RESPIRATORY SYSTEM

USE CLASS NOTES TO WRITE INTRODUCTION

The main function of the lungs is gas exchange i.e. getting O2 in and getting CO2 out. Normally during inhalation, the diaphragm pulls downwards and the chest muscles contract to open up the chest to allow the lung to expand and air comes in. During exhalation, the diaphragm relaxes and the chest muscles also relax which returns the lung back to normal size and CO2 is pushed out.

NB:- Inhaled air, high in O2 and low in CO2, travels through the respiratory tract deep into the terminal portions of the lungs, this is inspiration.

When you breathe in, air flows through the nostrils and enters the nasal cavity, whose cells release mucus (it is salty and sticky and releases lysozymes) which forms boogers in the nose that rests on the hair when the hair captures pathogens. Once in the nasal cavity, the air goes to the paranasal sinuses that are air-filled spaces that help air become warm and moist and also amplify the sound of voice (they get blocked when we have a clogged up nose and throat hence we sound differently). Fron the nasal cavity, air moves through the nasopharynx, oropharynx and laryngopharynx and then through the larynx (voice box) after which it goes to the trachea. The epiglottis ensures that air goes to the trachea and not the oesophagus when breathing (and food goes to the oesophagus and not the trachea when eating) {The smooth muscles of the trachea are innervated by the autonomic nervous system i.e. beta-2 adrenergic receptors for the sympathetic nervous system [increase diameter] and muscarinic receptors for the parasympathetic nervous system [reduce diameter]. The trachea is lined by ciliated pseudostratified columnar cells which have goblet cells that secrete mucus. This mucus moves towards the pharynx by the help of the mucocilliary escalator} From the trachea the air goes to the primary bronchi (mainstem bronchus) at the junction called carina (The right mainstem bronchus is wider and more vertical than the left one hence if anything enters the lung it has higher chances of entering the right lung hence there are higher chances of obstruction in the right lung. From the primary bronchi the air goes to the secondary bronchi (lobar bronchus) {the trachea, primary bronchi and secondary bronchi have the rings of cartilage to support them}. From the secondary bronchi, air moves to the tertiary bronchi (segmental bronchi) after which they move to the primary bronchioles (conducting bronchioles) {the conducting bronchioles are lined by the same cells in the trachea but have additional club cells which secrete glycosaminoglycans [protect the epithelium] and they have the ability to regenerate and replace the columnar cells} which open into the tertiary bronchioles and then into the respiratory bronchioles which open into alveolar ducts that open into the alveoli contained in the alveolar sac (the alveoli are lined by type I and type II pneumocytes. Pneumocyte type II secrete surfactant {decreases surface tension and keeps the alveoli open} and has the ability to regenerate and replace damaged cells. If a pathogen manages to reach the alveoli, the alveolar macrophages will ingest that pathogen and move up the respiratory tree using the mucocilliary escalator after which they are either spitted out or swallowed}. Once in the alveoli, gas exchange takes place. The blood-gas barrier is formed by the surfactant, the pneumocytes, the basement membrane of the pneumocytes, the basement membrane of the endothelial cells lining the capillaries and the endothelial cells of the capillaries (The basement membrane of the pneumocyte and the endothelial cells stick together but have potential space between them incase of the formation of an edema). Oxygen moves from the alveoli into the blood and CO2 moves from the blood into the alveoli. Oxygen from the blood goes to the heart and then to the systemic circulation.

NB:- The right lung has three lobes and the left lung has two lobes. The left lung has an additional cardiac notch.

NB:- The respiratory tract is divided into the upper respiratory tract and the lower respiratory tract. The upper respiratory tract consists of the nose, nasal cavity, sinuses and the pharynx. The lower respiratory tract consists of the larynx, trachea, bronchial tree and lungs.

-The bronchial tree (bronchi and bronchioles) are divided into two i.e. conducting zone and respiratory zone. The conducting zone consists of the primary, secondary and tertiary bronchi and the conducting and terminal bronchioles. The respiratory zone consists of the respiratory bronchioles, alveolar ducts, alveolar sacs and the alveoli

NB:- The upper part of the nose has olfactory mucosa where we smell from.

GAS LAWS AND RESPIRATION

BOYLE’S LAW

Boyle’s law states that “for a fixed mass of enclosed gas at constant temperature, the products of the pressure (P) and the volume (V) remains constant”

P1V1=P2V2

This means that when volume increases then pressure decreases and vice versa.

Boyle’s law operates in the pleural space and not in the alveoli because the pleural space is enclosed and when the diaphragm contracts the volume of the pleural space increases and the pressure in the pleural space decreases.

LAPLACE’S LAW

Laplace’s law relates the tension in a membrane to the pressure difference on either side.

D(DELTA)P=2T/R or Pi-Po=2T/R

Where Pi is pressure in the pleural space and Po is the pulmonary pressure inside the alveoli

This means that the pressure in a small alveolus will be greater than in a large alveolus if the surface tension was the same in both

DALTON’S LAW

P=nRT/V where RT/V is a constant and n is the number of moles hence pressure is directly proportional to the number of moles

Hence Ptotal = PgasA + PgasB + PgasC

HENRY’S LAW

Henry’s law states that concentration of a gas in a solution is equal to the partial pressure of the gas times the solubility coefficient of the gas e.g.

C(O2)=PO2\*SO2

At equilibrium, PO2 in air and water is equal.

LUNG VOLUMES AND CAPACITIES

During inspiration, about 1/2L of gas is inhaled.

There are no muscles for expiration at rest i.e. expiration is passive and is as a relaxation of inspiratory muscles

The tidal volume is the amount of air inspired and expired during rest. Inspiratory reserve volume (2.5L) is the maximum amount of air that can be inhaled. Expiratory reserve volume is the maximum amount of air exhaled. (True) Residual volume is the volume of air that is left in the lungs after the expiratory reserve volume. The residual volume prevents the alveoli from collapsing. This is important so that after expiration, the wet surfaces of the alveoli do not stick together as once they stick together it is not easy for them to inflate again i.e. a lot more force will be required when inspiring.

Functional residual capacity (3 L) is the true residual volume (1 and 1/2 L) plus the expiratory residual volume (1 and 1/2 L). This allows gas exchange when there is no breathing going on. Also, when the inhaled air comes to the lungs, only about 350ml of the fresh air mixes with the functional residual capacity and this is important in ensuring that the fluctuations in the partial pressures aren’t very high and this is important to prevent excessive homeostatic regulation.

The total lung capacity (6L) is the addition of the true residual volume, expiratory residual volume, tidal volume and the inspiratory residual volume i.e. the total volume of air that a lung has a capacity of holding onto.

The vital lung capacity is the total amount of air that can be breathed in and out i.e. expiratory residual volume plus the tidal volume plus the inspiratory residual volume.

The spirometer measures the volumes of air breathed in and out. However, it cannot measure the residual volume as it is never breathed out.

LV measurement equation...did not understand concept

As age increases, the elasticity of the lungs decreases as the elastic fibres become loose hence the elastic recoil is decreased hence the vital capacity also reduces.

Residual volume = functional residual volume – expiratory residual volume

The pathologies that affect the vital lung capacity are:-

1. Neuropathies i.e. poliomyelitis (viral infection in nerves i.e. phrenic nerve and intercostals nerves which leads to paralysis of inspiratory muscles) and myasthenia gravis (antibodies bind to the muscarinic receptors instead of acetylcholine)
2. Myopathies i.e. damage to muscle
3. Collapsed lungs and alveoli
4. Constricted airways e.g. in asthma

LUNG MECHANISMS

Lung mechanism is a study of those factors that are involved in breathing in and out.

The supporting factor is the muscles. The main muscle responsible for breathing in the resting state is the diaphragm. During aggressive breathing e.g. when exercising the external intercostal muscles (raises the ribcage anterolaterally), sternocleidomastoid, scalene muscles and psoas major come into play. During the resting phase, exhalation is passive. However, when aggressive exhalation is required the internal intercostal muscles and rectus abdominis (pushes abdominal contents into the abdominal cavity which moves the diaphragm upwards) come into play.

The opposing factors are the elasticity of the lungs, the friction between the tissues and the friction in the airways. When the lungs expand, the elastic fibres would want to go back to their original length so that they don’t get deformed. When the lungs expand, the two layers of the pleura glide against each other hence produce friction. When the air passes through the airways there is friction.

The main pressures measured are:-

1. Intra-alveolar pressure (pressure in alveoli)
2. Intra-pleuric pressure (pressure in pleura) usually -5
3. Atmospheric pressure (pressure outside the body wall) usually 0
4. Transmural pressure (Transpulmonary pressure, Transthoracic pressure and Transrespiratory pressure)

The transpulmonary pressure measures the pressure difference between the alveoli and the pleura. Transpulmonary pressure= Pressure in alveoli – Pressure in pleura. If the pressure difference is + then there is inflation, if the pressure difference is – then there is deflation and if the pressure difference is 0 then there is no net change. When the chest wall expands, the intrapleuric pressure becomes more negative which makes the transpulmonary pressure positive hence leading to inflation.

The transthoracic pressure measures the pressure difference between the pleura and the atmosphere. Transthoracic pressure = Pressure in pleura – Pressure in atmosphere.

The transrespiratory pressure measures the pressure difference between the alveoli and the atmosphere. Transrespiratory pressure = Pressure in alveoli – Pressure in atmosphere.

COMPLIANCE

Compliance is the ease with which a tissue can stretch while Elastance is the ease with which the tissue can recoil during stretching. Compliance and elastance are inversely proportionate i.e. when compliance increases the elastance decreases and when compliance decreases elastance increases.

USE NAJEEB TO WRITE NOTES

SURFACE TENSION AND ROLE OF SURFACTANT

Alveoli are lined by type 1 and type 2 pneumocytes. Type 1 pneumocytes are squamous while type 2 pneumocytes are cuboidal. The type 2 pneumocytes manufacture the surfactant. The luminal surfaces of the pneumocytes are wet i.e. water lies on the surface.

Water-air interface is the barrier between the water molecules and air molecules. The deep water molecules have forces in all directions hence there is no net force exerted, but for the superficial water molecules, there is no upward pressure towards the air molecules hence there is a net force exerted downwards which makes the water molecules move downwards and towards each other. This reduces the radius of the alveoli hence increasing surface tension. The increasing surface tension results in increased collapsing pressure of the alveoli. Alveoli follow the LaPlace’s Law which states that P=2T/r

The effects of surface tension are:-

1. Unequal ventilation perfusion ratio in unequal sized alveoli
2. Tendency to collapse
3. Tendency to edema formation

The lungs are made up of more than 300 million alveoli.

Alveoli cannot be too small as the radius will reduce hence increasing pressure resulting in collapsing of the alveoli (atelectasis)

Surfactant is 90% lipids and 10% proteins. Surfactant molecules form clusters to form lamilar bodies. When the lamilar bodies come towards the apical surface of the pneumocytes, they form tubular myelin. Tubular myelin are made out of surfactant too. The lipid component of the surfactant is called di palmityl phosphatidylcholine. The proteins are: 4 apo proteins (a,b,c and d), IgA and albumin. Hence surfactants are amphipathic molecules as they are both lipophilic and hydrophilic. Surfactant doesn’t cause surface tension because of the lipophilic part that gives an outward force hence no net inward pull. They replace water at the water-air interface. Apo protein a and d secrete opsonin which is a sticky compound that binds to both the macrophage and the pathogen allowing efficient phagocytosis (otherwise the pathogen can escape). Apo protein b and c allow the surfactant to spread across the surface. Apo protein a also allows surfactant release from the tubular myelin.

Effects of surfactant:

1. Improves lung compliance
2. Reduces surface tension
3. Cancels out effects of surface tension
4. Reduces chances of edema formation
5. Maintain equilibrium between smaller and larger alveoli i.e. equalizes the ventilation (The surfactant in the larger alveoli is spread out making it very thin which then allows water to come up and form part of the water-air interface which would increase surface tension. The surfactant in the smaller alveoli leads to expansion of the alveoli hence reducing surface tension)
6. Reduces use of muscles of inspiration hence reduced work of breathing

Respiratory distress syndrome in infants – surfactant production starts on week 24 and enough surfactant week is available at about the 35th week. Maternal glucocorticoids are high towards the last weeks of pregnancy which leads to enough production of surfactant. These infants don’t produce enough surfactant. (When babies are born, their alveoli are collapsed by when the umbilical cord is cut off, the oxygen supply is cut off and hence leading to hypoxia which stimulates the medullary respiratory centres that then lead to opening of the airways and this is represented by the crying of the babies.)

PULMONARY CIRCULATION

The pressures in the blood vessels are as follows; the left atrium is 2-6mmHg, the left ventricle is 120/0, the aorta is 120/80, the MAP in the aorta is 93mmHg, the systemic capillaries is 20mmHg, the right atrium is 0-2mmHg, the right ventricle is 25/0, the pulmonary artery is 25/8, the pulmonary capillaries is 7mmHg

The comparisons between the pulmonary and systemic circulation are:-

1. Pulmonary circulation is shorter than systemic circulation.
2. Pulmonary circulation is a low pressure system
3. The velocity of blood is higher in pulmonary circulation as there is a shorter distance to cover
4. The volume (flow) is the same in both circulation systems
5. Pulmonary vessels are thin walled hence are more compliant as they are more stretchable
6. Resistance to flow is low in pulmonary circulation

The pulmonary circulation is a low pressure system because under high pressure fluid would leak into the interstitium making the lung edematous. The systemic circulation is a high pressure system because blood needs to move longer distances to supply far distant organs and also blood moves anti-gravity.

The functions of the pulmonary circulation are:-

1. Gas exchange
2. Reservoir of blood i.e. the pulmonary circulation stores 500ml of blood from the 5L that it receives, and the capillaries store 70% of the stored blood
3. They have metabolic functions i.e. the endothelial cells of the pulmonary capillaries have angiotensin converting enzyme (ACE) which converts angiotensin 1 into angiotensin 2. ACE can also break down bradykinin hence enzyme works as bradykinase.
4. They act as a filter e.g. small thrombi moving in the circulation can be dissolved by the pulmonary circulation (Large thrombi can damage the lungs)

The blood in the pulmonary veins has 100% oxygen after gas exchange but before the blood reaches the left atrium the value reduces. This is as a result of shunts. There are four physiological shunts i.e.

1. The bronchial veins draining into the pulmonary veins.
2. The thebesian veins draining the blood in the myocardium (coming from coronary arteries) into the left ventricle.
3. Foramen ovale in the fetus
4. Ductus arteriosus in the fetus

NB:- In a fetus, as there is little oxygen in the lungs the pulmonary vessels constrict and hence blood cannot move from the right side of the heart to the pulmonary vessel hence there is an interatrial hole called foramen ovale which allows movement of blood from the right side of the heart to the left side of the heart. However, some of the blood (about 15%) goes to the pulmonary vessels and this is bypassed to the aorta by ductus arteriosus.

Resistance is low in pulmonary circulation but it is high in systemic circulation.

Resistance is measured by

RESISTANCE = PRESSURE / FLOW

The flow in both pulmonary and systemic circulation is 5L/min. The driving pressure is measured as MAP – Right Arterial Pressure. So, for:-

Systemic circulation

R= 93-2/5 (The MAP is 93 because BP in aorta is 120/80 and systole is 1/3 while diastole is 2/3 hence average is 93)

Pulmonary circulation

R=15-5/5

Hence, the pressure in the systemic circulation is about 10 times more than that in pulmonary circulation.

The factors that affect pulmonary vascular resistance are:-

1. Increased cardiac output reduces pulmonary resistance. This is because when there is increased cardiac output e.g. during exercise there is capillary recruitment (Physiologically, not all pulmonary capillaries are recruited for function but these few that are not recruited come into play when the cardiac output rises). Capillary recruitment leads to less pressure on the right atrium by lowering the pressure moving in the capillaries as the flow decreases. Also, the capillary recruitment increases the surface area allowing for gaseous exchange. There is also capillary distension of the previously opened capillaries as the capillaries are more compliant hence this reduces resistance and maintains the low pressure. When there is increased cardiac output, there is not a significant rise in resistance of the pulmonary capillaries.
2. Extremely increased lung volume increases resistance. When moving from resting lung volume (functional residual volume) to extremely increased lung volume, the alveoli dilate and this compresses the alveolar vessels (vessels surrounded by alveoli) and this increases resistance as pressure is high but the lumen is small. Also, the extra-alveolar vessels (vessels surrounded by elastic fibres) are stretched as when the lung expands the elastic fibres stretch and open up the vessels. Hence, there is increased resistance in the alveolar vessels. Extremely decreased lung volume increases resistance. When moving from resting lung volume to extremely decreased lung volume, the elastic fibres do not stretch and this constricts the extra-alveolar vessels hence blood cannot move to the alveolar vessels hence there is increased resistance in the extra-alveolar vessels.
3. In case of an obstruction at the alveolar duct, air cannot pass through the alveolar normally i.e. movement of air reduces hence the PO2 (Partial pressure of O2) in the affected alveoli reduces (less air coming in) while the PCO2 increases (less air going out). The oxygenated blood vessel coming from previously normally perfused and ventilated alveoli gets constricted and changes the direction of blood flow to other blood vessels where there is beter ventilation. This is because the K+ channels on the smooth muscles of the blood vessel lining the alveoli are extremely sensitive to the PO2. When PO2 is high, the K+ channels open making the smooth muscle cell more electronegative hence the chances of generating an action potential reduce. However, when the PO2 reduces, the K+ channels close making the smooth muscle cell more electropositive. When the smooth muscle cell becomes electropositive, the Ca2+ channels open and the Ca2+ bind to calmodulin and activate calmodulin kinase which activates myosin light chains which lead to contraction of the cell and eventually the entire muscle (CHECK WITH BCHEM MUSCLE NOTES) and that leads to constriction of the blood vessel. This is to prevent a concentration gradient between the perfused blood and underventilated alveoli which would lead to reduced oxygenation of blood. Also, the endothelial cells of the pulmonary capillaries are sensitive to the PO2. When the PO2 is normal then they stimulate their intracellular NO synthase to synthesise NO which goes to the smooth muscles and stimulates its respective serpentine receptor which activates guanylyl cyclase which converts GTP to cGMP. This relaxes the smooth muscle. However, when PO2 is less than normal then the endothelial cells inhibit NO synthase hence the smooth muscles contract. (CHECK WITH PHYSIO FIRST YEAR BOOK)

BLOOD CIRCULATION IN THE LUNGS

Physiologically, when standing, the apex of the lung has less blood flowing through as compared to the base and this is because of the effects of gravity. The apex which has a PA alveoli>Pa artery >Pv vein, the arteries will constrict hence there will be underperfusion but this is non-existent physiologically and it is called zone 1. The middle area of the lung is intermediately perfused i.e. no constriction during systole but constriction during diastole as Pa>PA>Pv and it is called zone 2. The base of the lung has Pa>Pv>PA and it is called zone 3.

NB:- However, pathologically, when there is a haemorrhage and bleeding in any part of the body, there could be a zone 1. This is because there is less blood returning to the right atrium hence less blood going to the lung i.e. zone 2 becomes zone 1. When using an artificial ventilator, if the ventilator overventilates the lung, then there is more pressure in the right atrium and the person can die i.e. zone 1 becomes zone 3.

-During exercise, the lung receives more blood hence there is capillary recruitment the zone 1 becomes zone 2 and zone 2 becomes zone 3.

FLUID EXCHANGE IN PULMONARY CAPILLARIES AND PULMONARY EDEMA

Physiologically, there are forces that govern the movement of fluid in and out of the blood vessel. The osmotic pressure of the plasma proteins retaining the fluid inside the vessel is 28mmHg, the hydrostatic pressure moving the fluid out of the vessel is 7mmHg, the osmotic pressure of the interstitial proteins is 14mmHg and the surface tension of the alveoli (pushing the fluid out of the blood vessel) is 8mmHg. Overall the forces are 29-28 hence 1mmHg of fluid moves out of the blood vessel and into the interstitium. This is, however, drained by the lymphatics i.e. from interstitial area to perivascular area to peribronchial area to lymphatics and then to circulatory system. This prevents accumulation of fluid into the interstitium.

However, when the hydrostatic pressure is 20mmHg or more e.g. when there is mitral stenosis (mitral valves do not open normally), left ventricle failure (left ventricle does not contract strongly) hence more fluid moves into the interstitium. However, this fluid is drained by the lymphatics hence there is no edema formation. But when the lymphatics are overwhelmed, the fluid accumulates in the interstitium leading to formation of pulmonary interstitial edema which can spread to also become pulmonary alveolar edema.

The reduction of the osmotic pressure of the plasma proteins can also lead to edema formation e,g hypoproteinemia i.e. protein losing nephropathy e.g. nephritic syndrome and protein losing enteropathy lead to proteinuria as a result of damage to glomerular basement membrane. This could also be as a result of cirrhosis where less plasma proteins are being produced. This could also happen when the diet is protein deficient.

Increase in the osmotic pressure of the interstitial plasma proteins can be because of damage to endothelial cells which increases the permeability to plasma proteins to move to the interstitium e.g. during infection and inflammation leading to edema formation.

Cancer can block lymphatics which can also lead to edema formation.

As a result of edema formation there is:-

1. Decrease in compliance by the pulmonary vessels
2. Difficulty in breathing because the muscles of respiration become fatigued
3. Airways narrow
4. Reduced gas exchange

DROWNING

There are two types of drowning i.e. salt water drowning and fresh water drowning.

In salt water drowning, when the salt water reaches the alveoli it pulls in water as it is a hyperosmolar solution. This reduces gaseous exchange and the person dies as a result of asphyxiation (death as a result of lack of oxygen).

In fresh water drowning, when the fresh water reaches the alveoli, the water moves into the blood vessel as it is a hypoosmolar solution. This makes the plasma diluted hence the water moves into the RBCs and the RBCs burst releasing K+ hence giving rise to hyperkalemia. The high levels of K+ stimulate the SAN and lead to increased cardiac contractions which lead to ventricular fibrillation which leads to cardiac failure.

XOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXOXO

Physiologically, the visceral pleura pulls the chest inside and the parietal pleura pushes the chest outside hence creating a negative pressure (The parietal pleura and visceral pleura are sticky but their forces create the pressure). Physiologically, the systemic vessels are next to the parietal pleura while the pulmonary vessels are next to the visceral pleura. Hence, the some of the fluid coming from the systemic vessels drains into the pleural cavity from where it drains into the pulmonary vessels and other lymphatic structures i.e. mediastinal lymphatics, diaphragmatic lymphatics and lymph nodes of the chest wall. However, when there is excess fluid draining into the pleural cavity there is pleural effusion and this results the same way as those of the pulmonary edema formation.

VENTILATION/PERFUSION RATIO

Alveolar ventilation is the amount of air coming to the alveoli for the purpose of gaseous exchange.

In a healthy person standing upright, the apex is less ventilated and less perfused as compared to the base i.e. perfusion and ventilation as you move from the apex to the base. This is because the pressure of the pleural fluid in the apex is -10 cm of water, in the middle are is -5 cm of water and in the base is -2.5cm of water. This and the effects of gravity pull the lung downwards. As the apex has the pleura pulling it upwards and gravity pulling it downwards it has a higher negative pressure and hence the alveoli are more distended. As you move to the base of the lung, the pleura and gravity are acting in the same direction hence the alveoli are only slightly stretched. Hence, when breathing, the change in the size of the alveoli is what allows air to move in and as the alveoli in the apex are already distended they cannot distend further (not significantly) hence they receive less fresh air as compared to those towards the base which can distend significantly and allow fresh air into the alveoli hence ventilation increases as you move from the apex to the base. As for perfusion, as blood comes to the lungs, the forces of gravity pull the blood towards the base making the base more perfused as compared to the apex. Also, as the alveoli of the apex are distended, the alveolar vessels become compressed and hence they constrict hence they are underperfused. As for the alveoli in the base, they are not distended significantly hence the alveolar vessels are open and allow blood to pass through significantly hence they are perfused. However, as moving from the apex to the base of the lung, ventilation increases significantly but perfusion increases dramatically.

Minute ventilation = Tidal volume \* Respiration rate =500\*12 =6000ml/min of air enters the respiratory system

However, about 150ml of this air is not in the alveoli i.e. it extends from the nose to the pharynx, larynx, trachea, bronchi, bronchioles upto the terminal bronchioles where there is no gas exchange taking place and this is termed as anatomical dead space.

Alveolar ventilation = (Tidal volume – Anatomical dead space) \* Respiratory rate = (500-150)\*12 =4200ml/min

Hence as about 4L of air goes to the alveoli and 5L of blood goes to the lung hence the ventilation/perfusion ratio is 4000/5000 = 0.8. This is an ideal situation and is only found in zone 2 of the lung substance. The ventilation/perfusion ratio is higher in the apex of the lung (apex is more ventilated than perfused) and it is lower in the base of the lung (base is more perfused than ventilated).

Normally, in the alveoli of zone 2 the PO2 is 104mmHg and the PCO2 is 40mmHg and in the blood coming to zone 2 PO2 of blood is 40mmHg and PCO2 is 46mmHg. As a result of the concentration gradient O2 moves from the alveoli to the blood and CO2 moves from blood to the alveoli hence the blood coming out has PO2 of 100mmHg and PCO2 of 40mmHg. In zone 1, the alveoli has PO2 of 100mmHg and PCO2 of 38mmHg hence when blood leaves the alveoli, the PO2 is 100mmHg but PCO2 is 38mmHg (<40mmHg). In zone 3, the alveoli has PO2 <100mmHg of and PCO2 >40mmHg of hence when blood leaves the alveoli, the PO2 <100mmHg is and PCO2 is >40mmHg.

Coming to the gas exchange in the body tissues, the PO2 in capillaries is 95mmHg, the PCO2 in capillaries is 40mmHg, the PO2 in the tissue fluid is 40mmHg, the PCO2 in tissue fluid is 45mmHg, the PO2 in the cells is 20mmHg and the PCO2 in the cells is 46mmHg. O2 diffuses from the capillary to the tissue fluid and from the tissue fluid to the cells. CO2 diffuses from the cell to the tissue fluid and from the tissue fluid to the capillaries.

When a person hyperventilates, they lose a lot of CO2. When this happens, the PCO2 in the alveoli drops and more CO2 is taken out of the blood. Hence this means that less CO2 forms carbonic acid hence less H+ and bicarbonate in the blood. CO2 + H20 = H2CO3 = H+ + HCO3- (EQUILIBRIUM SIGNS!!). Hence, there is a drop of H+ in blood and the pH rises above 7.4 hence leading to alkadosis. This is sensed by the negatively charged plasma proteins (which are bound to H+ and Ca2+). These proteins release H+ to stabilize the pH of blood. In the process, the plasma proteins bind to more Ca2+ hence the blood becomes hypocalcemia. These Ca2+ are used to block the voltage-gated Na+ channels by repels the Na+ (as Ca2+ is also positively charged). When the Ca2+ is not present, then the Na+ will move in and there will be irregular action potentials and hence leading to muscle spasticity (muscles continuously contract). This could also lead to fainting as there is change in neurological activity.

In the pathological condition of an obstruction of an alveoli, the movement of air reduces hence the PO2 (Partial pressure of O2) in the affected alveoli reduces (less air coming in) while the PCO2 increases (less air going out). The oxygenated blood vessel coming from previously normally perfused and ventilated alveoli gets constricted and changes the direction of blood flow to other blood vessels where there is better ventilation. This is because the K+ channels on the smooth muscles of the blood vessel lining the alveoli are extremely sensitive to the PO2. When PO2 is high, the K+ channels open making the smooth muscle cell more electronegative hence the chances of generating an action potential reduce. However, when the PO2 reduces, the K+ channels close making the smooth muscle cell more electropositive. When the smooth muscle cell becomes electropositive, the Ca2+ channels open and the Ca2+ bind to calmodulin and activate calmodulin kinase which activates myosin light chains which lead to contraction of the cell and eventually the entire muscle (CHECK WITH BCHEM MUSCLE NOTES) and that leads to constriction of the blood vessel. This is to prevent a concentration gradient between the perfused blood and underventilated alveoli which would lead to reduced oxygenation of blood. Also, the endothelial cells of the pulmonary capillaries are sensitive to the PO2. When the PO2 is normal then they stimulate their intracellular NO synthase to synthesise NO which goes to the smooth muscles and stimulates its respective serpentine receptor which activates guanylyl cyclase which converts GTP to cGMP. This relaxes the smooth muscle. However, when PO2 is less than normal then the endothelial cells inhibit NO synthase hence the smooth muscles contract. (CHECK WITH PHYSIO FIRST YEAR BOOK). This leads to chronic pulmonary hypertension.

In the case of a thrombi causing an obstruction in the blood vessel, the alveoli constricts to prevent air from passing through it as the air is underperfused and the air is directed to a better perfused area.

LARYNGEAL PHYSIOLOGY

USE NOTES FROM VIDEO NO. 5

OXYGEN TRANSPORT

Oxygen in blood is mainly carried by haemoglobin. Some of the oxygen is dissolved in plasma.

NB:- Haemoglobin is a tetrameric structure. It is made in erythroblasts during hematopoiesis. In the erythroblast, 4 pyroll rings are put together to form a protoporphyrin. Protoporphyrin adds a Fe2+ at the centre of the molecule and forms heme. A globin chain is then added to form a haemoglobin monomer. When four haemoglobin monomers are put together then a haemoglobin molecule is formed. If the haemoglobin molecule has 2 alpha chains and two beta chains then it is called Haemoglobin A (Adult). If the haemoglobin molecule has 2 alpha chains and two delta chains (CHANGE SYMBOL IN IMMUNO) then it is called Haemoglobulin A2. If the haemoglobin molecule has 2 alpha chains and two gamma chains then it is called Haemoglobulin F (Fetus).

-If the iron in haemoglobulin is Fe3+ instead of Fe2+ then that is called a methaemoglobin which is useless as it cannot carry O2.

-Free haemoglobin (outside of RBCs) is toxic to nephrons.

Oxygen bound to haemoglobin doesn’t determine PO2. This is determined by the O2 dissolved in plasma.

In deoxygenated blood, 75% of haemoglobin is saturated with O2 i.e. out of 4 binding sites only 3 are occupied. When deoxygenated blood reaches the alveoli, the PO2 in the alveoli is 104mmHg and the PO2 in the capillaries is 40mmHg hence O2 moves from the alveoli to the capillaries. When the PO2 in capillaries also rises to 104mmHg then O2 moves into the RBC and binds at the 4th binding site and makes the haemoglobin 100% saturated.

NB:- When the PO2 in plasma decreases then O2 moves from the haemoglobin to the plasma and when the PO2 in plasma increases then the O2 moves from plasma to the haemoglobin.

Males have 15gm Hb in 100ml of blood and female have 14gm in 100ml of blood. 1gm of Hb binds to 1.34ml of O2 if the Hb is 100% saturated. Hence, in 100ml of blood if the haemoglobin is 100% saturated then there is 20.1ml of O2 in 100ml of blood.

Oxygen dissolves poorly in plasma as it is not a highly soluble gas i.e. 0.003 ml of O2 dissolves in 100ml of blood under the PO2 of 1mmHg hence only 0.3ml of O2 in 100ml of blood.

97% of oxygen is bound to Hb and about 3% is dissolved in plasma (There is 20.4ml of O2 in 100ml of blood).

However, before the oxygenated blood reaches the left side of the heart, the deoxygenated blood from the bronchial veins drains into it. Also, in the left ventricle the thebesian veins drain into the oxygenated blood. This makes the PO2 reduce to 95mmHg and hence the haemoglobin becomes 97% saturated. This is called venous admixture and the amount of O2 in blood becomes about 20ml per 100ml of blood.

Coming to the gas exchange in the body tissues, the PO2 in capillaries is 95mmHg, the PO2 in the tissue fluid is 40mmHg and the PO2 in the cells is 20mmHg. O2 diffuses from the capillary to the tissue fluid and from the tissue fluid to the cells. CO2 diffuses from the cell to the tissue fluid and from the tissue fluid to the capillaries. When dissolved O2 in plasma moves from the capillaries to the tissue fluid, the PO2 in blood drops to 40mmHg and the haemoglobin releases one oxygen molecule and becomes 95% saturated. Hence, during venous return in 100 ml of blood PO2 of blood is 40mmHg, amount of dissolved O2 in blood in 0.12ml, 95% Hb are saturated and only 15ml of O2 is present in blood. Hence if in 100ml of blood 5ml of O2 went to the cells then in 5000ml (5L) 250ml of O2 goes to the cells.

OXYGEN ASSOCIATION DISSOCIATION CURVE

DRAW CURVE USING DR. NAJEEB

WRITE INTERPRETATION WHEN DRAWING CURVE

POLYCYTHEMIA

CO HAS 250\* MORE AFFINITY

CARBON DIOXIDE TRANSPORT

CO2 is a waste product of aerobic respiration.

CO2 is highly soluble (it is 25 times more soluble as compared to oxygen). Most of it is dissolved in the plasma. In a resting human being, about 200ml of CO2 is produced (250ml of O2 is transported to the cells and during aerobic respiration about 50ml makes water and 200ml makes CO2)

NB:- In arterial blood there is 48ml of CO2 in 100ml of blood and the pH is 7.4

-In venous blood there is 52ml of CO2 in 100ml of blood and the pH is 7.36

-4ml of CO2 is taken up from the cells

Coming to the gas exchange in the body tissues, the PCO2 in capillaries is 40mmHg, the PCO2 in tissue fluid is 45mmHg and the PCO2 in the cells is 46mmHg. CO2 diffuses from the cell to the tissue fluid and from the tissue fluid to the capillaries. In the capillaries about 5% is directly dissolved in plasma. 95% of the CO2 goes to the RBCs. Out of this 95%, 90% of CO2 combines with H2O to form H2CO3. This reaction is catalyzed by carbonic anhydrase. Then the H2CO3 is broken down into H+ and HCO3-. (WRITE REACTION)

The H+ is captured by the globin chain amino acids of the Hb and prevents a change in pH. The HCO3- is taken to the plasma by a membrane transporter called HCO3- Cl- countertransporter (BAND-3) that takes HCO3- out of the RBC and Cl- into the RBC. With Cl-, water follows into the RBC and hence the venous blood has 3% extra hematocrit as compared to the arterial blood as the RBCs swell up. The hydrogenated Hb has a lower affinity for O2 hence O2 is released to go to the tissues and this is called the Bohr effect.

The remaining 5% of CO2 in RBCs binds to the amino end of the globin chain of Hb and forms carboaminohaemoglobin. (Some of the CO2 also binds to the amino end of some other plasma proteins)

Normally, in the alveoli the PCO2 is 40mmHg and in the blood coming to the alveoli PCO2 is 46mmHg. As a result of the concentration gradient, CO2 moves from blood to the alveoli hence the blood coming out has PCO2 of 40mmHg. In the lung, as there is a higher concentration of O2, the O2 binds to Hb and reduces the affinity of Hb for H+ hence the H+ is released which binds to HCO3- to form H2C03 which is converted to CO2 and H2O. (WRITE REACTION WITH CARBONIC ANHYDRASE) The CO2 diffuses to the alveoli. This is called the Haldane effect.

NB:- The functions of Hb are:- a) oxygen transport b) CO2 transport c) acts as a buffer (captures the H+ made when CO2 dissociates to prevent acidosis and releases H+ when the pH rises to prevent alkalosis.) d) Binds to NO in the lungs and releases it in the systemic circulation to give rise to arterial dilation

REGULATION OF RESPIRATION (CONTROL OF BREATHING)

Breathing is controlled by the CNS by voluntary and autonomic innervation

The control by the autonomic nervous system is by:-

-The inspiratory centre is located in the dorsal part of the medulla oblongata (next to the nucleus of tractus solitarius) and it is also termed as a pacemaker or a RAMP pacemaker.

NB:- A pacemaker is a group of excitable cells that can undergo depolarisation spontaneously

-The inspiratory centre gives fibres which form the phrenic nerve (C3, C4 and C5) which innervates the diaphragm and the intercostal nerves which innervate the external intercostals muscles.

-In the lower pons, is the apneustic centre which can lead to apneusis (deep breath) if they are over simulated. The apneustic centre stimulates the inspiratory centre as a switch on.

-The upper pons has the pneumotaxis centre for the inhibition of inspiration.

-For resting breathing, expiration is a passive process

-Hence, during resting breathing, inspiration lasts for 2 seconds but when it onsets, it progresses as a ramp but after two seconds this stops suddenly for 3 seconds (expiration) and the same process continues again

-During intensity e.g. exercise, an anteroventrally located nucleus in the medulla oblongata (next to the nucleus ambiguous) has both inspiratory and expiratory neurones (inspiratory are dorsal to the expiratory ones). When the inspiratory centre fires it also stimulates the anteroventrally placed inspiratory neurones and enhances inspiration. And during forced expiration the expiratory centre is stimulated to enhance expiration.

Breathing is also regulated by emotions i.e. from the hypothalamus and limbic system.

Breathing is controlled by the voluntary nervous system:-

--Corticospinal tract is stimulated and the motor neurones send action potentials to the intercostals muscles and diaphragm e.g. when you take a deep breath consciously.

Breathing is controlled by the central and peripheral chemoreceptors which measure changes in PO2, PCO2 and pH.

Central chemoreceptors are found in the CNS. They are located anteroventrally in the medulla oblongata (very close to the exit point of the glossopharyneal nerve and the vagus nerve). They are sensitive to the PCO2 in arterial blood. They are, however, not sensitive to changes in pH and PO2. CO2 is a lipid soluble gas hence it can cross the blood-brain barrier and the blood-CSF barrier hence it can give information to the central chemoreceptors. The PCO2 in the CNS will equilibrate with that of the arterial blood i.e. 40mmHg hence e.g. when PCO2 in blood rises then CO2, in its molecular form, will cross the blood-brain barrier to enter the brain substance and dissociates into H+ and HCO3-. The central chemoreceptors measure the change in pH and stimulate the inspiratory centre respective of the changes in PCO2.

The peripheral chemoreceptors are carotid bodies (innervated by glossopharyngeal nerve) and aortic bodies (innervated by vagus nerve). They are sensitive to changes in PCO2, pH and especially changes to PO2. The peripheral chemoreceptors have the highest flow of blood so that there is no gaseous exchange and the PO2 of blood stays the same. When the PO2 in blood is normal then the K+ channels on the chemoreceptors are open and they make the chemoreceptors more electronegative hence not inducing a local potential. But when there PO2 in blood drops drastically i.e. below 40mmHg in arterial blood, the K+ channels close which makes the cell electropositive and then a local potential is induced as Ca2+ channels open and stimulate the dopamine loaded vesicles to exocytose the dopamine which binds to its specific receptors on the neurone innervating the chemoreceptor. When dopamine binds to its specific receptor then an action potential is induced and it stimulates the inspiratory centre. They are not sensitive to the amount of O2 in blood because otherwise anaemic patients would hyperventilate but they do not during resting breathing. The sensitivity of the chemoreceptors to pH and PCO2 is independent of PO2 i.e. when there is increased acidosis then the chemoreceptors notice the drop in pH and lead to hyperventilation to increase the loss of CO2 hence reducing the PCO2 and pH.

NB:- 90% of vagus is sensory while 10% is motor

There are also receptors in the lung that lead to stimulation or inhibition of the inspiratory centre. One of them is the lung stretch receptors which inhibits the inspiratory centre when the lung is inflated. This is called the Hering-Breuer reflex. Another is the irritable receptors lining the mucosa in the bronchioles which is sensitive to histamine and during inflammation when histamine is released, it binds to these receptors and stimulates the vagus nerve to cause bronchioconstriction. The third is the juxtacapillary receptor (J receptor) that are in the alveoli thatare activated during pulmonary edema and they produce rapid shallow breathing and lead to dysnea (unpleasant awareness of breathing).

The inspiratory system is also affected by proprioception i.e. during exercise and when you enter a cold shower.

RESPIRATION AT HIGH ALTITUDE

At high atmospheric pressure, the atmospheric pressure drops hence PO2 in the alveoli drops. Acclimitization is the process by which the respiratory system, cardiovascular system, blood and peripheral tissues undergo adaptive changes to maintain the normal supply of O2 to the tissues.

NB:- When a person goes 15000 ft above sea level then there is a significant decrease in PO2.

-At sea level, the total Pair is 780mmHg and as oxygen makes up 21% of the total air the PO2 in the atmosphere is 159mmHg. However, when air is entering into the body, it gets warmed in the nasal cavity by water vapour (Pwatervapour is 47mmHg) hence the PO2 in the lungs is decreased to about 147mmHg and the PO2 in the alveoli is decreased to 104mmHg.

At high altitude the PO2 in the atmosphere drops hence the PO2 in the alveoli drops to below 60mmHg and this is reflected in the arterial blood i.e. the PO2 in arterial blood is below 60mmHg and this is hypoxia. This drop is sensed by the peripheral chemoreceptors that send information via the glossopharyngeal nerve and vagus nerve to stimulate the inspiratory centre in the medulla oblongata hence the person starts to hyperventilate (5\* more than normal ventilation). The advantage of hyperventilation is that alveolar oxygen and atmospheric oxygen are mixed more hence the PO2 in alveoli increases hence this increases the PO2 in arterial blood.

During hyperventilation, more CO2 is lost from the body hence this leads to alkalosis as the H+ levels go down. Also, the CO2 going to stimulate the central chemoreceptors reduce hence the chemoreceptors do not stimulate the inspiratory centre but rather inhibit them hence the initial hyperventilation which was 5 times more than normal ventilation reduced to about one and a half to two times more hence the overall hyperventilation becomes mild as a result of the opposing actions of the central chemoreceptors and the peripheral chemoreceptors.

At the same time, the kidneys filter HCO3- which is normally absorbed into the proximal convulated tubule (In the lumen of the nephron, HCO3- combines with H+ released by the proximal convulated cells to form H2CO3 which then forms CO2 and H2O. These reactions are catalyzed by carbonic anhydrase. The CO2 enters the cells lining the proximal convulated tubules and CO2 is broken down into H+ and HCO3- by carbonic anhydrase. The HCO3- then goes back to the blood stream). However, at high altitudes, as the pH of blood drops, the pH sensitive carbonic ahydrase do not function hence HCO3- is not reabsorbed and the HCO3- is lost in urine i.e. bicarbonate uria. This helps make the pH neutral. Also, in the distal convulated tubules the same process occurs.

As the levels of HCO3- in blood reduce, the HCO3- that were formed in the CNS move to the blood hence the H+ in the CNS are free to stimulate the central chemoreceptors hence they stimulate the central chemoreceptors to stimulate the inspiratory centre to hyperventilate. This helps increase the PO2 in the alveoli which in turn increases the PO2 in the arterial blood.

NB:- Carbonic anhydrase is also involved in making of CSF hence at high altitudes, less HCO3- is made as the function of carbonic anhydrase is inhibited and this maintains the high levels of H+ in the CNS.

When someone is in high altitude areas for long, the endothelial cells and connective tissue of the peritubular capillaries in the kidney produce erythropoietin which goes to the bone marrow and prevents the erythroblasts from being stimulated to die by apoptosis hence more RBCs are formed and hence this increases the amount of Hb in the blood and this is called polycythemia. This increases the oxygen carrying ability of the blood.

Also, as a result of hyperventilation and increased blood volume the gas diffusion capacity of the lungs increases. This is because as a result of hyperventilation there is more oxygen in the lung and this leads to distension of the alveoli and as a result of increased blood volume the capillary walls are stressed and this increases the area for gas exchange hence increasing the rate of gas exchange.

Also, at high altitude, the cells release 2,3-DPG which goes to the RBCs and cross links the beta globin chains of the Hb and this leads to decreased affinity of Hb for O2 at the site of delivery of O2.

During chronic mild hypoxia, cells release angiogenic factors that go to the nearby capillaries and stimulate their endothelial cells to multiply and make more capillaries to increase the rate at which they receive O2.

Also, there is an increase in mitochondrial size and number and also increased number of enzymes involved into oxidative phosphorylation processes so that all the O2 is used efficiently.

Children born in high altitudes have a small body size but a big heart and a big chest. They have big hearts because they have hypoxia and hence they produce bronchioarterial constriction and this is overcome with higher BP produced by a bigger heart.

Some people may develop mountain sickness. It can either be acute or chronic. If it is acute then it is more fatal, however, if it is chronic then it can be treated as it is mild.

CONTINUE FROM PART 2

RESPIRATION IN EXERCISE

During exercise, there is no significant change in PO2 and PCO2 in the arterial blood. In mild to moderate exercise, there is no significant change is pH in the arterial blood. In severe exercise, pH will drop as a result of build up of lactic acid.

NB:- PCO2 in venous blood increases in exercise. There may be drop in PO2 of venous blood in exercise. During exercise there is increased cardiac output i.e. 6-7 times more.

When you want to exercise, the corticospinal tract sends neurones to the muscles to contract e.g. for running and at the same time the corticospinal tract gives some fibres to the inspiratory centre to stimulate it to increase ventilation. The golgi tendon organ and muscle spindles of the contracting muscles give sensory information to the inspiratory centre about proprioception.

In early exercise there is increase in tidal volume and in late exercise there is increase in respiratory rate and they both lead to an increase in ventilation.

During exercise there is a rise in PCO2 in venous blood and in intense exercise there is a drop in PO2 in venous blood. The ventilation/perfusion ratio in the apical part of the lung reduces as the total pulmonary blood flow increases.

Normally the Hb are saturated by the Imm of the 3mm of the capillary length and as during exercise more O2 is required, the remaining 2mm of the capillary length is to add more oxygen to the blood.

The oxygen association dissociation curve shifts to the right. According to the Haldane effect as more CO2 enters the blood from the tissues during exercise there is increased release of O2 from Hb. 2,3-DPG increases during intense exercise i.e. after an hour which cross links the beta globin chains of Hb and reduces their affinity for O2.

When the oxygen demand is not met then the body starts respiring anaerobically hence leading to an oxygen debt which leads to hyperventilation in order to pay the debt.

HYPOXIA

READ USING DR. NAJEEB

ASSESSMENT OF RESPIRATORY SYSTEM

READ USING DR. NAJEEB