord. The fibers concerned with expiration converge on the motor neurons in the spinal cord controlling the muscles of expiration, mainly internal intercostal muscles.
- The motor neurons to expiratory muscles are inhibited when those supplying the aspiratory muscles are active and vice versa through

reciprocal innervations. Exception to reciprocal innervation is a small amount of activity in phrenic axons in the early part of expiration. This is to put a brake to the lung's elastic recoil and make respiration smooth and not spasmodic.

❖ **Medullary Centers**

- **Pre-Botzinger complex:** Rhythmic respiration is initiated by a small group of maker cells in the Pre-Botzinger complex on both sides of medulla, between nucleus ambiguus and lateral reticular nucleus. These neurons can discharge rhythmically and are responsible for the rhythmicity of respiration. In addition, medulla also contains dorsal respiratory group (DRG) and ventral respiratory group (VRG) of neutons.
- **DRG** is located in and near the nucleus of tractus solitaries (NTS). DRG is made up of I (inspiratory) neurons which are controlled by the pacemaker cells in pre-Botzinger complex. They are active during inspiration. They also receive impulses from lungs, chemoreceptors and baroreceptors through vagus.
- **VRG** is located in the ventrolateral part of medulla. It extends through nucleus ambiguus and retroambiguus. VRG is made up of 'E' (expiratory) neurons mainly, but some (I) Neurons are also present in its mid-portion. E neurons inhibits I neurons in expiration. They remain almost totally inactive during quite inspiration, become active when there is increase in pulmonary ventilation, especially important in providing powerful expiratory force during expiration.

  ***Inspiratory Ramp Signal (IRS)*:** pattern of action potentials produced by the respiratory centre is called inspiratory ramp signal. Initially there is a latent period, then the intensity of action potentials increases and then decreases followed by a latent period. The cycle is repeated and normally the duration of one cycle is 4-5 seconds. The impulses pass to the inspiratory muscles and produce inspiration

❖ **Pontine centres:** Although the rhythmic discharge of medullary respiratory neurons is spontaneous, it is modified by neurons in the pons and afferents coming from receptors in airways and lungs through vagus.

- **Pneumotaxic center:** In the upper part of pons there is a pair of respiratory centers called pneumotaxic centre. Pneumotaxic centre has inhibitory effect on I neurons. When this area is stimulated, I neurons are inhibited and duration of inspiratory ramp signal is reduced. Rate of respiration will be increased and filling volume will be decreased, i.e., respiration becomes shallow and rapid. When pneumotaxic centre is damaged, respiration becomes slower and tidal volume will be increased, and if vagi are also simultaneously cut, it leads to apneusis, i.e., prolonged inspiratory spasms.

- **Apneustic center:** located in lower pons. It was thought to have an excitatory effect on I neurons, and stimulation of apneustic centre increased the duration of IRS producing sustained contraction of inspiratory muscles with expiratory gasps in between. This is called apneusis. The existence of this centre is yet to be proved.

❖ **Vagal Influences on Respiration:** Stretch of the lungs during inspiration stimulates stretch receptors in lung which generate impulses in afferent pulmonary vagal fibers. These impulses inhibit 'I' neurons and produce expiration. *The switch-off mechanism coming from pneumotaxic centre and vagus are the key factors which determine the rate and rhythm of respiration.*

❖ In experimental animals, brainstem is cut at different levels and respiratory movements are recorded

- Section above pons: Normal breathing is recorded since respiratory centers are intact.
- Just below pneumotaxic centre or midpontine section
  - Vagus intact →Rate of respiration decreases and depth increases.
  - After vagotomy → Apneusis
- Section at the junction of pons and medulla: Irregular breathing due to absence of impulses coming from pons.
- **Section below medulla – No respiration**

3. Reflex Control of Respiration: Receptors are classified into two:

❖ Receptors inside respiratory system

❖ Receptors outside respiratory system

Receptors inside Respiratory System

1. Stretch receptors
2. Pulmonary irritant receptors

Stretch Receptors

Hering-Breuer Reflexes

Hering-Breuer Inflation Reflex

When there is increase in the tidal volume to more than one litre, the stretch receptors of lung are stimulated to a greater extent and there is increase in the rate of afferent impulses passing through the vagus to the inspiratory centre. Vagus is inhibitory to the inspiratory centre and this leads to inhibition of inspiratory muscles and there will be increase in the expiration time. This brings back the lung volume back to normal. This reflex is called *Hering-Breuer Inflation Reflex*

This reflex operates only when the tidal volume exceeds1- 1.5 litres as in exercise and this reflex prevents overinflation of lung.

Stimulus – distention of lung which stimulates stretch receptors of lung
Receptors – stretch receptors in the airway smooth muscle i.e., trachea, bronchi and bronchioles
Afferent limb – vagus
Centre – inspiratory centre in medulla
Efferent – nerves supplying respiratory muscles especially muscles of expiration
Effect – inhibition of inspiratory centre and switching of IRS leading to expiration. Lung volume is thus brought back to normal.

Hering-Breuer Deflation Reflex

This reflex operates when there is excessive deflation of lungs. Extreme deflation of the lung occurs in collapse lungs, pneumothorax, sucking of air from trachea etc. here, there is stimulation of inspiration to bring back the lung volume to normal. This is Hering-Breuer deflation reflex.
Two theories are there to explain this reflex:

1. In severe deflation of lung, there is no stimulation of stretch receptors of lung and so, no inhibitor impulses pass through vagus from lung to the inspiratory centre. The IRS will be prolonged leading to increase in filling volume and lung size is brought back to normal.
2. J- reflex or pulmonary chemoreflex
   According to this view, stretch receptors are not involved; instead,J receptors or juxtacapillary receptors are involved. J receptors are nonmyelinated nerve endings (Cfibers) in alveoli which are in close proximity to pulmonary capillaries (hence the name juxta pulmonary capillary receptors). These receptors are stimulated in pulmonary embolism, pulmonary congestion, pulmonary edema etc. they donot function during normal quite respiration.
   The effects of stimulation of J receptors are:
   - Hypotension
   - Bradycardia
   - Tachypnea and dyspnea due to bronchospasm
   - Weakness of skeletal muscle

this is pulmonary chemoreflex or J-reflex. This reflex is similar to coronary chemoreflex or Bezold-Jarisch reflex. J receptors are responsible for hyperventilation in patients affected by pulmonary congestion and left heart failure**.**

Importance of Hering-Breuer Reflexes

1. This reflex prevents excessive inflation of lungs. It decides the filling volume of lungs especially in conditions of hyperinflation as in exercise.

2. It functions as an important feedback mechanism and may contribute to the rhythmicity of respiration in newborn babies.

Pulmonary irritant receptors

They are found in between airway epithelial cells. They are stimulated by smoke, dust, cold air, irritant gases like SO2 and chemicals like histamine. Stimulation of these receptors produces:

- Bronchoconstriction
- Hyperventilation
- Cough, sneezing etc**.**

Significance of Pulmonary Irritant Receptors

These receptors help to remove noxious agents from tracheobronchial tree. Bronchospasm is also beneficial as it prevents further entry of noxious agents into the alveoli.

Cough Reflex

This is a protective reflex. Stimulation of irritant receptors of larynx, trachea and bigger bronchi produces cough. Coughing begins with a deep inspiration followed by forced expiration against a closed glottis. The glottis is suddenly opened and air is expelled at very high velocity, i.e., there is explosive outflow of air. There is a great rise in intrapleural pressure during coughing. Excessive cough may lead to alveolar rupture, visual blackout, fainting attack, herniation etc.

Sneezing Reflex

Stimulation of irritant receptors of nasal cavity and upper airway produces sneezing. Mechanism is similar to coughing, but with a continuously open glottis.

- **Receptors outside Respiratory System**
  - ✓ **Those which stimulate respiration**
    - **Proprioceptors:** These are receptors in muscles, tendons, joints etc. Stimulation of these receptors reflexly stimulates I neurons. This helps to increase ventilation at the start of exercise even before changes in P_{CO2}, P_{O2}, and H^+ concentration occur.
    - **Nociceptors:** These are pain receptors which when stimulated stimulate the respiratory centre.
    - **Thermoreceptors:** present in the hypothalamus are stimulated when there is increase in body temperature as in fever, exercise etc. They send impulses to respiratory centre and produce increase in the rate of respiration.
    - **Emotional Stimuli:** These produce impulses from hypothalamus, limbic system etc., which stimulate the

respiratory centre. Thus emotional stimuli alter respiration as in crying, laughing, sighing etc.

- **Others:** Stretching the anal sphincter increases respiratory rate and is employed to stimulate respiration in a person who has stopped breathing.

✓ **Those which inhibit respiration**

- **Baroreceptors:** Increase in blood pressure stimulates baroreceptors leading to inhibition of respiration. Injection of adrenaline produce an increase in blood pressure, which in turn stimulates baroreceptors producing apnea called adrenaline apnea.
- **Visceroceptors**: In visceral reflexes like vomiting, swallowing etc., there is reflex inhibition of respiration. For example, deglutition apnea occurs during swallowing to prevent entry of food into respiratory passages.

Chemical control of respiration:

- Introduction: Changes in blood chemistry (P_{CO2}, P_{O2}, and pH) acts on respiratory centre and ventilation is adjusted to bring the blood chemistry back to normal. Changes in P_{CO2}, P_{O2}, and pH of blood act **on the** respiratory centre through a set of receptors called chemoreceptors. These are receptors which respond to changes in the chemical composition of blood or any fluid around it.
- **Chemoreceptors are classified into two: central chemoreceptors, and peripheral chemoreceptors**

Central chemoreceptors:

- Central chemoreceptors are a set of neurons located below the ventral surface of medulla on both sides near the exit of IX and X cranial nerves.
- Neurons in this chemosensitive area can sense changes in H^+ concentration especially in the brain interstitial fluid. Central chemoreceptors are surrounded by brain extracellular fluid.
- Increase in CO_2 of blood stimulates central chemoreceptors while increase in H^+ concentrationblood does not stimulate central chemoreceptors.
    1. The blood-brain barrier and blood-CSF barrier can be crossed by CO_2 very easily since it is lipid soluble but not so by H^+.
    2. Increase in blood P_{CO2} produces cerebral vasodilatation which enhances diffusion of CO_2 into CSF and brain interstitial fluid.
- Hypercapnia ($\uparrow P_{CO2}$) CO_2 enters the brain tissue and CSF) $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$ ($\uparrow CO_2$ in brain interstitial fluid$\rightarrow\uparrow H^+$). *Increase in H^+ in the brain interstitial fluid is the only direct stimulus of central chemoreceptors. CO_2 has only indirect action.*

Stimuli from central chemoreceptors go to inspiratory centre and stimulate respiration. Thus, CO_2 level in blood regulates ventilation by its effect on the pH of CSF and brain interstitial fluid. The resulting hyperventilation reduces blood P_{CO2} to normal.

- Central chemoreceptors are inhibited by anesthesia, cyanide, during deep sleep etc.
- Increase in H^+ has only acute action on central chemoreceptors, i.e., chemoreceptors respond only to abrupt changes in blood P_{CO2}. So, change in blood P_{CO2} has only a potent acute effect on controlling ventilation and only a weak chronic effect due to adaptation. *If the Pco_2 of brain interstitial 'fluid and CSF is persistently high, the action of it central chemoreceptors stops. Reason:* Normally, CSF has fewer buffers than blood and so increase in H^+ in CSF has more action on central chemoreceptors. But if hypercapnia is prolonged, HCO_3^- diffuses into CSF and neutralizes the H^+, and pH in the CSF will no longer be acidic but becomes alkaline.

Peripheral chemoreceptors (carotid and aortic bodies):

Peripheral chemoreceptors are situated in the carotid and aortic body. These are neurovascular structures. Another name for aortic and carotid body is glomus.

- Location: There is a carotid body near the carotid bifurcation on each side, and there are 2 or more aortic bodies near the arch of aorta. Carotid body is important in humans.
- *Innervation of PCR:* Carotid body is supplied by sinus nerve, a branch of IX (glossopharyngeal) cranial nerve. It is also called Hering's nerve. Sensory impulses from carotid body are carried through this nerve. Aortic body is supplied by aortic nerve, a branch of vagus. Sinus nerve and aortic nerve are together referred to as sinoaortic nerve.
- *Structure of Carotid Body:* Carotid body is composed of two types of cells surrounded by fenestrated sinusoidal capillaries:
  1) Type I cell (glomus cells) : are closely associated with cuplike ending of the afferent nerves; they have dense core granules containing catecholamines that are released upon exposure to hypoxia and cyanide. Hypoxia → transmitter release (dopamine) → D_2 receptors in nerve endings→ medulla
  2) Type II cells or Glial cells or Supporting cells or Sustentacular cells: These cells surround 4-6 glomus cells. Function is protection and support of glomus cells.

C Heyman was awarded Nobel Prize in 1938 for his Study on the role of carotid bodies in pulmonary ventilation.

Aortic bodies have a similar structure and are not much studied because of their anatomical location.

- *Mechanism of stimulation:* Type I glomus cells have O_2 sensitive K^+ channels. Hypoxia → decrease K^+ channels conductance →decrease K^+ efflux →depolarization of the cell → Ca^{++} influx → action potential and dopamine release.
  - Smooth muscles of pulmonary arteries contain similar O_2 sensitive K^+ channels, which mediate vasoconstriction caused by hypoxia.
  - Systemic arteries ATP-dependent K^+ channels (hypoxia→ ATP-dependent K^+ channels → K^+ efflux → vasodilatation).
- *Factors that stimulates PCR*:
  - Receptors not stimulated by *anaemia* and CO poisoning (although the combined O_2 is decreased but the dissolved O_2 is normal). It has a very high blood flow, i.e., 20 mL/g/min (0.04 mL/min) → O_2 needed of the cells met by dissolved O_2only.
  - Receptors stimulated by low P_{O2} and *vascular stasis*, *cyanide* (prevent O_2 utilization at the tissue level), sufficient doses of *nicotine* and *lobeline,* and by K^+ *infusion* (↑K^+ in exercise may contribute to exercise induced hyperpnea).

Ventilatory responses to CO_2

Ventilatory responses to increased CO_2:

- The arterial P_{CO2} is normally maintained at 40 mmHg.
- Increased P_{CO2} (↑metabolism) → (↑ventilation) → (↑pulmonary CO_2 excretion) → P_{CO2} fall to normal.
- Balance between CO_2 production and excretion.
- When a gas mixture containing CO_2 is inhaled → ↑alveolar P_{CO2}→ ↑arterial P_{CO2}→ ↑ventilation→↓ alveolar P_{CO2} (Linear relationship between respiratory minute volume and alveolar P_{CO2}).
- When the P_{CO2} of the inspired gas is close to the alveolar P_{CO2}, elimination of CO_2 become difficult.
- When CO2 content of the inspired gas is > 7%→ ↑alveolar and arterial P_{CO2} in spite of hyperventilation→ hypercapnia (accumulation of CO_2 in the body) →CNS depression including respiratory center, headache, confusion and eventually coma (CO_2 narcosis).

Ventilatory responses to Decreased PCO_2

When alveolar P_{CO2} is decreased to 30 mm Hg or if a person hyperventilates voluntarily, CO_2 is washed off leading to a reduction in arterial P_{CO2}. This causes depression of respiratory centre leading to apnea. When there is arrest of respiration, CO_2 accumulates leading to increase in P_{CO2}. During apnea there will be a decrease in alveolar P_{O2}. Both these factors stimulate respiration.

Hyperventilation → ↓Paco2 →Depression of respiratory centre → apnea → ↑PCO2 and ↓PO2→ Stimulation of respiratory center

Ventilatory response to oxygen lack:

- When the O_2 content of the inspired gas is decreased →↑respiratory minute volume (the stimulation is slight when the P_{O2} of the inspired gas is > 60mmHg and marked only at lower P_{O2}values).
- Any decline in P_{O2} below 100mmHg→ ↑discharge in nerves from carotid and aortic chemoreceptors → no increase in ventilation unless P_{O2} mmHg.
    1. Hb is weaker acid than Hb_{O2}. ↓ P_{O2} → Hb less saturated with O_2 →slight ↓in H^+→ inhibits respiration.
    2. . ↓ P_{O2} → ↑ventilation→ ↓ P_{CO2}→ inhibits respiration.
- The stimulatory effects of hypoxia on ventilation are not clearly manifested until they become strong enough to override the counterbalancing inhibitory effects of a decline in arterial H^+ concentration and P_{CO2}.

Effect of H^+ Concentration on Respiration

Acidosis

- Acidosis is defined as a condition in which there is addition of acid or removal of alkali from the system. Acidosis may be metabolic acidosis or respiratory acidosis. Metabolic acidosis is due to addition of acid or removal of bases. Respiratory acidosis is due to retention of CO_2 due to hypoventilation.
- Acidosis produces hyperventilation by stimulation of peripheral chemoreceptors. Hyperventilation decreases alveolar Pco_2 and thus produces a compensatory fall in blood H^+ concentration.

Metabolic Acidosis

Causes of Metabolic Acidosis

1. Diabetes mellitus: There is impaired fat and carbohydrate metabolism leading to increased production of ketoacids like acetoacetic acid.
2. Renal failure: There is inadequate renal excretion of acid metabolites leading to accumulation of these metabolites.
3. Severe exercise leads to lactic acidosis.
4. Starvation leads to ketoacidosis.
5. Loss of bases from ECF as in diarrhea leads to acidosis.
    - When acids stronger than HHb and other buffer acids are added to blood, metabolic acidosis is produced. The H^+ added is buffered and the reduced hemoglobin, protein (A-) and HCO_3^- level in plasma drop. The H_2CO_3 formed is converted to H_2O and CO_2, and CO_2 is rapidly excreted through lungs. The rise in plasma H^+ stimulates respiration and Pco_2 is reduced. This is the respiratory compensation in acidosis.

- The renal compensatory mechanisms bring about the excretion of the extra H^+ and return the buffer systems to normal. Urine buffer systems are HCO_3^- , HPO_4^{2-} and NH_3 buffer systems.

Respiratory Acidosis

- Hypoventilation that is not secondary to a fall in plasma H^+ concentration causes respiratory acidosis.
- ↓Pulmonary ventilation →↑P_{CO2}→ ↑H_2CO_3→↑ H^+
- *Causes of Respiratory Acidosis*
  - Respiratory centre depression
  - Obstruction to respiratory passage
  - Fibrosis of lung
  - Emphysema

Alkalosis

Alkalosis is defined as the condition in which bases are added or acids are removed excessively from the system. Alkalosis may be metabolic or respiratory in origin. When the arterial plasma pH is above 7.4, the resulting condition is alkalosis. Alkalosis may be produced by a decreased arterial P_{CO2} or an increase in plasma HCO_3^-.

Metabolic Alkalosis

- The primary abnormality is an increase in plasma HCO_3^- leading to an increase in pH.
- *Causes*:
  - ✓ Vomiting, where there is increased loss of gastric acid.
  - ✓ Loop diuretics and thiazides, which cause excretion of large volumes of acidic urine.
  - ✓ Cushing's syndrome
  - ✓ Primary hyperaldosteronism
  - ✓ Hypokalemia: in hypokalemia, H^+ shifts into the intracellular compartment. In addition, the renal loss of H+ is also increased in hypokalemia and this lead to alkalosis.

- *Respiratory Compensation: i*n alkalosis there is depression of respiratory centre which increases the P_{CO2} of blood, thus increasing the H^+ ion concentration and pH is brought back to normal. ↓H^+ →Depression of respiratory centre →Hypoventilation → ↑P_{CO2}→ ↑ H^+. But there is a limiting factor to this compensation. When there is hypoventilation there will be a reduction in P_{O2} which stimulates peripheral chemoreceptors leading to increase in ventilation (Hypoventilation→ ↓P_{O2}→Stimulation of PCR→↑ Ventilation)

Respiratory Alkalosis

- Hyperventilation that is not secondary to a rise in arterial H^+ concentration produces a drop in arterial P_{CO2} in turn lowers H^+ below normal leading to respiratory alkalosis.

- ↑Pulmonary ventilation —Elimination of more CO_2 from the body→↓aP_{CO2} →↓H_2CO_3→↓H^+ (Alkalosis)
- Causes of respiratory alkalosis:
  - ✓ Voluntary hyperventilation
  - ✓ High altitude.

Summary of the causes of acidosis and alkalosis

Condition	**Abnormality**
Respiratory acidosis	**Increase in aP_{CO2}**
Respiratory alkalosis	**Decrease in aP_{CO2}**
Metabolic acidosis	**Decrease in HCO_3^-**
Metabolic alkalosis	**Increase in HCO_3^-**

- 50% increase in Pa_{CO2} produces 10- fold increase in ventilation.
- Decrease of pH from 7.4 to 7 causes 3-4 fold increase in ventilation
- Decrease of Pa_{O2} from 100 to 40mmHg increases ventilation 1.5 fold.

Interaction of Chemical Factors in Regulation of respiration

***Interaction of* CO_2 *and* O_2**

a) When alveolar Pco_2 is kept constant

- If P_{CO2} in alveolar air is adjusted to *4-5* mm Hg above normal and if P_{O2} is decreased from 100 to 60 mm Hg, there is marked increase in ventilation.
- If alveolar P_{CO2} is kept 5mmHg lower than normal and if P_{O2} is decreased from 100 to 60 mm Hg, there is not much increase in ventilation. Below 60 mm Hg, there is marked increase in ventilation.

  This experiment shows that when alveolar P_{CO2} is increased, the person will be more sensitive to hypoxia.

b) When alveolar P_{O2} is kept constant

The ventilatory response is recorded on a graph by increasing alveolar P_{CO2} with alveolar P_{O2} kept constant. Three curves are plotted with alveolar P_{O2}100 mmHg, 55 mm Hg and 40 mm Hg. It is seen that the slope of the curve is increased when alveolar P_{O2} is less. This proves that hypoxia makes the individual more sensitive to increase in P_{CO2}.

Effect of H+ on CO_2 Response

The above experiment is repeated and two families of curves are plotted with pH 7.4 and 7.3. When pH is reduced, CO_2 response curve shifts to left, i.e., the same amount of respiratory stimulation is produced by lower arterial P_{CO2} levels when pH is reduced.

ABNORMALITIEIREGULATION OF RESPIRATION:

1. Respiratory centre depression

Causes

- Old age, due to thrombosis, hemorrhage etc., in the brain.
- Anesthetics

2. Periodic breathing

Periodic breathing consists of alternate waxing and waning of respiration or alternate hyperpnea and apnea. It may be normal or abnormal.

Types of periodic breathing are:

- **Voluntary hyperventilation**
- **Cheyne-Stokes respiration**
- **Biot's breathing**

Voluntary Hyperventilation

Hyperventilation in normal subjects is followed by a period of apnea, which in turn is followed by a few shallow breaths and then by another period of apnea followed again by a few breaths. This is a type of periodic breathing. The cycles lasts for some time before normal breathing is resummed.

Explanation for the Periodicity in Voluntary Hyperventilation

Apnea: Decrease in arterial Pco_2 due to hyperventilation.

Shallow breaths: Decrease in PO2 due to apnea leads to stimulation of peripheral chemoreceptors which stimulate respiration.

Again apnea: PCR stimulation corrects hypoxia leading to increase in Po, i.e., hypoxic stimulus is eliminated.

Normal breathing: Arterial Pco_2 comes back to normal.

Voluntary hyperventilation → washing off of CO2 →↓Arterial Pco2 → respiratory center depression →apnea →↑PCO2 and ↓PO2→ stimulation of respiration.

Cheyne-Stokes Respiration

This type of periodic breathing is seen in both physiological and pathological conditions. In this type, regular alternating periods of hyperventilation and apnea are seen.

The change over from one to the other occurs gradually.

Physiological Conditions

- Deep sleep
- Infants
- High altitude
- Prolonged hyperventilation

Theories Explaining Cheyne-Stokes Breathing

a) The respiratory centre over-responds to CO2 leading to hyperventilation followed by apnea. The cycle is repeated regularly.

CO_2 → Hyperventilation →↓$Paco_2$ → Apnea →↑$PaCO_2$→ Hyperventilation.

b) Prolongation of lung-to-brain circulation time as in CCF. Here it takes more time for changes in arterial gas tension to affect the respiratory centre. If this person hyperventilates there will be a decrease in $PaCO_2$ and when this blood reaches the brain their will be marked reduction in $Paco_2$, and respiratory center will be depressed leading to apnea. During apnea there is accumulation of CO_2 leading to increase in $PaCO_2$, folloed by increased ventilation.

Biot's Breathing

This type of breathing is always pathological. It consists of irregular periods of apnea and hyperventilation. The changes are abrupt. It is seen in:

- Meningitis
- Medullary lesions

Sleep apnea

The respiratory control mechanism is less effective during sleep and brief periods of apnea occur in normal sleeping adults. During sleep there is decreased sensitivity to decrease in PCO_2. Because of this decreased sensitivity, PCO_2 may fall during sleep which may lead to apnea. Some tmes it produces sleep apnea syndrome. i.e., when it occurs repeatedly the patient wakes up frequently and the loss of sleep causes headache, tiredness, confusion, and poor performance during daytime.

In normal adults, sleep apnea occur during REM sleep when, muscle are most hypotonic. Sleep apnea is said to be present if more than 5 apneic episodes occur per hour of sleep or more than 30 apneic episodes during night. Sleep apnea is diagnosed by polysommographic studies.

Causes of sleep apnea:

- Elderly
- Alcoholics
- Hypnotic which produce respiratory depression
- Aromegaly. Causes are prolapsed of enlarged tongue and and inspiratory collapse of hypopharynx.
  Sleep apnea can be relieved to some extent by advising to the subject to sleep on their backs.

Theories to explain sleep apnea:

Central cause:

Decrease in PCO_2 is the main cause for sleep apnea especially during REM sleep. The respiratory center is less sensitive to hypocapnia which causes further decrease in PCO_2 followed by apnea.

Obstructive sleep apnea:

Sleep apnea may be caused by obstruction of airways during inspiration. Two causes are known:

1. Pharyngeal muscles relax during sleep especially REM sleep, leading to respiratory obstruction
2. Failure of genioglossus muscle of tongue to contract during inspitation, and tongue falls back and obstructs the airways.

Sudden infant death syndrome:

SIDS may be a form of sleep apnea when, the apneic spells are so much prolonged leading to death. Healthy babies are dead in their cribs in this disorder.

Causes:

1. Prolonged sleep apnea
2. Prematurity
3. Cardiac arrhythmias
4. Babies of mothers who smoked during pregnancy
5. Increased β endorphine level in CSF and serum normal endorphine level in CSF=<15pg/mL, in serum= 100pg/mL

Hypercapnia:

Hypercapnia is retention of CO2 in the body, i.e., there is increased concentration of CO2 in the blood than normal. Hypercapnia initially stimulates respiration, but retention of larger amounts of CO2 produce depression of CNS and leads to CO2 narcosis, which is characterized by:

- Confusion
- Paresthesia (altered sensation)
- Coma with respiratory depression
- Finally death

There will be respiratory acidosis and plasma HCO3 may exceed 40mEq/L. urine becomes acidic.

Causes of hypercapnia:

- Ventilation-perfusion inequality.
- Inadequate alveolar ventilation as in pump failure, e.g., fatigue, respiratory center depression, mechanical defects, paralysis of respiratory muscles, obstruction to airways etc.
- Hypercapnia is exacerbated when CO2 production is increased as in fever (13% increase in CO2 production for each 1 C rise in body temperature); high carbohydrate diet increases CO2 production because of increase in RQ.

  Hypercapnia is rarely a problem in pulmonary fibrosis because CO2 is 20 times more soluble than O2 and diffuses with ease through the thickened membrane.

Hypocapnia

Decrease in the concentration of CO_2 in arterial blood below normal is called hypocapnia. The arterial PCO2 falls from 40 mm Hg to as low as 15 mm Hg. Hypocapnia occurs due to hyperventilation especially in neurotic patients. The alveolar Po2 rises to 120-140 mm Hg.

Effects of Hypocapnia

Cerebral blood flow may be reduced by 30% or more because of the direct constrictor effect of hypocapnia on cerebral vessels. Cerebral ischemia produces headache, dizziness, visual blackouts etc. Even though hypocapnia has a direct constrictor effect on many blood vessels, it does not increase blood pressure because it depresses vasomotor centre.

Reason for Tetany in Hyperventilation

Plasma calcium is partly bound to protein and the rest is ionized calcium (Ca^{2+}) and calcium in complex with bicarbonate and citrate. It is the free, ionized Ca^{2+} that is necessary for blood coagulation, muscle contraction and nerve function. Ionic Ca is a vital second messenger. Ca^{2+} is necessary for stabilizing the nerve and muscle membrane. A low ionic Ca level has an excitatory effect on nerve and muscle cells. It leads to hypocalcemic tetany (increased contraction of muscles) which is due to increased activity of motor nerve fibers. Carpopedal spasm and Chvostek's sign are manifestations of hypocalcemic tetany. Hypocalcemic tetany is characterised by spasms of skeletal muscles especially muscles of extremities, larynx etc.

Mechanism by which Blood pH Affects Ionic Calcium Level (Ca^{2+})

In hyperventilation there is increase in plasma pH. Even though the total plasma calcium level is normal, the ionic calcium level falls. This is because plasma proteins are more ionized when pH is high, providing more protein anion to bind with Ca^{2+}. Thus, the plasma level of ionic calcium falls and bound form increases.

There will be respiratory alkalosis and urine becomes alkaline. The plasma ionic Ca^{2+} level falls. Decrease in extra-cellular ionic calcium increases the excitability of nerve and muscle cells leading to tetany.

ASPHYXIA

Asphyxia is a condition where acute hypoxia and hypercapnia occur together.

Cause of asphyxia is obstruction to respiratory passage as in:

- Strangulation
- Choking
- Drowning, where there is reflex laryngeal spasm
- Hypocalcemic tetany with severe laryngospasm

Stages of Asphyxia

- Stage of exaggerated breathing
- Stage of convulsions
- Stage of coma

Stage of Exaggerated Breathing

Initially there is strong stimulation of respiration with violent respiratory efforts which ends in loss of consciousness due to severe hypoxia.

Stage of Convulsions

There will be increase in blood pressure, heart rate. acidosis and convulsions. This is due to increased secretion of catecholamines. It is associated with micturition and defecation. The patient can be revived at this stage by antificial respiration.

Stage of Coma

If artificial respiration is not started, respiratory movements become sluggish and gasping in nature and the person goes into coma state. Death occurs due to respiratory center depression and cardiac arrest within 5-6 minutes.

Hiccup I

Hiccup is spasmodic contraction of the diaphragm and other inspiratory muscles that produces an inspiration during which there is sudden closure of glottis. Sudden glottic closure is responsible for the characteristic sensation and sound. Function of hiccup is unknown. They respomds to measures that increase arterial Pco2 like breath holding. Hiccup also occurs in the fetus in-utero.

Yawning

Yawning is an "infectious" respiratory act!!! Yawing is involuntary deep inspiration whose significance is uncertain. It also occurs in the fetus in utero. Under-ventilated alveoli have a tendency to collapse. Yawning stretch open these alveoli and prevents their collapse or atelectasis. It also increases venous return to heart because of increase in negative intrapleural pressure.

HYPDXIA

Hypoxia is defined as O2 deficiency at the tissue level. This term should not be mistaken for anoxia which means absence of O2. Anoxia is not possible in the body during life.

Hypoxia is classified into four types depending on the following factors:

a. PO2 of arterial blood
b. O2 carrying capacity of blood
c. Rate of blood flow to the tissues

d. Utilization of O2 by the tissues

Types of hypoxia:

1. Hypoxic hypoxia
2. Anemic hypoxia
3. Stagnant or ischemic or circulatory or hypokinetic hypoxia
4. Histotoxic hypoxia

Hypoxic hypoxia:

It is a condition in which the Po2 of arterial blood is reduced. O2 content and O2 saturation are decreased.

Causes:

1. Decreased Po2 of inspired air, which occurs:
    - At high altitude
    - Breathing gas mixture with low Po2
    - Breathing in closed spaces
2. Hypoventilation or decreased pulmonary ventilation
    - Obstruction of respiratory passages in bronchial asthma or foreign body aspiration
    - Paralysis of respiratory muscles as in poliomyelitis
    - Respiratory centre depression
    - Bony deformities as in kyphosis and scoliosis
    - Pneumothorax
3. Cardiac disorders
    - Right-to-left shunt
    -
4. alveolar capillary diffusion block and ventilation-perfusion imbalance
    - Collapse
    - Pulmonary congestion
    - Pulmonary fibrosis
    - Pneumonia
    - Pulmonary edema

Hypoxic hypoxia is a problem in normal individuals at high altitudes.

Anemic Hypoxia

In anemic hypoxia, arterial Po2 is normal but the amount of hemoglobin available to carry O2 is reduced.

Causes

- Anemia
- Carbon monoxide poisoning

- Chemicals like nitrates, chloride and ferricyanide which convert hemoglobin to methemoglobin. (When iron in hemoglobin is oxidized to ferric form it is called methemoglobin.)

CO Poisoning
Normally, small amounts of CO are formed in the body which acts as chemical messenger in the brain and other parts of the body. In large amounts, CO is poisonous.

Sources of CO
1. By incomplete combustion of carbon
2. CO is a constituent of coal gas
3. From exhausts of gasoline engines

CO is toxic because it reacts with hemoglobin to form carbonmonoxyhemoglobin or carboxyhemoglobin (COHb). COHb cannot take up O2. So when CO combines with hemoglobin, the amount of hemoglobin available to combine with O2 is reduced. Moreover, COHb releases CO very slowly. 15% of inhaled CO combines with myoglobin.

The affinity of hemoglobin for CO is 210 times its affinity for O2. Further, the ODC shifts to left decreasing the amount of O2 released. This is why an anemic person with 50% of normal amount of HbO, can do moderate work, but an individual whose HbO2 is reduced to 50% due to formation of COHb cannot. When hemoglobin saturation with CO is 50%, death occurs.

Signs and Symptoms of CO *Poisoning*
Acute symptoms:
- Headache
- Nausea
- Loss of consciousness
- Cherry red discoloration of skin, mucous membrane and nail bed

Chronic symptoms:
- Progressive brain damage
- Mental changes

Fatal dose: >0.1 % in inspired air
Lethal blood level: 60-80% of COHb in blood.
Diagnosis: COHb level in blood can be measured by spectrophotometry.

Treatment of CO Poisoning
1. Termination of exposure and restriction of physical activity. Otherwise, it leads to extensive cerebral demyelination.
2. Adequate ventilation by artificial respiration preferably by:
    - Hyperbaric oxygenation which increases the dissociation of

COHb

- Using carbogen inhalation. Carbogen is a mixture of 5% CO2 and 95% O2, The CO2 will stimulate the respiratory centre.

Stagnant Hypoxia

In stagnant hypoxia, blood flow to the tissue is reduced so that adequate O2 is not delivered to the tissues. PO2 and hemoglobin content are normal.

Causes of Stagnant Hypoxia Generalized

- CCF
- Shock
- Polycythemia

Localized

- Thrombosis
- Embolism
- Vascular spasm (Raynaud's phenomenon)

Kidney, heart, liver and brain are damaged in severe shock and CCF. If hypotension is prolonged, it damages the lung leading to shock lung syndrome.

Histotoxic Hypoxia

Inability of tissues to utilize O_2 is called histotoxic hypoxia. Here there is inhibition of tissue oxidative process. The amount of O_2 delivered to the tissues is adequate but tissues cannot extract this O_2.

Causes of Histotoxic Hypoxia

- Cyanide poisoning
- Sulfide poisoning

Cyanide Poisoning

Cyanide inactivates cytochrome oxidase and other enzymes in tissues, and tissue oxidation is affected which leads to quick death. Acute poisoning affects CNS and CVS. Cyanosis is a late feature in cyanide poisoning.

Sources of Cyanide

1. Industry – plastic, synthetic rubber, electroplating, photographic processing
2. Laboratories
3. Pest control – HCN gas used in ships
4. Biological: bitter almond, seeds of apricot, peach, plum, pear, apple etc.
5. Medical: Sodium nitroprusside the antihypertensive drug produces cyanide as a metabolite.
6. Chronic exposure to tobacco smoke

Absorption and Metabolism of Cyanide

Cyanide is absorbed through all routes including intact skin. It is metabolized by the enzyme rhodanase in liver and kidney to thiocyanate and excreted through urine.

Cyanide poisoning is diagnosed by Lee-Jones test. There will also be the odour of bitter almond in the breath.

Fatal dose

HCN – 50 mg

NaCN – 200-300 mg

Treatment

1. Methylene blue or nitrites are used. These convert hemoglobin to methemooglobin which then reacts with cyanide to form cyanmethemoglobin which is a nontoxic compound.
2. Sodiumthiosulfate converts cyanide to thiocyanate.
3. Hyperbaric oxygenation may also be useful along with the above treatment.
4. Vitamin B12.

Clinical Features of Hypoxia

Severe Hypoxia of Sudden Onset

Loss of consciousness in 10-20 seconds and death in4-5 minutes

Hypoxia of Gradual Onset

- Drowsiness
- Headache
- Disorientation
- Anorexia or loss of appetite
- Nausea and vomiting
- Tachycardia
- Pulmonary and systemic hypertension.

O_2Therapy

Before O_2 therapy, the physiological basis of hypoxia should be considered. Administration of O_2 rich gas mixture is of limited value in stagnant hypoxia, anemic hypoxia and hypoxia due to heart disease with right-to-left shunt. In other forms of hypoxic hypoxia, O_2 therapy is of great benefit.

O_2 THERAPY ALONE IS OF NO USE IN HISTOTOXIC HYPDXIA.

O_2 therapy must be started with care inhypercapnic patients who are in severe pulmonary failure. The reason is that very high PCO_2 depresses the respirator^y center. These patients breathe only because of hypoxic drive by stimulation of peripheral chemoreceptors. When O_2 is administered, this hypoxic drive is lost and breathing stops and it becomes a vicious cycle.

O_2 toxicity:

While oxygen is necessary for life it is also toxic when present in excess. The

toxicity of O2 is due to the production of superoxide anion (O_2^-) which is a free radical and H_2O_2. When 80)-100% O_2 is administered for 8 hours there will *be irritation* of respiratory passage, nasal congestion and coughing.

Infants treated with O_2 for IRDS develop bronchopdysplasia characterized by lung cysts and densities. Another complication is retrolental fibroplasias which leads to serious visual defects. There will be spasm of central artery of retina leading to degeneration of retina and blindness.

symptoms of O2 Toxicity

symptoms of toxicity depend on the pressure at which O2 is give. They are:

- Mnscle twitching
- Dizziness
- Pulmonary edema leading to dyspnea
- Convulsions and coma when pressure is increased to 6 atmospheres

mechanism of O, Toxicity

Metabolic rate is increased in tissues and the temperature increases very much which affects the cellular enzymes damage of tissues occurs. Brain is predominantly affected.

hyperbaricO_2, Therapy

100% O_2 is administered at high pressure in hyperbaric O2 therapy. This is the most common cause of O_2 toxicity.

Indications for hyperbaric O_2 therapy:

- CO poisoning
- Gas gangrene which is produced by anaerobic bacteria. They cannot survive in excess of O_2.
- Decompression sickness
- Air embolism
- Organophosphorus poisoning

Complications of Hyperbaric O_2 Therapy

- Cerebral gas embolism
- Rupture of tympanic membrane
- Visual defects
- O2 toxicity (refer O_2 toxicity)

Contraindications

- Asthma and emphysema
- High fever, viral infections, chronic sinusitis
- Pregnancy

CYANOSIS

Cyanosis is bluish discoloration of skin and mucous membrane when the amount of reduced hemoglobin in capillary blood is >5 g/100 mL of blood. Usually cyanosis is noticed in areas where skin is thin like fingertips, ear lobe, tip of nose, nail bed, mucous membrane etc.

Cyanosis is classified into three:

1. Central cyanosis
2. Peripheral cyanosis
3. Mixed type

Central Cyanosis

Central cyanosis results from imperfect oxygenation of blood at the level of lung or heart, e.g., lung diseases, congenital cyanotic heart disease, heart failure etc. Here cyanosis is generalized and cyanosed extremities are warm due to peripheral vasodilatation. Pulse is bounding. It characteristically affects the tongue and lips.

Peripheral Cyanosis

Peripheral cyanosis is due to excessive reduction of oxyhemoglobin in capillaries when blood flow is slow. It is seen in conditions that produce stagnant hypoxia, e.g., venous obstruction, exposure to cold, circulatory shock etc. The cyanosed extremities are cold and tongue is unaffected. Pulse is thready.

Mixed Type

Both central and peripheral cyanosis occurs together as in heart failure.

Cyanosis is not seen in anemic hypoxia. This is because hemoglobin concentration is already less in anemia and hence the amount of reduced hemoglobin will be <5 g%. For cyanosis to occur, it should be > 5 g%.

Bluish discoloration of skin and mucous membrane will be produced by drugs like phenacetin due to methemoglobinemia. This may be mistaken for cyanosis, but here the patient will be cyanosed but not breathless.