Oxygen Transport in the Blood

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Dissolved O2 in the blood

- Dissolved O2 is free in solution and accounts for approximately 2% of the total O2 content of blood.

- At this concentration, dissolved O2 is grossly insufficient to meet the demands of the tissues.

Dissolved O2 in the blood

- the concentration of dissolved O2 is proportional to the partial pressure of O2; the proportionality constant is simply the solubility of O2 in blood, 0.003 mL O2/100 mL blood per mm Hg.

- Thus for a normal PaO2 of 100 mm Hg, the concentration of dissolved O2 is:
- 0.3 mL O2/100 mL (100 mm Hg × 0.003 mL O2/100 mL blood per mm Hg).

- At this concentration, dissolved O2 is grossly insufficient to meet the demands of the tissues.

Dissolved O2 in the blood

- In a person at rest, O2 consumption is about 250 mL O2/min.
- If O2 delivery to the tissues were based strictly on the dissolved component, then 15 mL O2/min would be delivered to the tissues:
- (O2 delivery = cardiac output × dissolved O2 concentration, or 5 L/min × 0.3 mL O2/100 mL = 15 mL O2/min).

O2 bound to hemoglobin

- 98% of the total O2 content of blood is reversibly bound to hemoglobin inside the red blood cells.

- Hemoglobin is a globular protein consisting of four subunits.

Hemoglobin

- Each subunit contains a heme moiety, which is an iron-binding porphyrin, and a polypeptide chain, which is designated either α or β.
- Adult hemoglobin (hemoglobin A) is called α2β2; two of the subunits have α chains and two have β chains.
- Each subunit can bind one molecule of O2, for a total of four molecules of O2 per molecule of hemoglobin.

Hemoglobin

- The percent of heme groups bound to O2 is called percent (%) saturation; thus 100% saturation means that all four heme groups are bound to O2.

- When hemoglobin is oxygenated, it is called oxyhemoglobin; when it is deoxygenated, it is called deoxyhemoglobin.

- For the subunits to bind O2, iron in the heme moieties must be in the ferrous state (i.e., Fe2+).

Pulse oximetry

- measures % saturation of arterial blood using dual-wavelength spectrophotometry.

- Because oxyhemoglobin and deoxyhemoglobin have different absorbance characteristics, the machine calculates % saturation from absorbance at two different wavelengths.

- Pulse oximetry does not directly measure PaO2. However, knowing % saturation, one can estimate PaO2

Hemoglobin

- O2 molecule combines loosely and reversibly with the heme portion of hemoglobin.
- When Po2 is high, as in the pulmonary capillaries, O2 binds with hemoglobin.
- when Po2 is low, as in the tissue capillaries, O2 is released from hemoglobin.

Variants of Hemoglobin molecule

- **Methemoglobin**.
- If the iron component of the heme moieties is in the ferric, or Fe3+, state (rather than the normal Fe2+ state), it is called methemoglobin.

- Methemoglobin does not bind O2.

- Methemoglobinemia has several causes including oxidation of Fe2+ to Fe3+ by nitrites and sulfonamides.
- There is also a congenital variant of the disease in which there is a deficiency of methemoglobin reductase, an enzyme in red blood cells that normally keeps iron in its reduced state.

Variants of Hemoglobin molecule

- **Fetal hemoglobin** (hemoglobin F, HbF).
- In fetal hemoglobin, the two β chains are replaced by γ chains, giving it the designation of α2γ2.
- The physiologic consequence of this modification is that HbF has a **higher affinity** for O2 than hemoglobin A, facilitating O2 movement from the mother to the fetus.
- HbF is the normal variant present in the fetus and is gradually replaced by hemoglobin A within the first year of life.

Variants of Hemoglobin molecule

- **Hemoglobin S**.
- Hemoglobin S is an abnormal variant of hemoglobin that causes sickle cell disease.
- In hemoglobin S, the α subunits are normal and the β subunits are abnormal.
- In its deoxygenated form, hemoglobin S forms sickle-shaped rods in the red blood cells, distorting the shape of the red blood cells (i.e., sickling them).
- This deformation of the red blood cells can result in occlusion of small blood vessels, causing many of the symptoms of sickle cell crisis (e.g., pain).
- The O2 **affinity of hemoglobin S is less** than the O2 affinity of hemoglobin A.

O2 content

- The O2 content is the actual amount of O2 per volume of blood. The O2 content can be calculated from the O2-binding capacity of hemoglobin and the percent saturation of hemoglobin, plus any dissolved O2.

$$O_2 \text{ content} = (O_2\text{-binding capacity} \times \% \text{ Saturation}) + \text{Dissolved } O_2$$

O2 binding capacity

- The O2-binding capacity is the maximum amount of O2 that can be bound to hemoglobin per volume of blood, assuming that hemoglobin is 100% saturated (i.e., all four heme groups on each molecule of hemoglobin are bound to O2).

O2 binding capacity

- To calculate the O2-binding capacity is that:
- 1 g of hemoglobin A can bind 1.34 mL O2 and:
- the normal concentration of hemoglobin A in blood is 15 g/100 mL.
- The O2-binding capacity of blood is therefore 20.1 mL O2/100 mL blood (15 g/100 mL × 1.34 mL O2/g hemoglobin = 20.1 mL O2/100 mL blood).

SAMPLE PROBLEM. A man who is anemic has a severely reduced hemoglobin concentration of 10 g/100 mL blood. Assuming that the patient has normal lungs and that the values of both $P_{A_{O_2}}$ and $P_{a_{O_2}}$ are normal at 100 mm Hg, *what is the* O_2 *content of his blood, and how does that value compare with the normal value?* Assume that for a normal hemoglobin concentration of 15 g/100 mL, the O_2-binding capacity is 20.1 mL O_2/100 mL blood, and that hemoglobin is 98% saturated at a $P_{a_{O_2}}$ of 100 mm Hg.

SOLUTION. (1) First, calculate the *O_2-binding capacity* (the maximum amount of O_2 that can be bound to hemoglobin) at a hemoglobin concentration of 10 g/100 mL blood. It is a given that at a normal hemoglobin concentration of 15 g/100 mL, O_2-binding capacity is 20.1 mL O_2/100 mL blood. Thus at a hemoglobin concentration of 10 g/100 mL, O_2-binding capacity is 10/15 of normal. Thus

$$\begin{aligned} O_2\text{-binding capacity} &= 20.1 \text{ mL } O_2/100 \text{ mL blood} \times \frac{10}{15} \\ &= 13.4 \text{ mL } O_2/100 \text{ mL blood} \end{aligned}$$

(2) Next, calculate the *actual amount of O_2 combined with hemoglobin* by multiplying the O_2-binding capacity by the % saturation. Thus

$$\begin{aligned} O_2 \text{ bound to hemoglobin} &= 13.4 \text{ mL } O_2/100 \text{ mL blood} \times 98\% \\ &= 13.1 \text{ mL } O_2/100 \text{ mL blood} \end{aligned}$$

(3) Finally, determine the *total O_2 content* by calculating the dissolved O_2 at Pa_{O_2} of 100 mm Hg and adding that amount to the O_2 bound to hemoglobin. The solubility of O_2 in blood is 0.003 mL O_2/100 mL per mm Hg. Thus

$$\begin{aligned} \text{Dissolved } O_2 &= 100 \text{ mm Hg} \times 0.003 \text{ mL } O_2/100 \text{ mL/mm Hg} \\ &= 0.3 \text{ mL } O_2/100 \text{ mL blood} \end{aligned}$$

$$\begin{aligned} \text{Total } O_2 \text{ content} &= O_2 \text{ bound to hemoglobin} + \text{dissolved } O_2 \\ &= 13.1 \text{ mL } O_2/100 \text{ mL blood} \\ &\quad + 0.3 \text{ mL } O_2/100 \text{ mL blood} \\ &= 13.4 \text{ mL } O_2/100 \text{ mL blood} \end{aligned}$$

An O_2 content of 13.4 mL O_2/100 mL blood is *severely* depressed. Compare this value with the O_2 content of 20.0 mL O_2/100 mL blood calculated at the normal hemoglobin concentration of 15 g/100 mL and 98% saturation. (Bound O_2 is 20.1 mL O_2/100 mL × 98% = 19.7 mL O_2/100 mL, and dissolved O_2 is 0.3 mL O_2/100 mL. Thus normal total O_2 content is the sum, or 20.0 mL O_2/100 mL blood.)

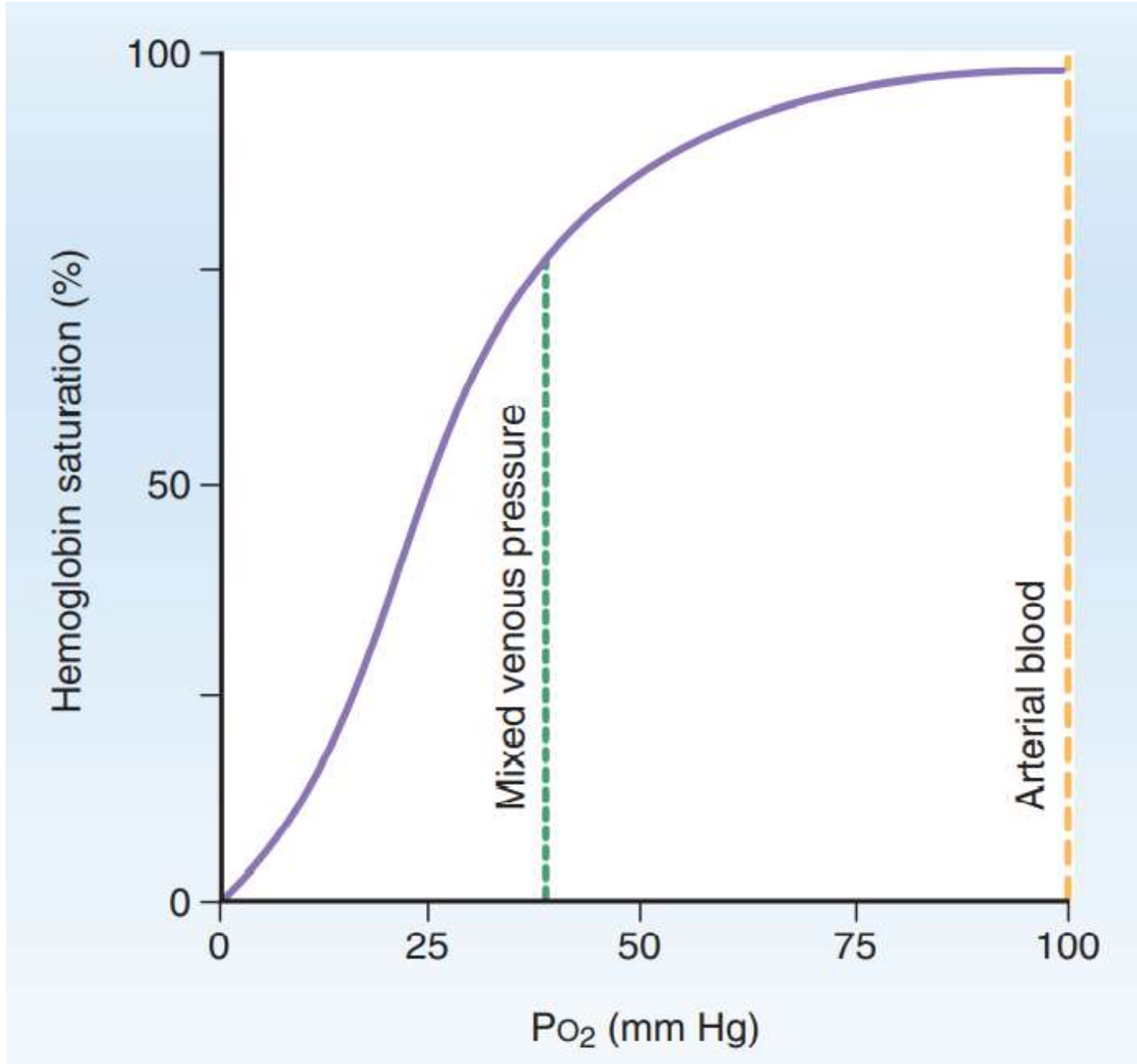
O2 delivery to tissues

- The amount of O2 delivered to tissues is determined by:
- blood flow
- the O2 content of blood.

- In terms of the whole organism, blood flow is considered to be cardiac output.

O2-Hemoglobin dissociation curve

- Percent saturation of hemoglobin is a function of the PO2 of blood.
- O2-hemoglobin dissociation curve is sigmoidal shape.
- In other words, the percent saturation of heme sites does not increase linearly as PO2 increases.
- Rather, percent saturation increases steeply as PO2 increases from zero to approximately 40 mm Hg, and it then levels off between 50 mm Hg and 100 mm Hg.


100
50
0
Hemoglobin saturation (%)
Mixed venous pressure
Arterial blood
0
25
50
75
100
P_{O_2} (mm Hg)

O2-Hemoglobin dissociation curve

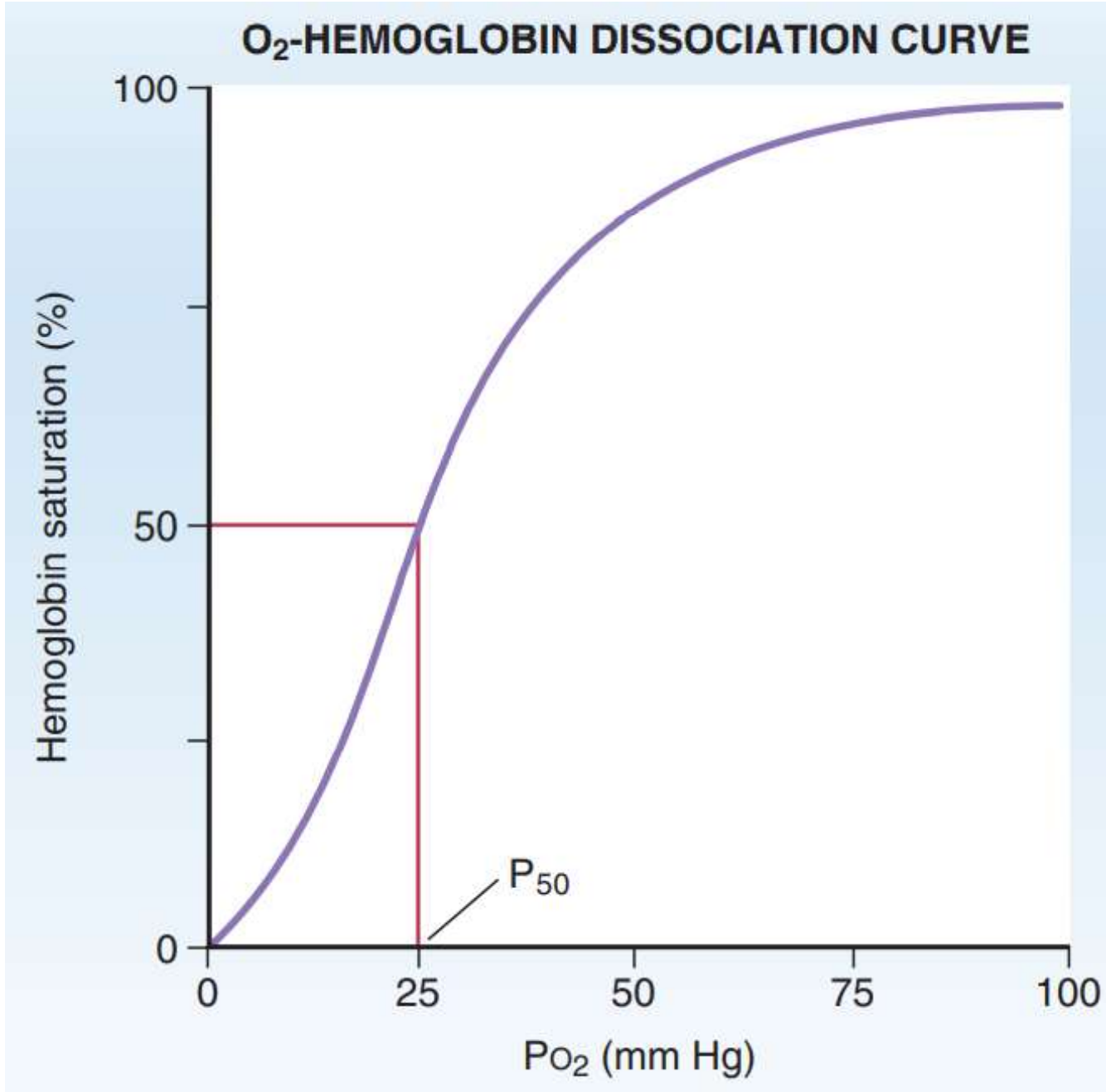
- The shape of the steepest portion of the curve is the result of a change in affinity of the heme groups for O2 as each successive O2 molecule binds.

- Affinity for the fourth molecule of O2 is highest and occurs at values of PO2 between approximately 60 and 100 mm Hg, where saturation is nearly 100%.

- This phenomenon is described as **positive cooperativity**

P50

- A significant point on the O2-hemoglobin dissociation curve is the P50.
- By definition, P50 is the PO2 at which hemoglobin is 50% saturated (i.e., where two of the four heme groups are bound to O2).
- A change in the value of P50 is used as an **indicator for a change in affinity** of hemoglobin for O2.
- An increase in P50 reflects a decrease in affinity, and a decrease in P50 reflects an increase in affinity.


O2-HEMOGLOBIN DISSOCIATION CURVE
100
50
0
Hemoglobin saturation (%)
P50
0
25
50
75
100
PO2 (mm Hg)

Values of Po_2 and Corresponding Values of Percent Saturation of Hemoglobin

Po_2 (mm Hg)	Saturation (%)
10	25
20	35
25	50
30	60
40	75
50	85
60	90
80	96
100	98

The Po_2 that corresponds to 50% saturation of hemoglobin is called P_{50}.

Loading and unloading of O2

- The sigmoidal shape of the curve reflects changes in the affinity of hemoglobin for O2, and these changes in affinity facilitate loading of O2 in the lungs (where PO2 and affinity are highest) and unloading of O2 in the tissues (where PO2 and affinity are lower).

Changes in the O2-Hemoglobin dissociation curve

- The O2-hemoglobin dissociation curve can shift to the right or shift to the left.

- Such shifts reflect changes in the affinity of hemoglobin for O2 and produce changes in P50.

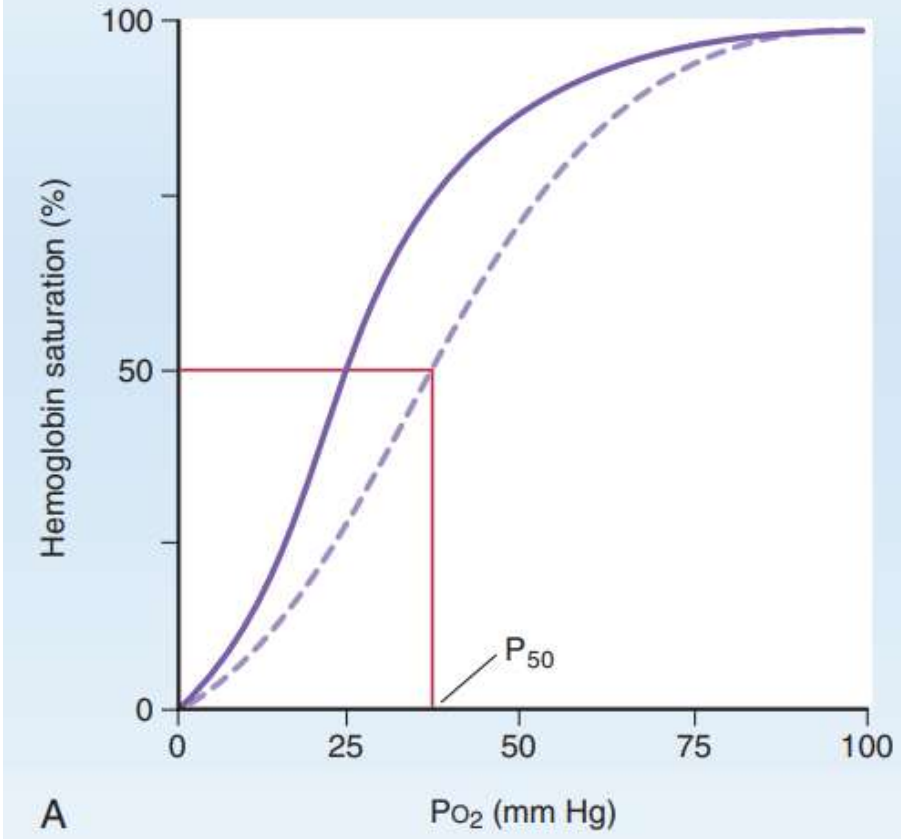
Shift to the right

- The occur when there is decreased affinity of hemoglobin for O2.

- reflected in an increase in P50, which means that 50% saturation is achieved at a higher-than-normal value of PO2.
- When the **affinity is decreased**, **unloading of O2** in the tissues is facilitated. Physiologically, the factors that cause a decrease in affinity and a right shift of the O2-hemoglobin dissociation curve are understandable:
- In each case, it is advantageous to facilitate unloading of O2 in the tissues.

Causes of shift to the right

- ↑ P_{CO_2}
- ↓ pH
- ↑ Temperature
- ↑ 2,3-DPG



A

Shift to the right

- **Increases in PCO2 and decreases in pH**.
- When metabolic activity of the tissues increases, the production of CO2 increases; the increase in tissue PCO2 causes an increase in H+ concentration and a decrease in pH.

- Together, these effects decrease the affinity of hemoglobin for O2, shift the O2-hemoglobin dissociation curve to the right, and increase the P50, all of which facilitates unloading of O2 from hemoglobin in the tissues.

- This mechanism helps to ensure that O2 delivery can meet O2 demand (e.g., in exercising skeletal muscle).

- The effect of PCO2 and pH on the O2-hemoglobin dissociation curve is called the **Bohr effect.**

Shift to the right

- **Increases in temperature.**

- Considering the example of exercising skeletal muscle, this effect also is logical.

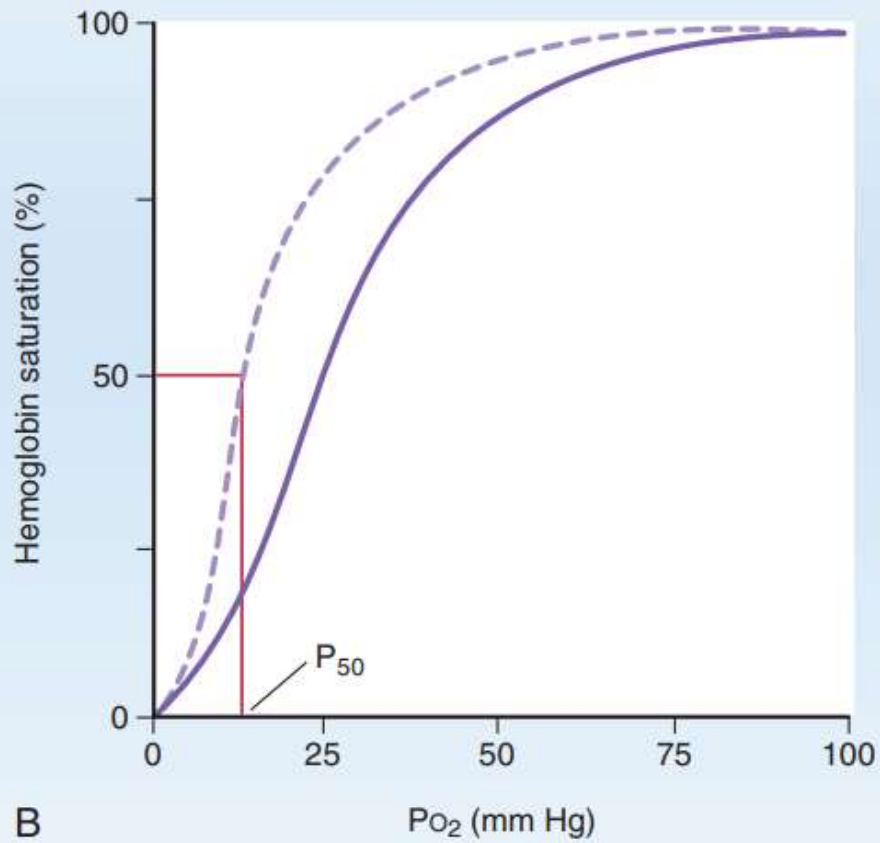
- As heat is produced by the working muscle, the O2-hemoglobin dissociation curve shifts to the right, providing more O2 to the tissue

Shift to the right

- **Increases in 2,3-diphosphoglycerate (2,3-DPG) concentration**.
- 2,3-DPG is a byproduct of glycolysis in red blood cells. 2,3-DPG binds to the β chains of deoxyhemoglobin and reduces their affinity for O2.
- This decrease in affinity causes the O2-hemoglobin dissociation curve to shift to the right and facilitates unloading of O2 in the tissues.
- 2,3-DPG production increases under hypoxic conditions.
- For example, living at high altitude causes hypoxemia, which stimulates the production of 2,3-DPG in red blood cells. In turn, increased levels of 2,3-DPG facilitate the delivery of O2 to the tissues as an adaptive mechanism.

Causes of shift to the left

- ↓ P_{CO_2}
- ↑ pH
- ↓ Temperature
- ↓ 2,3-DPG
- Hemoglobin F



B

Shift to the left

- The Shifts of the O2-hemoglobin dissociation curve to the left occur when there is increased affinity of hemoglobin for O2.
- An increase in affinity is reflected in a decrease in P50, which means that 50% saturation occurs at a lower-than-normal value of PO2.
- When the affinity is increased, unloading of O2 in the tissues is more difficult (i.e., binding of O2 is tighter).

Shift to the left

- **Decreases in PCO2 and increases in pH**.
- The effect of decreases in PCO2 and increases in pH is the Bohr effect again.
- When there is a decrease in tissue metabolism, there is decreased production of CO2, decreased H+ concentration, and increased pH, resulting in a left shift of the O2-hemoglobin dissociation curve.
- Thus when the demand for O2 decreases, O2 is more tightly bound to hemoglobin and less O2 is unloaded to the tissues.

Shift to the left

- **Decreases in temperature**.
- When tissue metabolism decreases, less heat is produced and less O2 is unloaded in the tissues.

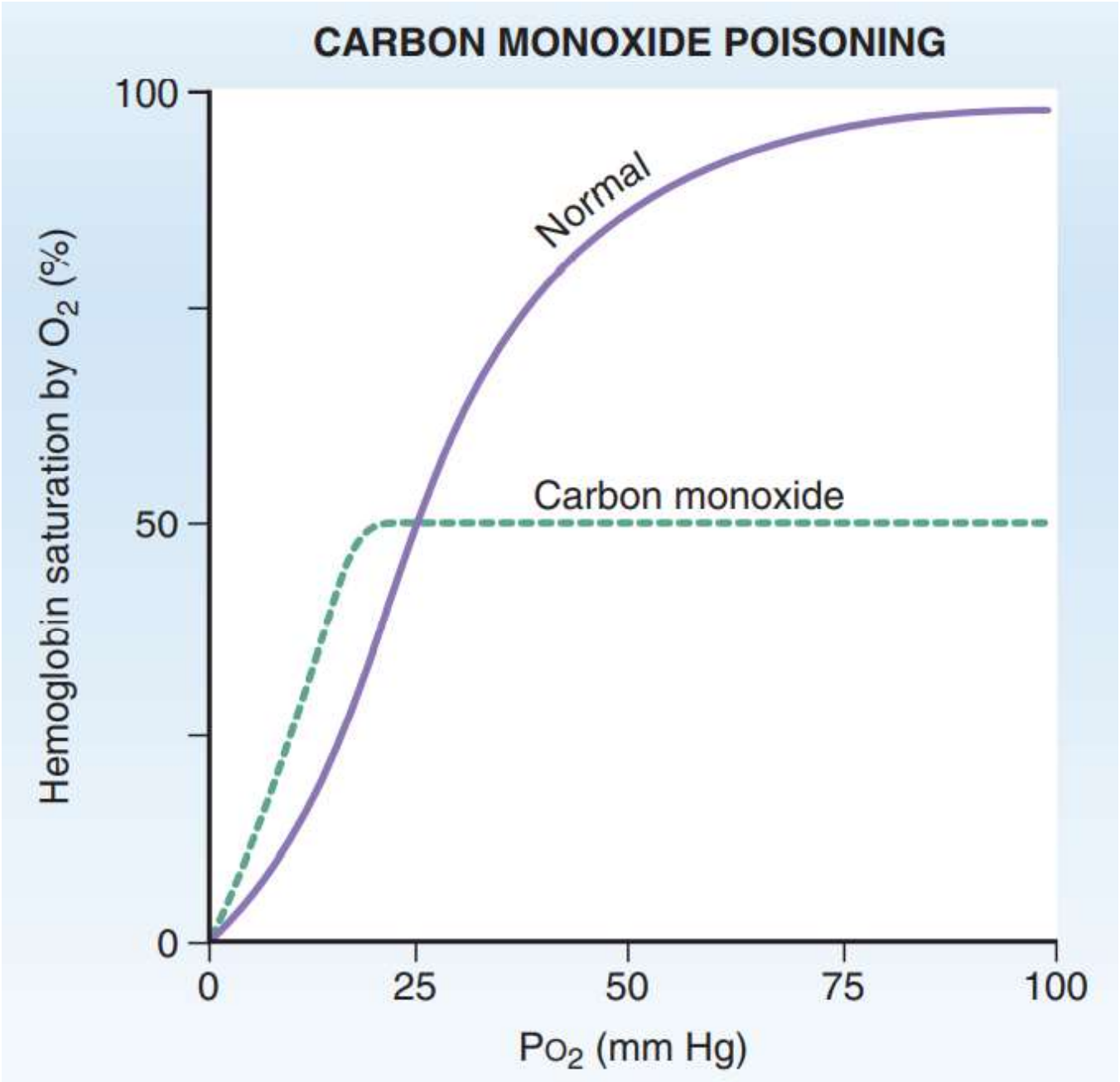
- **Decreases in 2,3-DPG concentration**.
- reflect decreased tissue metabolism, causing a left shift of the curve and less O2 to be unloaded in the tissues.

Shift to the left

- **Hemoglobin F**.
- The β chains of adult hemoglobin (hemoglobin A) are replaced by γ chains in HbF.
- This modification results in increased affinity of hemoglobin for O2, a left shift of the O2-hemoglobin dissociation curve, and decreased P50.
- 2,3-DPG does not bind as avidly to the γ chains of HbF as it binds to the β chains of hemoglobin A. When less 2,3-DPG is bound, the affinity for O2 increases.
- This increased affinity is beneficial to the fetus, whose PaO2 is low (approximately 40 mm Hg).

Carbon monoxide

- CO also causes a left shift of the O2-hemoglobin dissociation curve:
- Those heme groups not bound to CO have an **increased affinity for O2.**
- Thus P50 is decreased, making it more difficult for O2 to be unloaded in the tissues.
- Together, these two effects of CO on O2 binding to hemoglobin are catastrophic for O2 delivery to tissues.
- Not only is there reduced O2-binding capacity of hemoglobin, but the remaining heme sites bind O2 more tightly


CARBON MONOXIDE POISONING
100
50
0
Hemoglobin saturation by O_2 (%)
Normal
Carbon monoxide
0
25
50
75
100
P_{O_2} (mm Hg)

Thank you