B.Sc. Semester II, Physiology (General)

RESPIRATORY EXCHANGE OF GASES

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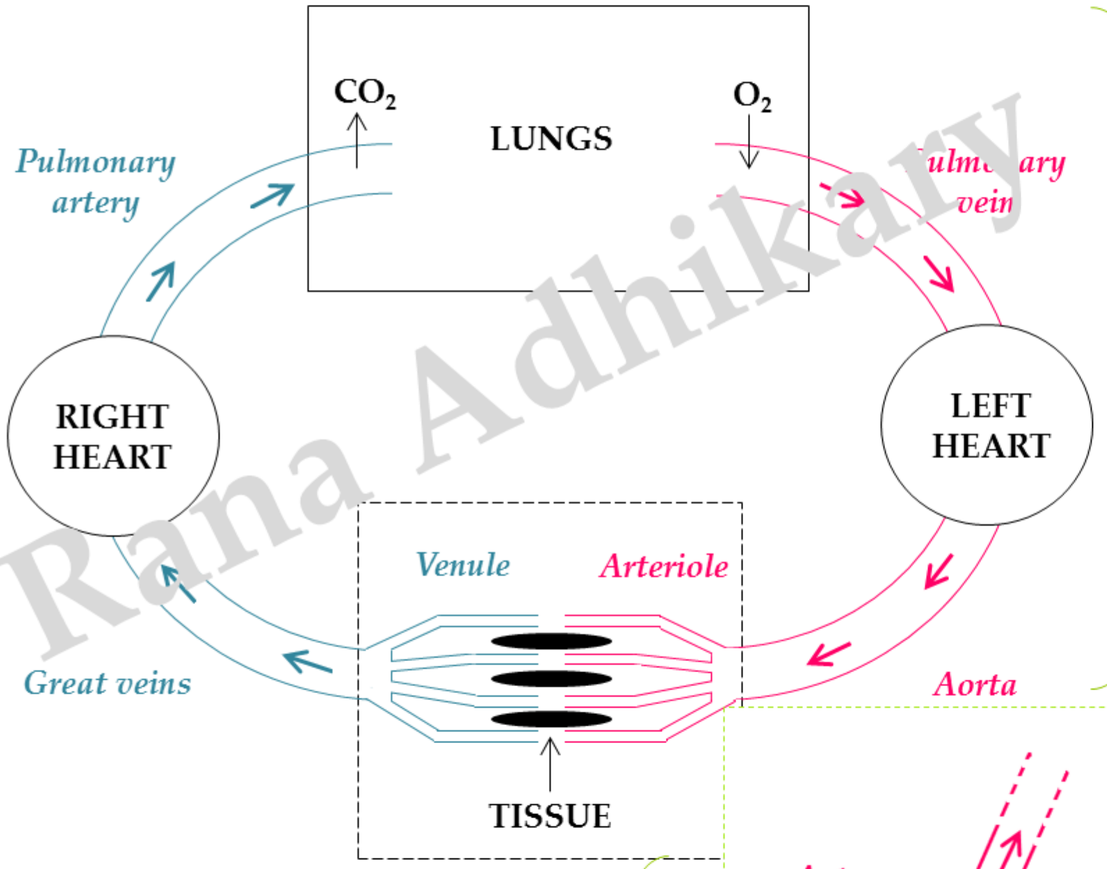
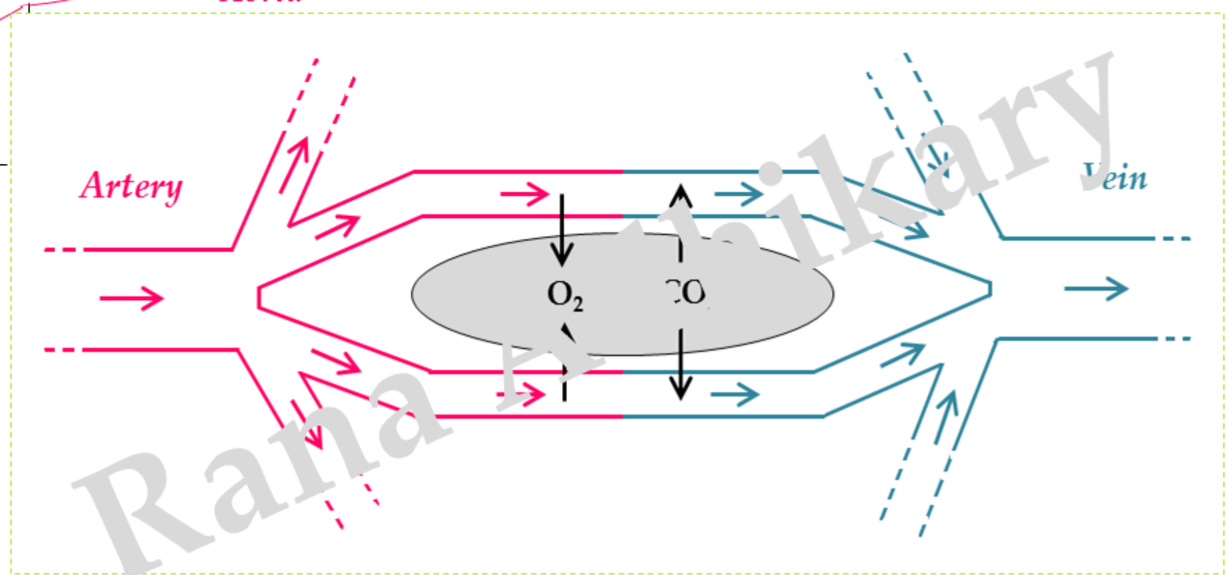
General idea about gaseous exchange

Gaseous exchange is an essential process for all living tissues in our body… gaseous exchange process involves reverse transport of O_2 and CO_2 … The source of O_2 into the lungs is 'pulmonary ventilation', and the source of CO_2 in extrapulmonary tissues is 'tissue respiration'…



Pulmonary ventilation: It refers to the amount of air going to lungs per minute.. (value is 6 Lit/min)

Tissue respiration



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Ventilation-perfusion (V_A/Q) ratio

Alveolar ventilation (V_A): It refers to the amount of air going to exchange zone per minute.. also written as V_A

V_A = (Tidal volume - Dead space) x Rate of respiration

V_A = (500 - 150) x 12 = 4.2 Lit/ min

Perfusion (Q): It refers to the amount of blood passing through the pulmonary capillaries per minute

Q = 5 Lit/ min

V_A/Q ratio
= 4.2 $L.min^{-1}$/5 $L.min^{-1}$
= 0.8

V_A/Q ratio

Bronchial asthma
Emphysema
Pneumothorax
Pulmonary fibrosis

- ✓ Normal pulmonary gas exchange
- ✓ Normal composition of alveolar air
- ✓ Normal gaseous composition of pulmonary venous blood

V_A/Q ratio

Pulmonary embolism
Anatomical shunts
Increased surface area
Pulmonary resistance

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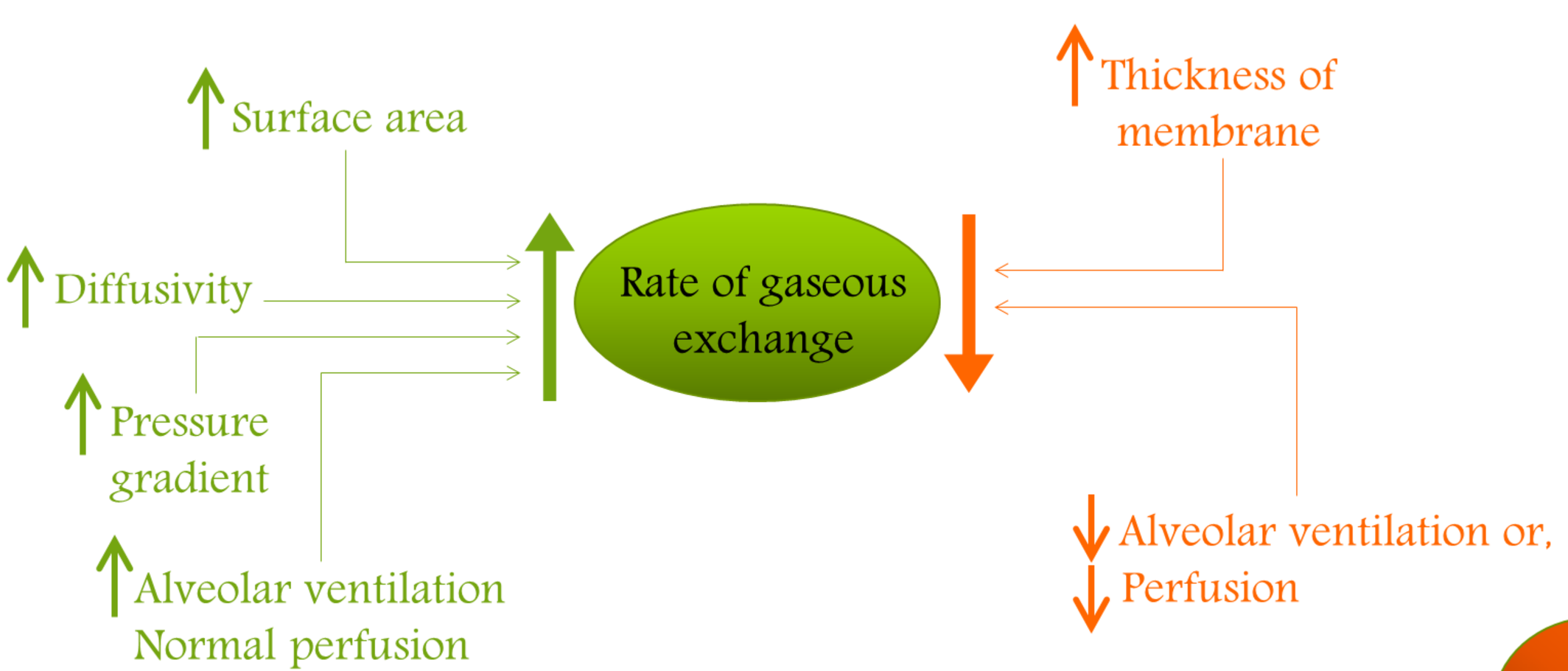
Factors affecting gaseous exchange

Fick's law states that '*volume of a gas passing through a membrane is directly proportional to the area of that membrane, diffusivity of that gas, and pressure gradient across the membrane; on the other hand it is inversely proportional to the thickness of the membrane*'

$$V_{gas} = \frac{A \times D}{T} \cdot (P_1 - P_2)$$



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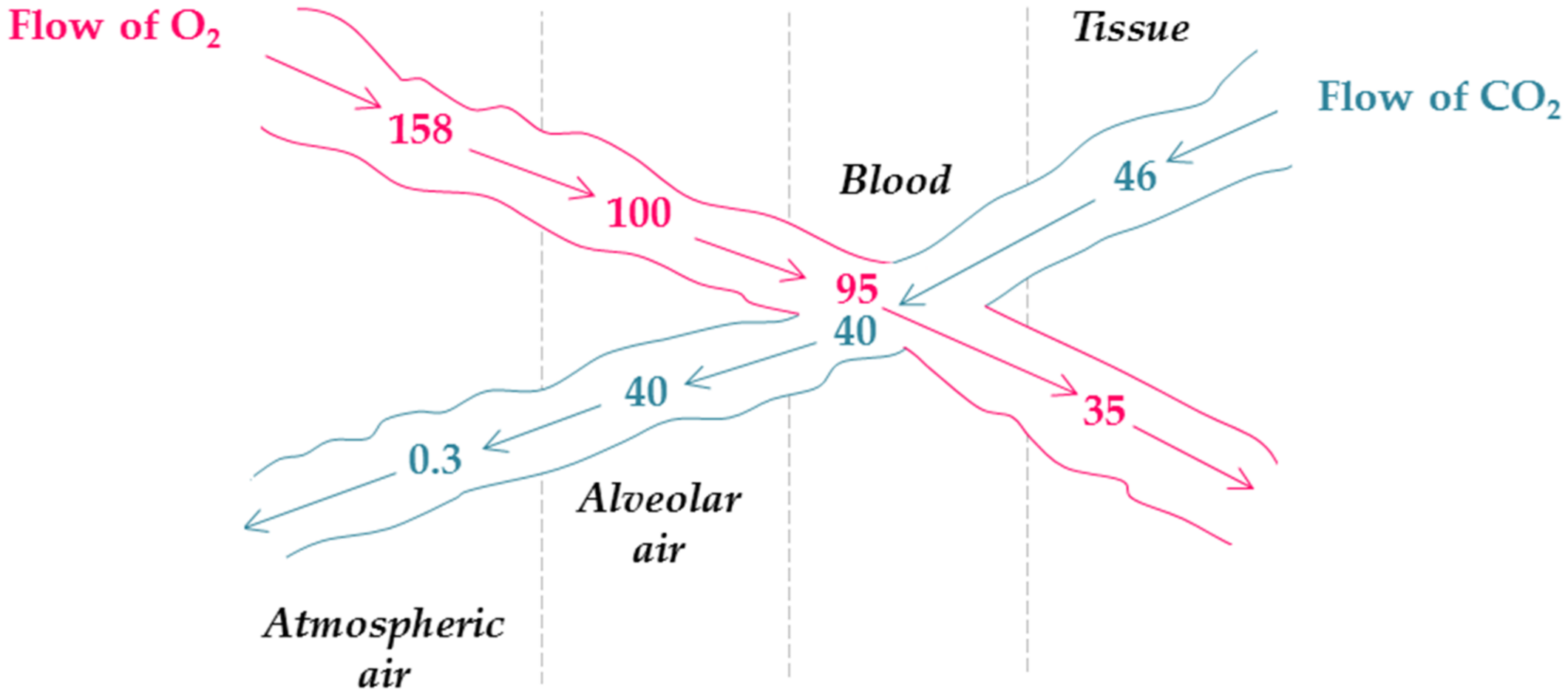
Transport of blood gases



O_2 transport: Atmospheric air ⇨ Alveoli ⇨ Blood ⇨ Tissue

CO_2 transport: Tissue ⇨ Blood ⇨ Alveoli ⇨ Atmospheric air

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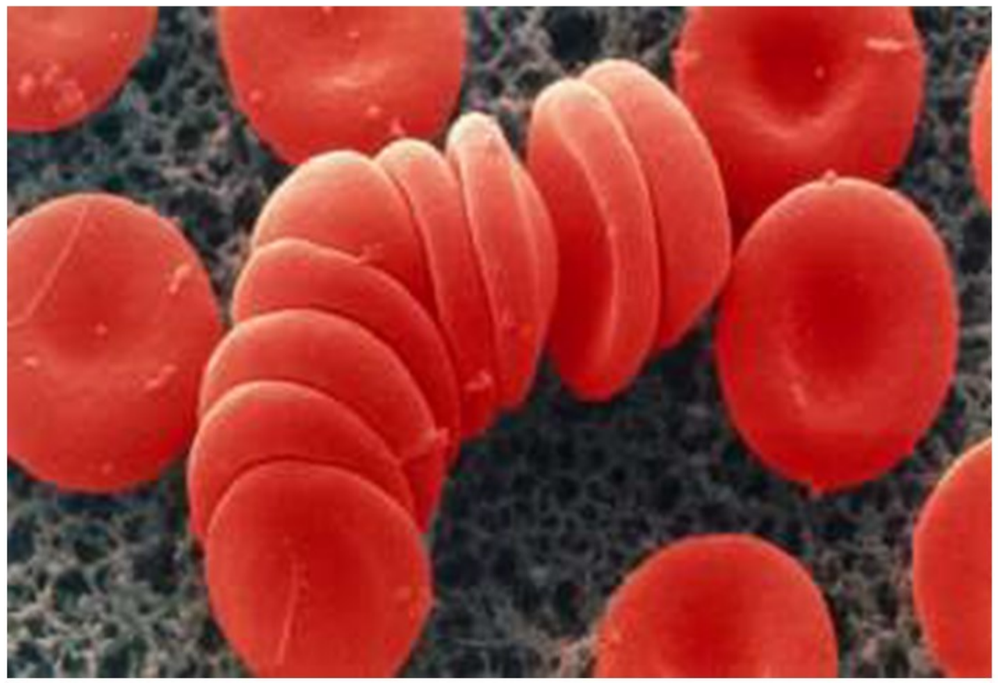
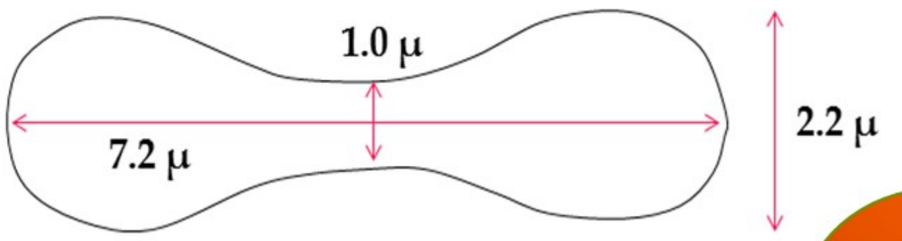
Role of erythrocytes in transport of gases

Erythrocytes are designed as efficient O_2 delivery system; erythrocytes are also involved in transport of various other gases too, e.g., CO_2, CO etc.

Besides huge content of hemoglobin (around 70% of the dry weight) which can interact and bind with various gases, erythrocytes have several structural peculiarities, some of which greatly assist in their gaseous exchange capabilities –

- Erythrocytes endow a biconcave shape, which is conferred by presence of proteins like spectrin and ankyrin. This biconcave shape effectively decreases the distance from centre to periphery and facilitates the exchange of gases across the cell, i.e., from one side to another side of the cell...
- Erythrocytes have an exceptionally large surface area to volume ratio, which makes them to avail greater surface area in comparison to a spherically shaped cell, this also enhances the rate of gaseous exchange...





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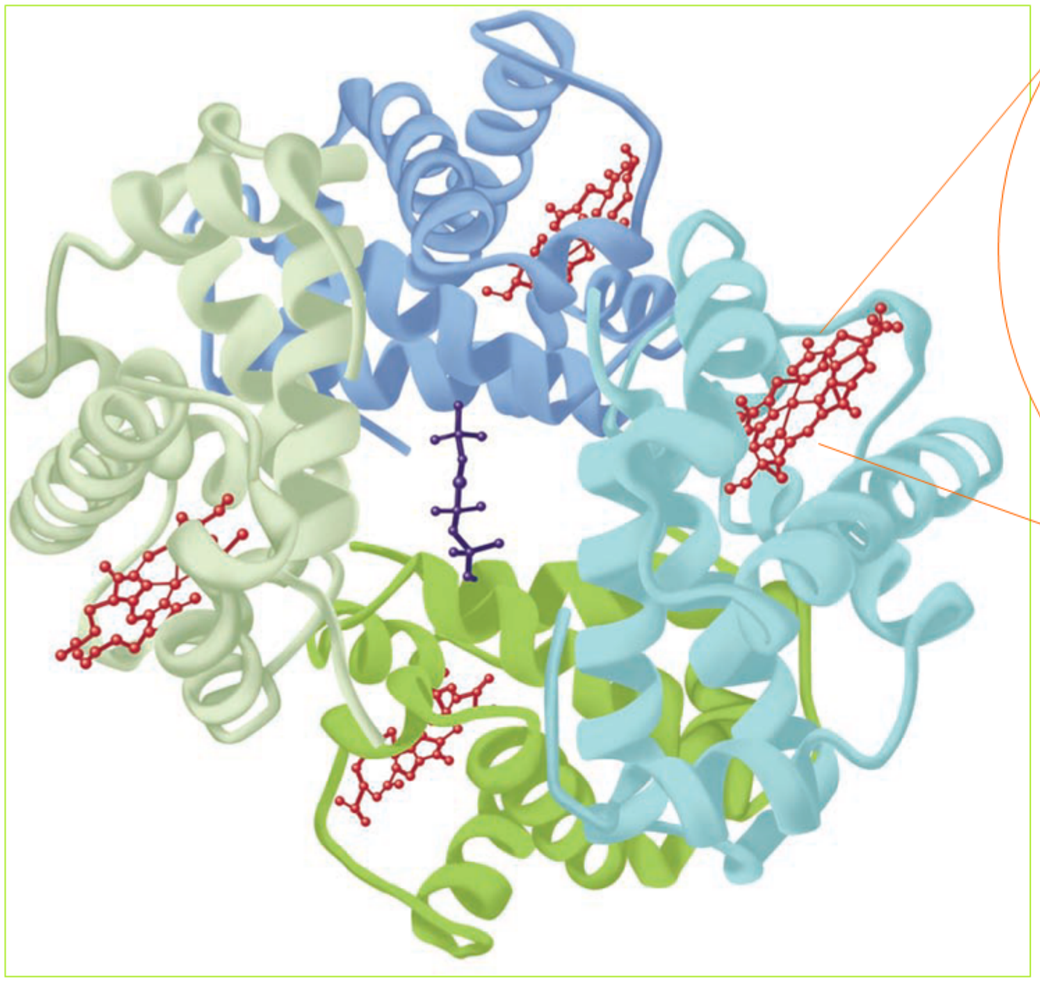
Oxygen transport in arterial blood

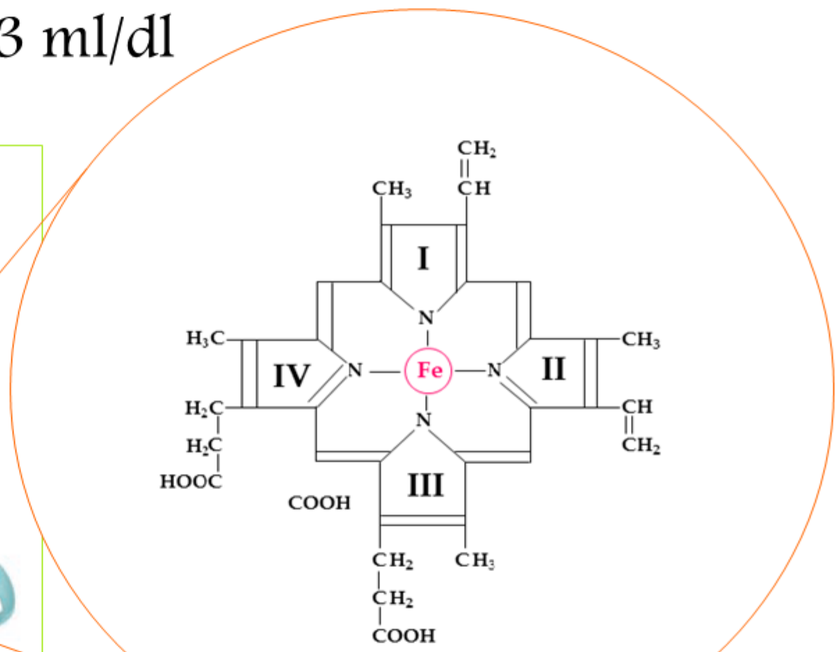
O_2 is transported in blood in two forms –

- as physical solution (0.3 ml/dl of blood)
- in combination with hemoglobin (19.43 ml/dl of blood)

O_2 carrying capacity of blood is = 19.73 ml/dl



Three-dimensional subunit structure of hemoglobin
[Harper's Illustrated Biochemistry, 30th Ed.]



Heme porphyrin ring

- Central iron in oxidized ferrus or Fe^{2+} state – capable of formation of six co-ordination bonds
- The central Fe^{2+} in heme can bind with both O_2 and CO
- One Hb can bind with four O_2
- 1 g of Hb combine with 1.34 ml of O_2

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Oxygenation of hemoglobin

Since combination of hemoglobin with O_2 do not alter ionic status of the large hemoglobin molecule, it better known as oxygenation...

$$Hb_4 + O_2 \longrightarrow Hb_4O_2$$
$$Hb_4O_2 + O_2 \longrightarrow Hb_4O_4$$
$$Hb_4O_4 + O_2 \longrightarrow Hb_4O_6$$
$$Hb_4O_6 + O_2 \longrightarrow Hb_4O_8$$

Combination of first O_2 molecule with one of the heme situated deep inside the three dimensional coiled coil structure of corresponding globin chain is difficult.. The globins are said to be in 'tout' (T) form due to strong interaction among the globin chains formed of salt bridges

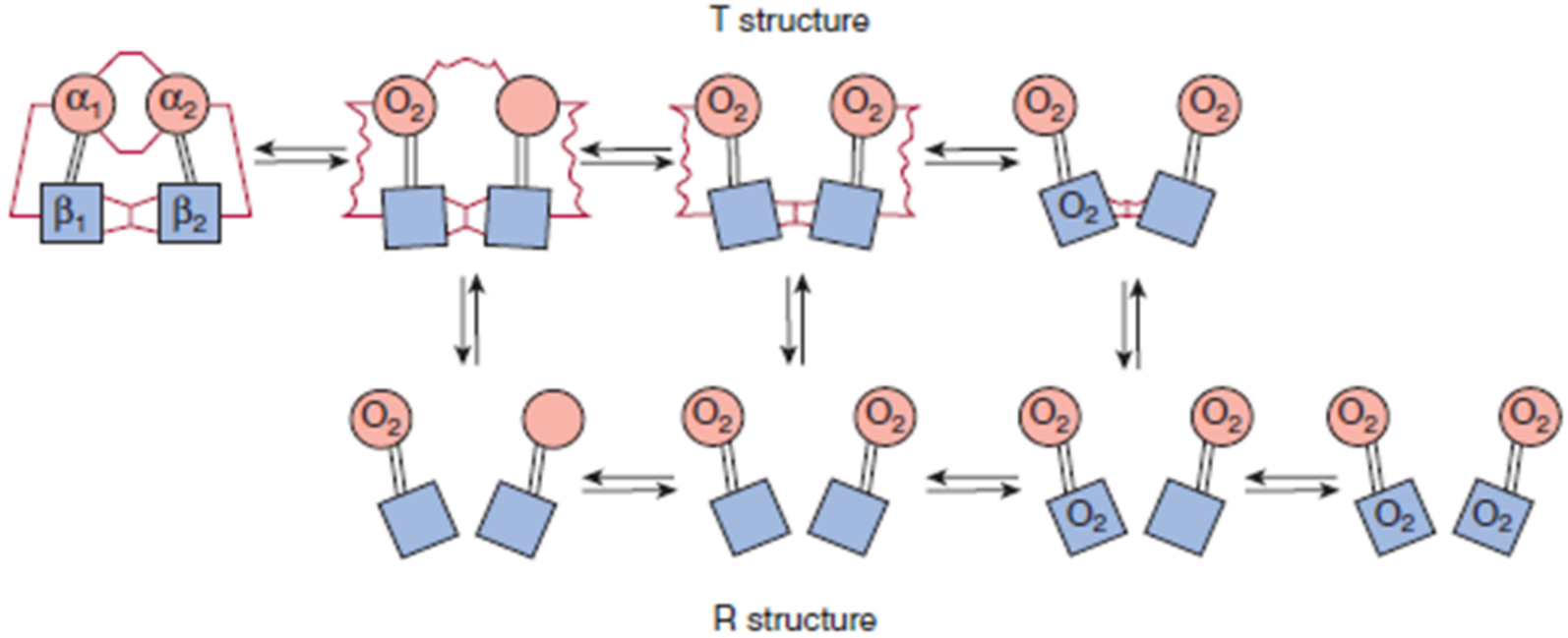

FIGURE 6–10 Transition from the T structure to the R structure. In this model, salt bridges (red lines) linking the subunits in the T structure break progressively as oxygen is added, and even those salt bridges that have not yet ruptured are progressively weakened (wavy red lines). The transition from T to R does not take place after a fixed number of oxygen molecules have been bound but becomes more probable as each successive oxygen binds. The transition between the two structures is influenced by protons, carbon dioxide, chloride, and BPG; the higher their concentration, the more oxygen must be bound to trigger the transition. Fully oxygenated molecules in the T structure and fully deoxygenate molecules in the R structure are not shown because they are unstable. (Modified and redrawn, wit mission, from Perutz MF: Hemoglobin structure and respiratory transport. Sci Am [Dec] 1978;239:

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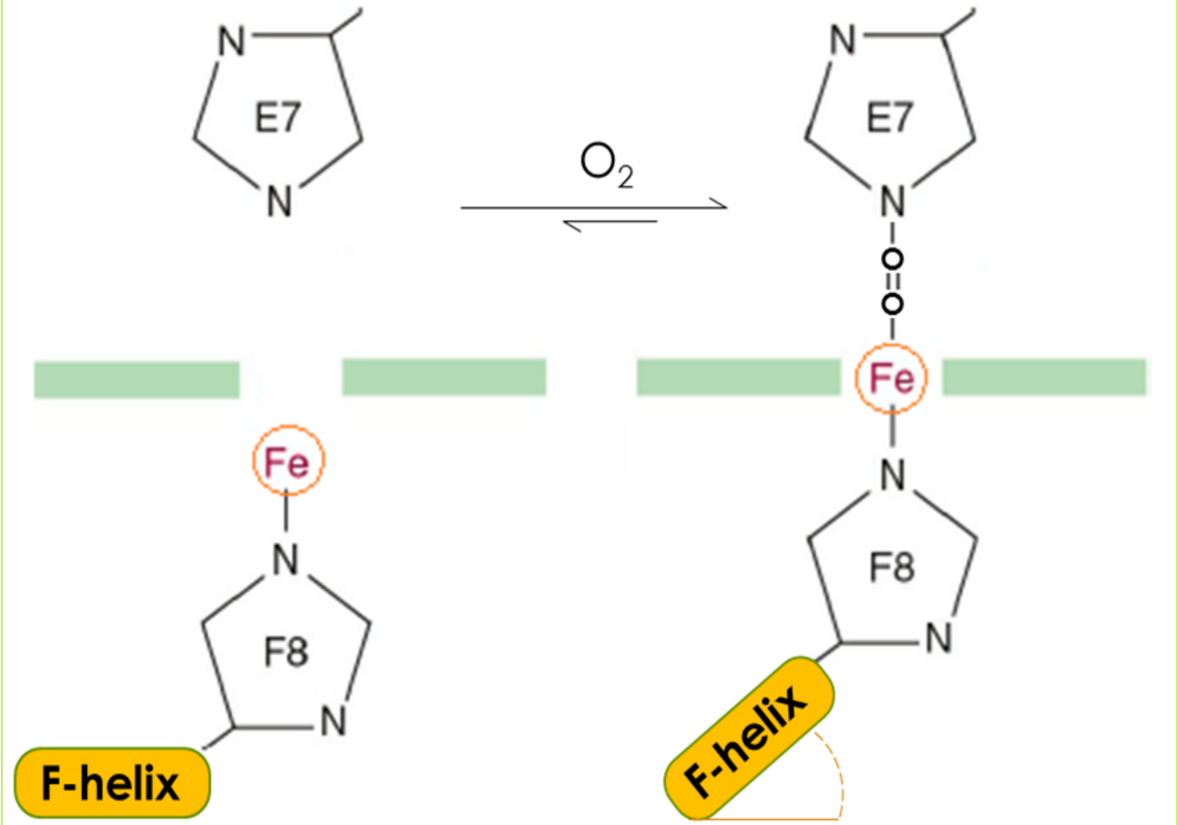
Molecular basis of oxygenation

At its 'tout' conformation within globin chains the iron (Fe^{2+}) at the centre of each heme tetrapyrrole rings are pulled 0.4Å out of the porphyrin planes due to interaction with one histidine residue (at 8^{th} position) of F-helix, i.e., His^{F8} which is also known as proximal histidine ... The oxygen first interacts with one histidine present at 7^{th} position of E-helix, i.e., His^{E7} which is known as distal histidine …

The oxygen in combination with distal histidine next interacts with the iron (Fe^{2+}) porphyrin ring… so the Fe^{2+} is dragged towards the porphyrin ring …

This displacement of iron also pulls the proximal histidine attached to it.. and induces some conformational changes in F-helix …

The conformational changes in F-helix is also transmitted to the other helices in the same globin chain… which tends to disrupt salt bridges formed by the globin chain with neighboring chains …



Conformational changes in F-helix due to oxygenation
Adopted from **Harper's Illustrated Biochemistry, 31st E**
[Modified and redrawn]

The three dimensional conformational changes in globin chain resulting in successive Bond breakages with neighboring globins transform it into 'relaxed' (R) state.

The other globins are also in partial R-state due to partial bond breakages… they interact with O_2 with greater affinity and more easily…

When Hb_4O_8 is formed the whole hemoglobin tetramer is said to be so relaxed that the $\alpha_2\beta_2$ pair in the molecule becomes free to rotate around 15° with respect to the $\alpha_1\beta_1$ pair…

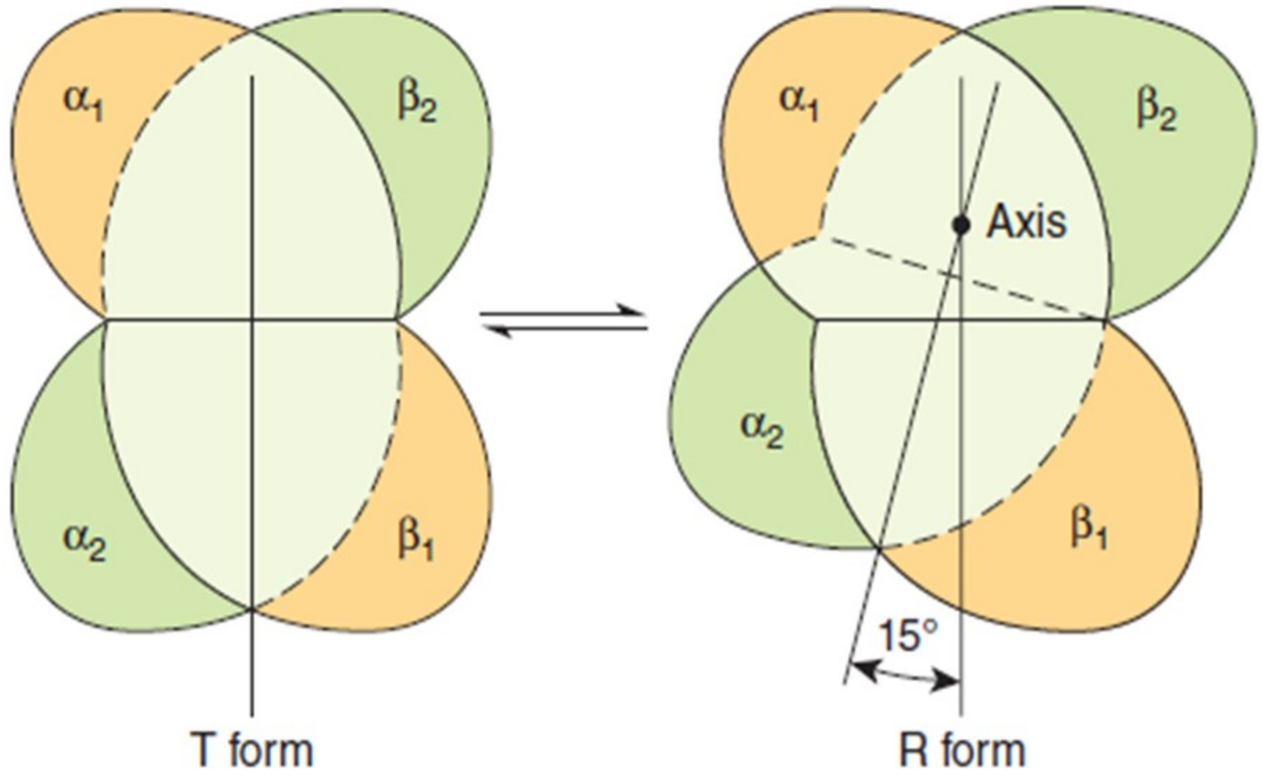


FIGURE 6–9 During transition of the T form to the R form of hemoglobin, the $\alpha_2\beta_2$ pair of subunits (green) rotates through 15° relative to the pair of $\alpha_1\beta_1$ subunits (yellow). The axis of rotation is eccentric, and the $\alpha_2\beta_2$ pair also shifts toward the axis somewhat. In the representation, the tan $\alpha_1\beta_1$ pair is shown fixed while the green $\alpha_2\beta_2$ pair of subunits both shifts and rotates.

Adopted from **Harper's Illustrated Biochemistry, 30th Edition**

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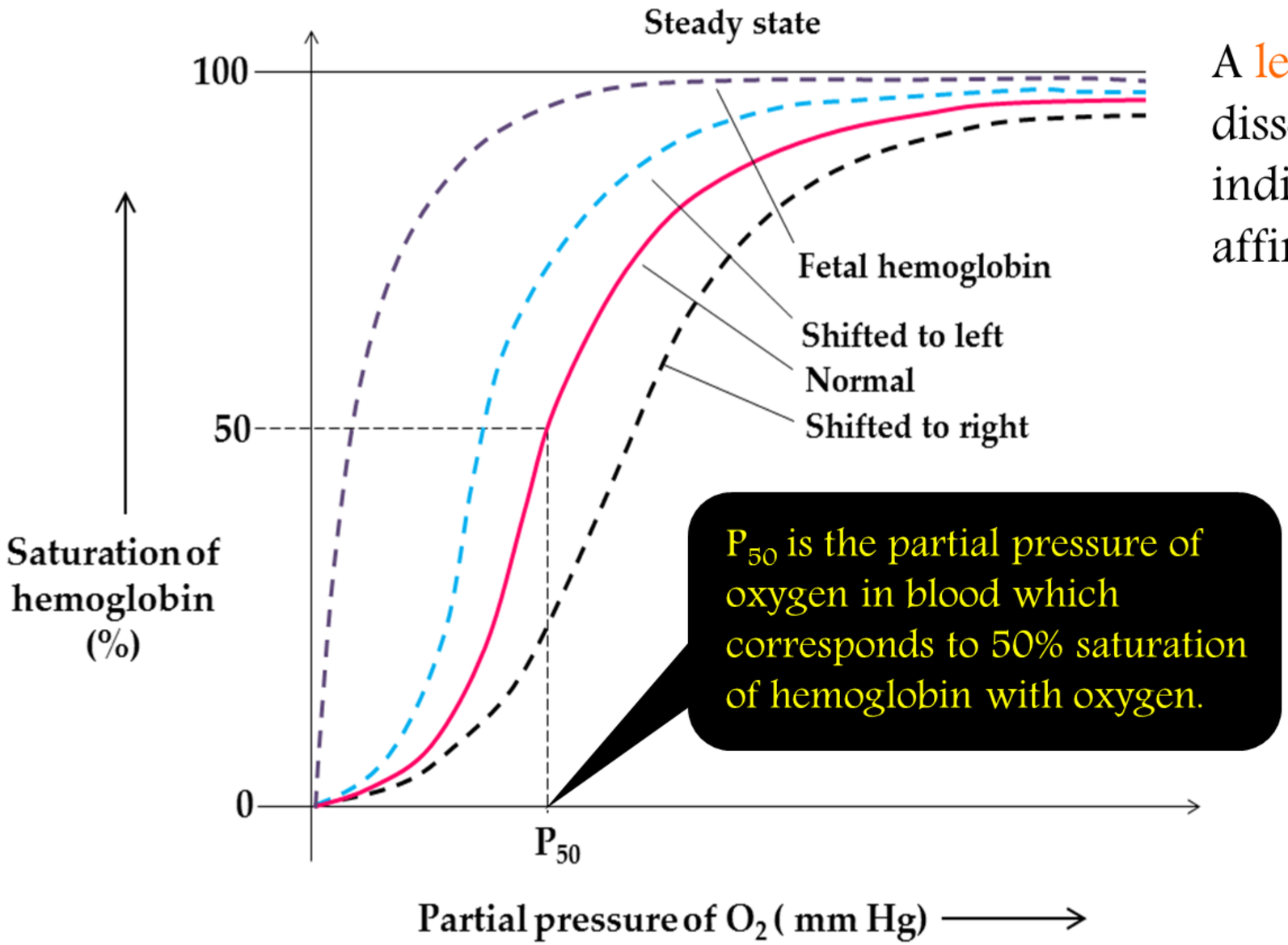
Kinetics of oxygenation

Oxygenation of hemoglobin follows sigmoid kinetics, i.e., the initial rate is slow, then it gradually increases and during the last part it decreases again to finally attain a steady state.. The graphical representation of which is also known as 'O_2 dissociation curve'



A left shift in the 'O_2 dissociation curve' indicates increase in O_2 affinity of the hemoglobins

A right shift in the 'O_2 dissociation curve' indicates decrease in O_2 affinity of the hemoglobins

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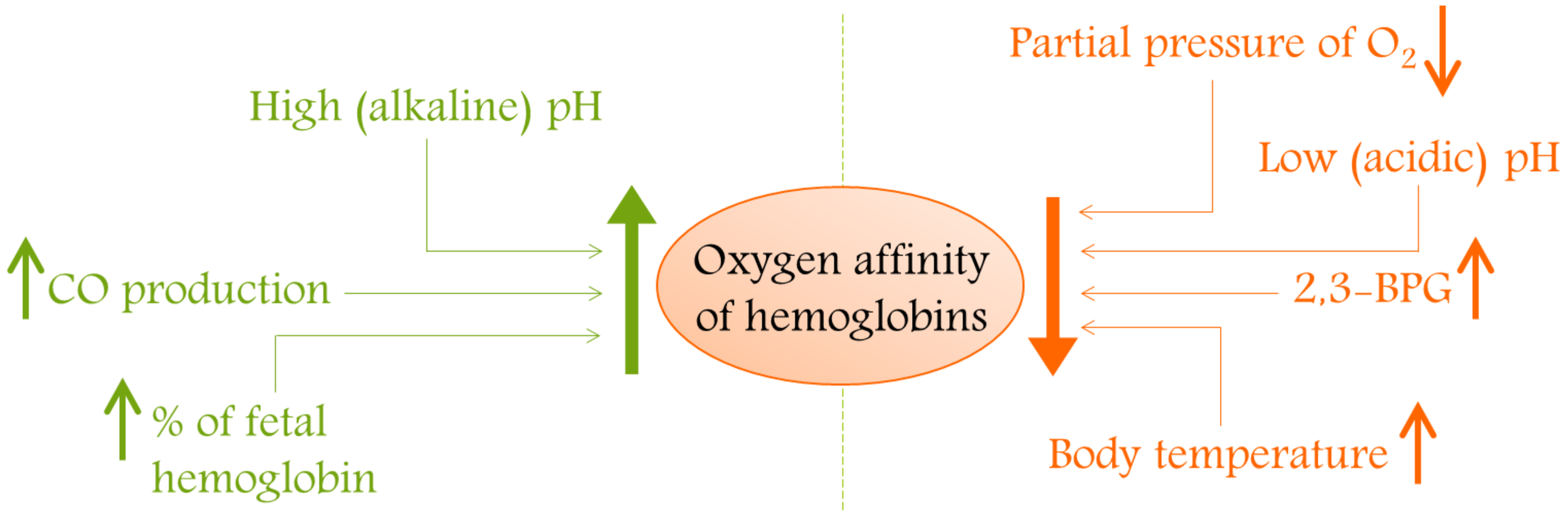
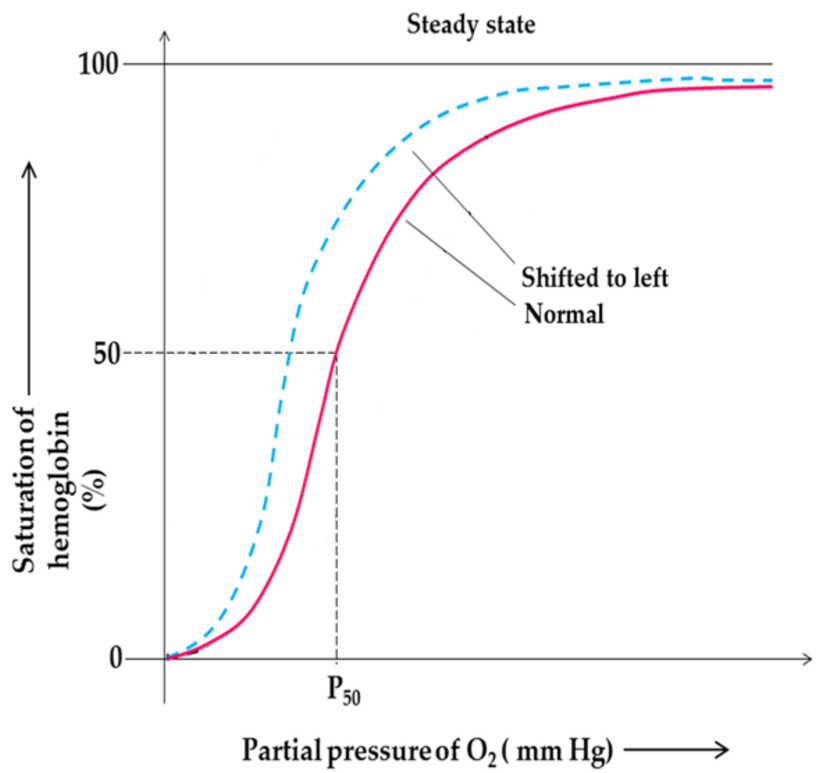
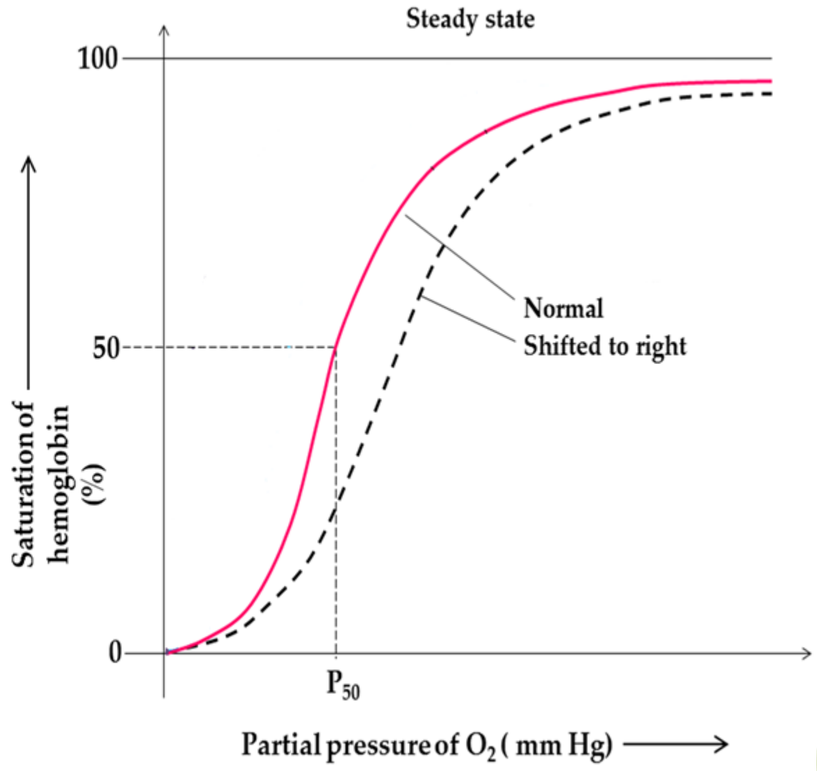
Factors affecting O_2 affinity of hemoglobins







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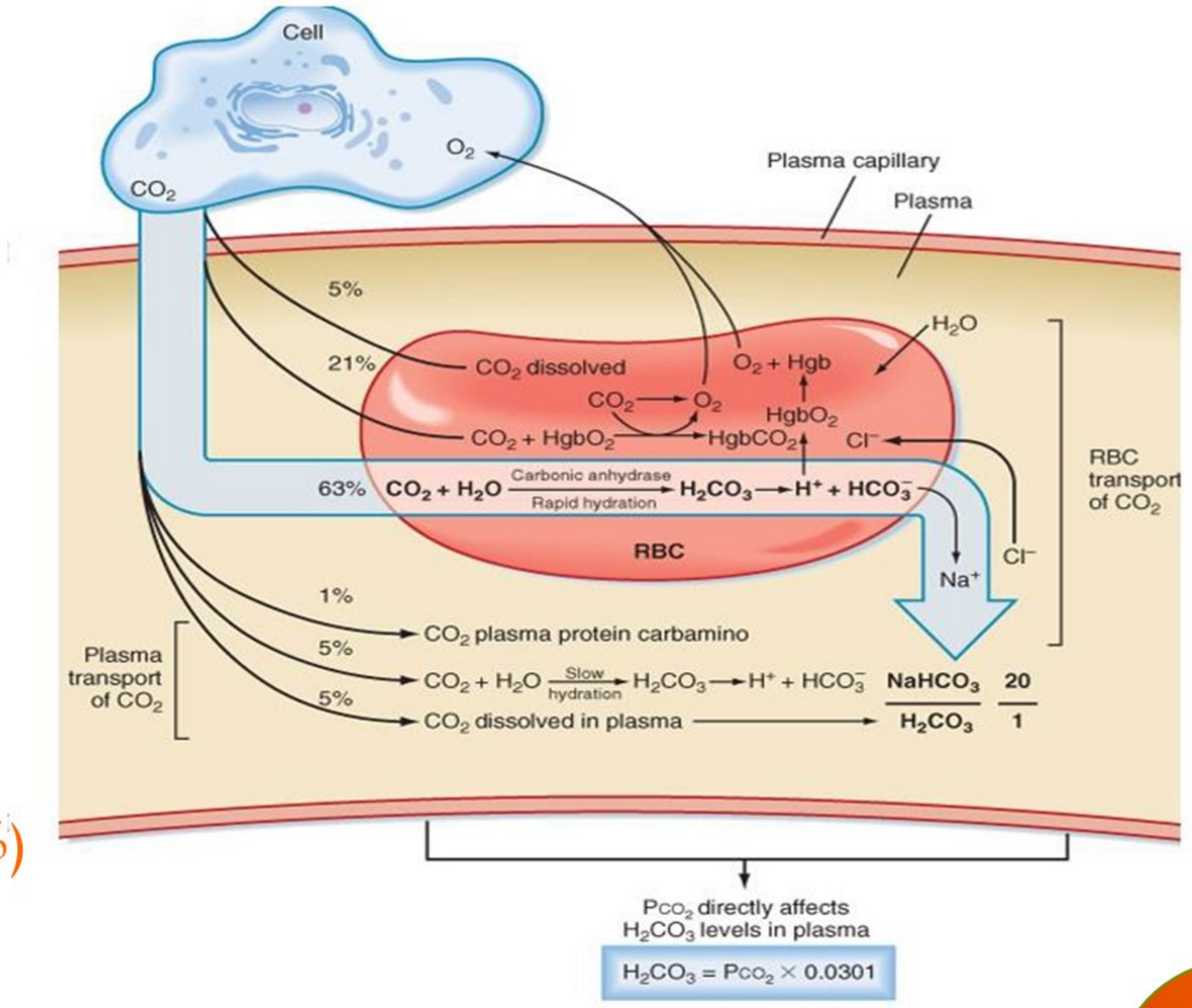
Carbon dioxide transport in venous blood

Unlike O_2, CO_2 do not bind to heme; hence CO_2 do not compete with O_2 (Although a rise in CO_2 is found to extract O_2 from oxyhemoglobin, which is known as 'Bohr effect'). CO_2 can combine with hemoglobin at specific amino acid residues present in globin chains forming carbamino compounds

- The source of CO_2 is tissue respiration (as byproduct of TCA cycle)
- O_2 delivery to the tissues promote oxidative metabolism which leads to production of CO_2

CO_2 is transported in blood in three forms –

- as physical solution (15%)
- as carbamino compound (22%)
- as bicarbonate (63%)



Adopted from **Berne & Levy Physiology, 6th Edition**

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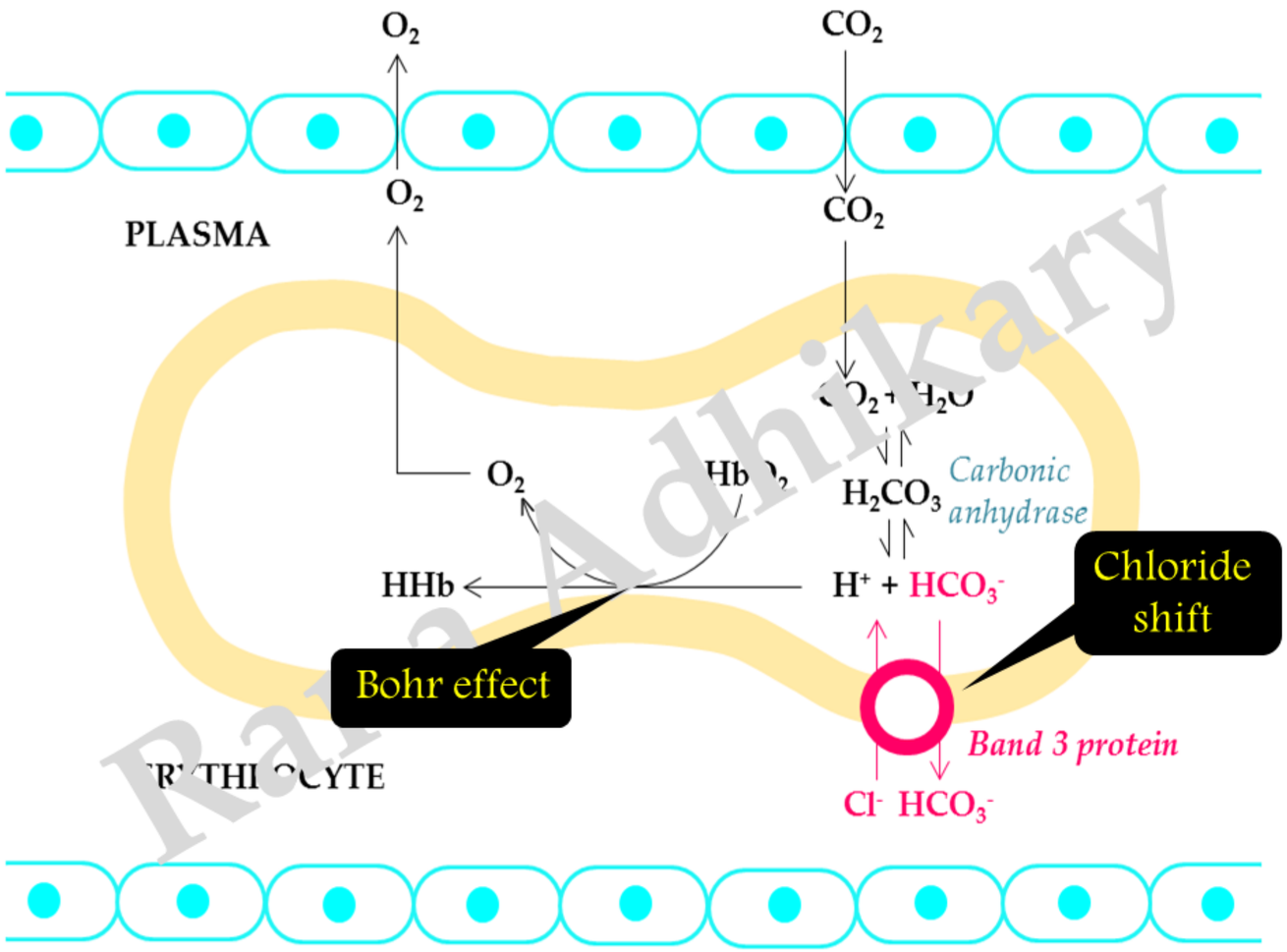
Hamburger effect: the chloride shift

CO_2 transport from tissues into blood occurs in association with O_2 transport, i.e., deoxygenation of HbO_2 helps in carriage of CO_2 in blood, which is known as 'Haldane effect'



Chloride shift mechanism

- CO_2 produced into tissues can easily diffuse through plasma membrane out of the cell
- Inside RBCs this CO_2 combines with H_2O to form H^+ and HCO_3^-
- CO_2 in form of HCO_3^- is frequently exported out of the erythrocytes through an antiporter present on the membrane, which is known as band 3 protein or HCO_3^-/Cl^- antiporter (Chloride shift)
- The H^+ produced as byproduct leads to deoxygenation

- H^+ has much higher affinity for heme in comparison to O_2, hence in presence of H^+, the O_2 is extracted from HbO_2, ensuring O_2 delivery to tissues (Bohr effec

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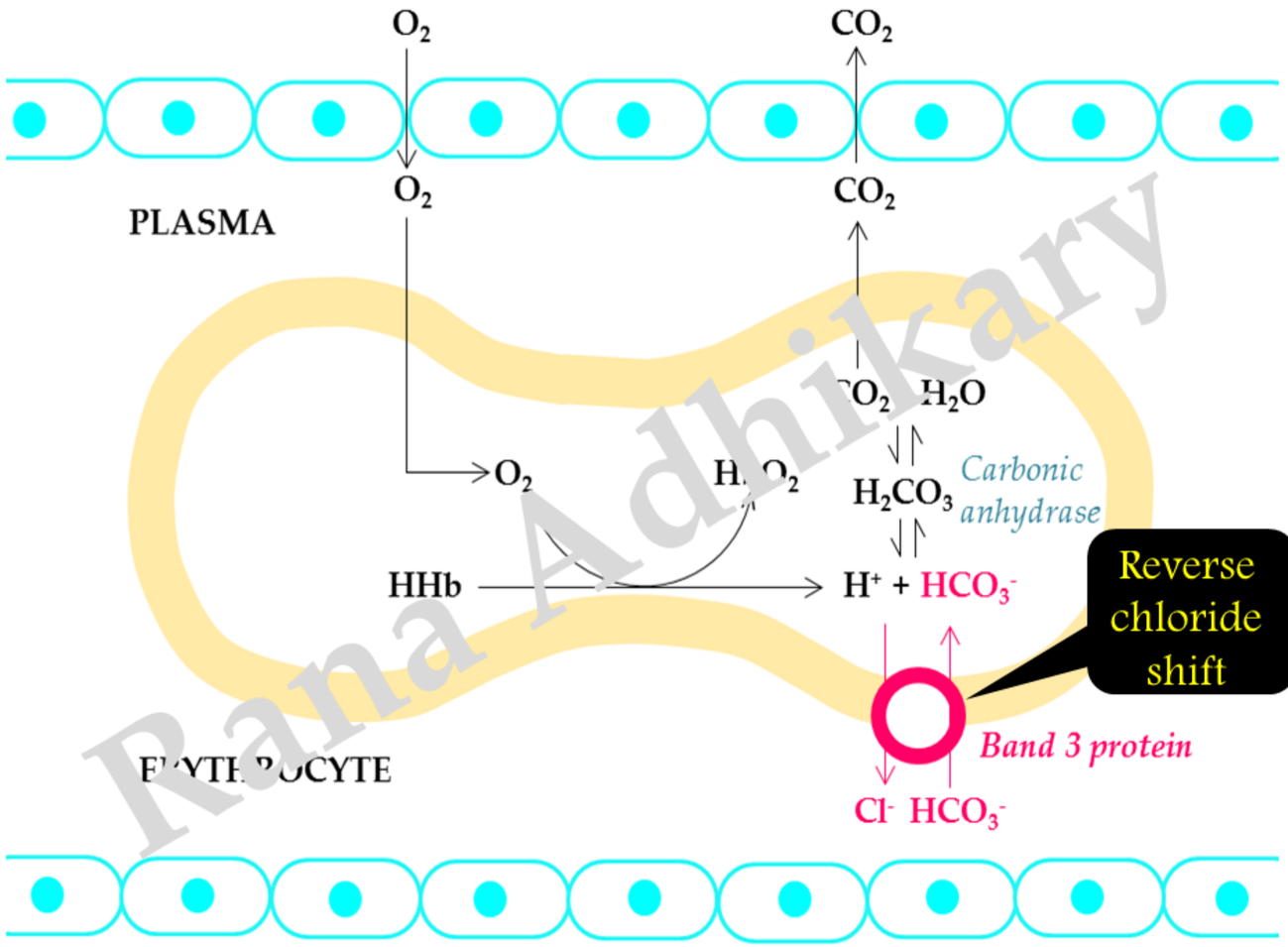
Reverse chloride shift

CO_2 transport from blood into lungs occurs in opposite direction and again in an association with O_2 transport, i.e., oxygenation of HbO_2 is facilitated by carriage of CO_2 in blood



Reverse chloride shift mechanism

- O_2 from lungs diffuses into RBCs, along its concentration gradient
- Since concentration of HCO_3^- is much higher in pulmonary circulation, the band 3 protein or HCO_3^-/Cl^- antiporter starts operating in reverse direction (Reverse chloride shift)

In presence of O_2 and its co-operative combination mode with hemoglobin H^+ is liberated (during breakdown of salt bridges). The HCO_3^- combines with H^+ to transform into CO_2 again

- CO_2 diffuses out of the erythrocytes along its concentration gradient and is exh out of the body during expiration

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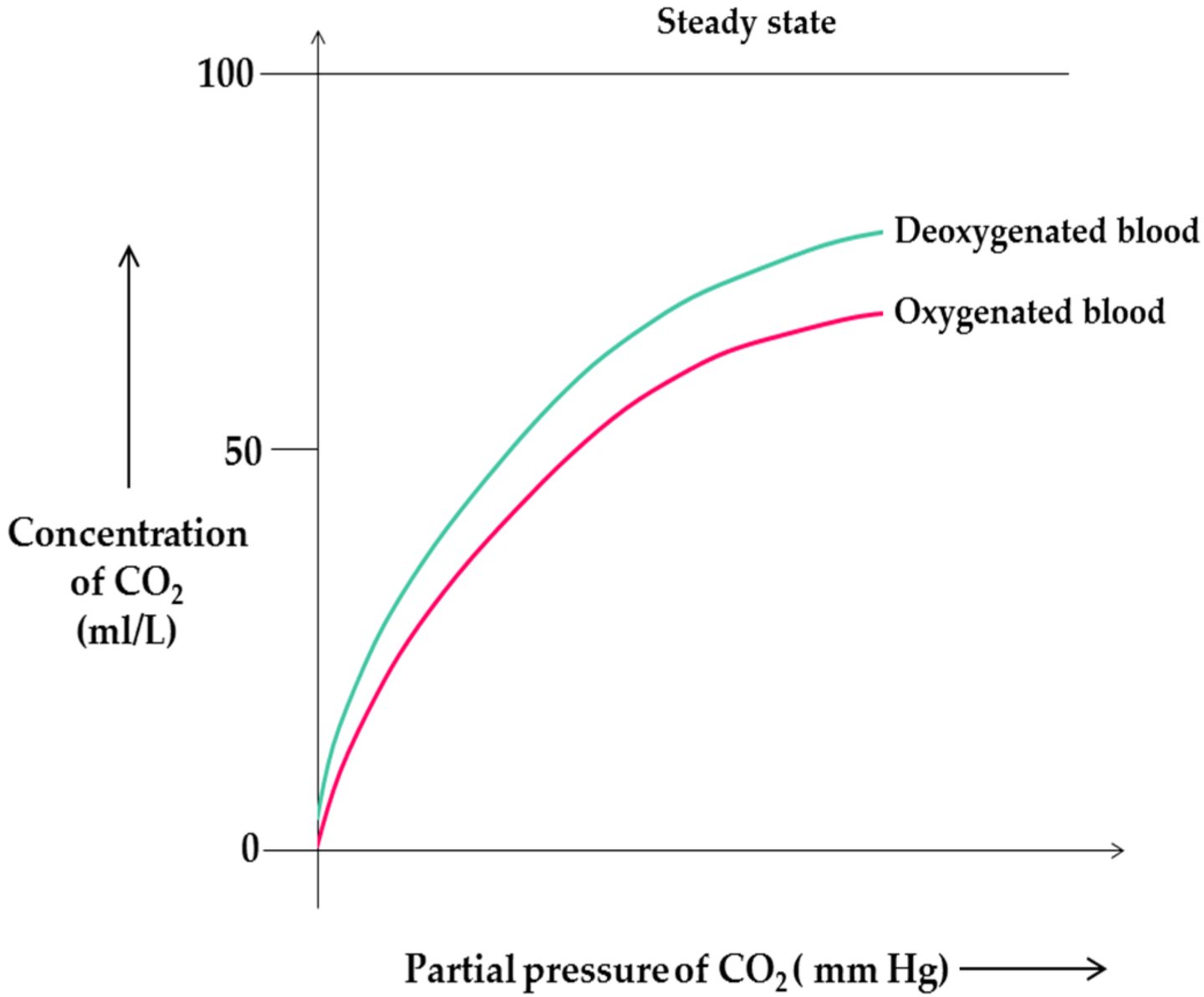
Carbon dioxide dissociation curve

It is a graphical presentation of the relationship between changes in partial pressure of CO_2 in mm Hg and its transport in blood in ml…



A left shift in CO_2 dissociation curve when blood is deoxygenated also explains the Haldane effect 'Deoxygenation of hemoglobins facilitates CO_2 transport'

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