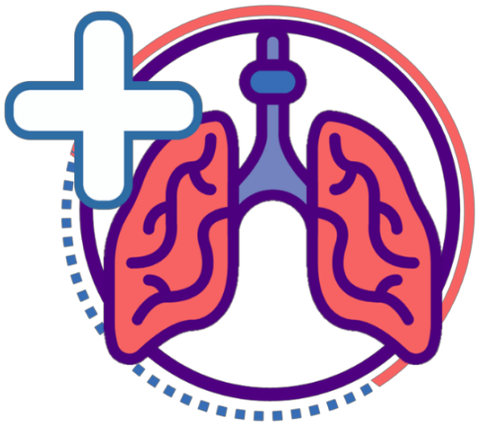

RESPIRATORY SYSTEM

Physiology

Sheet Slide

Number: -10

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Topics that are discussed in this sheet :

- Why the hemoglobin is located inside red blood cell ?
- CO_2 Exchange.
- Respiratory centers.
- Control of breathing.

Note

1. 2,3 BPG inside RBC. If no DPG the HbO_2 curve is no more sigmoidal, it becomes like that for myoglobin.
2. NADH-met-Hb reductase inside RBC converts methHb (ferric) to reduced Hb (ferrous).
3. Protection against degradation enzymes in plasma.
4. Protection against filtration through the kidneys.
5. Presence of C.A. which converts CO_2 to HCO_3, otherwise by using Acetazolamide (CA inhibitor) PCO_2 reaches 80 mmHg
6. Prevent in blood viscosity.

* Why does hemoglobin lie inside the RBCs, instead of being dissolved in plasma?

-There is a set of important enzymes lie inside the RBCs and are in help for Hb, these are: carbonic anhydrase, reductase (which converts Methemoglobin back to hemoglobin), mutase (which produces the regulator 2,3-DPG from 1,3-DPG).

-If the Hb is dissolved in the plasma, it will elevate the viscosity of the blood.

-The molecular weight of Hb = 64 kDa, so it would filter through the kidney thus, it will be lost in the urine.

CO2 exchange:

Forms of CO2 in blood

CO2 is carried in the blood in three forms: as **dissolved CO2**, as **carbaminohemoglobin** (CO2 bound to hemoglobin), and **as bicarbonate (HCO3 –),** which is a chemically modified form of CO2. By far, *HCO*3− *is quantitatively the most important* of these forms.

- CO2 is produced by cells, so the PCO2 in the interstitium is 45mmHg.

- Blood stays in the capillary bed for a certain period of time during which CO2 must be cleared from cells.

This CO2 diffuses to the capillaries, which contain RBC's (Hb.bound CO2; carbon anhydrase enzyme) and plasma (dissolved CO2).

* Respiratory exchange ratio (R) = CO2 production / O2 consumption

$$R = \frac{\dot{V}CO2}{\dot{V}O2} = \frac{200\ ml/min}{250\ ml/min} = 0.8$$

Normal cardiac output = 5L/min = 50 dl/min

- Each dl of arterial blood contains 20 ml O2, In capillary beds 5 ml will be extracted from each dl, leaving 15 ml O2 in venous blood.

So, in one minute, 50 dl blood will give off 5*50 = 250 ml O2 for cells to be used. O2 consumption = 250 ml/min.

- Each dl of blood in capillaries receives 4 ml of CO2, so total CO2 production = 50 * 4 = 200 ml/min.
  [In our next discussion we will define the forms through which these 200ml are transported]

If we were dependent only on carbohydrates in our diet, then according to the equation for the combustion of glucose(C6H12O6 + 6O2 -->6CO2 + 6H2O) O2 consumption equals CO2 production, so their ratio is 1:1, thus R would equals to 1. But this is not the case in our bodies due to mixed diet we take (proteins, fats,..) so it's 0.8 .

1) Dissolved CO2:

According to Henry's law, the concentration of dissolved CO2 is proportional to **the partial pressure** of CO2; the proportionality constant is simply the **solubility** of CO2 in blood, which is 20-folds the solubility of O2 (Solubility of CO2 = 20 * solubility of O2 (.003) = .06) . According to that: [$CO2$] = $Partial\ Pressure\ of\ CO2 \times solubility\ of\ CO2$

[CO2]arterial blood = 40 X 0.06 = 2.4 ml/dl

[CO2]venous blood = 45 X 0.06 = 2.8 ml/dl

2) Carbaminohemoglobin:

CO2 can bind hemoglobin, resulting with carbaminohemoglobin.

3) HCO3- :

When CO2 enters the RBC, it reacts with H2O to give off H2CO3. This reaction is catalyzed by the enzyme **carbonic anhydrase**. This scheme of catalyzing this reaction is important, to enable the blood to take up CO2 at the capillaries in a fast manner, since it does not have much time to do so. This reaction converts CO2 to another form (HCO3-) which will maintain a concentration gradient to drive the flow of CO2 into the blood.

- If carbonic anhydrase is deficient, there will be slow conversion of CO2 to bicarbonate, which will delete the driving force of CO2 uptake (No concentration gradient)

H2CO3 dissociates into HCO3 - and H+. After that, HCO3 - ions that get out of the cell are substituted with Cl-ions from the plasma (chlorine shift).

- [HCO3-] in venous blood > [HCO3-] in arterial blood , Cl- is the opposite.

- In the lungs:

O2 will replace CO2 and bind to Hb.
HCO3 - ions get back to the RBC's, replacing Cl ions that get back to the plasma. HCO3- reacts with H+ to form H2CO3 all over again. After that, H2CO3 gives off CO2 and H2O (catalyzed by carbonic anhydrase). Then, CO2 diffuses towards the alveoli.

CO_2 Transport; amounts summary:

CO_2	Arterial	Venous	A-V Difference	Percentage (of 4 ml/dl)
Dissolved	**2.4**	2.8	0.4	**10%**
Hb-CO_2	2.4	3.6	1.2	30%
Bicarbonate	43.2	45.6	2.4	**60%**
Total	48	52	**4**	100%

- Dissolved form is the least contributor.
- Bicarbonate ion form is the most important contributor.
- Significant numbers are in bold; the rest are not for memorization.
- Remember: dissolved CO_2 > dissolved O_2.

- What's the role of the respiratory system? **To maintain normal arterial blood gases (ABG).**
- Normal ABG:
  PO2= 95 mmHg [notice it isn't 100 mmHg, due to venous admixture & V/Q inequality.
  PCO2= 40 mmHg

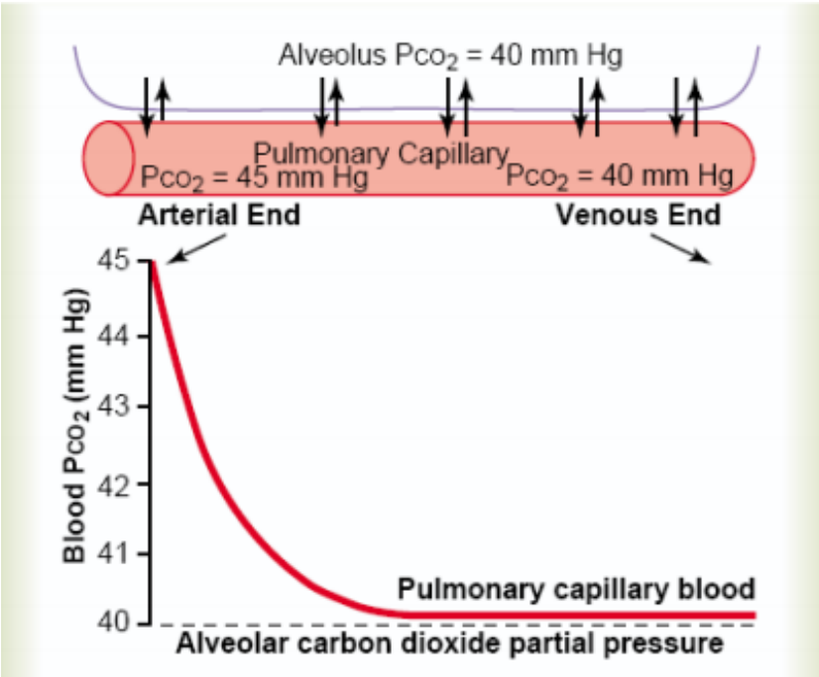
  Why is arterial PO2 95mmHg, while alveolar PO2 is 100mmHg? PaCO2 = PACO2; but PaO2 < PAO2

- For O2
  1- Venous admixture: Venous admixture is the result of mixing of non-reoxygenated blood with reoxygenated blood. This "pollution" has three

sources: 1- Bronchial veins 2- Cardiac veins (that empty in the left heart/atrium) 3- Physiologic A-V shunt (right to left): some blood from the pulmonary artery bypasses the alveoli without undergoing gas exchange. Approximately, 2% of the cardiac output is shunted.

2- Inequality in V/Q ratio: In the base of the lung, PO2 is 90mmHg, while in the apex, PO2 is 130mmHg. This 130mmHg does not compensate for the 90mmHg. This is a result of the S-shaped Hb-O2 dissociation curve. At PO2 of 130mmHg, saturation is 100%, and at PO2 of 90mmHg, saturation is nearly 100%, too. So, for oxygen, the hyperventilated area does not compensate for the hypoventilated area, because of the S-shaped Hb-O2 dissociation curve. (If the curve was linear, then 30% increase in the x-axis is accompanied with a 30% increase in the y-axis.)

- For CO2:



Notice that the curve in the figure is "linear". CO2 is self-compensatory; if one lung is hypoventilated and the other lung is hyperventilated, the hyperventilated one would

not compensate for the hypoventilated in terms of oxygen. However, CO2 levels would be compensated for.

- In order to achieve respiration, we need to contract the diaphragm. Because the diaphragm is a voluntary muscle it needs an external stimulus [**it lacks automaticity**, no intrinsic ability to initiates its own action potential like the SA node(no sodium leakage channels)]. So, if we increase the number of stimuli, we are achieving increased ventilation (be careful it is not hyperventilation!), and vice versa (less stimuli→ decreased ventilation).
- Goals of increased ventilation is to increase PO2, decrease PCO2 and decrease H+.

- **How to calculate blood pH**
  Henderson-Hasselbalch Equation:

$$pH = 6.1 + log \frac{[HCO_3^-]}{[.03 \times P_{CO_2}]}$$

- Normally, [HCO3-] =24 mmol , pCO2 = 40 so pH=7.4
- Acidosis (low pH) is caused by : increase of PCO2, decrease of HCO3-, or both.
- So, getting rid of CO2 is more important than bringing O2 in, because CO2 will be converted into H+ which in turn affects each enzyme in the body, by changing the body's pH from their optimal ones.
- If H+ increases, some enzymes in CNS will stop working → coma & death.
- If H+ decreases, some enzymes start firing too much in respiratory muscles! → convulsions& death.
  Therefore, [H+](40*10^-9) must be precisely maintained. Although its concentration is 3.5 million times less than [Na+](140*10^-9) but it is more important and we care a lot about it.

<u>Respiratory Centers</u> -controllers of respiration-

Three take-home messages:

1) The objective of the controller system is to guarantee normal ABG.

2) The tools used to achieve this goal are: increased ventilation or decreased ventilation.
3) The nature of the feedback regulation of this system is the level of O_2, CO_2 and H^+.

Feedback regulation:

- By O_2 level: + Increased O_2 level doesn't affect the respiratory center.
  - decreased O_2 level below 60 mmHg, will activate the center.
- By CO_2 level: High CO_2 will activate the center. (to wash out CO_2 by increased ventilation)
  Low CO_2 will suppress the center. (to retain some CO_2)

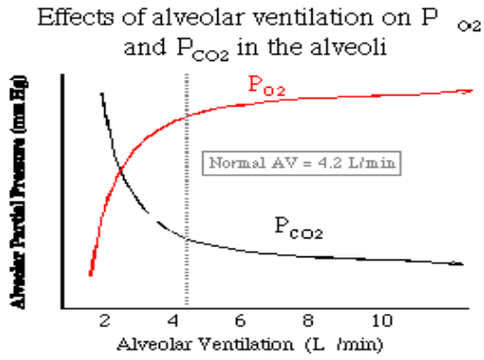
**Notice that both, increase or decrease in PCO_2 will affect the center, because CO_2 must be precisely maintained normal.
Also H^+ does the same as Co_2.

** Clinical application:
If a child with type 1 diabetes presented to your clinic while he is in a coma or semi coma, and you need to determine the cause whether it is due to hypoglycemia (because of high dose of insulin) or hyperglycemia with ketoacidosis.
A clue may present, if he has acidosis he will have hyperventilation (increased number of breaths).
Meaning that, his body is trying to fix the acidosis, by converting H^+ in the presence of HCO_3^- back to CO_2 by carbonic anhydrase, to be expired by lungs.
By doing that, we are losing a very important ion which is the bicarbonate, which may ultimately cause the depletion of HCO_3^- (there are limits in our bodies for that).

Control of breathing

First: what affects the gases?

Notice here that we are talking about the arterial PO2



-PO2 depends on:

1- Alveolar Ventilation VA (O2 delivery to alveoli).

2- O2 consumption VO2(Rate of O2 absorption to blood).

So :

PaO2 = (VA/VO2)*k.

(**k** here is a constant as the relation is not liner).

-Arterial PO2 is directly proportional to alveolar ventilation but inversely proportional to oxygen consumption.

-Now if you wanted to increase(from 100 to 120 for example) arterial PO2(or alveolar PO2), you can either increase the rate of ventilation, decrease your oxygen consumption.

-if you wanted to decrease(from 100 to 90 for example) arterial PO2, you can either decrease the rate of ventilation, or increase your oxygen consumption.

-But normally, arterial PO2 is kept around normal values(100) because of our regulatory mechanisms that will be described in the next lecture.

-During exercise, alveolar ventilation and oxygen consumption are increased in a proportional way, and thus not affecting arterial PO2.

- But notice that the maximum arterial PO2 that can be achieved is 150(here, we breath an atmospheric air(160) which is humidified via H2O to become 150). We can increase the PO2 above 150 only by increasing the O2 fraction of air(more than 21%).

Very important take home messages:

The 1st " Increase ventilation is when the lungs try to make the alveolar air composition closer to the atmospheric air(try to make PO2 150 & PCO2 around 0).

The 2nd "Decreased ventilation will try to shift PO2 and PCO2 to their values in mixed venous blood (increase PCO2 around 45 and decrease PO2 around 40).

We are done with PO2, let's study the PCO2

-PCO2 and hydrogen ion:

PaCO2 = (VCO2/VA)*K

-K is a constant and it equals 0.863mmhg.lit/ml

-If ventilation is doubled then PaCO2 decreases to half.

-If ventilation is halved then PaCO2 is doubled.

The tools by which the respiratory center will use to maintain normal ABGs are:.

* increased ventilation which tries to shift PO2 and PCO2 to their values in atmospheric air (decrease CO2 and increase O2).

* decreased ventilation which tryies to shift PO2 and PCO2 to their values in mixed venous blood (increase CO2 and decrease O2).

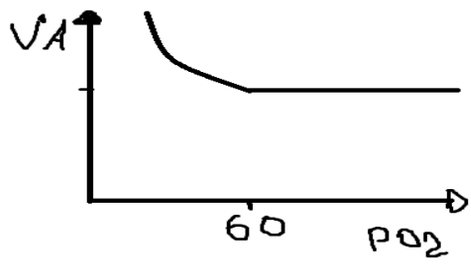
The alveolar – arterial difference of CO2 is zero(self-compensatory), while the difference of O2 is less than 5 mmHg (due to the venous admixture & Inequality in V/Q ratio).

We mentioned how does the ventilation affect gases, now we will discuss how do gases affect or regulate ventilation:.

-Starting with O2:. <u>Notice the curve.</u>

- When PO2 increases:

If PO2 is increased above 100, the control system does nothing. This is because any increase in PO2 over 100 will not cause more saturation of



hemoglobin because it is already 100% saturated. So, ↑PO2 over 100 doesn't affect the control system.

- When PO2 decreases:

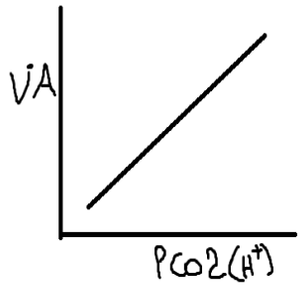
When PO2 decreases from 100 to 60, the control system also does nothing. But once the PO2 is decreased to less than 60, ventilation increases. (This will be explained more in the next lecture)

- CO2 as a regulator:.

When PCO2 increases → hyperventilation to return it back to normal

When PCO2 decreases → hypoventilation to retain CO2.

So, both ↓ PCO2 and ↑PCO2 causes a response (unlike O2). The relation is liner.



Let's have an example:.

-If we take a normal person and bring him to a higher altitudes what will happen?

- When a person ascends to high altitudes, atmospheric pressure will drop, so PO2 will drop(but its fraction stills 21% of the atm), leading to hypoxia which drives the ventilation.
- But hyperventilation will lead to hypocapnia(low CO2) which suppresses ventilation.
- So in first few days, the patient will suffer from mild hypoxia, and hypocapnia. As hypoxia(stimulates ventilation) and hypocapnia(suppresses ventilation) antagonize each other.
- In the coming 5 days in mount top, this person will tolerate CO2 drop.(more details in the next lecture)
- In the coming days, after tolerating low CO2 , Suppression for ventilation (alkalosis) will be removed, hypoxia will be the only driver of the ventilation, so ventilation will increase and usually successfully compensate for hypoxia.

-And this person will live in peace there for now.

The doctor will discuss in more details this example in the next lecture :)

{ قُلْ سِيرُوا فِي الْأَرْضِ فَانظُرُوا كَيْفَ بَدَأَ الْخَلْقَ ۚ ثُمَّ اللَّهُ
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و الحمد لله