

# OXYGEN TRANSPORT AND HEMOGLOBIN

## COFEXPRESS

### Hemoglobin

- Each Hb molecule: 4 heme groups ( $\text{Fe}^{2+}$  center) + 4 globin chains.
- Major subtypes:
  - HbA ( $\alpha_2\beta_2$ ): predominant adult form
  - HbA<sub>2</sub> ( $\alpha_2\delta_2$ ): minor adult form
  - HbF ( $\alpha_2\gamma_2$ ): fetal form; lower 2,3-BPG binding → higher  $\text{O}_2$  affinity
- Tetrameric structure → allosteric behavior → sigmoidal  $\text{O}_2$  dissociation curve.
- **Positive cooperativity:** each  $\text{O}_2$  binding increases affinity of remaining sites.

### Carbon Dioxide Transport

- Bicarbonate ( $\text{HCO}_3^-$ ): ~70%
  - $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^-$  (carbonic anhydrase).
- Carbaminohemoglobin ( $\text{HbCO}_2$ ): ~25%
  - $\text{CO}_2$  bound to Hb's N-terminus.
- Dissolved  $\text{CO}_2$ : ~5%

### Oxygen Content and Delivery

- $\text{O}_2$  arterial content = Hb-bound  $\text{O}_2$  + dissolved  $\text{O}_2$
- Hb-bound  $\text{O}_2$ : main contributor; depends on Hb and  $\text{SaO}_2$ .
- Dissolved  $\text{O}_2$ : small contribution; depends on  $\text{PaO}_2$
- $\text{O}_2$  delivery = cardiac output × arterial  $\text{O}_2$  content

### Oxyhemoglobin Dissociation Curve

- Sigmoidal shape: due to positive cooperativity.
- Right shift (easier  $\text{O}_2$  unloading): ↑  $\text{CO}_2$ , ↓ pH, ↑ temp, ↑ 2,3-BPG, exercise, chronic hypoxia.
- Left shift (harder  $\text{O}_2$  unloading): ↓  $\text{CO}_2$ , ↑ pH, ↓ temp, ↓ 2,3-BPG, HbF, CO, methemoglobinemia.

### Response to High Altitude

- ↓ barometric pressure → ↓  $\text{PiO}_2$  → ↓  $\text{PaO}_2$  → hyperventilation → respiratory alkalosis.
- Chronic adaptations: ↑ Ventilation; ↑ Erythropoietin; ↑ 2,3-BPG; Renal  $\text{HCO}_3^-$  excretion; Pulmonary vasoconstriction.

### Clinical Conditions Affecting $\text{O}_2$ Transport

- Carbon Monoxide (CO) poisoning: CO binds Hb with 200× higher affinity than  $\text{O}_2$  →  $\text{HbCO}$
- Methemoglobinemia:  $\text{Fe}^{2+}$  oxidized to  $\text{Fe}^{3+}$  → can't bind  $\text{O}_2$
- Cyanide poisoning: Blocks oxidative phosphorylation



## HEMOGLOBIN

Hemoglobin is the protein that carries the majority of oxygen in blood. Each Hb molecule contains **four heme groups** (each with an  $\text{Fe}^{2+}$  ion at the center → binds  $\text{O}_2$  reversibly), each embedded in a **globin** polypeptide chains.

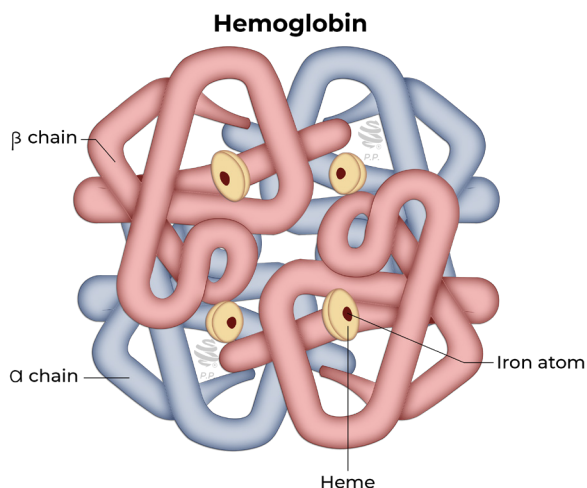


Figure 1: Hemoglobin A representation.

- Hemoglobin subunit composition:
  - HbA =  $\alpha_2\beta_2$  (adult predominant)
  - HbA<sub>2</sub> =  $\alpha_2\delta_2$  (minor adult component)
  - HbF =  $\alpha_2\gamma_2$  (fetal; less 2,3-BPG → higher  $\text{O}_2$  affinity)

The tetrameric arrangement (two  $\alpha$  and two non- $\alpha$  chains) creates an allosteric molecule: **binding at one site affects the others**. This property creates the **sigmoidal oxygen–dissociation curve** and allows rapid loading in the lungs and effective unloading in tissues.

- **Positive cooperativity:** successive  $\text{O}_2$  bindings increase affinity for more binding  $\text{O}_2$ ; unbinding favors subsequent unbinding.

### Clinical pearls

- Structural changes or abnormal chains (thalassemias, Hb variants) alter  $\text{O}_2$  carrying capacity and/or curve position.

### MYOGLOBIN VS HEMOGLOBIN

- Myoglobin (Mb) has a **single globin chain** and a **single heme group**. Its  $\text{O}_2$ -binding curve is hyperbolic (because there is no cooperativity). Mb has **greater  $\text{O}_2$  affinity** than Hb and provides an  $\text{O}_2$  storage in muscle for use during high demand (releases  $\text{O}_2$  only at very low  $\text{PO}_2$ ).

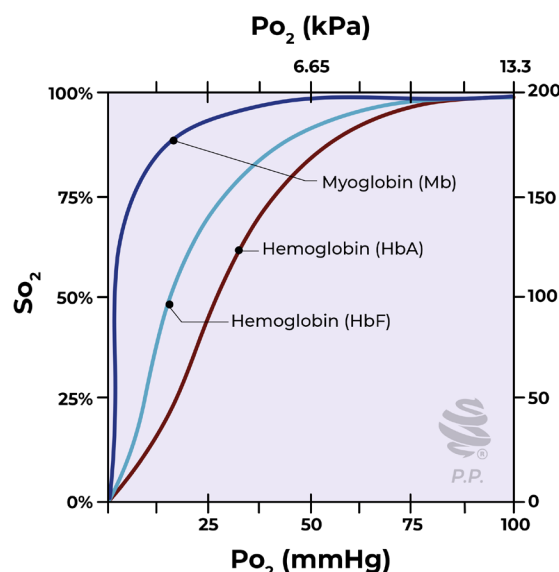


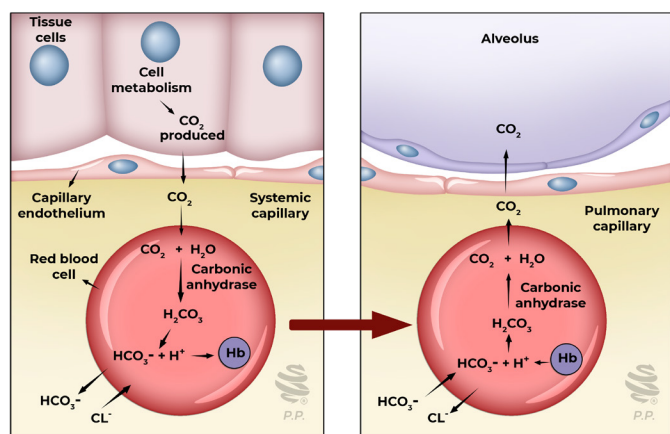
Figure 2: Myoglobin, hemoglobin A, and hemoglobin F dissociation curve (affinity to oxygen).

## CARBON DIOXIDE TRANSPORT

CO<sub>2</sub> travels from tissues to lungs in three main forms:

- **Bicarbonate (HCO<sub>3</sub><sup>-</sup>) ~70%:** formed inside RBCs by **carbonic anhydrase** ( $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$ ). HCO<sub>3</sub><sup>-</sup> is exchanged out for Cl<sup>-</sup> (chloride shift).
- **Carbaminohemoglobin (HbCO<sub>2</sub>) ~25%:** CO<sub>2</sub> bound to N-terminus of globin chain (not bound to heme); in tissues, carbaminohemoglobin formation favors O<sub>2</sub> unload from Hb.
- **Dissolved CO<sub>2</sub> ~5%:** directly dissolved in plasma.

**Haldane effect:** Oxygenation of Hb in the lungs lowers Hb's affinity for CO<sub>2</sub> and H<sup>+</sup>; this promotes CO<sub>2</sub> release (the reverse occurs in tissue). Clinically, this improves CO<sub>2</sub> unloading in the lungs when Hb is oxygenated.



**Figure 3:** Transport of carbon dioxide (CO<sub>2</sub>) between tissues and lungs through bicarbonate. In systemic capillaries (left), CO<sub>2</sub> produced by tissue metabolism diffuses into red blood cells, where carbonic anhydrase catalyzes its hydration to carbonic acid (H<sub>2</sub>CO<sub>3</sub>), which then dissociates into bicarbonate (HCO<sub>3</sub><sup>-</sup>) and protons (H<sup>+</sup>). Bicarbonate exits the cell in exchange for chloride (Cl<sup>-</sup>) in the "chloride shift," while H<sup>+</sup> is buffered by hemoglobin (Hb). In pulmonary capillaries (right), the process reverses: bicarbonate reenters the red cell, combines with H<sup>+</sup> to reform carbonic acid, which dissociates into CO<sub>2</sub> and H<sub>2</sub>O, and CO<sub>2</sub> diffuses into the alveolus for exhalation. The Haldane effect explains how oxygenation of hemoglobin in the lungs promotes CO<sub>2</sub> and H<sup>+</sup> release, facilitating CO<sub>2</sub> exhalation.

## OXYGEN CONTENT AND DELIVERY

**Oxygen arterial content = oxygen carried by hemoglobin + dissolved oxygen**

**Oxygen carried by hemoglobin:**

- Most of the O<sub>2</sub> is carried by hemoglobin → high contribution to O<sub>2</sub> arterial content.
- Determined by **Hb concentration and SaO<sub>2</sub>** (percentage of Hb bound to O<sub>2</sub>).
  - Small changes in Hb concentration (eg, anemia) or desaturation (eg, COPD exacerbation, CO poison) drastically change O<sub>2</sub> content.

**Dissolved oxygen:**

- Small contribution to O<sub>2</sub> arterial content.
- Determined by **partial pressure of O<sub>2</sub> (PaO<sub>2</sub>)** in arterial blood.

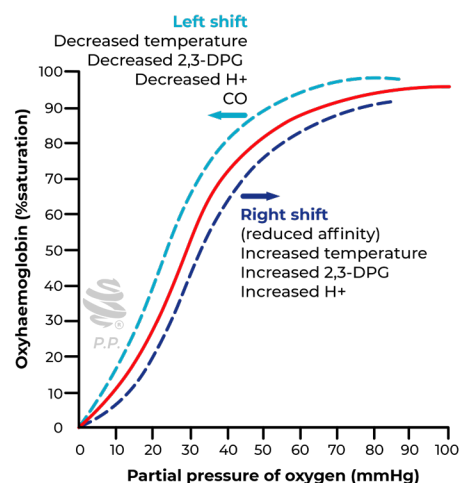
**Oxygen delivery to tissues** is the product of **cardiac output and arterial O<sub>2</sub> content**.

## OXYHEMOGLOBIN DISSOCIATION CURVE

The oxyhemoglobin dissociation curve (ODC) plots SaO<sub>2</sub> against PaO<sub>2</sub>. Its **sigmoidal** shape reflects **positive cooperativity** and allows a wide dynamic range of O<sub>2</sub> loading/unloading.

### WHAT CHANGES THE CURVE?

- **Right shift (facilitates O<sub>2</sub> unloading to tissues):**
  - ↑ CO<sub>2</sub> (local metabolism - Bohr effect)
  - ↓ pH (acidosis)
  - ↑ temperature
  - ↑ 2,3-BPG (hypoxia)
  - Exercise, chronic hypoxia
- **Left shift (inhibits O<sub>2</sub> unloading; tighter binding):**
  - ↓ CO<sub>2</sub> (lungs)
  - ↑ pH (alkalosis)
  - ↓ temperature
  - ↓ 2,3-BPG
  - HbF, CO, methemoglobinemia



**Figure 4:** Oxyhemoglobin dissociation curve.

## RESPONSE TO HIGH ALTITUDE

At high altitude, the fraction of inspired oxygen (FiO<sub>2</sub>) remains the same, but barometric pressure (P<sub>B</sub>) decreases. This leads to a **lower partial pressure of inspired oxygen (P<sub>I</sub>O<sub>2</sub>)**, which in turn **reduces arterial oxygen (PaO<sub>2</sub>)**. The immediate response is an increase in **ventilation**, lowering PaCO<sub>2</sub> and causing respiratory alkalosis. This acute imbalance contributes to **altitude sickness**, with symptoms such as headaches, nausea, fatigue, lightheadedness, and sleep disturbances.

Over time, the body undergoes several adaptations to improve oxygen delivery and utilization:

- **Ventilation:**
  - Chronic increase in ventilation maintains higher oxygen intake despite low PaO<sub>2</sub>.
- **Erythropoiesis:**
  - Hypoxia stimulates erythropoietin release.
  - Leads to increased hematocrit (Hct) and hemoglobin (Hb), improving oxygen-carrying capacity.
- **2,3-Bisphosphoglycerate (2,3-BPG):**
  - Levels rise in red blood cells.
  - Causes a rightward shift of the oxyhemoglobin dissociation curve (facilitates oxygen unloading to tissues).

- **Cellular changes:**
  - Mitochondrial adaptations enhance efficiency of oxygen use at the cellular level.
- **Renal compensation:**
  - Kidneys excrete more bicarbonate ( $\text{HCO}_3^-$ ) to compensate respiratory alkalosis.
- **Pulmonary circulation:**
  - Chronic hypoxia causes pulmonary vasoconstriction → results in increased pulmonary vascular resistance.
  - Long-term consequence: pulmonary hypertension and right ventricular hypertrophy (RVH).

## CLINICAL CONDITIONS THAT AFFECT $\text{O}_2$ TRANSPORT

### CARBON MONOXIDE (CO) POISONING

- **Mechanism:** CO binds Hb with  $\sim 200\times$  the affinity of  $\text{O}_2$  to form carboxyhemoglobin (HbCO), occupying binding sites and shifting the ODC **left** (inhibits  $\text{O}_2$  unloading from remaining sites).
  - **Net effect:** reduced  $\text{SaO}_2 \rightarrow$  reduced  $\text{O}_2$  arterial content  $\rightarrow$  tissue hypoxia.
- **Presentation:** headache, dizziness, confusion, nausea, **cherry-red skin** (classic but not always present), multiple victims common (eg, faulty furnace).
  - Pulse oximetry can read falsely normal/high because it cannot distinguish oxyhemoglobin from carboxyhemoglobin.
- **Diagnosis:** co-oximetry (measures percent carboxyhemoglobin); arterial  $\text{PaO}_2$  will be normal.
- **Treatment:** 100% oxygen; hyperbaric oxygen for severe cases.

### METHEMOGLOBINEMIA

- **Mechanism:** Oxidation of heme iron to  $\text{Fe}^{3+}$  (methemoglobin)  $\rightarrow \text{Fe}^{3+}$  cannot bind  $\text{O}_2$ .
  - **Net effect:** reduced  $\text{SaO}_2 \rightarrow$  reduced  $\text{O}_2$  arterial content  $\rightarrow$  tissue hypoxia.
- **Causes:** local anesthetics (benzocaine), nitrates, dapsone.
- **Clinical features:** cyanosis, **chocolate-brown blood, does not correct with supplemental  $\text{O}_2$** .
  - Pulse oximetry will be decreased.
- **Treatment:** methylene blue (reduces  $\text{Fe}^{3+}$  back to  $\text{Fe}^{2+}$ ); ascorbic acid (vitamin C).

### CYANIDE POISONING

- **Mechanism:** Cyanide impairs oxidative phosphorylation by inhibiting **cytochrome c oxidase (complex IV)**  $\rightarrow$  tissues cannot use  $\text{O}_2 \rightarrow$  lactic acidosis.
- $\text{PaO}_2$  and  $\text{SaO}_2$  are normal.
- **Treatment:** hydroxocobalamin (binds cyanide  $\rightarrow$  renal excretion); Nitrites (oxidize heme iron  $\rightarrow$  methemoglobin  $\rightarrow$  binds cyanide  $\rightarrow \downarrow$  toxicity); Sodium thiosulfate (cyanide  $\rightarrow$  thiocyanate  $\rightarrow$  renal excretion).

## CLASSIC BOARD-STYLE VIGNETTES

1. A 32-year-old man is rescued from a house fire. He is confused and tachypneic. Pulse oximetry shows 100%  $\text{O}_2$  saturation.  
**Answer:** CO poisoning.  
**Explanation:** Pulse oximeter cannot distinguish between oxyhemoglobin and carboxyhemoglobin.
2. A 24-year-old woman on dapsone develops cyanosis. Blood appears chocolate-brown.  
**Answer:** Methemoglobinemia ( $\text{Fe}^{3+}$  Hb). Treat with methylene blue.
3. A climber at 4500 m has dyspnea, headache, and respiratory alkalosis. Which change helps him adapt?  
**Answer:**  $\uparrow$  2,3-BPG  $\rightarrow$  right shift to improve  $\text{O}_2$  unloading.

## NOTES



# FLASHCARDS - FINAL REVIEW



1. What is the main difference between Hb and myoglobin dissociation curves?

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2. What causes a right shift of the dissociation curve?

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3. What causes a left shift of the dissociation curve?

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4. Why does HbF have higher O<sub>2</sub> affinity?

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5. How does altitude affect the Hb curve?

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6. Which condition gives chocolate-colored blood?

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7. Why is pulse oximetry unreliable in CO poisoning?

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8. Treatment for methemoglobinemia?

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9. Treatment for CO poisoning?

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# ANSWERS – FINAL REVIEW



1. What is the main difference between Hb and myoglobin dissociation curves?  
**Hb = sigmoidal (cooperativity); Myoglobin = hyperbolic (no cooperativity).**
2. What causes a right shift of the dissociation curve?  
**↑CO<sub>2</sub>, acidosis, ↑temperature, ↑2,3-BPG, exercise.**
3. What causes a left shift of the dissociation curve?  
**HbF, ↓CO<sub>2</sub>, alkalosis, ↓temperature, CO, MetHb.**
4. Why does HbF have higher O<sub>2</sub> affinity?  
**Poor binding of 2,3-BPG.**
5. How does altitude affect the Hb curve?  
**Chronic hypoxia → ↑2,3-BPG → right shift.**
6. Which condition gives chocolate-colored blood?  
**Methemoglobinemia.**
7. Why is pulse oximetry unreliable in CO poisoning?  
**It cannot distinguish oxyHb from carboxyHb.**
8. Treatment for methemoglobinemia?  
**Methylene blue, vitamin C.**
9. Treatment for CO poisoning?  
**100% O<sub>2</sub>, hyperbaric O<sub>2</sub> if severe.**

## NOTES