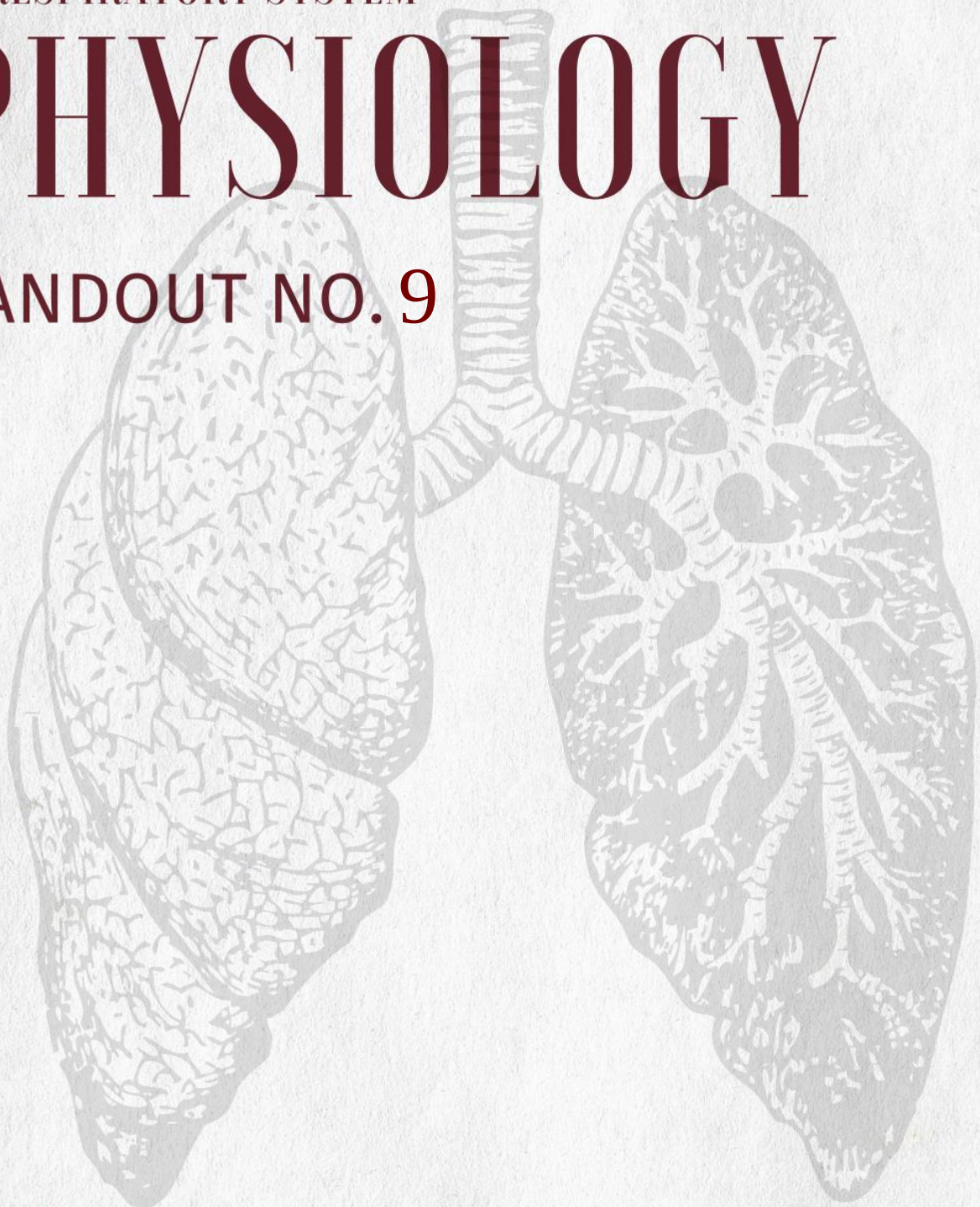
RESPIRATORY SYSTEM

PHYSIOLOGY

HANDOUT NO. 9



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Color code

slides

doctor

important

Gas Transport

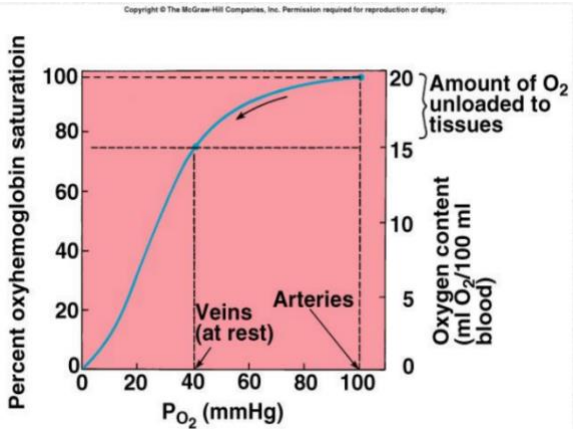
Important concepts (additional tables)

Aspect	Description
Forms of O_2 in Blood	Oxygen is carried in two forms: dissolved O_2 and O_2 bound to hemoglobin. Dissolved O_2 alone is insufficient for tissue demands, so hemoglobin-bound O_2 is essential.
Dissolved O_2	Accounts for **~2%** of total blood oxygen concentration. Dissolved O_2 generates partial pressure, which drives oxygen diffusion, but has a minimal role in oxygen transport.
O_2 Bound to Hemoglobin	Constitutes **~98%** of total oxygen concentration. Hemoglobin binds oxygen reversibly, enabling efficient oxygen transport to tissues.
Oxygen Concentration and Hemoglobin	Most of the oxygen concentration in blood is determined by hemoglobin as **oxyhemoglobin**. Total O_2 concentration depends on hemoglobin's O_2-binding capacity, saturation percentage, and dissolved oxygen.

Aspect	Partial Pressure of Oxygen (PO_2)	Oxygen Concentration
Definition	The pressure exerted by oxygen molecules dissolved in blood plasma.	The total amount of oxygen present in the blood.
Units of Measurement	Millimeters of mercury (mmHg)	Milliliters of O_2 per deciliter of blood (mL O_2/dL) or grams per deciliter (g/dL)
Components Included	Only oxygen dissolved in plasma.	Oxygen dissolved in plasma **plus** oxygen bound to hemoglobin.
Measurement Methods	Arterial blood gas (ABG) analysis.	Hemoglobin saturation tests, ABG, or calculated using PO_2 and hemoglobin levels.
Physiological Significance	Indicates the ability of oxygen to diffuse from the lungs into the blood and from the blood to tissues.	Represents the total oxygen available for transport to tissues.
Dependence on Hemoglobin	Independent of hemoglobin; only accounts for dissolved oxygen.	Dependent on hemoglobin levels; most oxygen is carried bound to hemoglobin.
Relationship Formula	**Oxygen Dissolved (mL O_2/dL) = PO_2 (mmHg) × 0.0031**	**Oxygen Concentration (mL O_2/dL) = (Hemoglobin × 1.34 × SaO_2) + (PO_2 × 0.0031)**

*O2 concentration and O2 content are the same thing

The importance of oxygen concentration [O2]:



⇒ if the hemoglobin is 7.5g or 15g, the curve will not change

⇒So, even in 7.5g hemoglobin, P_AO2 = 100, O_2 sat =100%, but [O2] = 10

⇒while 15g hemoglobin, when P_AO2 = 100 & O_2 sat =100%, the [O2] = 20

Why is O2 concentration more important than O2 saturation and O2 partial pressure?

1. The importance of [O2] is manifested in **anemia**, decrease in RBCs leading to ↓ **[O2], but O sat= 100% & PaO2 =100**, because PaO2 represents oxygen in plasma not bound to hemoglobin.
2. **CO poisoning**
   carbon monoxide bound to hemoglobin, significantly impairs hemoglobin ability to carry oxygen, because it binds to hemoglobin with 250 times greater affinity than O2. ↓ **[O2],** is reduced, as COHb displaces oxygen on hemoglobin and prevents proper oxygen transport,
   O2 sat is reduced because it is bound to CO rather than O2.
   PaO2 =100 , When PO2 is less than 60, the respiratory center will respond, but in this case when PO2 is 100 the center will not respond.

Even if P_aO2 is 100, this doesn't mean that they have enough oxygen, that's why most of them die (**CO** -carbon monoxide- **poisoned patients**) because of CO strong binding (250x than O2) so it's difficult to be released, what's worse is that the symptoms are mild and mistaken (as if they are drinking alcohol) and they are not bluish (in early cases).

Oxygen carrying capacity

❖ Depends on two factors

1. Number of hemoglobin molecules (polycythemia vs anemia)
2. Saturation of Hb

A) Oxygen-carrying capacity of blood is determined by its hemoglobin concentration.

* Anemia:

• [Hemoglobin] below normal.

*Polycythemia:

• [Hemoglobin] above normal.

B) Hemoglobin production controlled by erythropoietin.

• Production is stimulated by a decrease in renal PO2

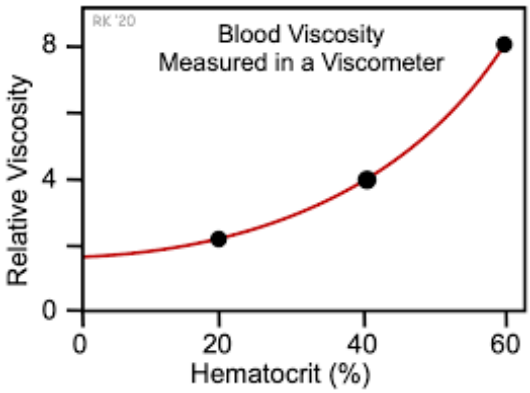
Hemoglobin production in bone marrow is stimulated by erythropoietin which is secreted by the kidney when there is hypoxia in the kidney.

At high altitudes, generalized hypoxia in the kidney ➔ stimulates erythropoietin secretion, after 4-6 weeks:

- Hemoglobin ➔ 20g/dl (instead of 13.8 – 17.2 in men, and 12.1 – 15.1 in women)
- Hematocrit ➔60% (instead of 40-45%)

⇒ This results in increased viscosity, which increases resistance and leads to a greater load on the heart

- When hematocrit increases, the viscosity also increases, but it is not in a linear relationship, <u>at some point,</u> the curve will be shifted to the left, meaning that even a small increase in hematocrit causes viscosity to rise exponentially, leading to a high increase in the resistance and pressure. But a problem arises, there's pulmonary **vasoconstriction** leading to pulmonary **hypertension**, pulmonary arterial blood pressure will increase from 14 to 30, leading to increased pressure on the right atrium and potentially causing **cor pulmonale**



  - P = Q (cardiac output) x TPR (total peripheral resistance)

Values to remember

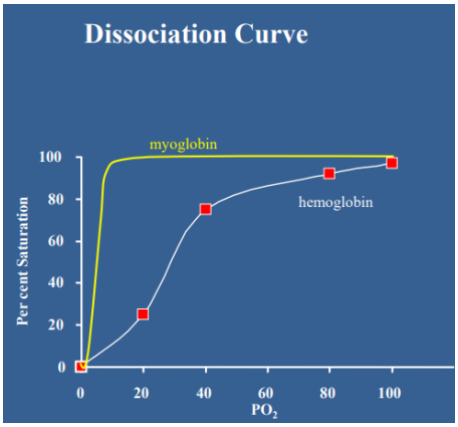
PO2	O2 Sat (%)	
10	25	
20	35	
26	50	P50
30	60	
40	75	Venous
50	85	
60	90	Respiratory center stimulation
80	96	
100	98	Almost Fully saturated

Remember this rule…it is close enough! (not precise)

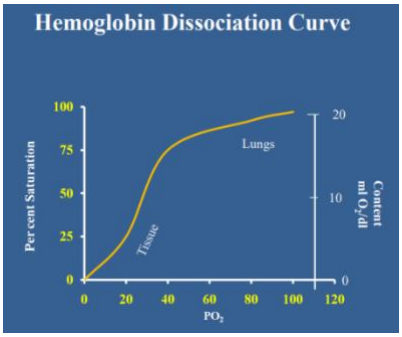
4,5,6	7-8-9
Po2 (mmHg)	40 50 60
%Sat	70 80 90

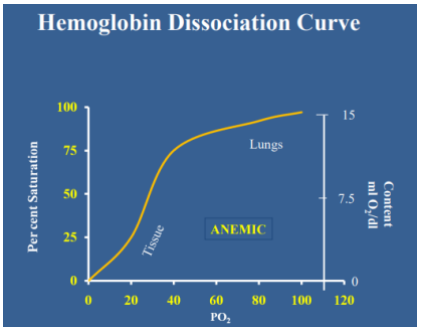
Myoglobin curve

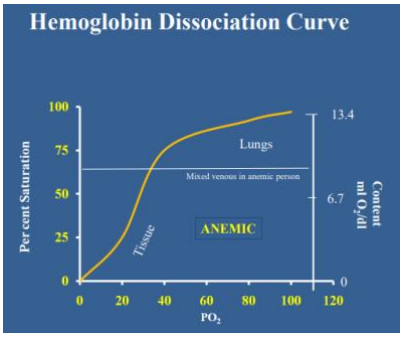
Myoglobin, which is found in heart and skeletal muscles, has a higher affinity for oxygen than hemoglobin, and a decreased ability to release O2. In the heart, myoglobin acts as an oxygen reservoir, ensuring oxygen availability to heart muscle cells during ischemia, when blood supply is compromised. Myoglobin's P50 is approximately 1 mmHg, which means that it binds oxygen even at very low partial pressures. In contrast, hemoglobin has a higher P50 (around 26 mmHg), reflecting its tendency to release oxygen more readily in tissues where oxygen concentration is lower.



Hemoglobin dissociation curve







- In **anemia the curve doesn't change, only the [O2] change, however**
- Normally, when the pO2=100 saturation is 100% → [O2] = 20 ml of O2/dl
  At P50 → [O2] = 10 ml O2/dl
  Remember: 15g hemoglobin *1.34 = 20 ml O2/dl

In anemia, for example, when pO2 = 100 and saturation is 100%, but the Hb content is decreased, [O2] = less than 20ml O2/dl. At P50 → [O2] = less than 10 ml O2/dl

- **In an anemic patient, what happens to the venous PO2? It will decrease,**

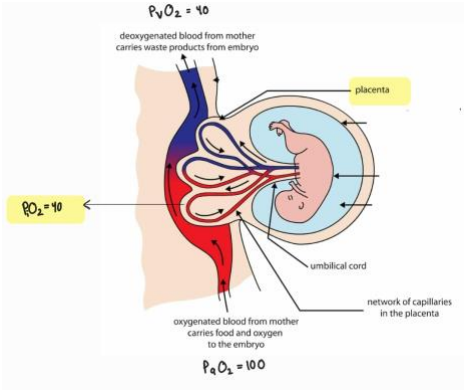
Let's see this example:

If the arterial O2 concentration is 10 ml O2/dl (as mentioned before, only the [O2] changes) at rest, what is the expected venous pO2?

- From the 10 mlO2/dl (100% saturated Hb), the tissue takes 5 ml O2/dl at rest, leading to a saturation of 50% at the venous side (5-10=5 ml/dl O2 left after tissue gas exchange, which is half the original O2 content of 10ml/dl) and a PO2 of 26mmHg (compared to 75% saturation and a PO2 of 40mmHg in the venous side in a normal person)
  The O2 saturation of the mixed venous in anemia will be less than 75%

Changes in the O2-Hemoglobin Dissociation Curve

1. Fetal hemoglobin

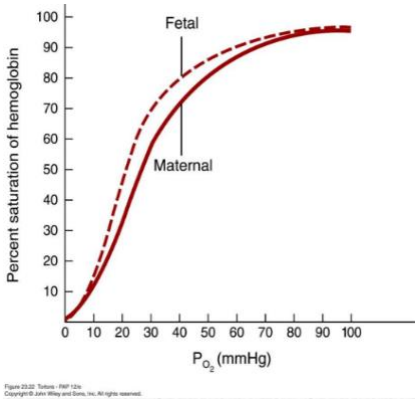


- Placenta (the membrane that acts as the lung for the fetus before birth - intrauterine period).

  The mother's placental PO2 is low (<40 mmHg), which reflects The P_iO2 of the interstitium.

While the fetus is growing, it needs a large amount of oxygen, since Fetal hemoglobin has 2 γ-chains in place of the β-chains

γ- chain does not bind 2,3 DPG therefore, HbF has higher affinity towards O2

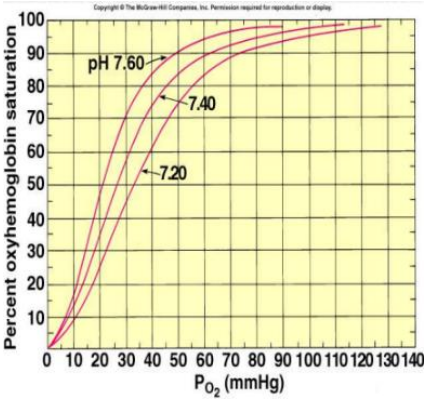


- So the curve will be **shifted to the left** leading to **higher** affinity of oxygen.
- So instead of when P_AO2 is 40 and O2 Sat is 75% as in hemoglobin A, in **hemoglobin F, when P_AO2 is 40, O sat is 95%**
- After the fetus takes its first breath, hemoglobin F production in the bone marrow is shifted to hemoglobin A

Fetal and Maternal Hemoglobin

- Fetal hemoglobin has a higher affinity for oxygen than adult hemoglobin
- Hb-F can carry up to 30% more oxygen
- Maternal blood's oxygen readily transferred to fetal blood

Effect of PH & Temp



- Normally, P50 is 26mmHg
- when the Curve shifts to the **right** due to ↓PH (acidosis) → **P50** is **more** than normal
- when the curve shifts to the **left** due to ↑ pH (alkalosis)→ **P50** is **less** than normal

!! the following topics (during exercise + high altitude) both topics will be explained in handout 10

So during exercise: exam question

1. Alveolar ventilation **increases**

2. Diffusion capacity of the lung for O2 **increases,** because there is more area for exchange (from 1/3 of the capillary to the entire capillary)

$$\text{Diffusion capacity} \propto \frac{(\text{area of the site of exchange})}{\text{thickness}}$$

3.P50 **increases** (notice the above pic)

4. cardiac cycle duration **decreases**

5. **Hyperventilation** during **intense** exercise **only**

Hyperventilation attempts to change the composition of alveolar air to match the composition of outside air more closely.

Hyperventilation is ONLY during intense or sever exercise when the person develops acidosis (not in mild exercise)

$$\text{P alveolar CO2} = \frac{\text{V co2 (co2 production)}}{\text{V R (alveolar ventilation)}} \text{x } 0.863$$

↑ PO2, ↓ PCo2

So, by definition, the Hyperventilation decreases arterial P_aCO2

Why doesn't hyperventilation happen during normal exercise?
Because arterial **Blood gases (ABG) remain normal**, since the production of **CO2 is increased**, and the **alveolar ventilation is increased**

Notice that by definition, hyperventilation is when PaCO2 decreases, and in mild exercise PaCO2 remains the same

$$\text{P alveolar Co2} = \frac{\uparrow \text{V co2 (co2 production)}}{\uparrow \text{VR (alveolar ventilation)}} \text{x } 0.863$$

Respiratory Exchange Ratio (RER):

- The cardiac output Q = 50 dL/min = 5L/min
- **At rest**, we extract **5mlO2/1dl** →50 * 5 = 250ml/min VO2 (O2 consumption)
- Similarly, the tissues release **4ml CO2/1 dl** →50x4 = 200 ml/min V_{CO2} (CO2 production)

(every one dl of blood (as we move towards the venous side) contains extra 4ml of CO2 and 5ml less of O2)

Respiratory exchange ratio (RER) =

$$\frac{\text{VCO2 (CO2 production)}}{\text{VO2 (O2 consumption)}} = \frac{4}{5} = \frac{200}{250} per\ minute = 0.8$$

* This value is less than 1 because we don't consume only carbohydrates (as discussed in GI physiology if you remember)

⇒ **carbohydrates** respiratory exchange ratio = 1

$C_6H_{12}O6 + 6O_2 \rightarrow 6CO_2$

* 6O2 → 6CO2 →This is a 1:1 ratio of number of O2 molecules consumed to number of CO2 molecules produced

⇒in **fats** = 0.7

⇒ in **protein** = 0.8

⇒ in **mixed** food = 0.8

At high attitude → hypoxia → hyperventilation

At high altitude: → PO2 ↓, O_2 sat ↓, [O2] ↓

Regulation of respiration:

we said before that hyperventilation ↑ PO2, ↓ PCo2, so in high altitudes, **two opposite stimuli occur:**

1. **Decreased** PO2 **drives** ventilation
2. **Decreased**PCO2 **inhibits** ventilation, (not a direct effect of CO2 on the respiratory center, but it's an indirect effect through the decreased H+ produced from CO2)

At sea level, the ventilation = 6L/min, when you ascend to **high altitude the ventilation increases to (e.g., 10),** then **after days it increases again to (e.g., 20),** so it's increased even when pCO2 is reduced, why?

> **First you should know how the respiratory center works** :the respiratory center in the medulla oblongata responds to Hydrogen ion not directly to CO2 , in the CSF, CO2 will bind to H2O → H2CO3 → $H^+ + HCO3^-$, the hydrogen ions will go to the respiratory center stimulating it. Thus an increase in arterial Pco2, results in increasing the PCO_2 of CSF, which results in an increase in H+ concentration of CSF (decrease in pH) A decrease in pH then signals the inspiratory center to increase the breathing rate (hyperventilation). (That's what is supposed to be)
>
> *(Henderson-Hasselbalch Equation) pH= 6.1 +log $(\frac{[HCO3-]}{[CO2]})$

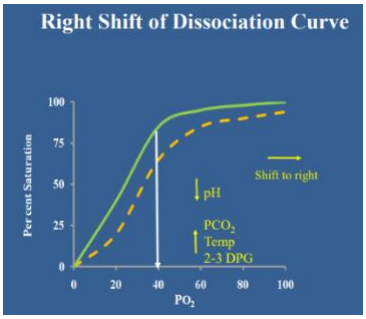
However in high altitude (we have higher ventilation along with the decreased CO2 and H+!!)

According to the equation above:

Where $HCO3^-$ is regulated by the kidney, and CO2 is regulated by the lungs, when the CO2 **decreases** when we ascend to high altitude (due to the decrease in the overall atmospheric pressure and due to the compensatory mechanism of hyperventilation(10)), the kidney compensates by excreting $HCo3^-$ in the urine, **decreasing** the level of $HCO3^-$ in the blood, leading to **normal** pH, and since the pH is normal, there is no inhibition on the respiratory center. As a result, after several days at high altitude, the kidney will **return the pH to normal, allowing low PO2 (hypoxia)to be the main driver of ventilation.**

➢ **Bohr Effect:**

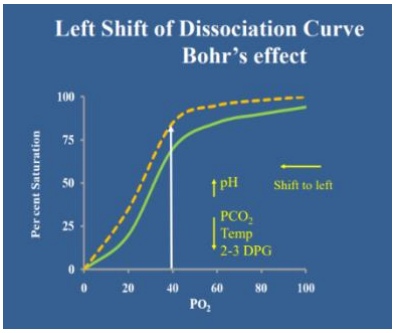
- Right shift occurs at tissue level
- ↑PaCO2 or ↑ arterial H+⟶ ↓ affinity for oxygen or increase O2 release…this occurs at the tissue level



- When oxygenated hemoglobin goes to **tissues**, the **CO2 or hydrogen ions bind** to hemoglobin, causing the **O2 to be released**

➢ **Haldane's effect:**

- Left shift at lung
- Haldane's effect is the reverse of Bohr's effect
  - loss of carbon dioxide at lungs ⟶ ↑affinity of Hb towards oxygen
- When deoxygenated hemoglobin reaches the **lungs**, **O2 binds** to hemoglobin, while the **CO2 or hydrogen ions get released.**



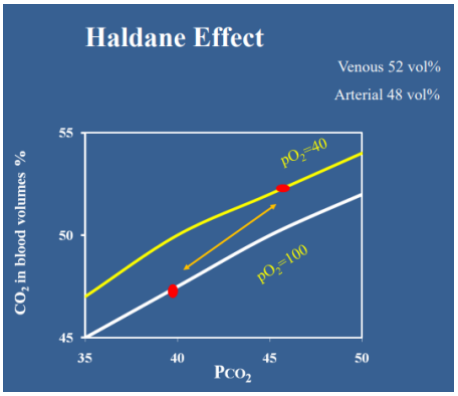
CO2 dissociation curve

!! will be explained later

The curve will differ according to the difference in PO2

There are 2 conditions:

1. PO2 =100 (the white curve, arterial)
2. PO2 =40 (the yellow curve, vinous)

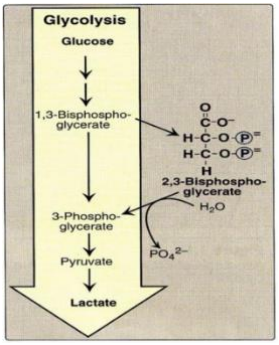


Look at the red dot,

At PO2 =40 , PCO2 = 45

At PO2 =100 , PCO2 = 40

3. Effect of 2,3 DPG on O2 Transport



1) **Anemia**: –

When RBCs or blood [hemoglobin] levels falls, each RBC produces greater amount of 2,3 DPG.

• <u>Since RBC lacks both nucleus and mitochondria</u>, it produces ATP through **anaerobic** metabolism, which makes enough 2,3-DPG available

• Glucose → G-6-P → 1,3 DPG → **mutase** → (2,3 DPG) →→ G-3-P →→

The RBC will produce high amount of 2,3 DPG, for every one hemoglobin there will be one 2,3 DPG molecule, and since the one RBC contain 280 million hemoglobin, there will be 280 million 2,3 DPG molecules.(2,3 DPG increases O2 release from Hb to be delivered to the tissues, compensating for the low O2 in tissues due to anemia)

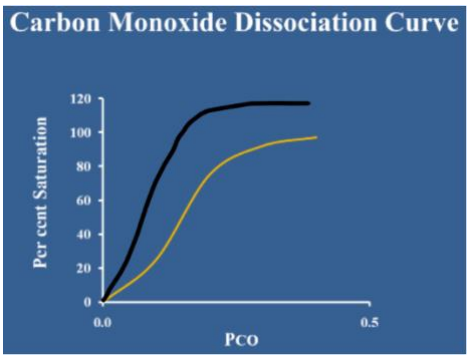
➢ **So, the question is what is the benefit of having hemoglobin inside the RBCs (not inside the plasma for example)?**

1. Inside the RBCs, there are high concentrations of **mutases**, **reductase** (ferric to ferrous conversion), and **carbonic anhydrase** ($CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$)
2. Protecting the hemoglobin and **prevent** it from being **degraded** by plasma proteases, and **preventing** the **viscosity** of plasma from increasing (as free hemoglobin in plasma would raise its viscosity). RBCs also **prevent** hemoglobin from being **filtered** and lost in the urine (the molecular weight of hemoglobin is 64,500 ; in the kidney anything having molecular weight below 70K will be filtered and lost in urine).
   In **hemolysis**, the RBCs rapture and release hemoglobin in the plasma,
   - In plasma, hemoglobin binds to albumin, but if the concentration of hemoglobin exceeds the binding capacity of albumin, hemoglobin may appear in urine (**hemoglobinuria**).
3. **2,3 DPG is found inside the RBCs as a regulator for the affinity of oxygen toward hemoglobin**

2) Fetal hemoglobin (HbF): –

Has 2 y-chains in place of the ß-chains… y-chain <u>does not bind</u> 2,3,DPG..therefore, HbF has higher affinity towards O2

4. Carboxyhemoglobin CoHb:



- the curve is **shifted to the left.** (the black curve on the pic)
- Why? This happens because CO bound to hemoglobin alters hemoglobin's conformation, This increases the oxygen affinity of the remaining binding sites. CO reduces the number of binding sites available for oxygen while increasing the affinity of hemoglobin to the already bound oxygen, As a result, less oxygen dissociates and is available to tissues, leading to the **leftward** shift of the curve.

Explained before in **CO poisoning**

Summary

A) Oxygen-carrying capacity of blood determined by its hemoglobin concentration.

1. Anemia:
   - [Hemoglobin] below normal.
1. Polycythemia:
   - [Hemoglobin] above normal.
2. Hemoglobin production controlled by erythropoietin.
   - Production is stimulated by the decrease in renal PO2

B) Loading/unloading depends:

1. PO2 of the environment.

2. Affinity between hemoglobin and O2

- The loading and unloading of O2 are influenced by the affinity of hemoglobin for O2.

Affinity is decreased by:

- ↓blood pH ↑ H+ (acidic)
- ↑temperature
- ↑ 2,3-DPG
- ↑ PCO2

– All Shift the curve to the right.

- (mainly by Co2 & pH)
- All these changes occur during **exercise** to increase the extraction ratio, which is 25% at rest (and from 100% to 75% oxygen saturation).
  all the above factors, change the 3-dimensional structure of hemoglobin from relaxed to **tight** (R relaxed-binding →T Tight-release)
- On the X-axis, at any given pO2, the amount of oxygen **bound** is **less**, indicating more released oxygen.
  Hemoglobin Dissociation Curve
  - Alveoli
    - Over wide range hemoglobin will be highly saturated
    - Example: PO2 of 60 mmHg correspond to 90% saturation
  - Tissue:
    - Normal: consume 5 ml O2 /100 ml blood (PiO2 is 40 mmHg)
    - During exercise: 15 ml of O2 /100 ml blood (PiO2 is only 20 mmHg)

Questions:

1) A person has a hemoglobin concentration of 10 gm/dl. The arterial oxygen content is 6.5 ml O2 /dl. What is the saturation?

A. 25% B. 50% C. 75% D 100%

Calculation: 10gm/dl x 1.34 = 13.4 ml O2 /dl (the normal arterial concentration of oxygen - This is max oxygen carrying capacity -)

$\frac{6.5 \text{ ml O2/dl}}{13.4 \text{ ml O2/dl}}$ = ~50%

Answer: B. 50%

2) Calculate oxygen content, Patient has saturation of 60%, Hb of 15 gm/dl?

Answer:

15 gm/dl x 1.34= ~20 ml O2/dl - This is max oxygen carrying capacity -

$\frac{?}{20.1}$ = 60% 20.1 x 60% = ~12 ml O2/dl = oxygen concentration

3) Assume Hb is 10 gm/dl,100% saturation give a content of 13.4 ml of O2/dl in blood. At rest body uses 5 ml O2 /dl, this leaves a mixed venous content of 8.4 ml/dl, venous saturation is?

Answer:

Venous saturation is 8.4/13.4 = 63%

4) Which of the following is least important for the transport of carbon dioxide?

a. hydrogen ions bound to hemoglobin

b. carbonic anhydrase

c. CO2 dissolved in plasma

d. CO2 bound to plasma proteins

Answer: d. CO2 bound to plasma proteins

Carbon Dioxide

❖ **Oxygen in blood is found in two forms one is <u>dissolved</u> & the other is <u>bound</u>.**

- bound → **98.5%**
- dissolved → **1.5%**
- solubility coefficient is 0.003
- dissolved oxygen content in arterial blood **[O2]** = 100mmHg (P_aO_2) x 0.003 = **0.3 ml** of O2 per 100 ml of blood

- **Carbon dioxide in blood is found in three forms: dissolved, bound to hemoglobin, and as bicarbonate.**
  The solubility of Co2 is 20x more than oxygen as you remember, so solubility coefficient is, 0.003 x 20 = 0.06
- dissolved carbon dioxide content in arterial blood **[CO2]** = 40mmHg (P_aCO_2) x 0.06 = 2.4 ml of CO2 per 100 ml of blood
- to determine how much Co2 is dissolved, we look at the **venous** CO2 pressure which is =45mmHg
- dissolved carbon dioxide content in venous blood **[CO2]** = 45mmHg (P_VCO_2) x 0.06 = **2.8 ml** of CO2 per 100 ml of blood
- the difference between venous and arterial is, 2.8 – 2.4 = 0.4
- Previously, we mentioned that the blood carry 5ml of O2, and 4ml of CO2
  0.4 / 4ml = 10%

Dissolved CO2 accounts for ~10% of the 4 ml, the total CO2 in blood (some textbooks may report 7%)."

The End

Version 2:

- **P6:** diffusion capacity ≠ Area/thickness, but is proportional to them
  (DLO2= area/thickness * solubility$\sqrt{MW}$)