Sheet No. 4

Physiology

Hematolymphatic System

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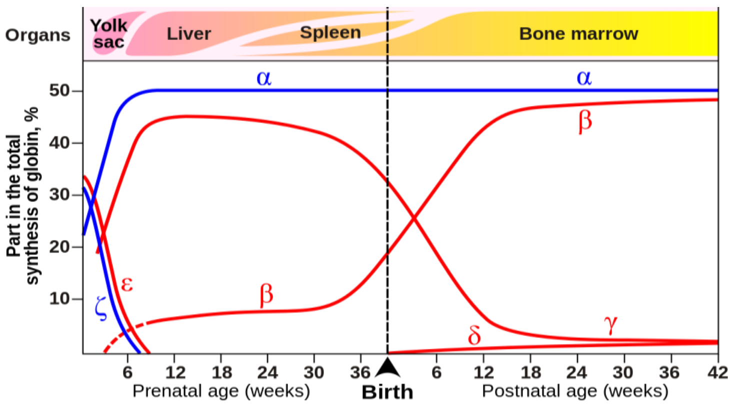
Normal hemoglobin concentration :- in males 15 g/100ml blood , in females 14 g/100ml blood

Usually, 1g HB carries 1.34 ml O2, so in 100ml blood there is about 20 ml O2, and oxygen can be found even in plasma (0.3 ml O2 in 100 ml plasma).

Hemoglobin consists of 4 subunits (2 alpha, 2 beta), and each subunit contains heme moiety (protoporphyrin + iron), so each hemoglobin molecule contains 4 iron molecules.

Name	Designation	Molecular structures	Proportion in adults	Proportion in newborns
Adult hemoglobin	A	α2β2	97%	20%
Hemoglobin A2	A2	α2δ2 α2γ2	2.5%	0.5%
Fetal hemoglobin	F	ζ2γ2 ζ2ε2 α2ε2	**>1%**	80%

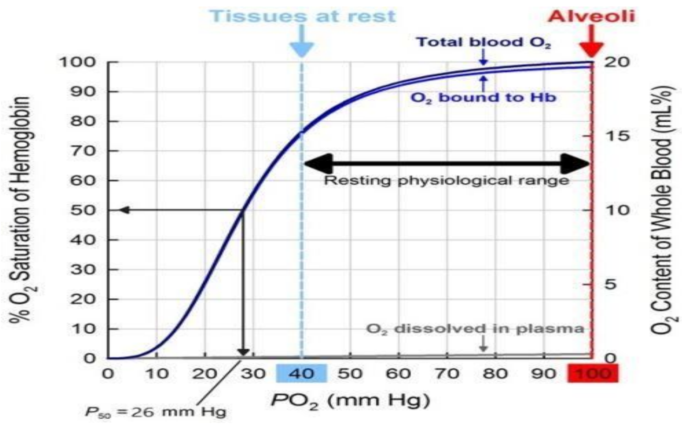
Fetal hemoglobin is replaced almost totally by adult hemoglobin by the end of the 6th month after birth, sometimes it takes longer time to be replaced, but usually not more than a year.



Heme is also a part of myoglobin structure (an oxygen-binding protein found in red muscles), as well as neuroglobin (an oxygen-binding globin found in the brain).

Note:- in one RBC there are about 300 million hemoglobin molecules.

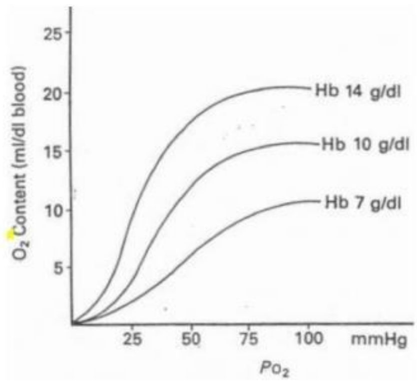
Hemoglobin oxygen dissociation curve



1- When the pO2 in the lungs is 100 mm Hg not all hemoglobin molecules become saturated, the doctor said about 90% of them become saturated, however, the figure shows that the percentage is 97% which is more accurate.
2- At the tissue level, when pO2 is 40 mm Hg not all oxygen molecules are released into tissues, just about 25% of the oxygen is released.
3- The P50 of saturation is about 26 mm Hg.

- This hemoglobin oxygen dissociation curve doesn't change from person to person whatever the hemoglobin concentration is.

☒ We can get different diagrams for different people depending on the hemoglobin concentration by plotting O2 content against pO2 as shown in the next figure.



It is evident that the quantity of oxygen carried in a volume of blood is dependent on pO2 as well as the hemoglobin concentration. The percentage saturation of hemoglobin with oxygen is dependent on pO2 and totally independent of hemoglobin concentration.

So the oxygen content depends on :-

1- pO2 :- the higher the pO2 the higher the O2 content in the blood.
2- The concentration of hemoglobin:- the higher the hemoglobin concentration the higher the content of O2 in the blood.

$Hb_4 + O_2 \longleftrightarrow Hb_4O_2$

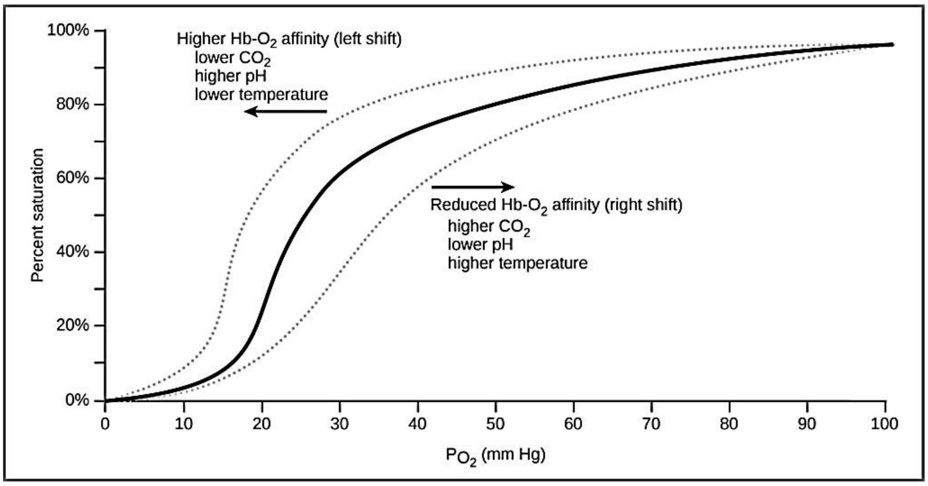
$Hb_4O_2 + O_2 \longleftrightarrow Hb_4O_4$

$Hb_4O_4 + O_2 \longleftrightarrow Hb_4O_6$

$Hb_4O_6 + O2 \longleftrightarrow Hb_4O_8$

As we said before one hemoglobin molecule contains four heme molecules and each one of them binds one oxygen molecule, and the binding process doesn't occur all at once, instead, each heme molecule bind to one oxygen molecule solitary one by one.

The binding of the first heme in the hemoglobin molecule with O2 increases the affinity of the second heme for O2, and oxygenation of the second one increases the affinity of the third one and so on.



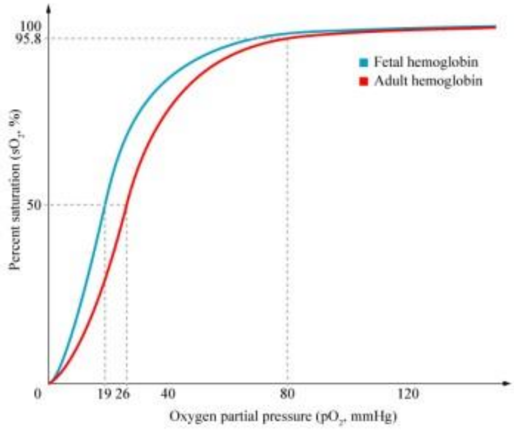
1. The shifted curve to the right means :-

A. Hemoglobin affinity towards oxygen decreases, so the hemoglobin releases oxygen easily so it needs more oxygen.
B. P50 increases. And this can be due to :- a- decreased pH. b- increased temperature. c- increased pCO2. d- increased 2,3-BPG.

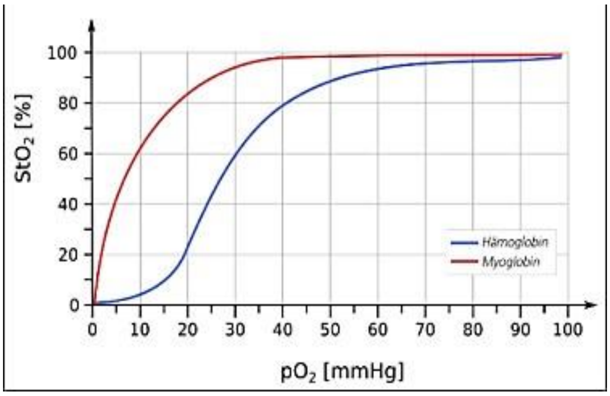
2. The shifted curve to the left means:-

A. Hemoglobin affinity towards oxygen increases, so the hemoglobin doesn't release oxygen easily.
B. P50 decreases. And this can be due to:- a- increased pH. b- decreased temperature. c- decreased pCO2. d- decreased 2,3-BPG.

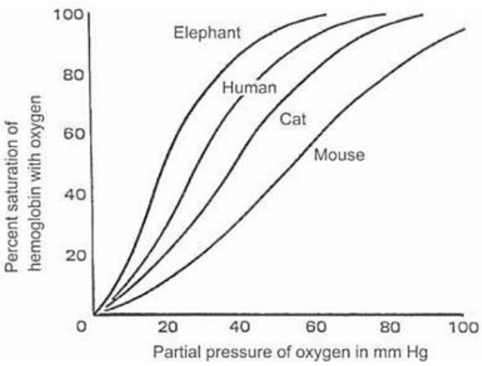
- there are two types of hemoglobin in this figure, adult and fetal hemoglobin, the affinity of fetal hemoglobin towards oxygen is higher than that of the adult hemoglobin so its curve is shifted to the left.



- The affinity of myoglobin is higher than both adult and fetal hemoglobin as shown in the figure.



☒ This figure represents the oxygen dissociation curve of different kinds of mammalians and it shows the following:



- The elephant curve is shifted to the left -compared to human curve- meaning its Hb has higher affinity (lower oxygen need).
- As for the cat and the mouse curves they are shifted to the right -compared to human curve- meaning that their Hb has lower affinity (higher oxygen need).

☞ The reason behind this difference in affinities is that the demand of oxygen in each mammalian differs from the other according to its activity.

❖ **Blood parameters** (which we already discussed):-

1- [Hb] :- in males -> 15 g/100 ml blood, in females -> 14g/100ml blood

2- Red cell count (RCC) :- in males -> about 5 million/µl, in females -> about 4 million/µl
3- Hematocrit (HTC):- in males-> 45% , in females -> 40% 4- Mean cell volume (MCV):- 80-90 μm^3or fl.

And by calculations we can conclude other two parameters:

1- **Mean cell/corpuscular hemoglobin** (**MCH**):- The MCH indicates the average weight of hemoglobin in one red blood cell, with a normal range of (28-32) picograms (pg) for both males and females.

$$MCH = \frac{\text{Weight of hemoglobin in 1 } \mu l \text{ of blood}}{\text{Number of red blood cells in 1 } \mu l \text{ of blood}}$$

$$MCH = \frac{\text{Hemoglobin} \times 10}{\text{Red blood cell count in millions}} \text{ pg}$$

The MCH indicates the amount of hemoglobin in the red blood cell and should always correlate with the MCV and MCHC. An MCH lower than 28 pg is found in microcytic anemia and also with normocytic, hypochromic red blood cells. An elevated MCH occurs in macrocytic anemias and in some cases of spherocytosis in which hyperchromia may be present.

2- **Mean cell/corpuscular hemoglobin concentration** (**MCHC**):- the MCHC indicates how much of the hemoglobin in one RBC occupies of the MCV, It gives the ratio of the weight of hemoglobin to the volume of the red blood cell, with a normal range of (32%-36%) for both males and females.

$$MCHC = \frac{\text{Hemoglobin in g/dl}}{\text{Hematocrit/dl}} \times 100 \text{ (to convert to \%)}$$

$$MCHC = \frac{\text{Hemoglobin} \times 100}{\text{Hematocrit}} \%$$

The MCHC indicates whether the red blood cells are normochromic, hypochromic, or hyperchromic. An MCHC below 32% indicates hypochromia, an MCHC above 36% indicates hyperchromia, and red blood cells with a normal MCHC are termed normochromic.

The red blood cell indices are used as an aid in differentiating anemias. When these indices are combined with an examination of red blood cells on the stained smear, a clear picture of red blood cell morphology may be obtained.

❖ **Mean cell volume (MCV)**

The MCV indicates whether the red blood cells appear normocytic, microcytic or macrocytic. If the MCV is less than 80 fl, the red blood cells are microcytic. If the MCV is greater than 97 fl, the red blood cells are macrocytic. If the MCV is within the normal range, the red blood cells are normocytic.

$$MCV = \frac{\text{Volume of red blood cells in femtoliters (fl)}/\mu l \text{ of blood}}{\text{Red blood cells}/\mu l \text{ of blood}}$$

$$MCV = \frac{\text{Hematocrit} \times 10}{\text{Red blood cell count in millions}} \text{ fl}$$

Normal value for the MCV: 80–97 fl

Examples the doctor mentioned: -

1- MCV = 91 fl

MCH = 31 pg Normocytic Normochromic.

MCHC = 34%

2- MCV = 67 fl

MCH = 22 pg Microcytic Normochromic.

MCHC = 33%

3- MCV = 67 fl

MCH = 20 pg Microcytic Hypochromic.

MCHC = 30%

4- MCV = 115 fl

MCH = 38 pg Macrocytic Normochromic.

MCHC = 33%

5- MCV = 91 fl

MCH = 26 pg Normocytic Hypochromic.

MCHC = 29%

Anemia (**erythrocytopenia**) **:** Anemia is a name given for a group of disorders that develop when your blood lacks enough healthy red blood cells or hemoglobin, i.e. it is either characterized by low RBCs or low hemoglobin.

Classification of Anemia :-

1. Based on Morphology:
    a) Normochromic, Normocytic: - The size and hemoglobin content of the RBCs are within normal limits, but the problem is in the count (lower than the normal).
    b) Hypochromic, Normocytic: - the problem is in the hemoglobin content ratio.
    c) Hypochromic, Microcytic: - RBCs' size is smaller than usual, with decreased hemoglobin content.
    d) Macrocytic: - Unusually large RBCs and the count is low such as in pernicious anemia.
    e) Micro-spherocytic: A hereditary rare disorder where RBCs look like spheres, leading to premature breakdown of red blood cells.

2. Based on Etiology :-
    A. Increased blood loss, which could be caused by : a- Acute or chronic hemorrhage b-Hemolysis, a problem which can be :-

    a) **Corpuscular** :- The problem is either in the cell itself or its membrane. Like a deficiency of some enzymes such as G6PD (Glucose-6-phosphate dehydrogenase) or pyruvate kinase.
    b) **Extra corpuscular** :- The problem is outside the cells, in the plasma for example because of toxins or infections like malaria.

    B. Decreased blood production :-

    a) **Nutritional** :- Inadequate dietary intake of some essential substances for erythropoiesis such as deficiency in vitamin B12, folic acid, pyridoxine (vitamin B6), ascorbic acid(vitamin C) or proteins.
    b) **A problem in the bone marrow** (bone marrow failure), as the bone marrow is the place where erythropoiesis takes place. Could be primary, or secondary to drugs, chemicals, or irradiation.

Effects of anemia on the circulatory system

1- In severe anemia the **blood viscosity may fall to as low as 1.5** times that of water rather than the normal value of approximately 3 times the viscosity of water.
2- The greatly decreased viscosity decreases the resistance to the blood flow in the peripheral vessels so that far greater than normal quantities of blood returns to the heart.
3- Moreover, hypoxia due to diminished transport of oxygen by the blood, causes the tissue vessels to dilate, allowing further increase in the return of blood to the heart, increasing the cardiac output to a still higher level. **(+ an increase in the heart rate)**
4- Thus, one of the major effects of anemia is greatly **increased workload on the heart.**
5- Consequently, during exercise, which greatly increases tissue demand for oxygen, extreme tissue hypoxia results, and acute cardiac failure often ensues.

Polycythemia (erythrocytosis)

Polycythemia is defined as an increase in the number of the RBCs in the circulation.

Classification of Polycythemia (erythrocytosis) :-

1- Relative erythrocytosis :-

Results from dehydration, in which the plasma volume decreases so the total volume of blood decreases, while the RBCs number is still the same. As a result, the RBCs concentration increases relatively to the volume of the blood. This case usually occurs during fasting.

2- **True erythrocytosis**, which is further divided into :-

a- With increased erythropoietin :- physiologically due to high altitude or drugs such as Cobalt and androgens.
b- With low or normal erythropoietin (polycythemia vera):- because of cancer.

Effect of polycythemia on the circulatory system

1- The greatly **increased viscosity** of the blood in polycythemia, increases the workload on the heart.
2- **The flow of blood** through the vessels is often very **sluggish**.
3- It is obvious that increasing the viscosity tends to **decrease** the rate of **venous return to the heart.**

4- On the other hand, the **blood volume is greatly increased** in polycythemia, which tends to increase the venous return.
5- The blood passes sluggishly through the skin capillaries, a larger than normal proportion of the hemoglobin is deoxygenated. The bluish color of this deoxygenated hemoglobin masks the red color of the oxygenated hemoglobin. Therefore, a person with polycythemia ordinarily has a ruddy complexion but often with a bluish color to the skin.

- Not all RBCs of a polycythemia patient are oxygenated because there are too many of them (can reach 7- 8 million/ml)
- **In both cases**, anemia and polycythemia, the **heart work is increased** but due to different causes, and this may lead to heart failure. In polycythemia, increased blood volume causes increased venous return and heart load. Whereas, in anemia decreased resistance due to decreased RBCs and vasodilation is what increases the venous return.