Transport of Oxygen

Transport in arterial blood:

- Oxygen is carried in the blood in two forms,
- 1. Dissolved (3.0%) and
- 2. Combined with haemoglobin (Hb)(97%).

Dissolved Oxygen:

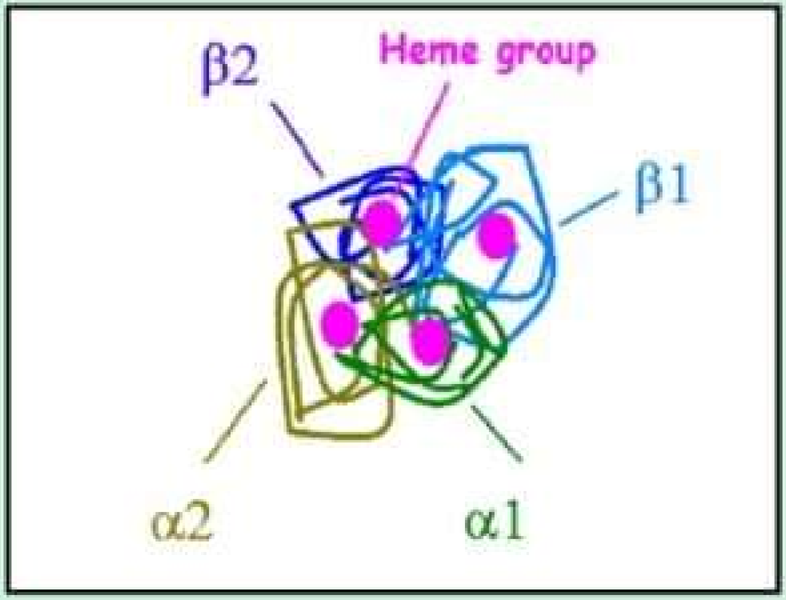
- The amount of oxygen dissolved in the blood is proportional to its partial pressure (Henry's Law).

- 100 ml of arterial blood with normal oxygen PO_2 (100 mm Hg) contains 0.3 ml oxygen.

- By this way amount of oxygen delivered to the tissues is only about 90 ml/min.

- But, tissue requirements are about 3000 ml oxygen/min, Therefore, this way of transporting oxygen is not adequate.

Combination with haemoglobin (Hb)



Haemoglobin:

Haemoglobin (Hb) = Heme (iron-porphyrin) + globin (protein)

Globin has 4 protein polypeptide chains:

2 alpha (each has 141 aa) and
2 beta (each has 146 aa).

- Differences in the amino acid sequence of these chains give rise to various types of Hb.
- Hb-A: Normal adult Hb
- Hb-F: Foetal Hb, which makes part of the total Hb at birth and is gradually replaced by Hb-A.
- Hb-S: In sickle cell anaemia. This Hb has valine in the beta chain instead of glutamic acid. Deoxygenated form of this Hb is poorly soluble and crystallises in the RBC which results in changes in red cell shape (crescent or sickle-shaped). The fragility of the red cells is increased and there is a tendency to thrombus formation.

- Each polypeptide chain combines with one heme group.

- In the centre of each heme group there is one atom of iron, which can combine with one oxygen molecule.

- Thus one Hb molecule can bind 4 oxygen molecules. Heme contains iron in the reduced form (Fe++, ferrous iron).

- In this form the iron can share electrons and bond with oxygen. Oxygen forms a reversible combination with Hb.

  $O_2 + Hb \rightarrow HbO_2$ (oxyhemoglobin)

- However, since the molecule contains 4 Hb units, the haemoglobin molecule can be represented as Hb_4 and can combine with 4 molecules of O_2 to form Hb_4O_8.

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

Combination of oxygen with Hb

- Oxygen carrying capacity:
- One gram of Hb can combine with 1.39 ml oxygen
- Because normal blood has 15 mg of Hb/100 ml the oxygen capacity of 100 ml blood is 20.8 ml.

- Oxygen saturation:
- The proportion of Hb in combination with O2 depends on the PO_2 irrespective of the amount of HB present.
- Arterial blood (PO_2=100 mm Hg) is 97.5 % while oxygen saturation of the venous blood (PO_2= 40 mm Hg) is 75 %.

Combination of oxygen with Hb

- **Oxygen content:**
- depends on PO_2 and Hb content. If blood is anaemic, then even with complete saturation of HB with oxygen, a liter of blood will contain only half the normal amount of oxygen.

Combination of oxygen with Hb

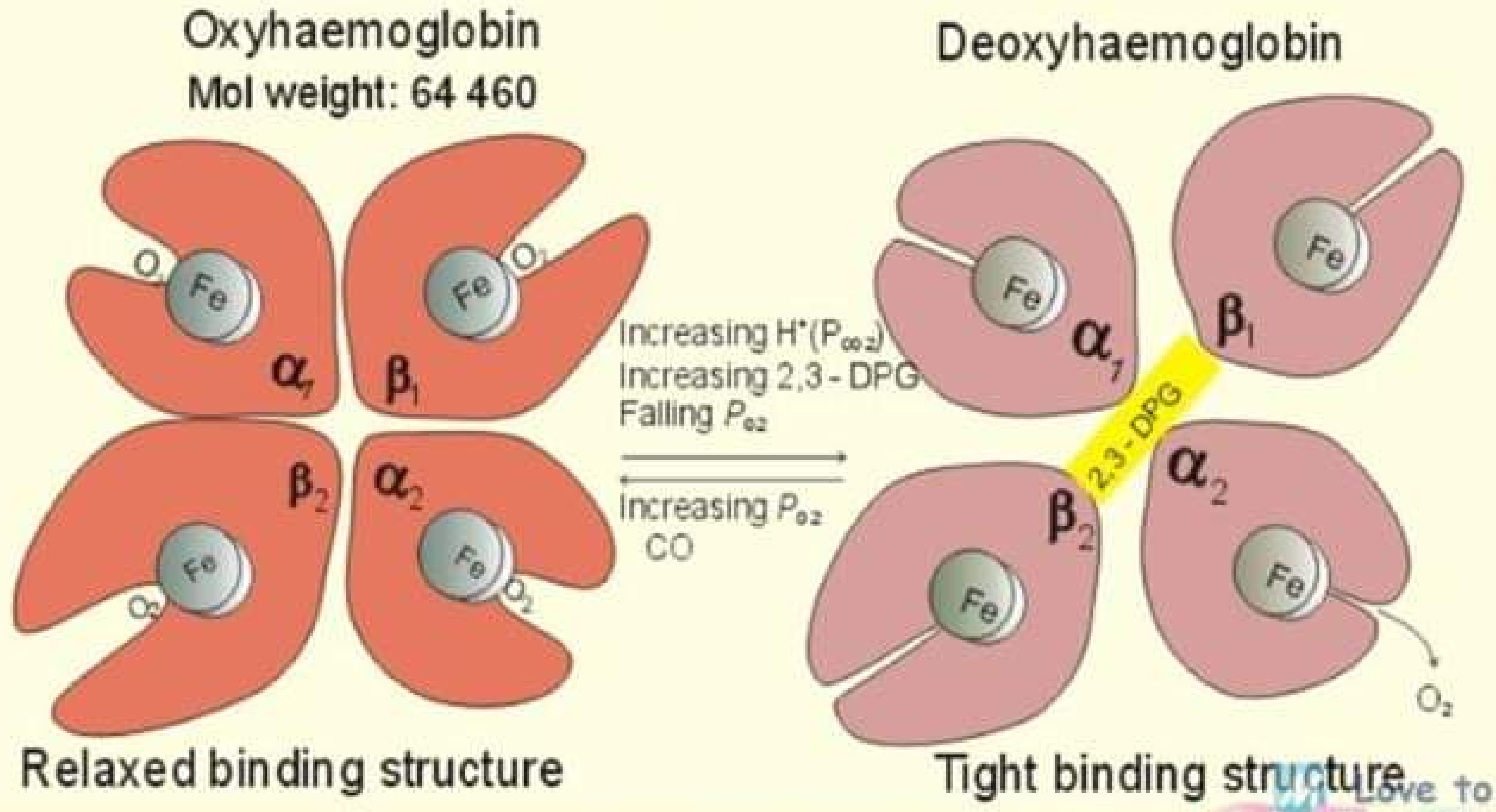
- The reaction is
  - $Hb + 4O_2 \rightarrow$ oxygenation
  - (not oxidation as Fe^{++} stays in the reduced form).

- The reaction is rapid (< 0.01 sec), and results in movement of the peptide chains, with an associated change in affinity of the haem moiety.

- 1. R = relaxed state $\rightarrow\uparrow$ affinity for O_2

- 2. T = tense state $\rightarrow\downarrow$ affinity for O_2

Oxygen Binding and Unloading



relaxed (R) configuration **tense (T) configuration**

Transfer between blood and alveolar air

- In deoxyhaemoglobin, globin units are tightly bound in a tense (T) configuration which reduces the affinity of the molecule for oxygen.

- When oxygen is first bound, the bonds holding the globin units are released producing the relaxed (R) configuration which exposes more binding sites.

- The net result is a 500-fold increase in O_2 affinity.

- In the tissues, this reaction is reversed releasing oxygen.

Amount of Oxygen in blood:

- The Hb in systemic arterial blood at rest is only 97% saturated (due to venous admixture). The arterial blood therefore contains 19.5 mL in combination with Hb and 0.29 mL in solution.
- In venous blood at rest, Hb is 75% saturated and the total O_2 content is about 15.2 mL (0.12 mL in solution and 15.1 mL bound to Hb.
- Thus, at rest, the tissues remove about 4.6 mL O_2 from each deciliter of blood (Oxygen extraction ratio).
- In this way 250 mL of O_2 is transported from the blood to the tissues at rest.

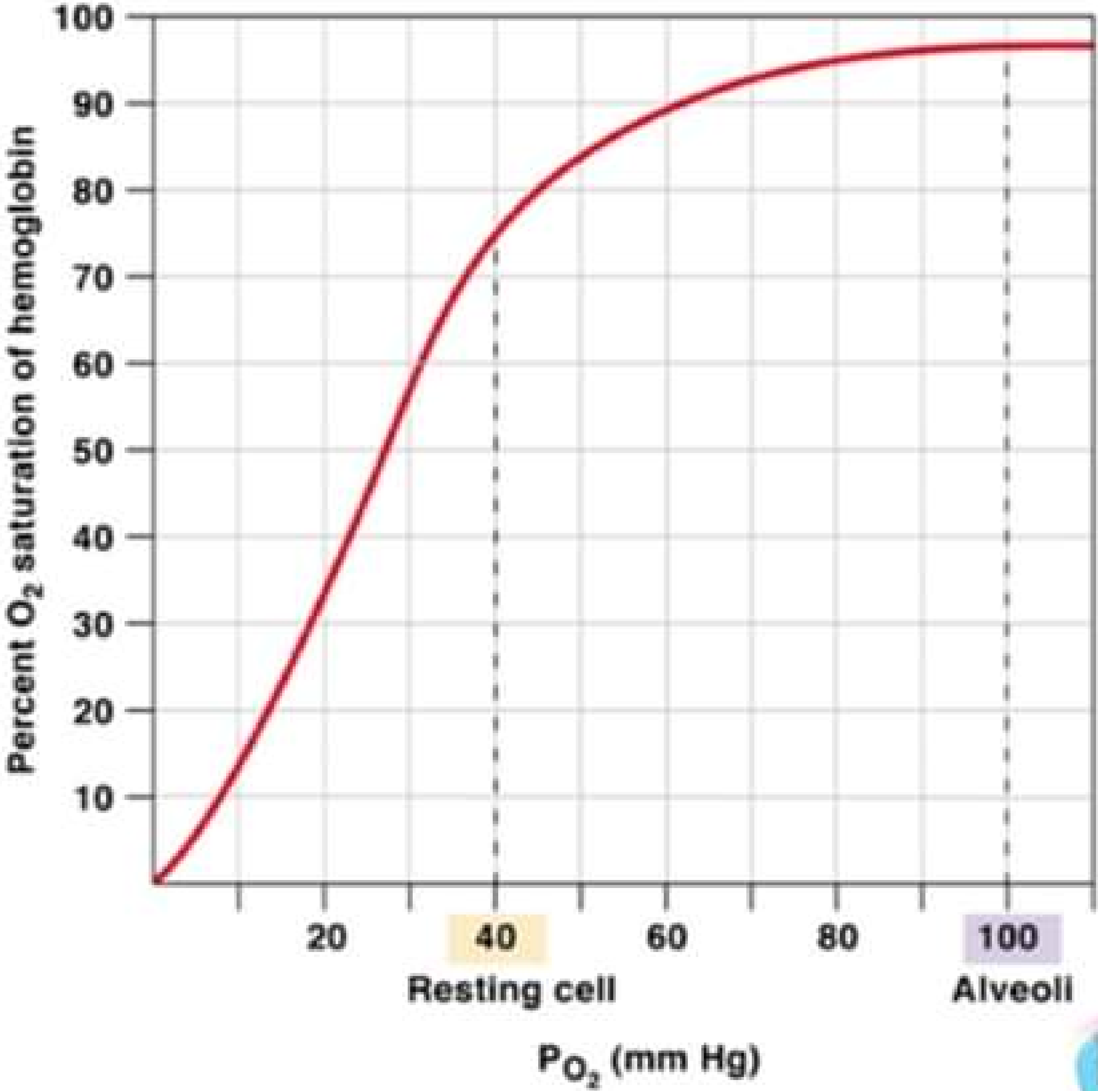
The oxygen-haemoglobin dissociation curve

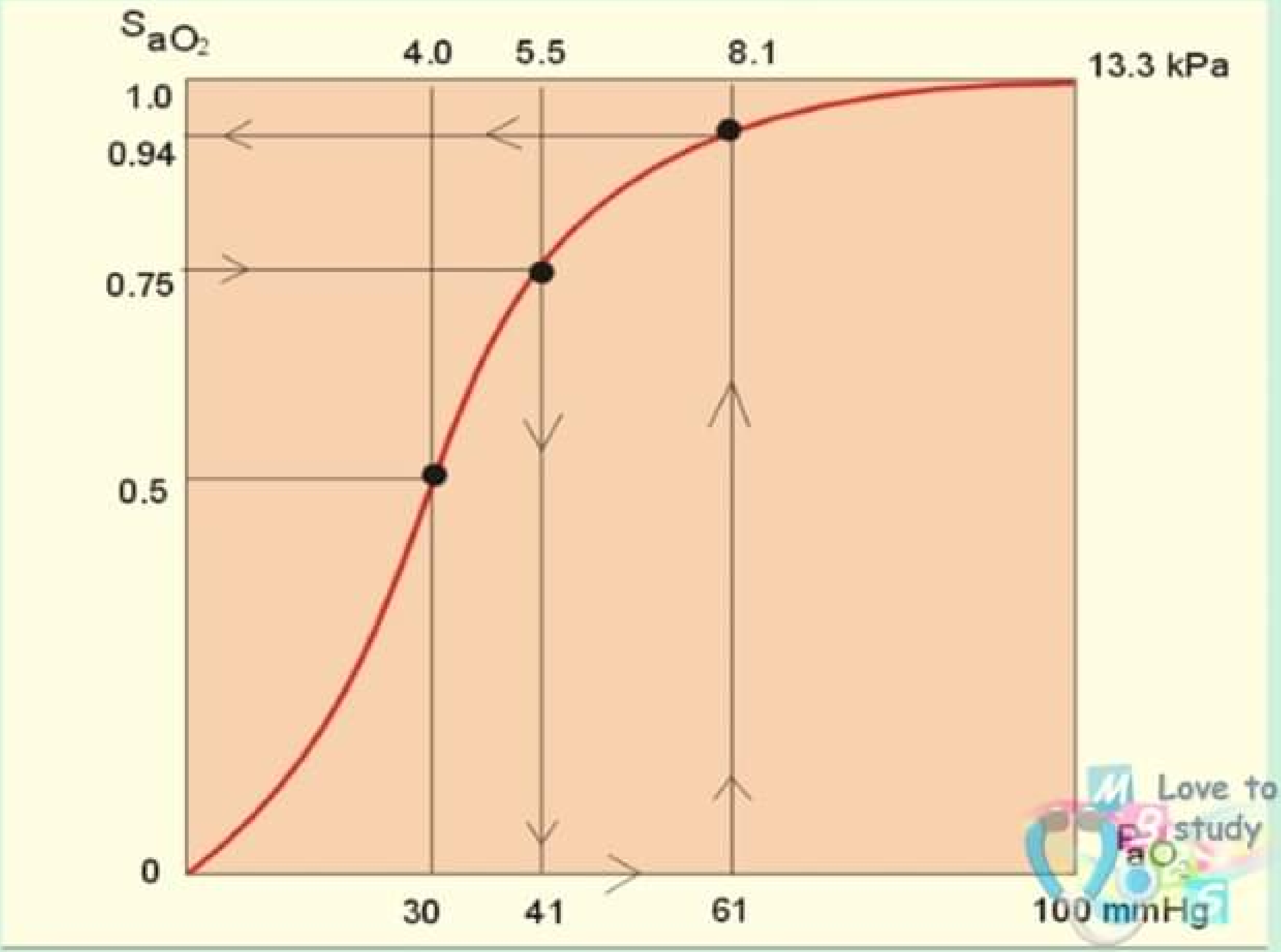
The oxygen-haemoglobin dissociation curve:

- Is the curve relating percentage saturation of Hb with O_2 to PO_2.
- It has a characteristic sigmoid shape due to the T-R interconversion.
- Combination of the first heme in Hb with O_2 increases the affinity of the second heme for O_2 and oxygenation of the second increses affinity for third heme molecule etc., so that the affinity for the fourth O_2 is many times that for the first.

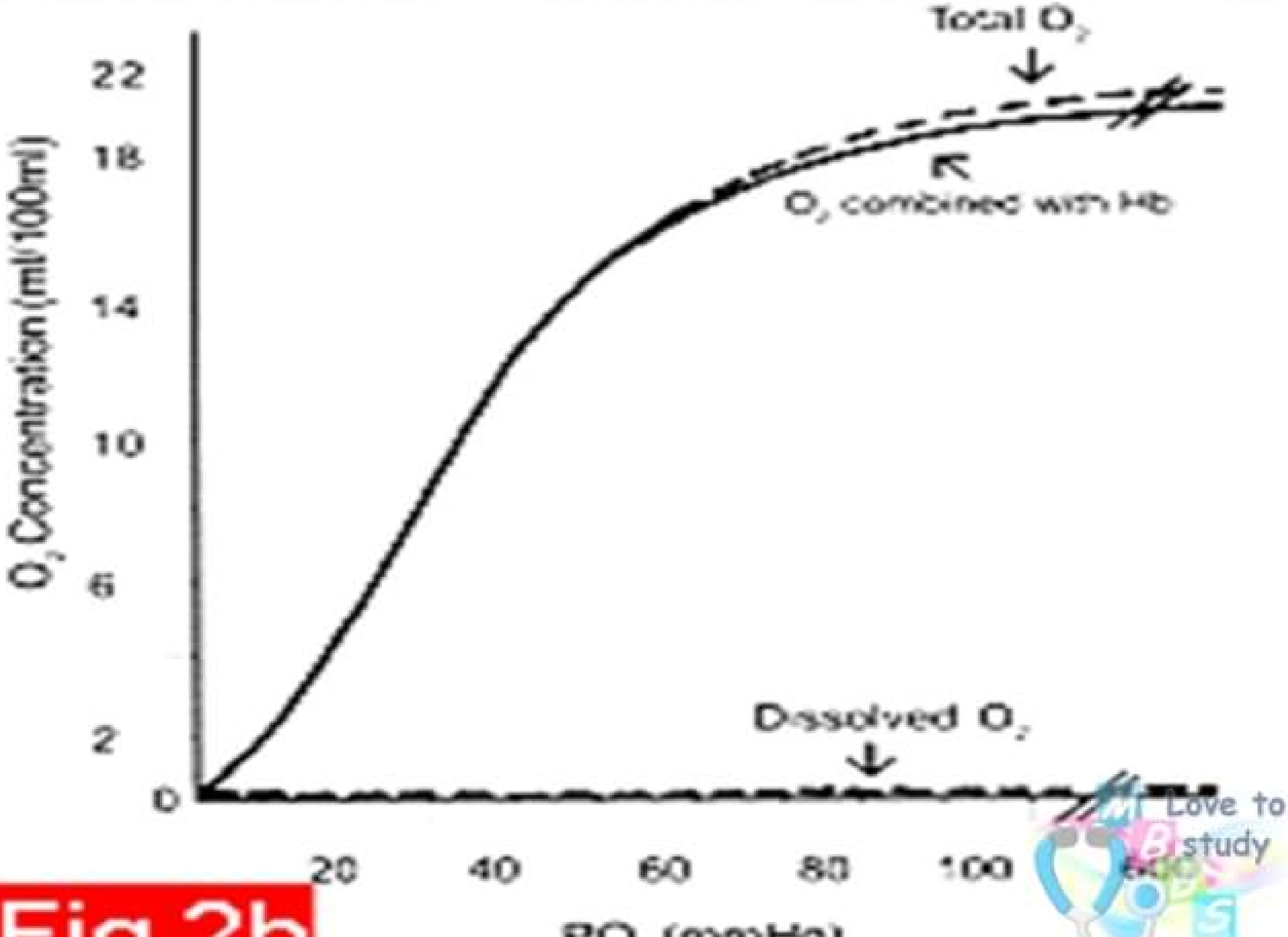
The oxygen-haemoglobin dissociation curve:

- When fully saturated, each gram of Hb contains 1.39 mL of oxygen.
- However, blood contains inactive Hb derivatives and the measured value in vivo is lower - the traditional value being 1.34 mL.
- The Hb in normal blood is about 15 g/dL. One dL of blood would contain 20.1 (1.34 x 15) mL when Hb is 100% saturated.


100
90
80
70
60
50
40
30
20
10
Percent O_2 saturation of hemoglobin
20
40
60
80
100
Resting cell
Alveoli
P_{O_2} (mm Hg)



SaO2
4.0
5.5
8.1
13.3 kPa
1.0
0.94
0.75
0.5
0
30
41
61
100 mmHg
PaO2
Love to study



Total O_2
O_2 combined with Hb
Dissolved O_2
O_2 Concentration (ml/100ml)
22
18
14
10
6
2
0
20
40
60
80
100
PO_2 (mmHg)

Fig 2b

Factors Affecting Oxy-Hb Dissociation Curve:

- **Affinity** is measured by the P_{50} , which is the PO_2 when Hb is 50% saturated.
- at pH = 7.4, T = 37°C P_{50} = 26.3 mm Hg

- ↓ Affinity of Hb for O_2 → a shift of the curve to the right and an↑ P_{50}

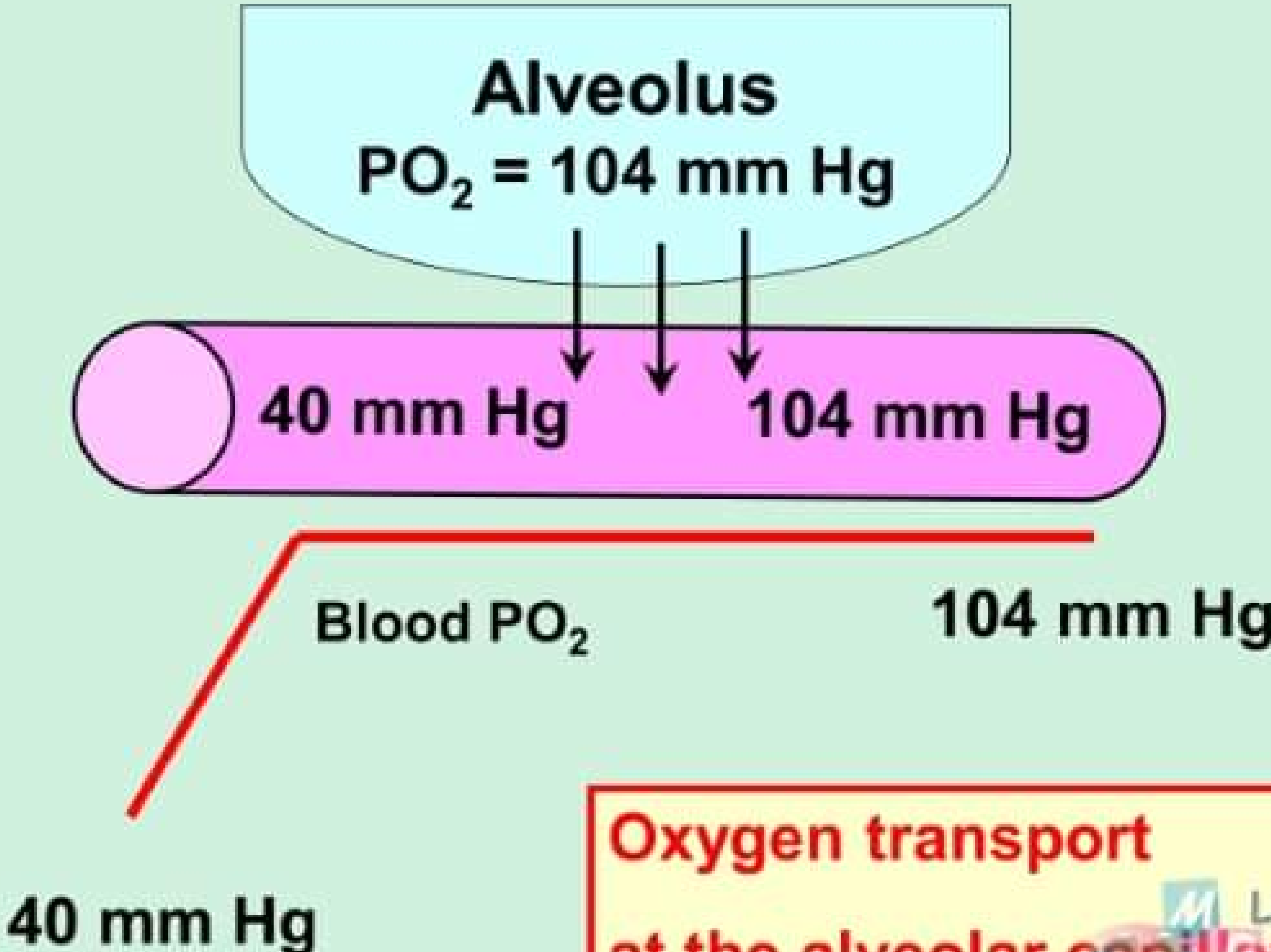
- ↑ affinity of Hb for O_2 → a shift of the curve to the left and a↓ P_{50}

The higher the P_{50}, the lower the affinity.

Physiological implications:

- 1. When PO_2 increases above 70 mm Hg Hb does not take up much more O_2 because it is almost fully saturated. Thus, alveolar ventilation can decrease by about 20-30% without much variation of the blood O_2 level. Thus, large changes in normal day to day activity does not change the O_2 content of blood leaving the lungs.

- 2. At low PO_2 in the tissues, a small decrease in PO_2 will cause a large transfer of O_2 to supply the tissues.

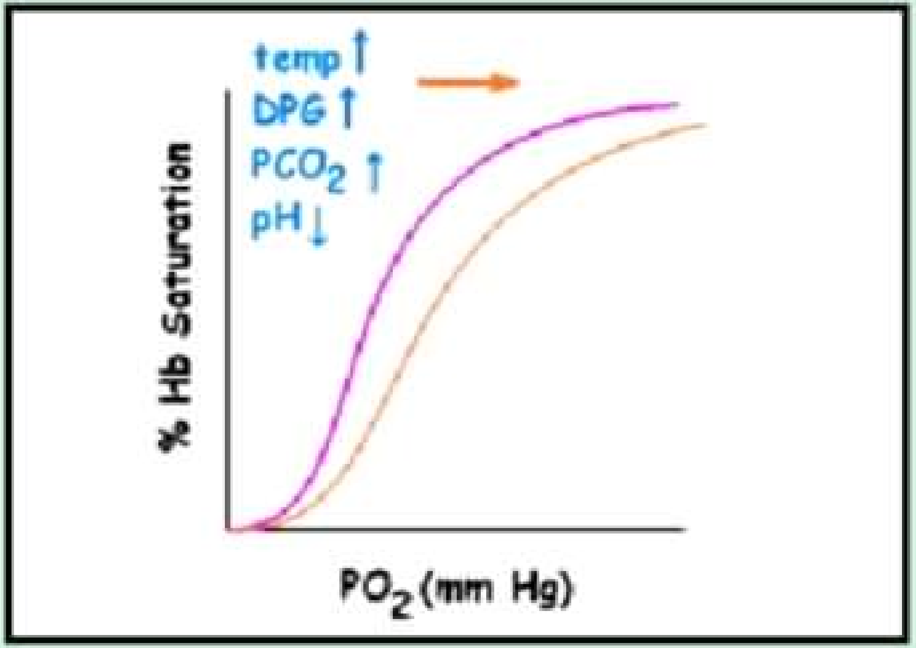


Oxygen transport at the alveolar capillary

Factors affecting the affinity of HB for O_2:

1. pH
2. Temperature
3. 2,3-diphosphoglycerate (2,3-DPG)
4. Carbon dioxide tension (PCO_2)

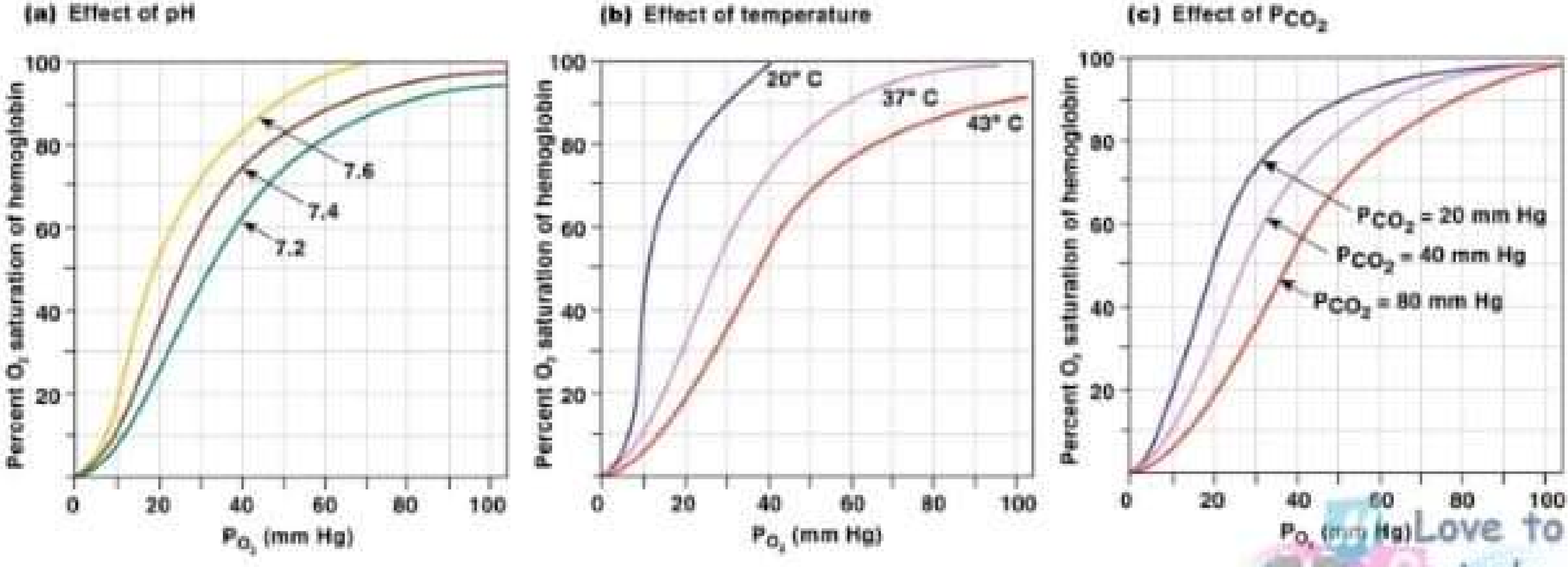
A rise in temperature or a fall in pH shifts the curve to the right. This means that a higher PO_2 is required for Hb to bind a given amount of O_2.



This means that the affinity is lower and P_{50} is higher.

pH, Temp and P_{CO2}

- (2,3-DPG also has a role)



Factors affecting concentration of 2,3-DPG:

5. High altitude triggers a substantial rise in 2,3-DPG secondary to the respiratory alkalosis. P_{50} increases more oxygen is available to the tissues. The rise in DPG is secondary to the rise in blood pH.

6. 2,3-DPG has a low binding affinity for the γ-chains of HbF. This results in the higher affinity of HbF for O_2, thereby enabling placental transfer of greater amounts of O_2.

7. Red cell DPG is increased in anaemia and conditions with chronic hypoxia. P_{50} is raised and more O_2 is released to tissues.

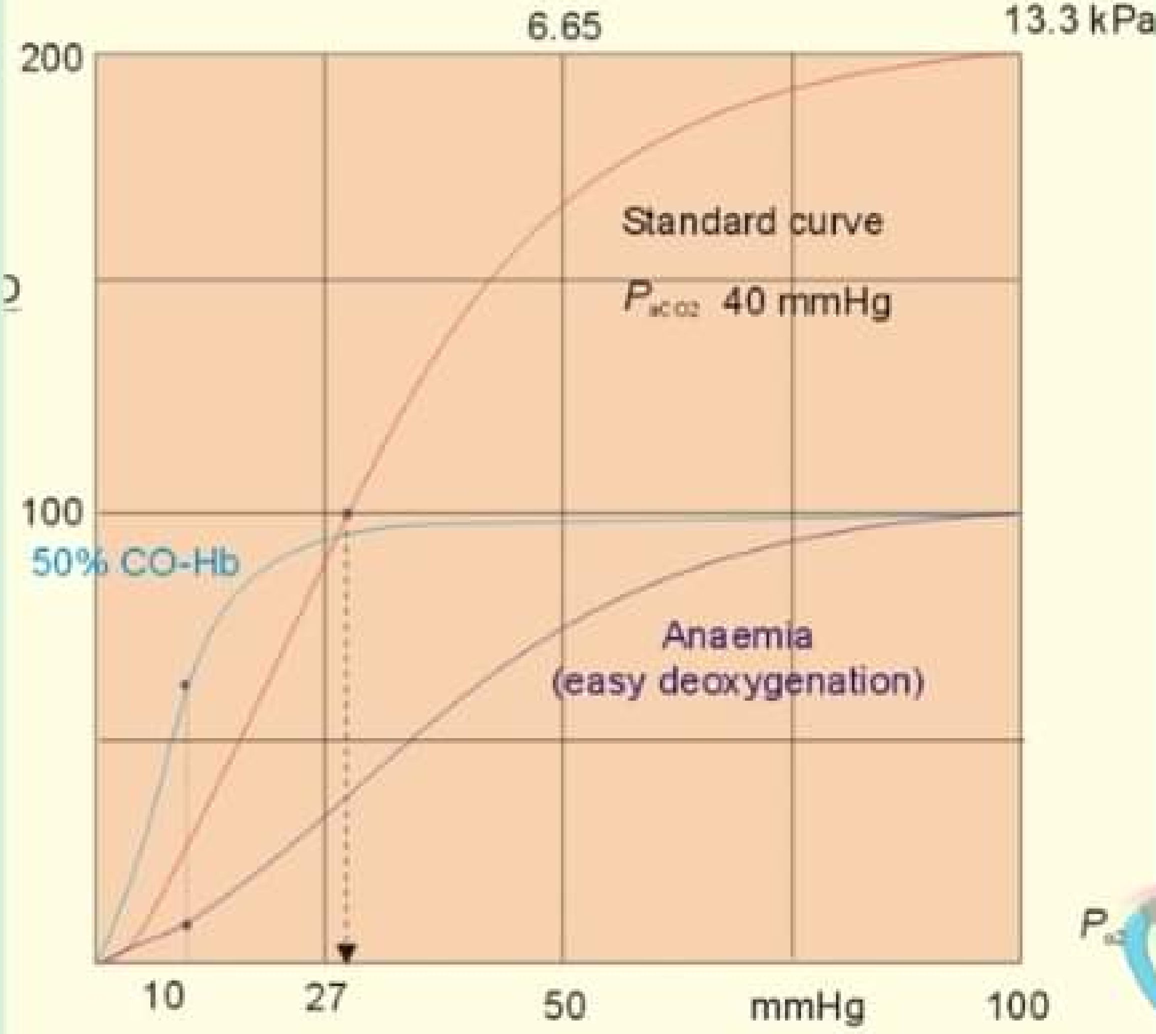
In summary:

- The following factors shift the oxygen dissociation curve to the right (increase P_{50} decreased affinity):
- 1. Increasing P_{C02} (the Bohr effect),
- 2. increasing $[H^+]$,
- 3. increasing 2,3-DPG,
- 4. increasing temperature.
- The metabolic activity of the cells augment these factors, and means that less O_2 is bound to haemoglobin at a given P_{aO2} (metabolic activity facilitates unloading of O_2).

- The factors that shift the oxygen dissociation curve to the left (low P_{50}) are
- 1. Increasing O_2 tension (the Haldane effect),
- 2. decreasing $[H^+]$ and P_{aCO2},
- 3. low temperature in the lungs.
- 4. Increasing CO tension,
- 5. Reduced 2,3-DPG production in chronic acidosis, and by
- 6. Foetal haemoglobin.
- The leftward shift in the lung facilitates the binding of O_2 to haemoglobin.

- **CO poisoning:**
- CO competes with oxygen for binding sites on Hb, Thus, exposure to CO reduces the oxygen binding to Hb (COHb).
- Persons with a 50% CO-block of a normal Hb concentration have a leftward shift of the oxy-CO-Hb dissociation curve.
- All the binding sites that are bound to CO do not respond to falling oxygen tension.
- The remaining oxygen molecules on the Hb molecules are much more avidly bound and unload slower than normal.

Anaemia & Carbon Monoxide (CO) Poisoning



- **Effects of CO poisoning:**
- High affinity for oxygen (240 times)
- Left shift of the curve - more difficult to unload oxygen
- Arterial PO_2 (dissolved) normal
- No physical signs of hypoxia; blood is bright red
- CO is odourless, colourless, non-irritating

- Anaemia:
- Patients with CO poisoning and anaemia and with the same arterial oxygen concentration can be compared.
- At an oxygen tension of 10 mm Hg feeding the peripheral tissues, the CO-blood keeps most of its oxygen bound,
- whereas the anaemia-blood unloads almost all its oxygen.
- This is why the anaemia patient can go to work and the carbon monoxide poisoned person is dying.

Transfer between blood and alveolar air

- **Oxygen is transported from the alveolar air to the red cells by diffusion across the alveolar-capillary barrier.**

- **The transit time for the red cells to pass through the 1 mm long lung capillaries (3/4 s) is adequate for the haemoglobin to become fully saturated with oxygen.**
- **Thus, in normal, physiological conditions, oxygen transfer is <u>perfusion limited</u>.**

- **Nitric oxide transport:**

- Oxygen binding sites also bind NO and there is an additional binding site on the β chains.

- The affinity of this site is increased by O_2.

- Therefore Hb binds NO at the lungs and releases it in the tissues where it promotes vasodilatation.

Functions of haemoglobin:

1. Facilitates O_2 transport
2. Facilitates CO_2 transport
3. Role as a buffer
4. Transports NO

- **Nitric oxide transport:**

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Diffusion and Perfusion Limitations

- **Diffusion-limitation is not present** in healthy persons.
- In exercise, oxygen requirement increases much more than at rest. Therefore, there is likelihood of inadequacy but normally there are **built-in safety factors**.
- 1. Diffusing capacity increases due to **increased capillary surface area** which helps to achieve normal V_a/Q ratios in the upper zone.
- 2. Since normally blood is saturated with oxygen only $1/3^{rd}$ the way down the capillary, there is a lot of reserve.

Venous admixture:

- Refers to the degree of admixture of mixed venous blood with arterialised pulmonary end capillary blood.
- 98% of blood to the left ventricle is fully oxygenated and has an oxygen tension of 104 mm Hg. 2% of flow is through the bronchial circulation and is unsaturated. This blood enters directly to the pulmonary veins having bypassed the lungs (venous admixture).
- Therefore, PO_2 of blood in the left ventricle and the aorta is only 95-97 mm Hg and is about 95% saturated.

Components of Venous Admixture

- Absolute Shunt
- 1. physiological
- a. coronary blood enters LV via the thebesian veins
- b. some bronchial artery blood enters the pulmonary veins
- 2. pathological
- a. congenital heart disease with R to L shunt
- b. perfusion of non-ventilated alveoli
- c. pulmonary arterio-venous shunts

- Regions of Low V/Q
- 1. physiological
- a. normal scatter of V/Q ratios
- b. changes with posture - ie. erect vs. supine
- 2. pathological
- a. abnormal scatter of V/Q ratios
- b. alveolar-capillary block