Lung surfactant, Lecithin / sphingomyelin (L / S) ratio & oxygen dissociation curve

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Lung surfactant

- It is produced by **pneumocyte type II** cells.

❑ **Composition:**

A) Lipids: ~ 90%

<u>1. Phospholipids:</u> 80-90%

- ✓ **Mainly dipalmitoylphosphatidylcholine (dipalmitoyl lecithin) &**
- ✓ **Other phospholipids (**phosphatidyl glycerol, phosphatidylserine, phosphatidylethanolamine & sphingomyelin)

<u>2. Neutra fat:</u> 3-10% (mainly cholesterol),

B) Proteins: ~ 10%

- ✓ **4 surfactant-associated proteins (SP-A, SP-B, SP-C, and SP-D)**

- Dipalmitoyl lecithin, SP-B & SP-C lower the surface tension
- SP-A, and SP-D for host defense & immunity

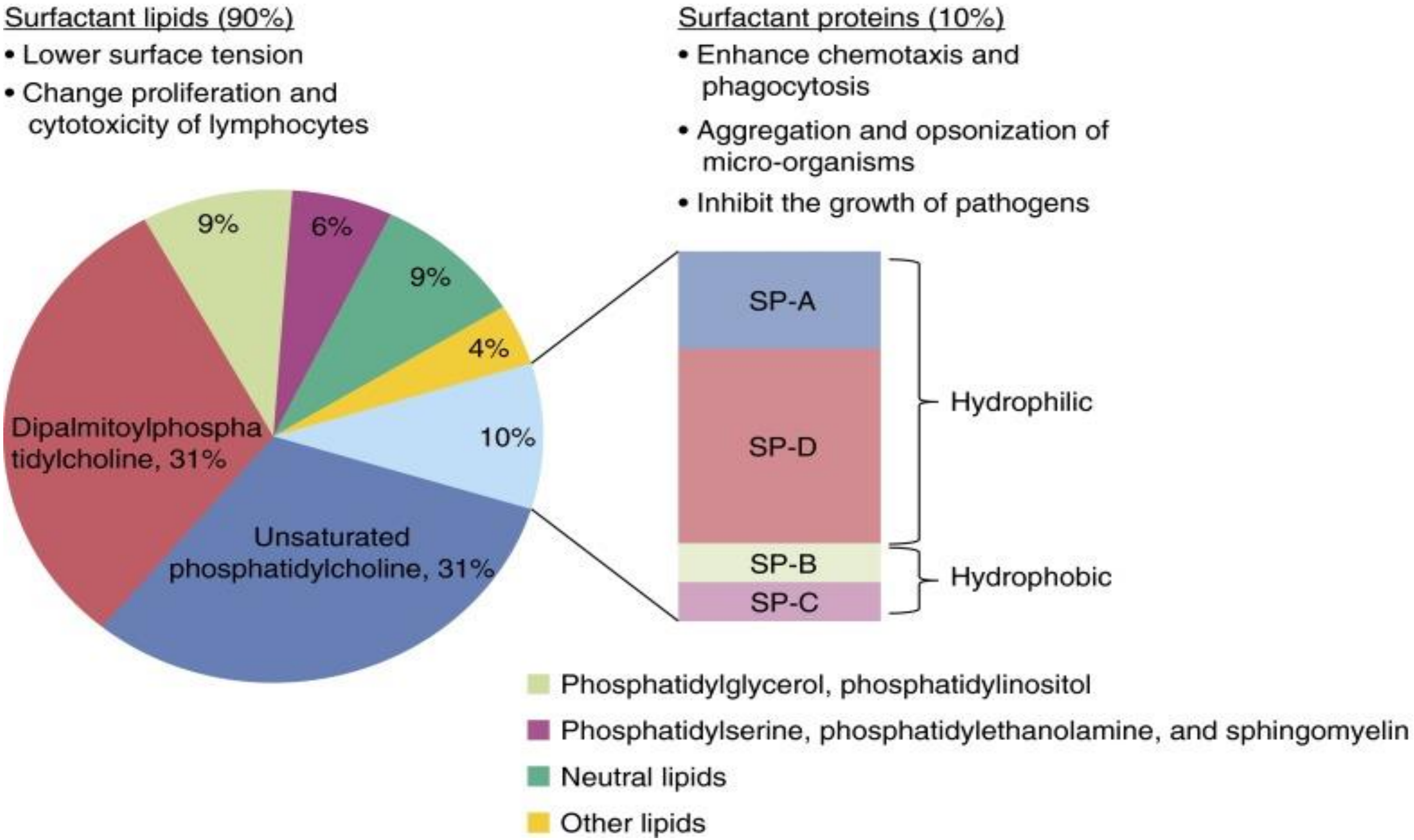
Lungs surfactant

❑ Functions:

1. **It lowers the surface tension** at the air–liquid interface & prevents collapse of lung alveoli.
   (Dipalmitoyl lecithin, SP-B & SP-C)
2. **Host defense** (kills pathogens or prevents their dissemination)
   (SP-A, and SP-D)
3. **Modulates immunity**
   (SP-A, SP-B, SP-C & SP-D)

❑ Storage:

- It is stored and secreted by organelles called **lamellar bodies.**


Surfactant lipids (90%)
• Lower surface tension
• Change proliferation and cytotoxicity of lymphocytes
Surfactant proteins (10%)
• Enhance chemotaxis and phagocytosis
• Aggregation and opsonization of micro-organisms
• Inhibit the growth of pathogens
9%
6%
9%
4%
10%
Dipalmitoylphosphatidylcholine, 31%
Unsaturated phosphatidylcholine, 31%
SP-A
SP-D
SP-B
SP-C
Hydrophilic
Hydrophobic
Phosphatidylglycerol, phosphatidylinositol
Phosphatidylserine, phosphatidylethanolamine, and sphingomyelin
Neutral lipids
Other lipids

Lecithin to sphingomyelin (L / S) ratio:

- It evaluates the lung maturity
- Normal L / S ratio: ≥ **2:1** (2 - 2.5) indicates **mature** fetal lungs
- An L/S ratio < **2.0** indicates **immature** fetal lung.

- **Sample collection:**
  - **Amniotic fluid by amniocentesis after 34 weeks of gestation**
  - **Vaginal pooling** in preterm premature rupture of membranes
- **Method of analysis: thin layer chromatography**

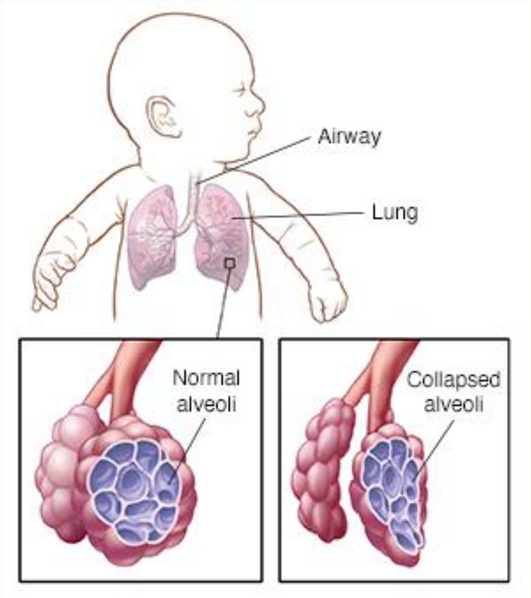
❑ Clinical significance

- The L/S ratio guides clinicians in determining the timing of delivery of neonates to minimize the risk of developing **neonatal respiratory distress syndrome**.
- The evidence of immature fetal lungs is used to support the **administration of glucocorticoids** for promoting lung maturation.

Infant (newborn) Respiratory distress syndrome:

- **Risk of respiratory distress syndrome (RDS) increases with:**

1. **Prematurity**
2. **Multifetal** pregnancies
3. Maternal **diabetes**,
4. Being a **white** male.

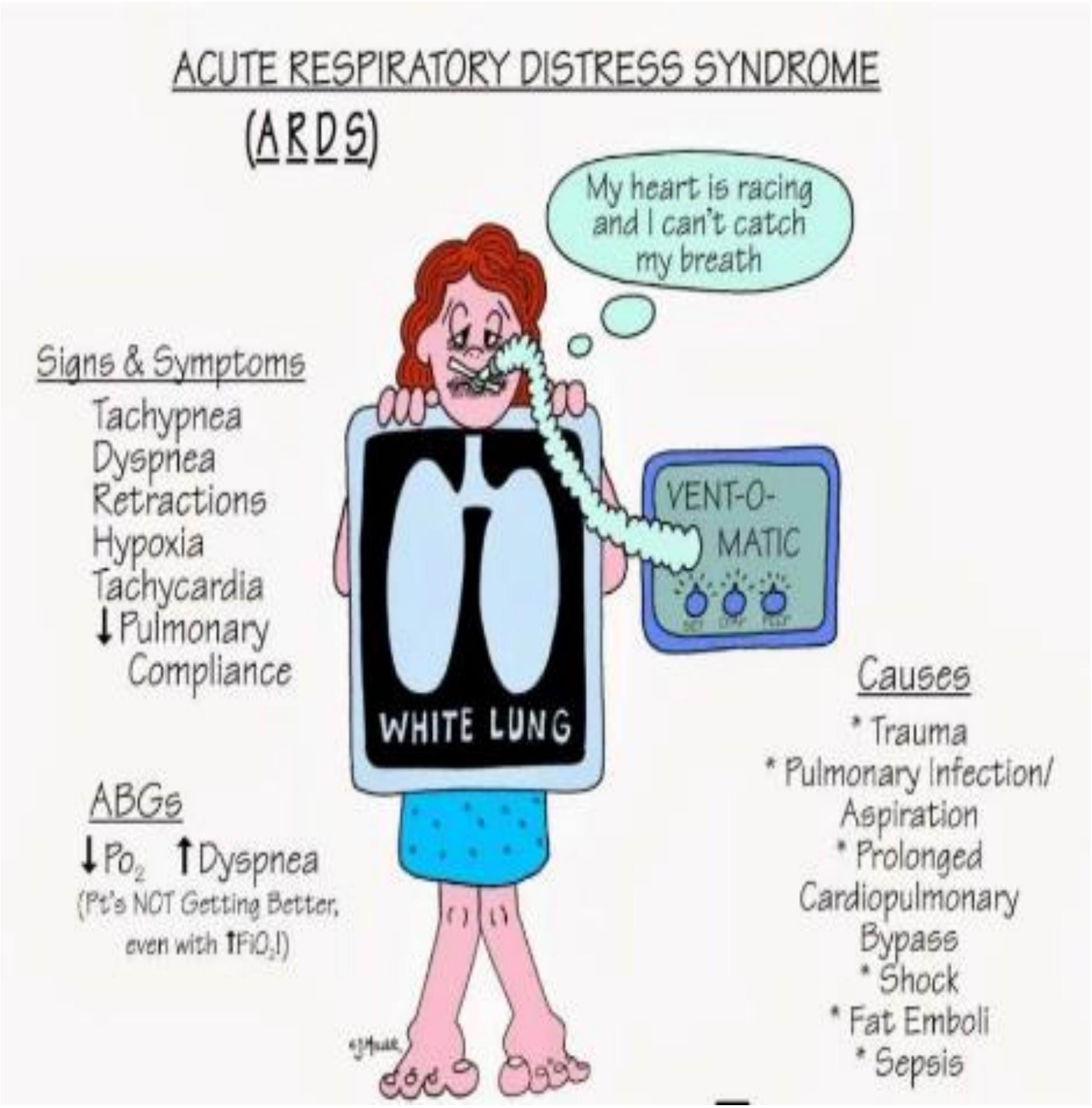


- **Risk of RDS decreases with:**

1. Fetal growth **restriction**
2. Preeclampsia or eclampsia, maternal **hypertension**
3. Prolonged **rupture** of membranes,
4. Maternal **corticosteroid** use.

- **Pathophysiology:**
- Lung surfactant is essential for life (it **lines alveoli → ↓ surface tension →** prevents atelectasis during breathing.
- **With surfactant deficiency**:
- A greater pressure is needed to open alveoli.
- Lungs become diffusely collapsed, triggering inflammation & pulmonary edema.
- Blood passing through collapsed portions of lung is not oxygenated, the infant becomes hypoxemic.
- ↓ Lung compliance → ↑ the work of breathing.
- In severe cases, the diaphragm and intercostal muscles fatigue, → CO_2 retention and respiratory acidosis

Acute respiratory distress syndrome (ARDS): surfactant deficiency may be due to **loss** of the **alveolar epithelium**



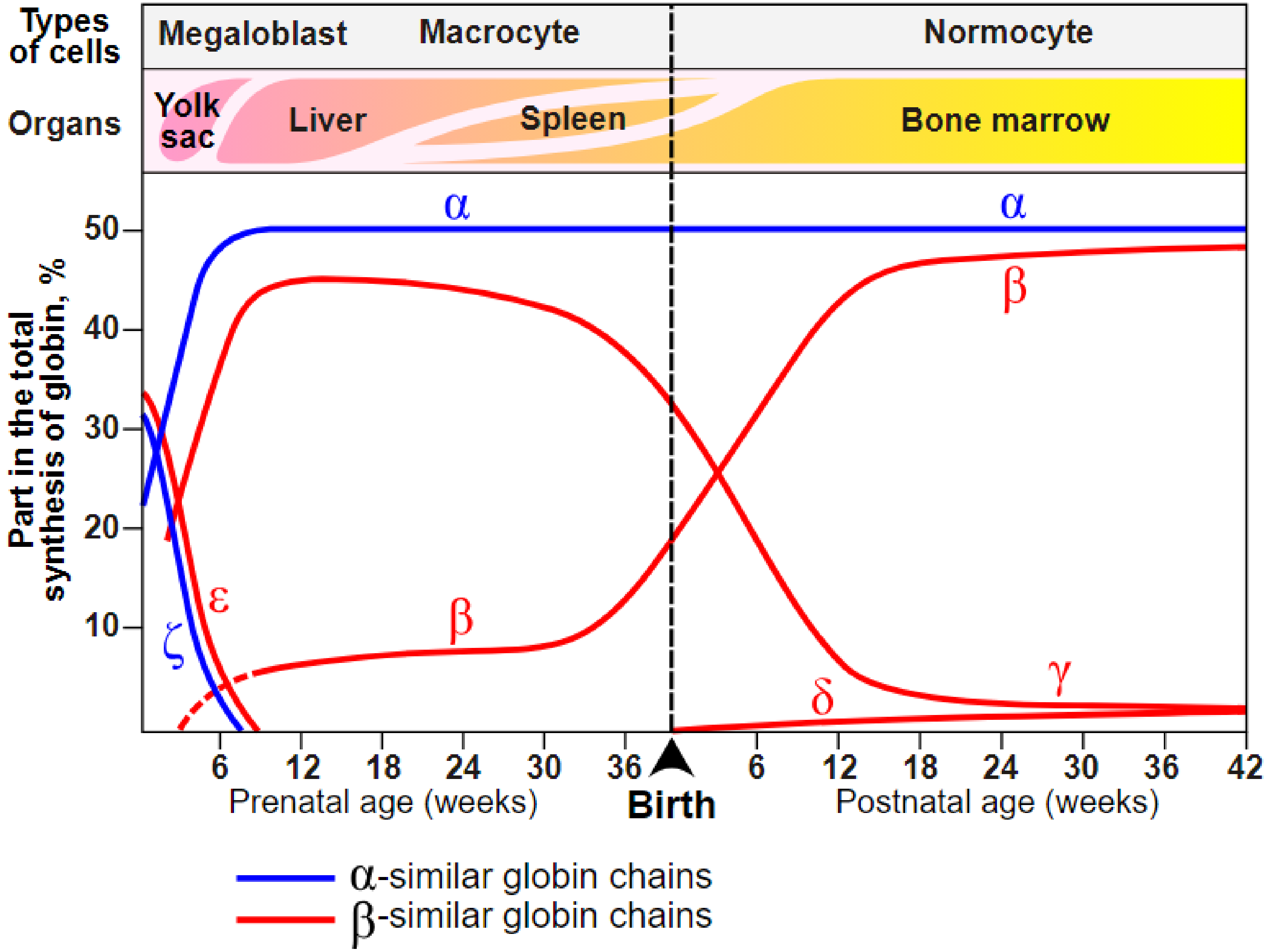
Treatment

Approach Considerations

- Corticosteroids
- Surfactant Replacement Therapy **(Surfactant may be natural or synthetic & it reduces mortality from RDS by 50%)**
- Oxygenation and CPAP **(continuous positive airway pressure)**
- Vapotherm **(mix of O2 & air via nasal cannula (or tracheostomy mask, replaces CPAP)**
- Assisted Ventilation
- High-Frequency Ventilation
- Nitric Oxide
- Supportive Therapy
- Parent and Family Support

Form	Chain composition	Fraction of total hemoglobin
HbA	$\alpha_2\beta_2$	90%
HbF	$\alpha_2\gamma_2$	<2%
HbA_2	$\alpha_2\delta_2$	2–5%
HbA_{1c}	$\alpha_2\beta_2$-glucose	3–9%

Normal adult human hemoglobins.



Developmental changes in hemoglobin.

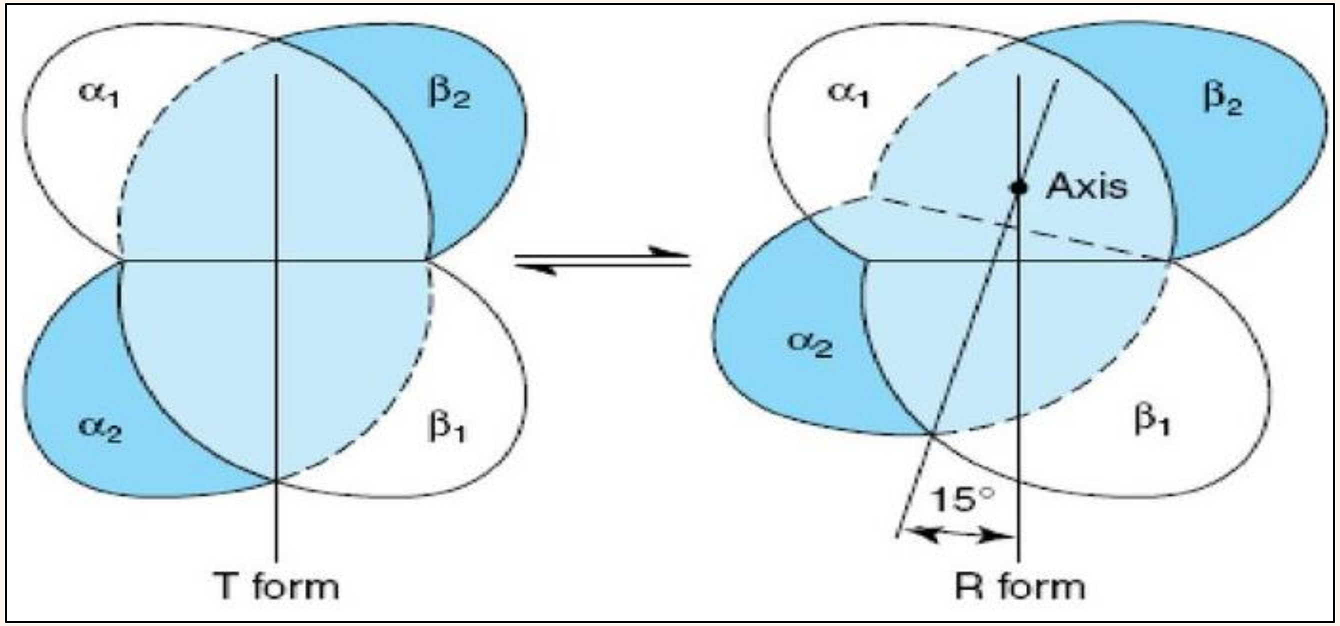
Forms of Hb:

a. T form: The **deoxy** form of Hb "**taut**" or (tense) form.

The **T** form is the **low** oxygen-affinity form of Hb

b. R form: The **oxy** form of Hb "**Relaxed**" or (tense) form.

The **R** form is the **high** oxygen-affinity form of Hb

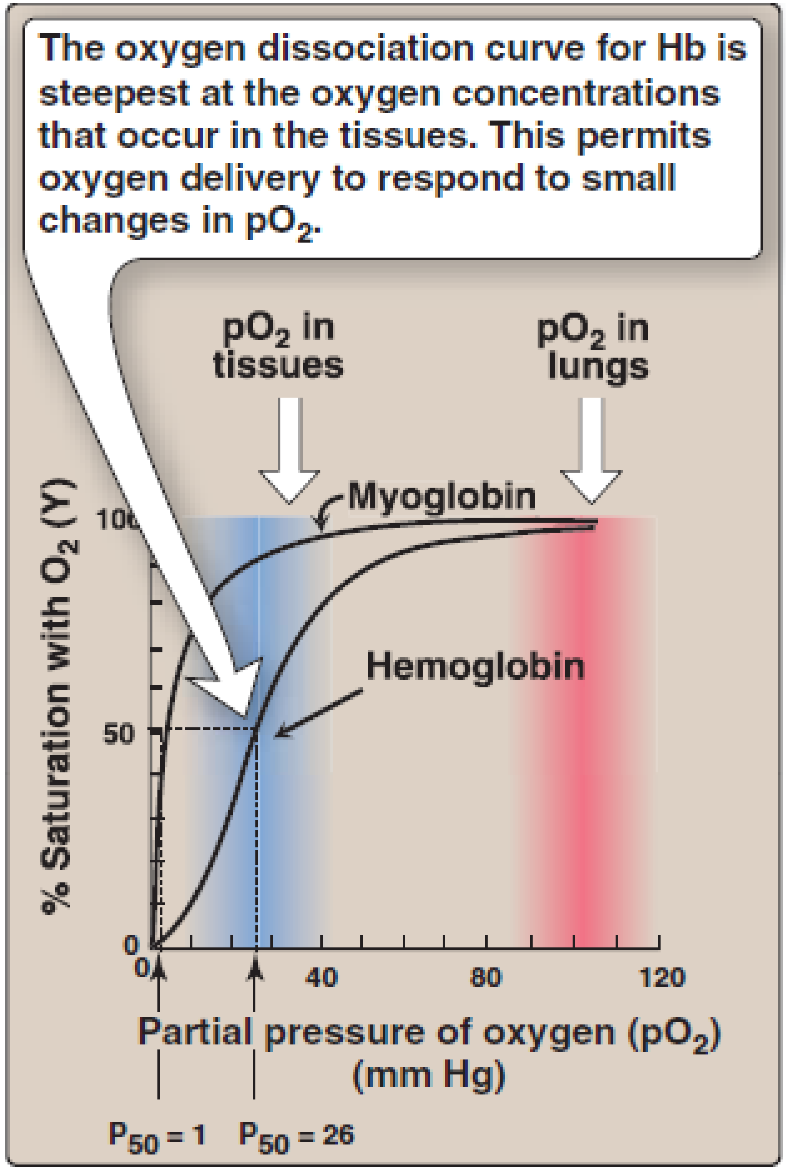


Binding of O_2 to Hb:

- Hb can bind 4 O_2 (oxygenation not oxidation).
- Degree of saturation of O_2 – binding sites can vary (from 0% to 100%).

Oxygen dissociation curve for Hb:

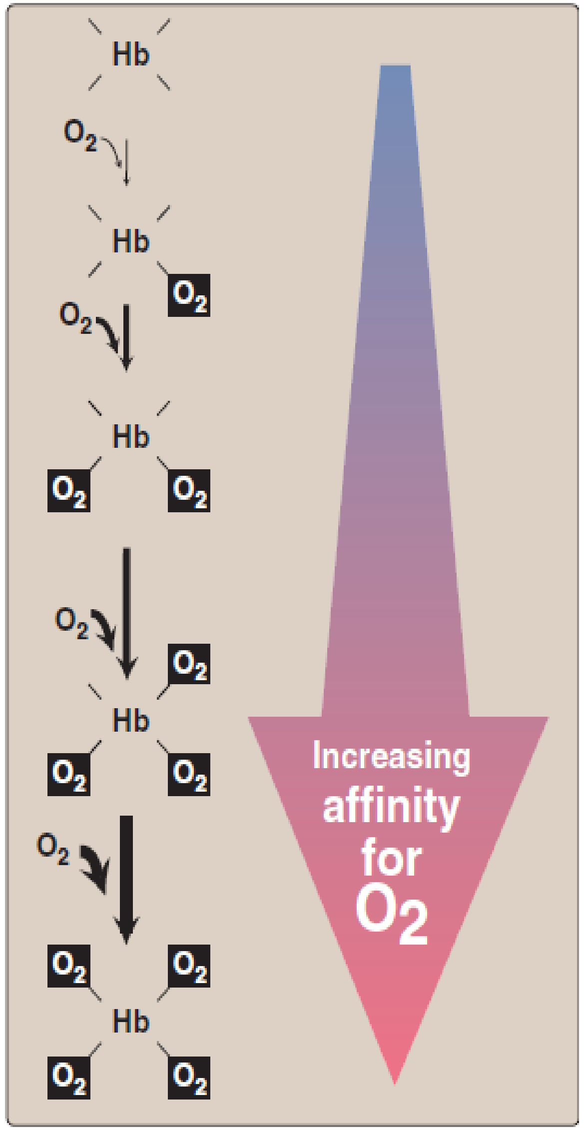
- A plot of degree of saturation at different pO_2
- pO_2 to achieve half-saturation of binding sites (p50) is ~ 26 mm Hg for Hb.
- The higher O_2 affinity (the more tightly O_2 binds), the lower the p50.



Oxygen dissociation curve for Hb:

- It is **sigmoid shaped**
- **Cooperative binding of O_2:**

- Binding of an O_2 at one heme → ↑ O_2 affinity of remaining heme groups in the same Hb molecule (heme-heme interaction).
- Although it is more difficult for the first O_2 to bind Hb, the subsequent binding of O_2 occurs with high affinity (**steep upward curve)**
- The affinity of Hb for the last $\mathbf{O_2}$ is ~ 300 times greater than the first $\mathbf{O_2}$.



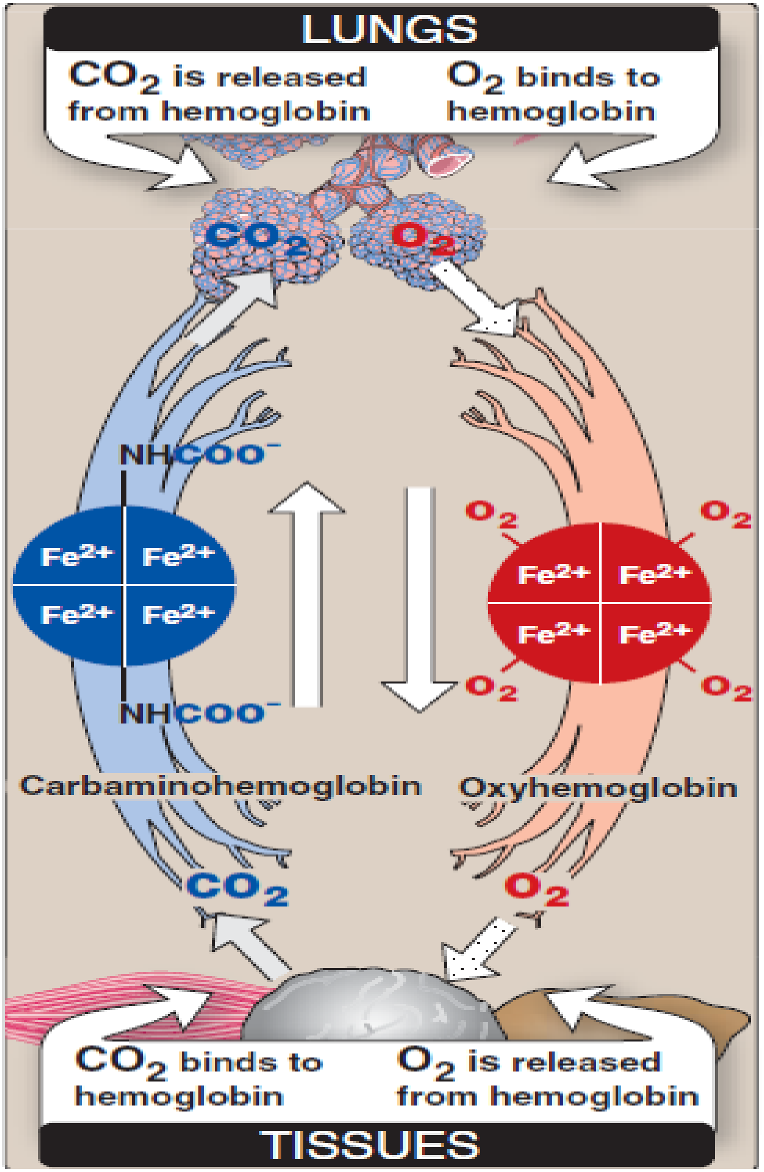
- At lungs, O_2 concentration is high → Hb becomes saturated "loaded" with O_2.
- At peripheral tissues, oxyhemoglobin releases (or "unloads") much of its O_2 for oxidative metabolism of tissues.

Factors affecting Hb affinity for O_2 :

A. **pH**

B. **2, 3 bis-phospho-glycerate (2, 3 BPG)**

C. **pCO_2**



Bohr effect:

- **O_2 release from Hb is enhanced with ↓ in pH or ↑ in pCO_2.**
- Both result in ↓ **O_2 affinity** of Hb → **shift to the right** in O_2 dissociation curve, & stabilization of the **T state**. This change in oxygen binding is called the Bohr effect.

The Bohr effect can be represented schematically as:

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

oxyhemoglobin — deoxyhemoglobin

- Conversely, ↑ pH or ↓ CO_2 → ↑ affinity for O_2 → shift to left in O_2 dissociation curve & stabilization of the R state.

(at lungs, CO_2 dissociates from Hb, and is released in breath)

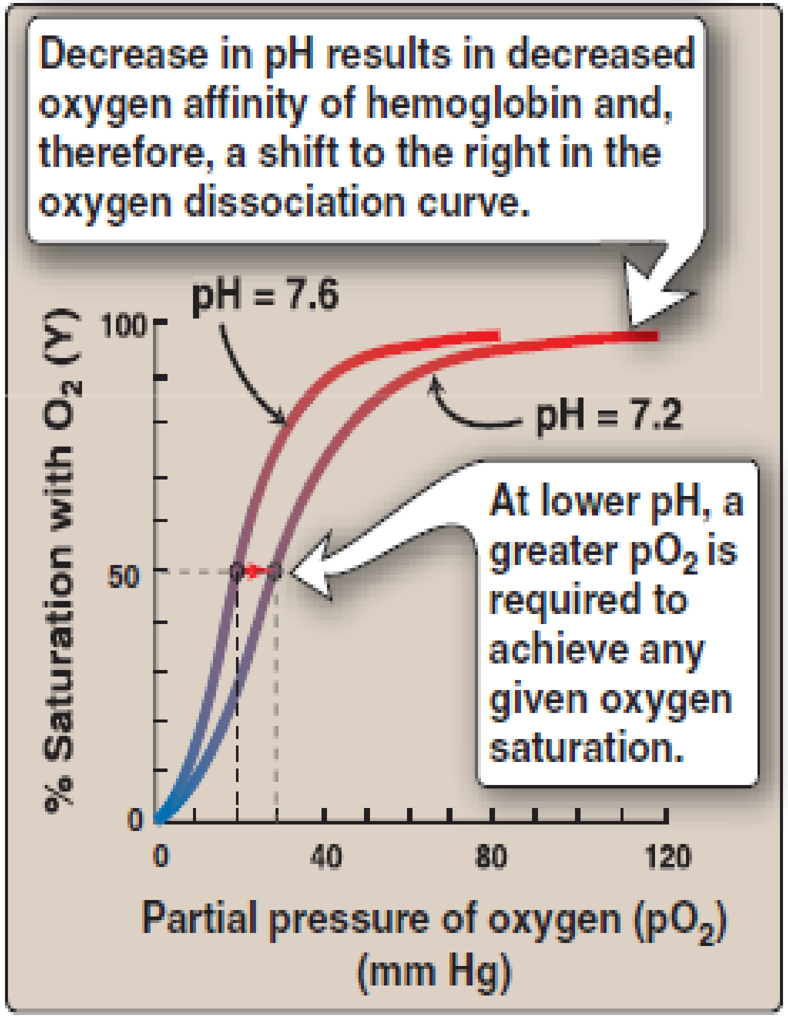
Differential pH gradient:

- The lungs (↑ pH) & tissues (↓ pH) → unload of O_2 in tissues & load of O_2 in lungs
- E.g. Organic acids (as lactic acid) produced during anaerobic metabolism in rapidly contracting muscle (source for protons)
- In tissues, CO_2 is converted by carbonic anhydrase to carbonic acid:

$$CO_2 + H_2O \rightleftarrows H_2CO_3$$

- H_2CO_3 spontaneously loses a proton → bicarbonate (major blood buffer):

$$H_2CO_3 \rightleftarrows HCO_3^- + H^+$$



Effect of 2,3- BPG on O_2 affinity:

- 2,3-BPG is an important regulator of O_2 binding to Hb.
- It is the most abundant organic phosphate in RBC
- Its concentration is nearly that of Hb.
- It is synthesized from an intermediate of glycolytic pathway
- It ↓ O_2 affinity of Hb by **binding to deoxy-Hb** but not to oxy-Hb.
- This preferential binding **stabilizes the taut (T)** state of deoxy-Hb.

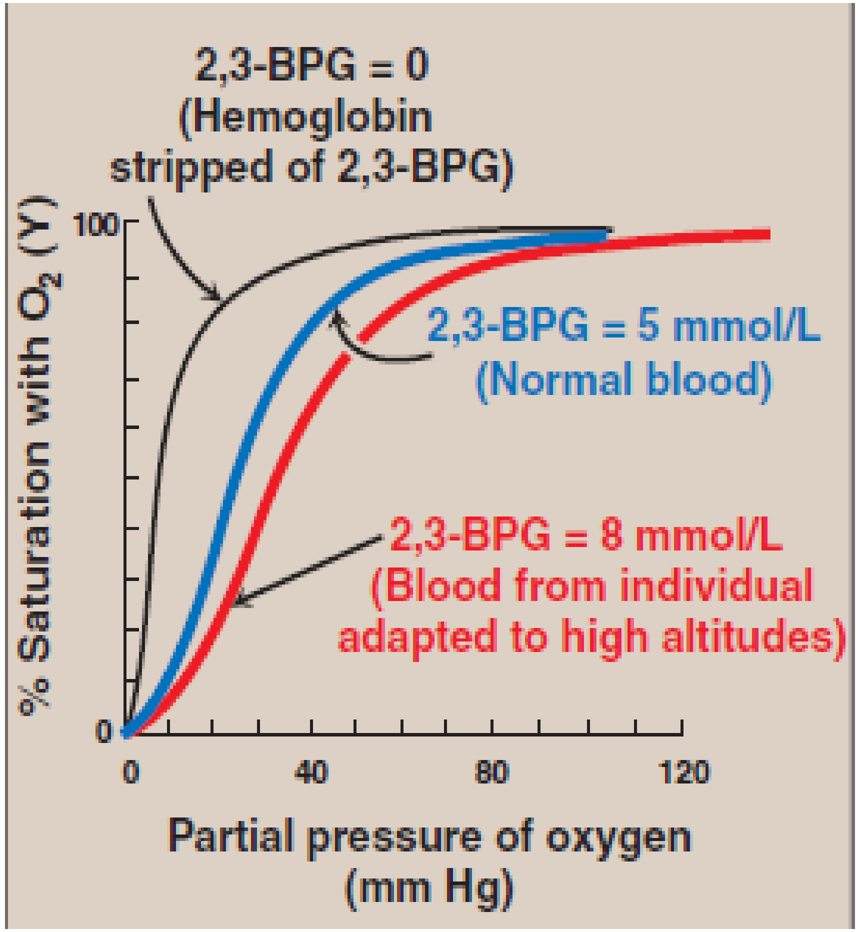
$$\underset{\text{oxyhemoglobin}}{HbO_2} + \text{2,3-BPG} \rightleftarrows \underset{\text{deoxyhemoglobin}}{\text{Hb–2,3-BPG}} + O_2$$

In RBCs, 2,3-BPG → ↓ **affinity** of Hb for O_2 → **Shift of** O_2 **dissociation curve to right.**

Response of 2,3-BPG to chronic hypoxia:

2,3-BPG in RBCs ↑ in response to **chronic hypoxia**, as in chronic obstructive pulmonary disease (COPD) like emphysema, or at high altitudes, where circulating Hb may have difficulty receiving sufficient O_2.

↑ 2,3-BPG levels →↓ O_2 affinity of Hb → ↑ delivery of O_2 to the tissues.

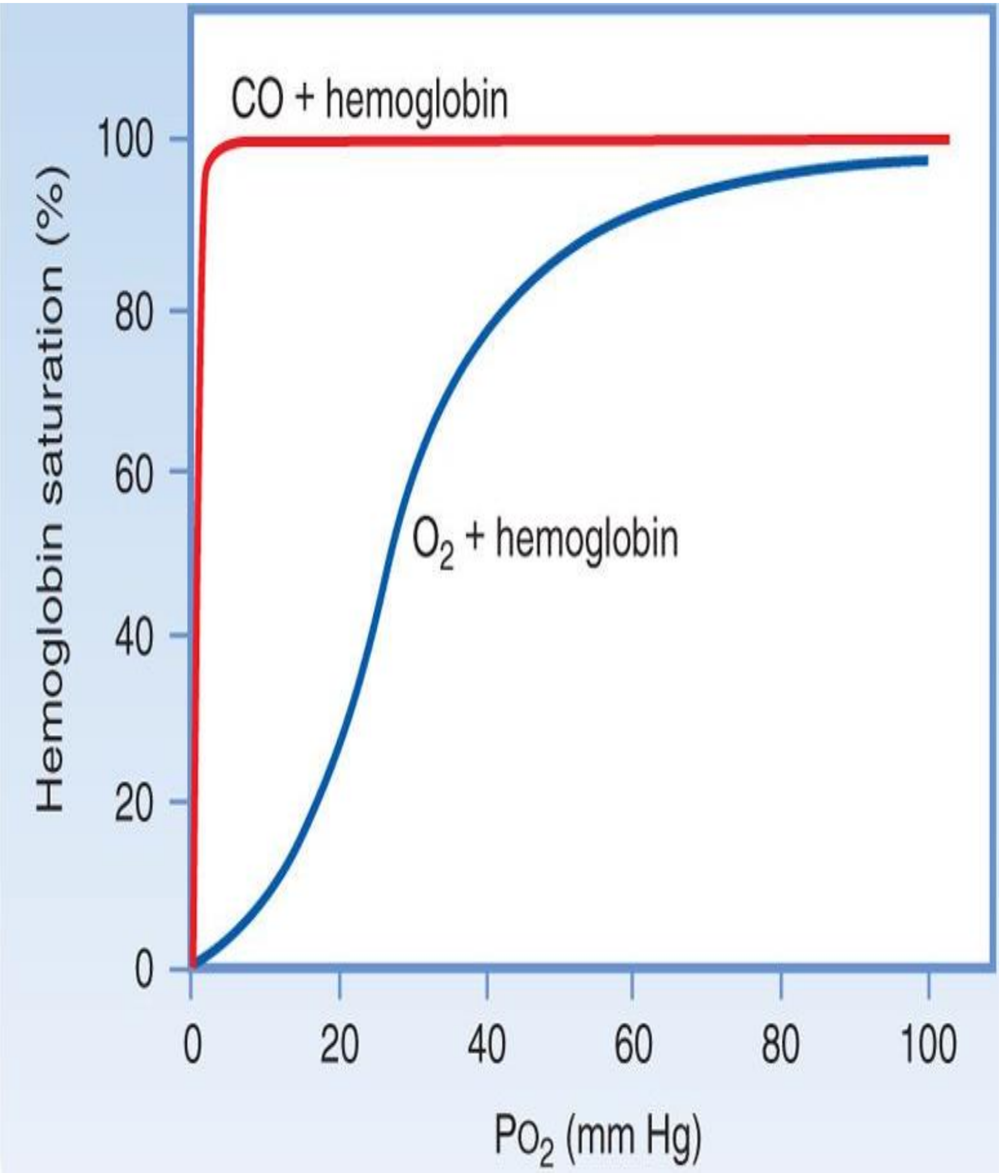


Role of 2,3-BPG in transfused blood:

- Storing blood in currently available media → ↓ in 2,3-PBG → abnormally ↑ O_2 affinity & ↓ delivery of O_2 to tissues.
- Hb deficient in 2,3-BPG is an O_2 **"trap"** rather than transport.
- Transfused RBCs **restore** depleted 2,3-BPG in **6–24 hours**.
- Severely ill patients may be compromised if transfused with large quantities of 2,3-BPG–"stripped" blood.
- Maximum storage time is doubled (21 to 42 days) by changes in **H^+, phosphate & hexose sugar concentration, & by adding adenine**
- 2,3-BPG content is not greatly affected by these changes but **ATP** production ↑ and improved RBC survival.

Binding of CO to Hb:

- CO binds Hb tightly (but reversibly) → carboxyhemoglobin
- When CO binds one or more of 4 heme sites, Hb shifts to **R state** → the remaining sites bind O_2 with high affinity → **shift to left**, & changes the normal sigmoidal shape toward a **hyperbola**.
- Affected Hb is unable to release O_2 to tissues.
- Hb affinity for CO is 220 times greater than for O_2.

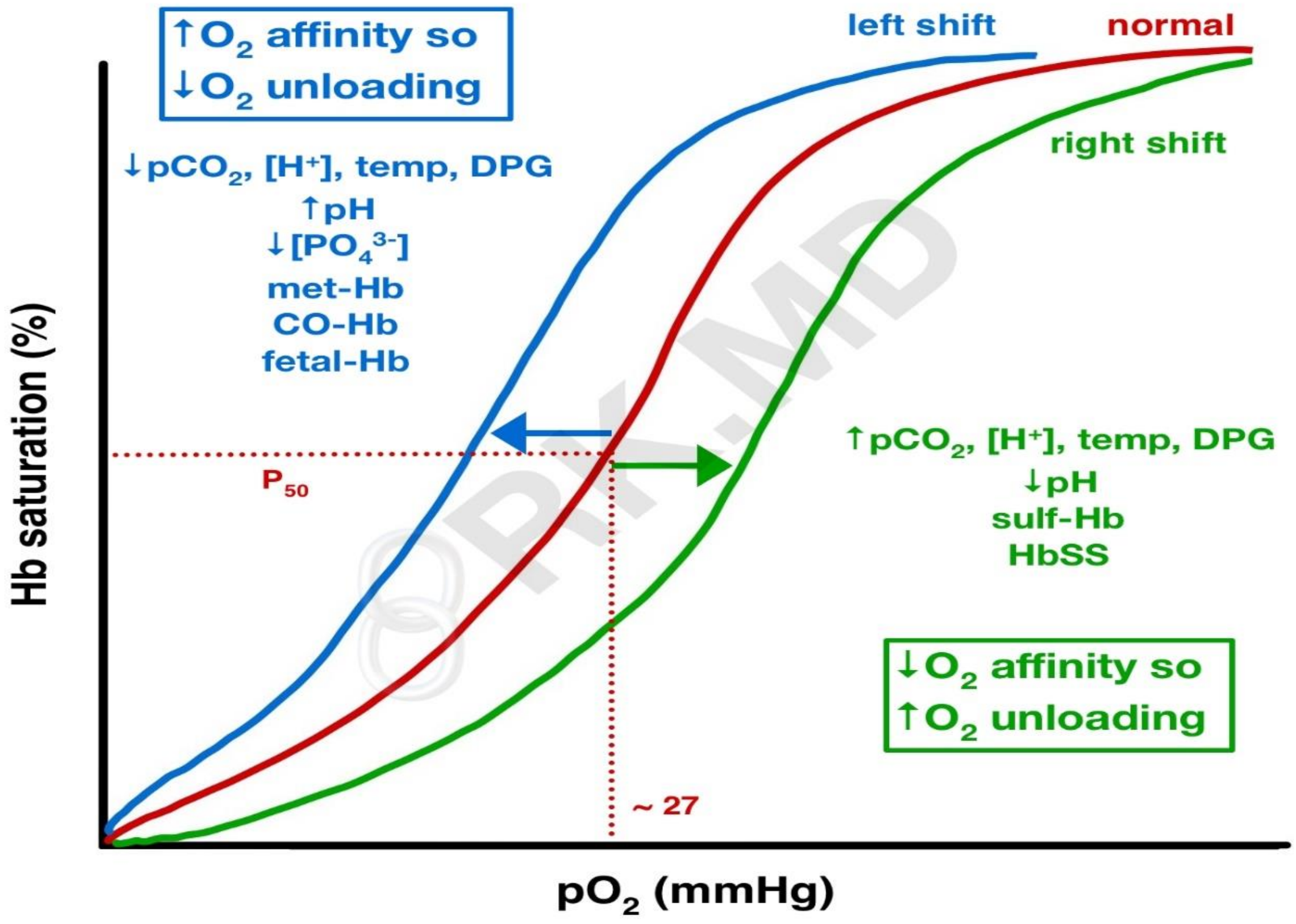


- Thus in the presence of CO, a person can experience severe tissue hypoxia while maintaining a normal PO_2. Patients with CO poisoning show symptoms as headache, malaise, altered mental status, shortness of breath, seizures, or cherry red lips. A pulse oximeter would usually be normal because the machine is unable to detect carboxyhemoglobin from oxyhemoglobin.

- **Fetal Hemoglobin:**
- HbF ($\alpha 2\gamma 2$) has a ↓ **affinity for 2,3-BPG**, → ↑ **affinity for O_2** at lower levels of partial pressure → **shift to left** of dissociation curve.
- This state is advantageous in the womb, as the fetus can pull O_2 from maternal circulation with greater ease.
- At the placenta, **2,3-DPG interacts more readily with adult Hb**, inducing O_2 unloading. Whereas, HbF is unaffected by 2,3-BPG and can bind O_2 easily.

Womb: الرحم

OXYHEMOGLOBIN DISSOCIATION CURVE



Questions

An infant, born at 28 weeks of gestation, rapidly gave evidence of respiratory distress. Lab and x-ray results supported the diagnosis of infant respiratory distress syndrome. Which of the following statements about this syndrome is true?

A. It is unrelated to the baby's premature birth.

B. It is a consequence of too few type II pneumocytes.

C. The lecithin/sphingomyelin ratio in the amniotic fluid is likely to be greater than two.

D. Concentration of dipalmitoylphosphatidylcholine in amniotic fluid would be expected to be lower than that of a full-term baby.

E. RDS is an easily treated disorder with low mortality.

Hemoglobin shows maximum affinity with:

A. Carbon monoxide

B. Carbon dioxide

C. Oxygen

D. Ammonia

E. H^+

Which one of the following statements concerning the hemoglobins is correct?

A. Fetal blood has a higher affinity for oxygen than does adult blood because Hb F has a decreased affinity for 2,3-BPG.

B. Purified Hb F (stripped of 2,3-BPG) has a higher affinity for oxygen than does purified Hb A.

C. The globin chain composition of Hb F is $\alpha 2\delta 2$.

D. Hb A1c differs from Hb A by a single, genetically determined amino acid substitution.

E. Hb A2 appears early in fetal life.

One of the following statements concerning the binding of oxygen by hemoglobin is correct?

A. The Bohr effect results in a lower affinity for oxygen at higher pH values.

B. Carbon dioxide increases the oxygen affinity of hemoglobin by binding to the C-terminal groups of the polypeptide chains.

C. The oxygen affinity of hemoglobin increases as the percentage saturation increases.

D. The hemoglobin tetramer binds four molecules of 2,3-BPG.

E. Oxyhemoglobin & deoxyhemoglobin have the same affinity for protons (H+).

THANK YOU