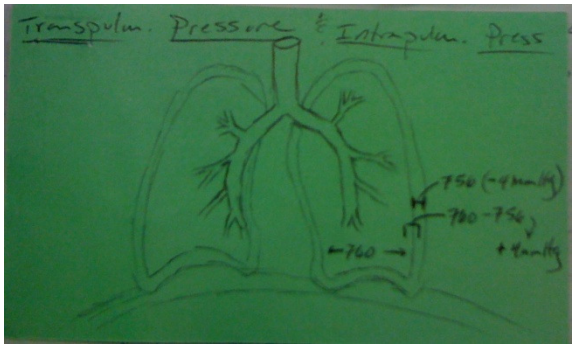
Pulmonary Ventilation

- Goals of respiration:
  - Provided O_2 to the tissues/remove CO_2
- To achieve these goals, resp. is divided into 4 events:
  1. Pulm. Ventilation = exchange of resp. gases between ATM and alveoli
  2. Diffusion of Resp. Gases = movement of O2 and CO2 b/w the alveoli and blood
  3. Transport of Resp. Gases = how it is carried in the blood and tissues
  4. Regulation of Ventilation = Resp. groups in the medulla and pons

I. Mechanism of Pulmonary Ventilation
- Req. the expansion and contraction of the lungs
- 2 ways:
  1. Movement of the diaphragm (lengthen/shorten the chest cavity)
  2. Elev/dep. of the ribs (inc/dec. diameter of chest cavity)
- Normal breathing occurs via #1
  - Inspiration = diaphragm move down, pulling the lungs down
  - Expiration = relaxes the diaphragm through **elastic recoil**
- Heavy breathing occurs via #2
  - req. extra force (need to use abdominal muscles)
  - Inspiration = ext. intercostals (elevate the chest)
  - Expiration = int. intercostals and rectus abdominus (depress the chest)

A. Movement of Air
- The lungs are not attached to the chest cavity; free floating/suspended in pleural fluid
- Continual suction of fluid from capillaries into the lymphatic system, creates a suction b/w the parietal pleura and visceral pleura (pleural pressure)…usually slightly negative
  - What happens if the suction/pressure is lost? = Pneumothorax (collapsed lung)
- Pleural Pressure = pressure between the pleura (visceral and parietal)
- Alveolar Pressure = pressure of air within alveoli
  - Open to the ext. atm
  - All pressure in the respiratory tree is equal to the atmospheric pressure
- Compliance
  - This is the extent to which the lungs expand for each increase in **transpulmonary pressure** (difference b/w the Pleural Pressure and Alveolar Pressure)
  - $C_L = \Delta V_L / \Delta(P_{pl}-P_{alv})$



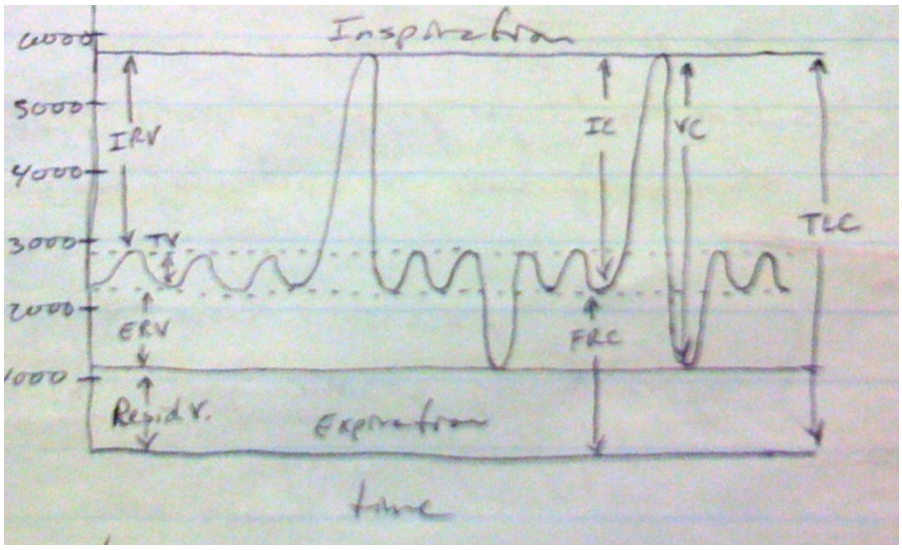
- Surfactant
  - Surface active agent
  - Reduces surface tension
  - Produced/secreted by type II alveolar epith. Cells
- Physical Factors influencing Insp/Expiration:

- Resistance → $F = \Delta P / R$
- The relationship b/w pressure and volume can be expressed through Boyle's Law:
  - At a constant temp, pressure and volume are inversely related and it is represented by the equation – $p_1v_1 = p_2v_2$

II. Pulmonary Capacities and Volumes

A. Spirometry

- Simple method for measuring pulmonary volumes
- Typical spirometer consists of the following:
  - Drum inverted in a tub of H20
  - Weight to counterbalance the drum
  - Tube connecting the mouth to the gas chamber
- When a person breaths into the tube, the drum will rise/fall in proportion to the volume of air expired and is also recorded on a piece of paper
- Pulmonary Volumes:
  - 4 volumes can be measured:
    - Tidal volume (TV) = normal inspiration/expiration (~500ml)
    - Inspiratory Reserve Volume (IRV) = the extra volume of air that can be inspired above the normal tidal inspiration (~3000ml)
    - Expiratory Reserve Volume (ERV) = the extra volume of air that can be expired above the normal tidal expiration (~1100ml)
    - Residual Volume (RV) = volume remaining in lungs after a forceful expiration (~1200ml)
- Pulmonary Capacities:
  - Can be calculated by combining two or more pulmonary volumes
  - 4 capacities:
    - Inspiratory Capacity (IC) = TV + IRV
    - Functional Residual Capcity (FRC) = ERV + RV
    - Vital Capacity (VC) = IRV + TV + ERV
    - Total Lung Capacity (TLC) = VC + RV or IC + FRC



III. Functions of Respiratory Passages

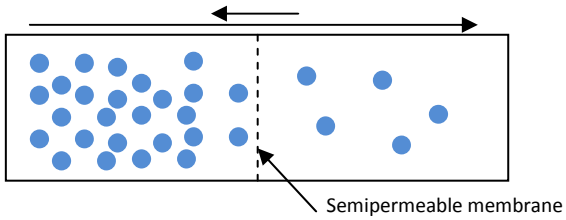
- Air enters lungs in 3 ways:

    - Trachea
    - Bronchi
    - Bronchioles
- Respiratory passages also consist of cartilage to keep the conducting areas open
    - 5/6 of the trachea is composed of "c" shaped hyaline cartilage
    - The proportion of cartilage decreases from the Trachea → Bronchi, allowing free contraction and expansion of the lungs
    - No cartilage in bronchioles (kept open via transpulmonary pressure)…as alveoli open, bronchioles open.
    - Where there is no cartilage, walls are comprised of smooth muscle
    - Bronchioles are almost entirely smooth muscle
        - Exception = respiratory bronchiole (the most terminal end)
- Many obstructive pulmonary diseases result from narrowing, often b/c of excessive contraction of smooth muscle
- Sympathetic dilation of bronchioles is relatively weak due to not many nerve fibers penetrating the central portion of the lungs
    - However, Epi and NE do not have an effect…they stim. β-receptors, causing dilation
- Parasympathetic constriction of bronchioles is caused by penetration of the vagus (X) nerve into the lung tissue
    - Nerves secrete ACh, which causes mild-moderate constriction
    - In asthmatics, parasymp. Stimulation and asthma attacks have serious effects
        - Treatment with atropine can cause some relaxation

Physical Principles of Gas Exchange

- After alveoli are filled w/air, the next step is diffusion of O_2 from alveoli into blood and diffusion of CO_2 in the opposite direction
- So what is diffusion?
    - Random molecular motion in all directions in the respiratory membrane and surrounding fluids
    - In respiratory physiology we are not only concerned with the mechanism, but also the **rate** at which diffusion occurs

I. Physics of Diffusion and Partial Pressures
- All gases of concern in respiratory physiology are simple molecules, free to move among one another (diffusion)…this is also true for dissolved gases in the body
- …For diffusion to occur, there must be a source of energy. This energy is provided by the kinetic motion of each gas molecule



Dissolved gas molecules will follow a concentration gradient. Net diffusion will occur from an area of high concentration to low, while some molecules will travel in the opposite direction. The energy for this diffusion comes from the kinetic energy of the molecules as they move and hit each other or bounce off the membrane walls.

A. Partial Pressures of Individual Gases

- How is pressure created?
    - Constant impact of molecules against a surface
    - Pressure generated is directly proportional to the concentration of the gas
- In respiratory physiology we don't just deal with O2, we deal with mixtures of gases (O_2, CO_2, N_2…)
- The rate of diffusion of each gas is directly proportionate to the pressure caused by each gas alone…this is called the **Partial Pressure** of the gas***
    - Example:
        - Air = 79% N_2 and ~20.9% O_2
        - Total pressure = ~760 mmHg
            - Pressure from N_2 = 600 mmHg (pN_2)
            - Pressure from O_2 = 160 mmHg (pO_2)

B. Pressure Differences Cause Net Diffusion

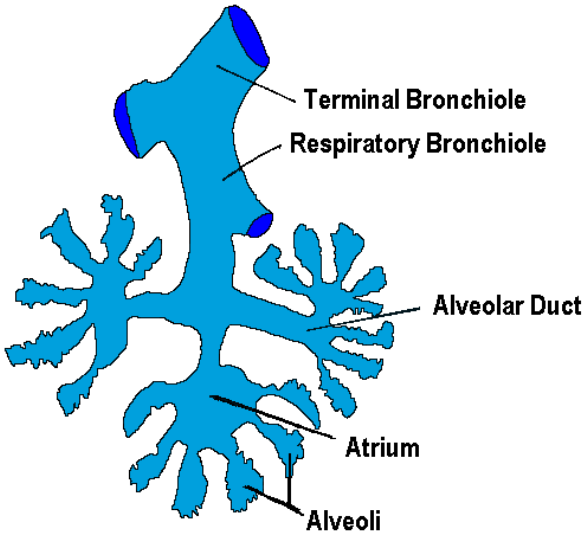
- When the pressure of a gas is greater in one area than in another, there will be net diffusion from the area of high pressure to the area of low pressure.
- In addition to the ΔP, other factors influence the rate of diffusion:
    - **Solubility** of gas in the fluid (CO_2 is 20x more soluble in the blood than O_2)
    - **Cross sectional area** of fluid (> area = > # of molecules)
    - **Distance** through which the gas has to travel (thicker = slower)
    - **Molecular weight** of the gas
    - **Temperature** of the fluid (usually remains constant)

C. Diffusion of Gases through Tissues

- All gases important to respiratory physiology are highly lipid soluble (O_2 and CO_2)
- This makes them highly soluble in cell membranes (i.e. phospholipid bilayer)
- The only major limitation in the gases is the rate they diffuse through tissue H_2O, not cell membrane

II. Diffusion of Gases through the Respiratory Membrane

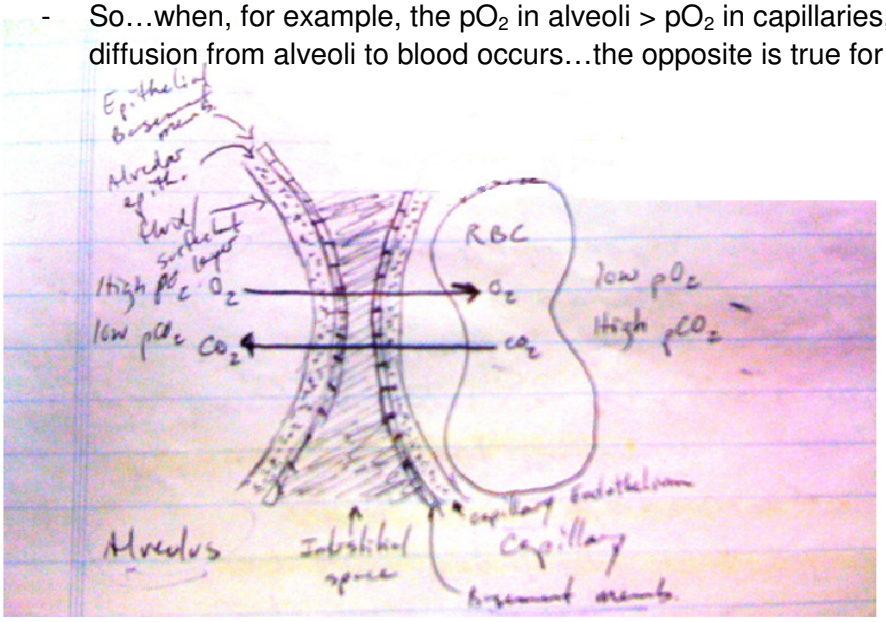
- Respiratory Unit:



- w/in this system there is a continuous network of interconnecting capillaries…creating a flowing "sheet" of blood around the alveolar walls
- b/c alveolar gases are in such close proximity, gas exchange takes place through all membranes of the terminal portion of the respiratory unit
- there are **6** different layers of the respiratory membrane:
    - Surfactant
    - Alveolar epithelium
    - Epithelial basement membrane
    - Interstitial space b/w capillary and alveoli
    - Capillary basement membrane
    - Capillary endothelial membrane
- From a histological standpoint, the alveoli cover a shockingly large area:
    - Estimated to be ~70 m^2
    - This is equivalent to a room 25x30ft
    - This should give a better understanding of the rapidity of gas exchange

A. Factors Affecting the Rate of Diffusion
- Thickness of Respiratory Membrane:
    a. Sometimes thickness increases (i.e. result of edema)
        - In this case, respiratory gases must now pass through the membrane and the fluid
    b. Also, some diseases cause fibrosis in lungs, increasing portions of the respiratory membrane
    c. Any factor that increases the thickness by a factor of 2-3x can significantly influence the rate of gas exchange
- Surface Area of Respiratory Membrane:
    a. Many conditions can decrease S.A. (i.e. removal of a lung)
    b. The best example/disease is Emphysema
        - This disease causes alveoli to coalesce, w/dissolution of many alveolar walls
        - New chambers are much larger, but the total S.A. for gas exchange has decreased by as much as 5x.
    c. Surface area becomes most important during periods of strenuous activity
    d. Any decrease in surface area can severely inhibit gas exchange
- Diffusion Coefficient:
    a. This is the measure of the transfer of gas through the respiratory membrane
    b. Depends mainly on the gas's solubility
        - CO_2 = 20.3
        - N_2 = .53
        - O_2 = 1.0
    c. The rate of diffusion in the respiratory membrane is almost exactly the same as it is for H_2O
        - Therefore, for a given ΔP, CO_2 diffuses 20x as fast as O_2…and O_2 diffuses at a rate ~2x as fast as N_2
- Pressure Difference:

a. This is the difference b/w the partial pressures of gas in alveoli (pO_2 and pCO_2) and the pressure of gas in the capillaries
b. The partial pressure is a measure of the total # of molecules of a particular gas, striking a unit area of the alveolar surface
c. The pressure of gas in blood equals the number of molecules that attempt to escape from the blood in the opposite direction
d. Therefore, the difference b/w these two pressures will give the net tendency for the gas molecules to move across the membrane
    - So…when, for example, the pO_2 in alveoli > pO_2 in capillaries, net diffusion from alveoli to blood occurs…the opposite is true for CO_2



B. Diffusion of O_2
- In men, the avg. diff. capacity for O_2 is ~21 ml/min/mmHg (it is a little less than this in women)
- This means:
    - The mean O_2 pressure difference across the respiratory membrane is ~11 mmHg
    - Multiplication of this pressure by the diffusing capacity (11*21) gives 230 ml of O_2 diffusing through the respiratory membrane each minute.

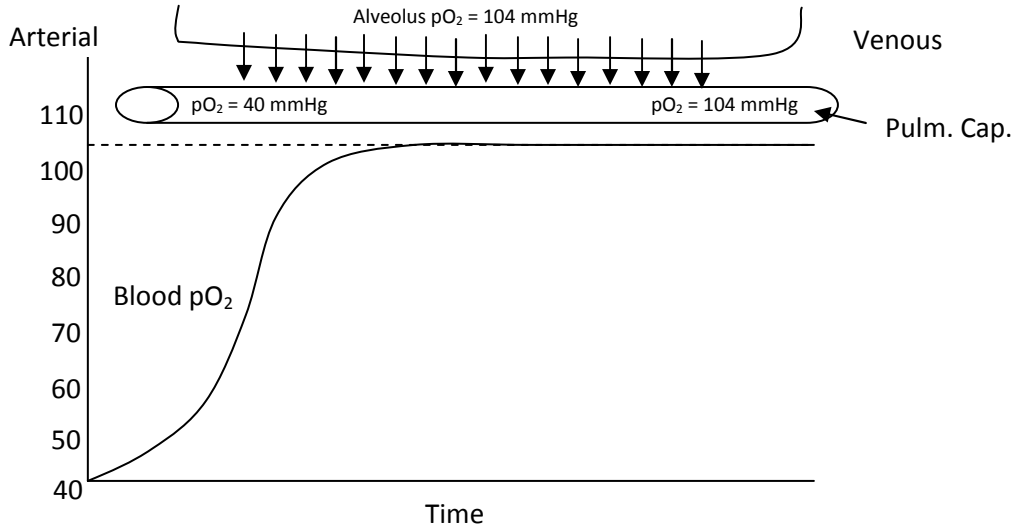
C. Diffusing Capacity of CO_2
- Interestingly, this value can't be measured directly
- This is because CO_2 diffuses so rapidly that the avg. pCO_2 in pulmonary blood is not that different than the pCO_2 in the alveoli…the difference is <1 mmHg (too small to measure accurately)
- However, b/c the diffusing capacity is 20x faster than that of O_2, one would expect the value to be between ~410-450 ml/min/mmHg at rest.

Transport of O_2 and CO_2 in Body Fluids

- Once O_2 is in the blood it binds w/Hb (allows for 30-100x more O_2 to be transported) and is carried to the tissue capillaries
- In tissues O_2 reacts w/food stuffs and cellular respiration takes place
    - What is the equation for cellular respiration? What is the by-product?
        - $C_6H_{12}O_6 + 6O_2 \rightarrow \underline{6CO_2} + 6H_20 + ATP$
- CO_2 is a by-product of cellular respiration and is transported back to the lungs

I. Pressures of O_2 and CO_2 in Lungs, Blood, and Tissues
- We have already discussed that gases move via diffusion caused by pressure differences
    - Therefore O_2 diffuses into blood if:
        - $pO_{2\ alveoli} > pO_{2\ capillaries}$
    - In the same way, O_2 diffuses into tissues if:
        - $pO_{2\ cap} > pO_{2\ tissues}$
    - The same is true for CO_2, only in the opposite direction
- So it is fair to say that you must have <u>diffusion</u> and <u>blood flow</u> for transport of respiratory gases.

A. Uptake of O_2 in Blood

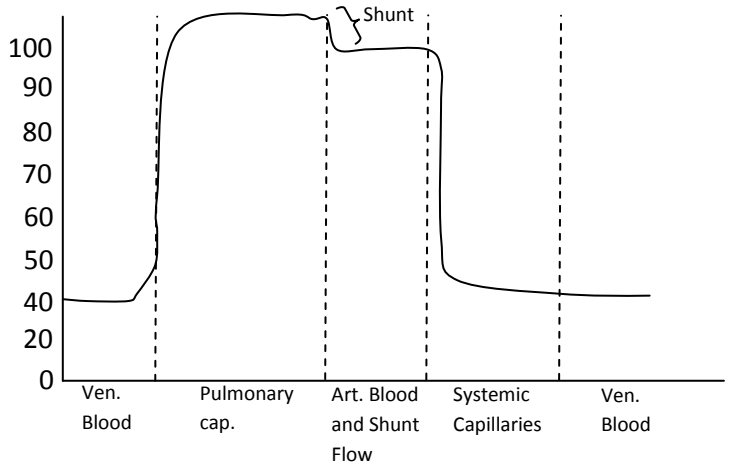


- Shows the pulmonary alveolus adjacent to pulmonary capillaries w/diffusion of O_2 molecules
- pO_2 in alveolus averages 104 mmHg, whereas pO_2 from the body averages 40 mmHg
- This curve shows the rapid rise in blood pO_2 as the blood moves through the capillary
- How does exercise influence O_2 uptake?
    - You need ~20x as much O_2 during exercise compared to rest
    - Cardiac output increases, decreasing the time blood spends in the capillaries surround the alveoli
    - For this reason, oxygenation of blood could suffer, but it doesn't…here is why:
        - As you increase activity, more respiratory surface area is opened up for diffusion

- Look at the graph, blood becomes fully saturated after only passing through the first 1/3 of the pulmonary capillaries, so there is extra time to take up more O_2 if needed.

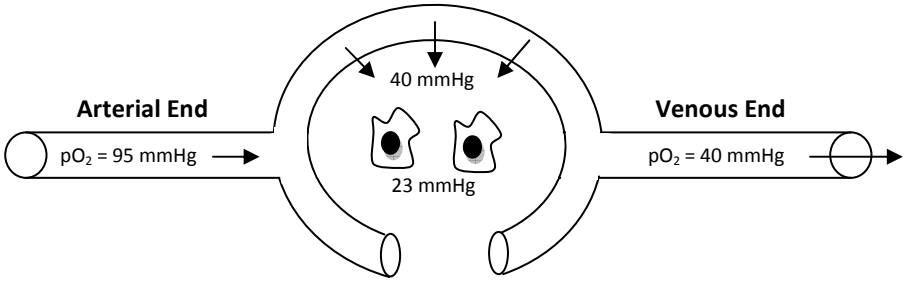
B. So, the O_2 that reaches tissue capillaries is only 95 mmHg, What???

- Why not 104 mmHg?...98% of blood that enters the left atrium has gone past the alveolar capillaries, this accounts for the 104 mmHg.
- ~2% has passed directly from the aorta through the bronchiolar circulation, this is referred to as the "shunt" flow.
    - The pO_2 of this blood is ~40 mmHg, similar to the venous blood
    - "shunt" blood combines w/oxygenated blood from the alveolar capillaries (called venous admixture) and causes the pO_2 to fall to 95 mmHg



C. Diffusion of O_2 from **<u>Peripheral Capillaries into Tissues</u>**

- What is the pO_2 of blood when it reaches the tissues? (95 mmHg)
- The pO_2 of the surrounding tissue fluid is only ~40 mmHg
    - This pressure difference causes O_2 to diffuse rapidly from the blood into the tissue spaces
- So, after diffusion, what is the pO_2 of blood leaving the tissues?
    - ~40 mmHg when it goes from tissue capillaries into the venous circulation

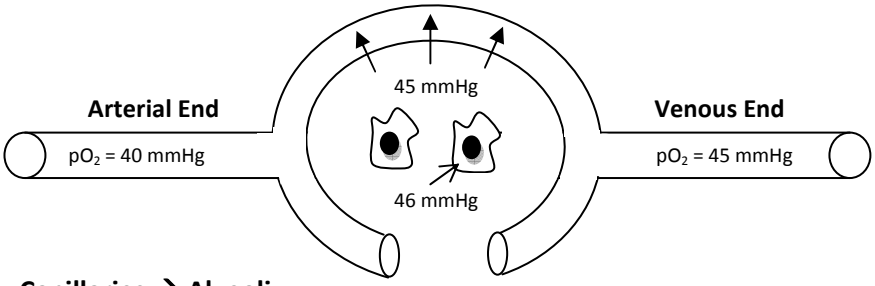


- Where does the 23 mmHg factor in?
    - O_2 is always being used by cells and in many cases there is considerable distance b/w capillaries and cells
    - Therefore, the normal, intracellular range of pO_2 goes from as little as 5 mmHg to a maximum of 40 mmHg, averaging to ~23 mmHg

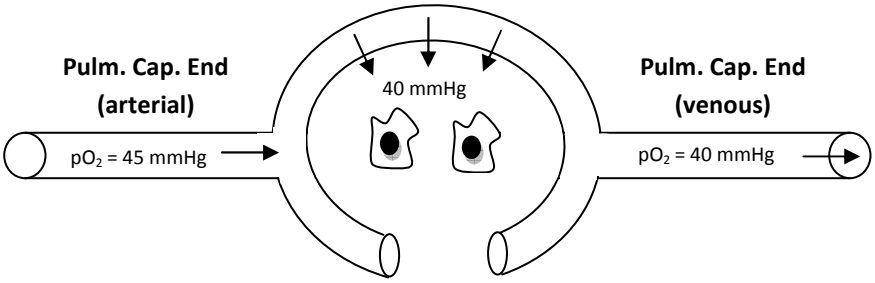
- This is more than enough b/c tissues only need ~1-3 mmHg for normal, resting conditions

D. Diffusion of CO_2 from **<u>cells into tissue capillaries</u>**…and **<u>Pulmonary Capillaries to Alveoli</u>**

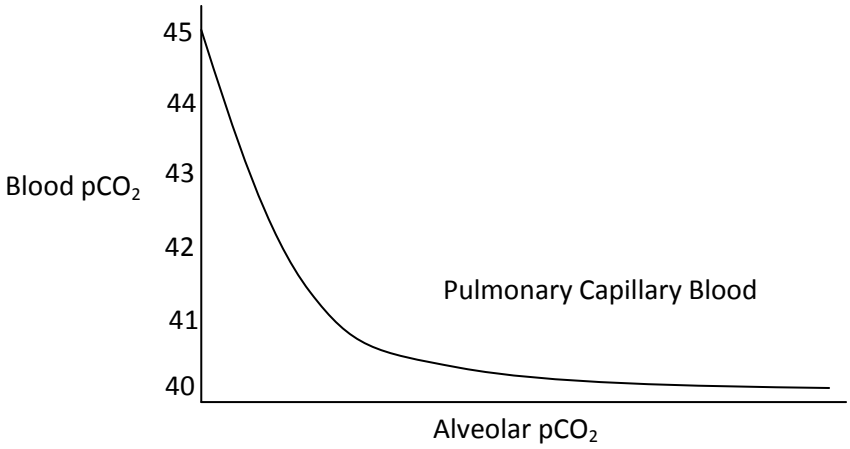
- After diffusion of O_2, O_2 is used in cellular respiration and a byproduct is CO_2
- CO_2 diffuses from the cells into tissue capillaries where it is then carried to the lungs
- In the lungs, it diffuses from the pulmonary capillaries into the alveoli
- At every point in the respiratory cycle, CO_2 diffuses opposite to O_2
- However, there is 1 major difference, CO_2 diffuses 20x faster!
- What does this mean for the pressure difference?.....IT CAN BE FAR LESS!!!!!
- <u>For Example:</u>
  - Intracellular pCO_2 = 46 mmHg; Interstitial pCO_2 = 45 mmHg
    - There is only a 1 mmHg pressure difference
  - pCO_2 of arterial blood entering tissues = 40 mmHg; pCO_2 of venous blood = 45 mmHg
    - the tissue capillary blood is almost in equilibrium w/the interstitial pCO_2.
  - pCO_2 of blood in the pulmonary capillaries = 45 mmHg; pCO_2 of alveolar air = 40 mmHg
    - only a 5 mmHg pressure difference causes all of the CO_2 diffusion out of the pulmonary capillaries and into the alveoli.
- **<u>Cells → Tissue Capillaries:</u>**



- **<u>Pulmonary Capillaries → Alveoli:</u>**

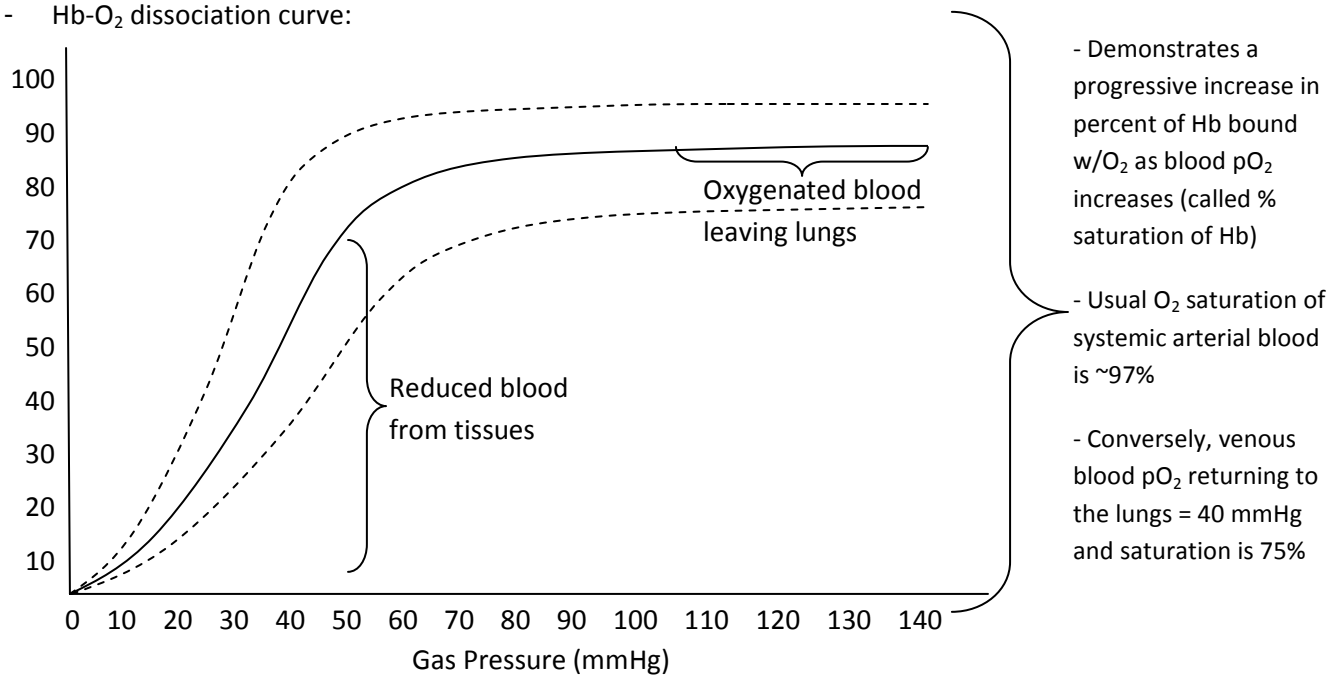


- Also:



II. Transport of O_2 in Blood (Hb)

- Hb-O_2 dissociation curve:



- Normally, 98% of O_2 is carried by Hb in the RBC's
- The other 2% is dissolved in plasma H_2O (this number is low b/c O_2 is not very soluble in H_2O)
- O_2 bound to Hb combines loosely w/the heme groups, allowing the attachment to be reversible
    - ↑pO_2 (pulm. cap.) induces O_2-Hb; ↓pO_2 (tissue cap.) releases O_2 from Hb.
- The combination of O_2 and Hb is called oxyhemoglobin, or HbO_2
- Hb that has released O_2 is called deoxyhemoglobin, or HHb.
- The equation for this reaction is as follows:
    - $HHb + O_2 \leftrightarrow HbO_2 + H^+$
- The rate at which O_2 is unloaded from Hb is regulated by pO_2, temperature, blood pH, pCO_2, and BPG (DPG)
    - BPG (2,3 – Bisphosphoglycerate) reversibly binds w/Hb and is produced by RBC's as they utilize glucose during glycolysis
    - So:
        - ↑ temperature, pCO_2, H^+, or BPG = ↓Hb affinity for O_2 (Bohr Effect)
            - Remember, ↑H^+ = ↓pH
            - This causes the Hb-O_2 curve to shift to the right
            - This in turn increases the rate at which O_2 is unloaded from Hb in blood
        - ↓ in any of the above factors leads to increased Hb affinity for O_2 (Haldane Effect)
            - Causes the curve to shift to the left

A. Hb-NO and Gas Exchange

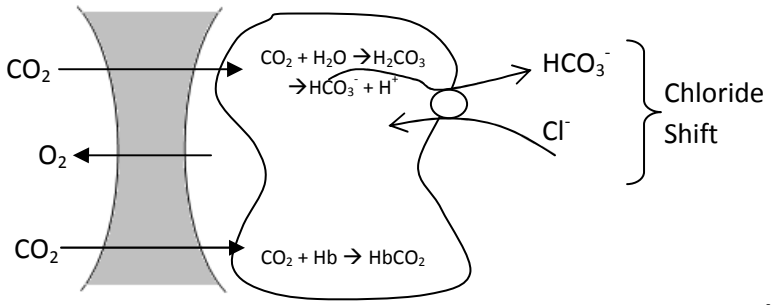
- NO (nitric oxide) is actively secreted by vascular endothelial cells and causes vasodilation
- Hb acts as a NO scavenger
- Another side effect of Nitrogen is that it is a major cause of hypoxia (inadequate supply of O_2 to the tissues)
    a. 4 Types:
        i. Anemia Hypoxia

ii. Ischemic Hypoxia
iii. Histotoxic Hypoxia
iv. Hypoxemic Hypoxia
v. CO Poisoning
    - Basically a subclass of Hypoxemic Hypoxia
    - Hb affinity for CO is >200x that of O_2, therefore it displaces O_2 on Hb.
        a. HbCO = carboxyhemoglobin

III. Transport of CO_2

- Blood transports CO_2 from tissues to the lungs in 3 forms:

1. Dissolved in plasma (7-10%)
2. Chemically bound to Hb ($HbCO_2$) – carbaminohemoglobin
    - Reaction = $CO_2 + Hb \leftrightarrow HbCO_2$
    - Reaction is rapid, does not require a catalyst
    - Bind to amino acids of the globin group, not the heme group
    - Loading and unloading is directly influenced by pCO_2
3. As bicarbonate ions in plasma (~70%)
    - Vast majority of CO_2 transport is by HCO_3^-
    - When CO_2 diffuses into RBC's it combines with H_2O, forming carbonic acid (H_2CO_3)
        a. H_2CO_3 is highly unstable and quickly dissociates
            i. $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$
    - H^+ ions released bind to Hb, triggering the Bohr effect
    - At the same time, Chloride (Cl_2^-) ions are rushing from the plasma into RBC's, this is called the **<u>Chloride Shift</u>**… (this is as HCO_3^- moves to the plasma)
    - In the lungs, the process is reversed…HCO_3^- moves into RBC's while chloride ions move into the plasma
        a. HCO_3^- binds with H^+ to form carbonic acid, which dissociates into water and carbon dioxide...the carbon dioxide move along the pressure gradient into the alveoli



IV. Bicarbonate Buffer System
- Typically H^+ ions released during H_2CO_3 dissociation is buffered by Hb (HHb)
- HCO_3^- generated in the reaction in RBC's diffuses into plasma where it acts as an alkaline reserve
- The HCO_3^- buffer system is very important in maintaining blood pH
    a. i.e. → if hydrogen concentration increases in blood, excess hydrogen ions bind with bicarbonate to form carbonic acid (weak acid), which dissociates very little at physiological pH or acidic pH
    b. if the concentration of hydrogen ions decreases, carbonic acid is converted back to biocarbonate, the pH will become more acidic.

V. Control of Respiration
- Most normal breathing is controlled by networks of neurons in the medulla and pons
    1. Medulla:
        - sets the respiratory rhythm
        - 2 critically important areas →
            a. dorsal respiratory group (DRG)
                - integrates input from peripheral stretch and chemoreceptors
                - transfers information to the VRG
            b. Ventral respiratory group (VRG)
                - rhythm regulation and integration center
                - contains neurons controlling inspiration and expiration
                    - stim. of inspiratory fibers = phrenic/intercostals nerves activ.
                    - stim. of expiratory fibers = inhib. of above; elastic recoil
    2. Pons:
        - influence and modify signals from the VRG
            - smooths out the transition between inspiration and expiration
        - the PRG (pontine respiratory group) also sends signals to the VRG

VI. Homeostatic Imbalances
- Hyperventilation
    a. Rapid breathing decreases concentration of CO_2 in blood (hypocapnia)
    b. Cerebral vessels constrict
    c. Increased H^+ concentration in blood → decrease blood pH (acidosis)
    d. pCO_2 is abnormally low, apnea (or cessation of breathing) occurs until pCO_2 levels are restored and stimulates breathing
    e. ***sometimes swimmers induce hyperventilation…allows them to remove CO_2 from their body, thereby decreasing the effect it has on respiration. The benefit is that they can hold their breath longer, but the risks (passing out) outweigh the benefits.
- COPD (chronic obstructive pulmonary disease)
    a. Common examples = chronic bronchitis or emphysema
    b. These conditions share 4 common features:
        i. ~>80% are smokers
        ii. Exhibit dyspnea, or labored breathing
        iii. Chronic coughing
        iv. Development of respiratory failure manifested as hyperventilation, causing respiratory acidosis and hypoxemia
- Asthma

    a. Characterized by coughing, wheezing, dyspnea, etc…
    b. Similar to COPD, but reversible
    c. In asthmatics, active inflammation comes first, caused by T lymphocytes secreting interleukins (IL), increasing the concentration of Immunoglobulin E (IgE) in the blood
- Tuberculosis
    a. Caused by bacterial infection (*Mycobacterium tuberculosis*)
    b. Usually not a problem due to fast immune responses and antibiotics
    c. Some strains are becoming antibiotic resistant
- Lung Cancer
    a. Leading cause of cancer related deaths
    b. Can be prevented…nearly 90% of all cases are due to smoking
    c. Because it grows rapidly and metastasizes widely, it is not recognized until it is well advanced
    d. Smoking increases the risk due to:
        i. Inactive mucus membrane/cilia that usually carry disease and toxins/chemicals out of the body
    e. 3 common types:
        i. Squamous cell carcinoma
        ii. Adenocarcinoma
        iii. Small cell carcinoma