Respiratory System and Disorders

Lesson 2

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Diffusion

- Diffusion through tissues is described by **Fick's law:**

- As a result, carbon dioxide diffuses more rapidly than does oxygen (20 times more).

Alveolar Gas Pressures

- Athmosperic gas pressures:
  - Po_2 = 160 mmHg
  - Pco_2 = 0,3 mmHg

- Typical alveolar gas pressures:
  - Po_2 = 105 mmHg
  - Pco_2 = 40 mmHg

- The factors that determine the precise value of alveolar Po_2:
  1. The Po_2 of atmospheric air
  2. The rate of alveolar ventilation.
  3. The rate of total-body oxygen consumption.

- ***Hypoventilation*** exists when there is an increase in the ratio of carbon dioxide production to alveolar ventilation.

- ***Hyperventilation*** exists when there is a decrease in the ratio of carbon dioxide production to alveolar ventilation.

Diffusion and Perfusion Limitations

Diffusion and Perfusion Limitations

- **Carbon monoxide (CO):** Binds tightly to Hb. Large amount of CO can be taken up by the cell with almost no increase in partial pressure.

- It is clear, therefore, that the amount of carbon monoxide that gets into the blood is limited by the diffusion properties of the blood-gas barrier and not by the amount of blood available.

- The transfer of carbon monoxide is therefore said to be ***diffusion limited***.

Diffusion and Perfusion Limitations

- **Nitrous oxide (N_2O):** No combination with hemoglobin takes place. The partial pressure rises rapidly.
- The amount of this gas taken up by the blood depends entirely on the amount of available blood flow and not at all on the diffusion properties of the blood-gas barrier.
- The transfer of nitrous oxide is therefore ***perfusion limited*.**

Diffusion of Oxygen

- **Oxygen (O_2):** O_2 combines with hemoglobin (unlike nitrous oxide) but with nothing like the avidity of carbon monoxide.

- Under resting conditions, the capillary Po_2 virtually reaches that of alveolar gas in 0,25 sec. Under these conditions, O_2 transfer is perfusion limited like nitrous oxide.

- However, in some abnormal circumstances when the diffusion properties of the lung are impaired, it may become diffusion limited as well.

Diffusion of Oxygen

- The diffusion reserves of the normal lung are enormous.
- In severe exercise, the time available for oxygenation is less (1/3), but in normal subjects breathing air, there is generally still no measurable fall in end-capillary Po_2.
- Abnormality: Thickenin of alveolar wall by disease so that rate of oxygen diffusion is slowed

Diffusion of Oxygen

- Another way of stressing the diffusion properties of the lung is to lower the alveolar Po_2.

- Subject is either going to high altitude or inhaling a low O_2 mixture.

Impairment of Diffusion

- The total surface area of all of the alveoli in contact with pulmonary capillaries may be decreased:
  - In ***pulmonary edema,*** some of the alveoli may become filled with fluid.
  - Alveolar walls become severely thickened with connective tissue (fibrotic), as, for example ***diffuse interstitial fibrosis.***
- Typical symptoms of these types of diffusion diseases: shortness of breath and poor oxygenation of blood.
- Pure diffusion problems of these types are restricted to oxygen and usually do not affect the elimination of carbon dioxide, which diffuses more rapidly than oxygen.

Matching of Ventilation and Perfusion

- **Ventilation–perfusion inequality** is the mismatch of alveolar air flow and capillary blood flow.

- Because of gravitational effects on ventilation and perfusion, there is enough ventilation–perfusion inequality in healthy people to decrease the arterial Po_2 about 5 mmHg. (105 → 100)

The Ventilation-Perfusion Ratio

- The Po_2 in any lung unit is determined by the ratio of ventilation to blood flow. This is true not only for O_2 but also for CO_2.

Regional Gas Exchange in the Lung

- Ventilation increases slowly from top to bottom of the lung and blood flow increases more rapidly.
- As a consequence, the ventilation-perfusion ratio is abnormally high at the top of the lung (where the blood flow is minimal) and much lower at the bottom.

Matching of Ventilation and Perfusion

- Disease states can cause marked ventilation–perfusion inequalities:
  1. There may be ventilated alveoli with no blood supply at all (dead space or wasted ventilation) due to a blood clot, for example.
  2. There may be blood flowing through areas of lung that have no ventilation (this is termed a ***shunt***) due to collapsed alveoli, for example
  3. Thebesian veins in heart.

- There are several local homeostatic responses within the lungs that minimize the mismatching of ventilation and blood flow and thereby maximize the efficiency of gas exchange.

Local Control of Ventilation–Perfusion Matching

1. Low oxygen in alveoli causes local vasoconstriction
2. Low perfusion causes local bronchoconstriction

Transport of Oxygen in Blood

- The oxygen is present in two forms in blood:
  1. Dissolved in the plasma (2%)
  2. Reversibly combined with hemoglobin molecules in the erythrocytes (98%)

- According to **Henry's law**, the amount dissolved O_2 is proportional to the partial pressure
  - For each mm Hg of Po_2; there is 0,003 ml O_2 /100ml blood.

- Dissolved O_2 is insufficent for metabolism. Clearly, an additional method of transporting O_2 is required

Transport of Oxygen in Blood

Hemoglobin

- Each **hemoglobin** molecule is a protein made up of four subunits bound together.

- **Heme** is an iron-porphyrin compound that is joined to each of four polypeptide chains that together constitute the protein globin.

- The chains are of two types, **alpha** and **beta**, and differences in their amino acid sequences give rise to various types of human hemoglobin.

Transport of Oxygen in Blood

Hemoglobin

- Each of the four heme groups in a hemoglobin molecule contains one atom of iron (Fe^{2+}), to which molecular oxygen binds.
- Each iron atom can bind one molecule of oxygen, a single hemoglobin molecule can bind four oxygen molecules.
- Hemoglobin can exist in one of two forms—**deoxyhemoglobin** (**Hb**) and **oxyhemoglobin** (**HbO_2**).

$$O_2 + Hb \rightleftharpoons HbO_2$$

Hemoglobin Saturation

- In a blood sample containing many hemoglobin molecules, the fraction of all the hemoglobin in the form of oxyhemoglobin is expressed as the **percent hemoglobin saturation.**

- Percent Hb saturation = $\dfrac{O_2 \text{ bound to Hb}}{\text{Maximal capacity of Hb to bind } O_2} \times 100$

- The denominator in this equation is also termed the **oxygen-carrying capacity** of the blood.

Oxygen–Hemoglobin Dissociation Curve

Oxygen–Hemoglobin Dissociation Curve

- By far the most important is the blood Po_2.
- The curve is sigmoid. Because the reactions of the four subunits occur sequentially, with each combination facilitating the next one.
- The globin units of deoxyhemoglobin are tightly held by electrostatic bonds in a conformation with a relatively low affinity for oxygen.
- The binding of oxygen to a heme molecule breaks some of these bonds between the globin subunits, leading to a conformation change that leaves the remaining oxygen-binding sites more exposed.

Tense (T) State
Low Affinity State

↔

Relaxed (R) State
High Affinity State

Oxygen–Hemoglobin Dissociation Curve

- As a summary,
  - Hb has high affinity to O_2 in lung capillaries (High Po_2) (loads the O_2)
  - Hb has low affinity to O_2 in systemic capillaries (Low Po_2) (unloads the O_2)

- This **plateau portion** at higher Po_2 values has a number of important implications (a safety factor).
  - In many situations, including at high altitude and with pulmonary disease, a moderate reduction occurs in alveolar $Po_{2.}$
  - Even if the Po_2 decreased from the normal value of 100 to 60 mmHg, the total quantity of oxygen carried by hemoglobin would decrease by only 10%.

Oxygen–Hemoglobin Dissociation Curve

- The **plateau portion** also explains;
  - A healthy person at sea level, increasing the alveolar Po_2 either by hyperventilating or by breathing 100% oxygen does not increase Hb saturation.
  - Only a small additional amount dissolves.

- **BUT!** If a person initially has a low arterial Po_2 because of lung disease or high altitude, then increasing the alveolar Po_2 would result in significantly more oxygen transport on hemoglobin.

- The **steep portion** of the curve (from 60 mmHg down to 20 mmHg) is ideal for unloading oxygen in the tissues:
  - A small decrease in Po_2 due to diffusion of oxygen from the blood to the cells, a large quantity of oxygen can be unloaded in the peripheral tissue capillaries.

Oxygen–Hemoglobin Dissociation Curve

- The factors that influence hemoglobin saturation other than Po_2:
  - Blood Pco_2,
  - H^+ concentration $p[H^+]$,
  - Temperature,
  - **2,3-diphosphoglycerate**(**DPG**) (also known as bisphosphoglycerate [BPG])
- DPG, which is produced in erythrocytes reversibly binds with hemoglobin, causing it to have a lower affinity for oxygen:
  - Whenever DPG concentrations increase, there is enhanced unloading of oxygen from hemoglobin.
  - Increase in DPG concentration is triggered by inadequate oxygen supply or hypoxia (high altitude).

Oxygen–Hemoglobin Dissociation Curve

←

CO
Fetal Hb

Temperature ↑
2,3-diphosphoglycerate(DPG) ↑
p[H^+] ↑

→

Oxygen–Hemoglobin Dissociation Curve

- The more metabolically active tissues, have greater Pco_2, H^+ concentration, and temperature.
- At any given Po_2, this causes hemoglobin to release more oxygen during passage through the tissue's capillaries.
- It is another local mechanism that increases oxygen delivery to tissues with increased metabolic activity.

Carbon monoxide (CO) Poisoning

- ***Carbon monoxide (CO)*** is a colorless, odorless gas. Inhalation of CO is a common cause of sickness and death due to poisoning
- CO has extremely high affinity—210 times that of oxygen—for the oxygen-binding sites in hemoglobin so it occupies these sites.
- CO exerts a second deleterious effect.
  - Upon binding to hemoglobin it increases affinity of O_2
  - Hb cannot unload O_2 for tissues.

Transport of Carbon dioxide (CO_2) in Blood

1. In bicarbonate (HCO3-) form (60% to 65%)
   - CO_2 is converted to HCO_3^-

$$CO_2 + H_2O \underset{}{\overset{\text{carbonic anhydrase}}{\rightleftharpoons}} \underset{\text{carbonic acid}}{H_2CO_3} \rightleftharpoons \underset{\text{bicarbonate}}{HCO_3^-} + H^+$$

2. In carbamino form (25% to 30%)
   - CO_2 react reversibly with the amino groups of hemoglobin to form **carbaminohemoglobin.**

$$CO_2 + Hb \rightleftharpoons HbCO_2$$

3. Dissolved in plasma (10%)
   - CO_2 is much more soluble in water than oxygen

Transport of Carbon dioxide (CO_2) in Blood

- This reaction is too slow unless catalyzed in both directions by the enzyme **carbonic anhydrase.**
- This enzyme is present in the erythrocytes but not in the plasma, so this reaction occurs mainly in the erythrocytes.
- Once formed, most of the HCO_3^- moves out of the erythrocytes into the plasma via a transporter that exchanges one HCO_3^- for one chloride ion (this is called the "**chloride shift**" which maintains electroneutrality).

$$CO_2 + H_2O \underset{}{\overset{\text{carbonic anhydrase}}{\rightleftharpoons}} \underset{\text{carbonic acid}}{H_2CO_3} \rightleftharpoons \underset{\text{bicarbonate}}{HCO_3^-} + H^+$$

TISSUE CAPILLARIES

LUNG CAPILLARIES

Transport of H^+ Between Tissues and Lungs

- Deoxyhemoglobin has a much greater affinity for H^+ than does oxyhemoglobin, so it binds (buffers) most of the H^+.
- When deoxyhemoglobin binds H^+, it is abbreviated HbH.

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

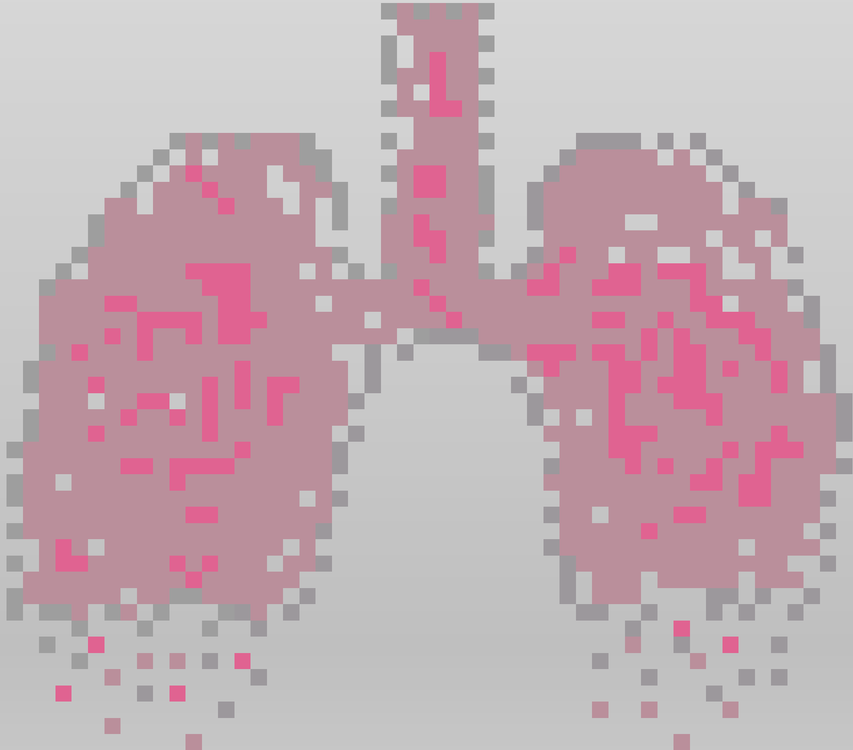
- In this manner, only a small amount of the H+ generated in the blood remains free. This explains why venous blood (pH = 7.36) is only slightly more acidic than arterial blood (pH = 7.40).

Transport of H^+ Between Tissues and Lungs

- As the venous blood passes through the lungs, this reaction is reversed.

- When a person is hypoventilating;
  - Not only would arterial Pco_2 increase as a result, but so would arterial $[H^+]$. Increased arterial $[H^+]$ due to CO_2 retention is termed ***respiratory acidosis***

- Conversely, hyperventilation;
  - Would decrease arterial Pco_2 and $[H^+]$, produce ***respiratory alkalosis.***



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Thank you for your patience!