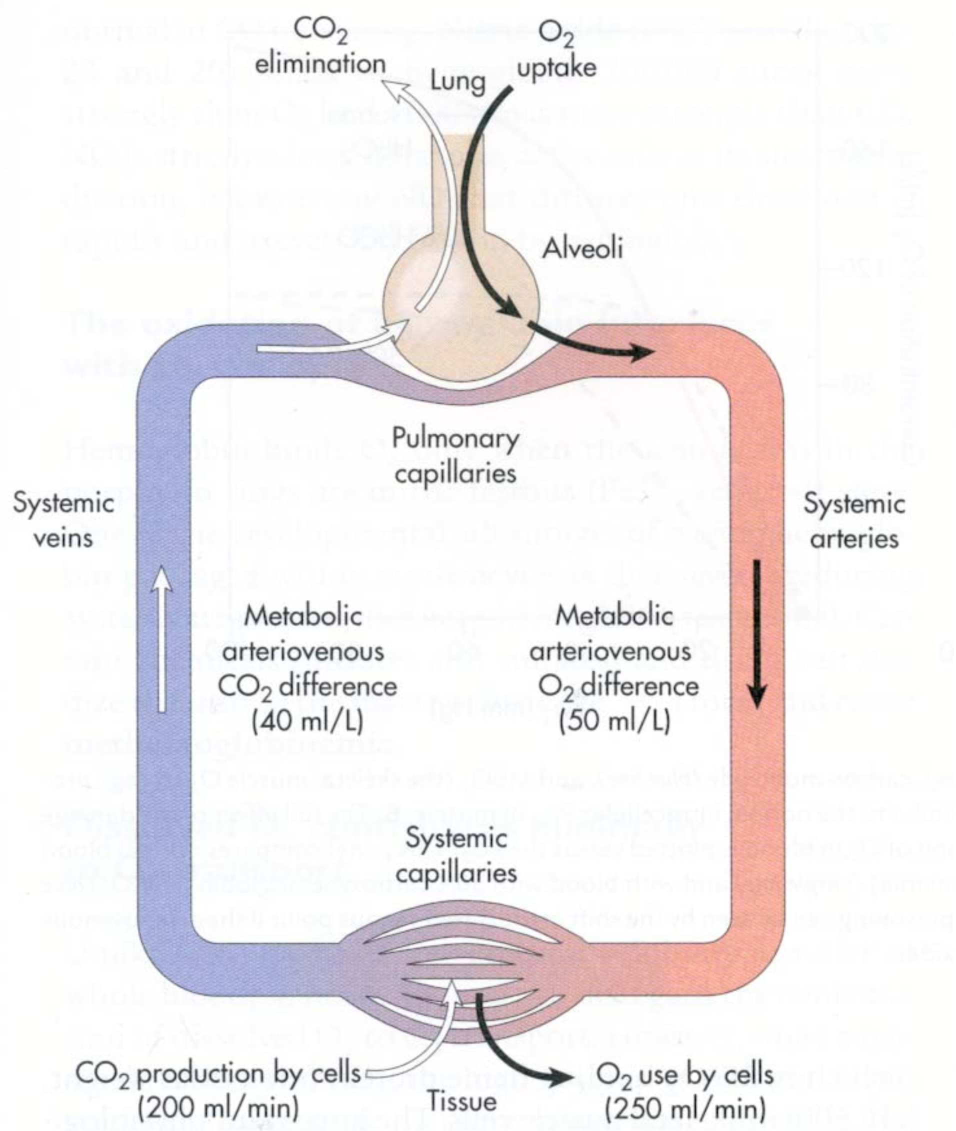


TRANSPORT OF OXYGEN AND CARBON DIOXIDE IN BLOOD

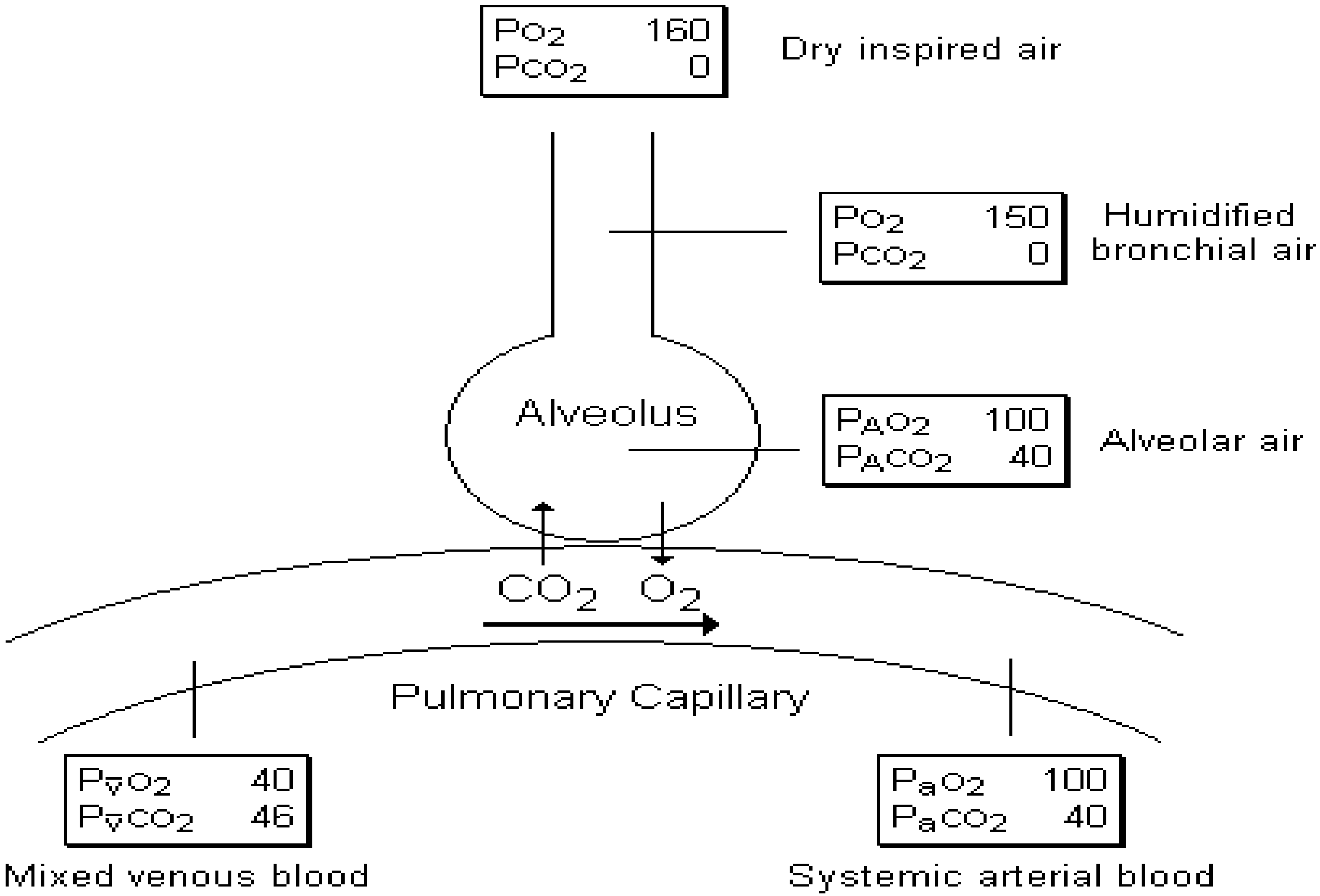
CONTENTS

O2 TRANSPORT

REQUIREMENTS FOR OXYGEN TRANSPORT SYSTEM

Match O2 supply with demand

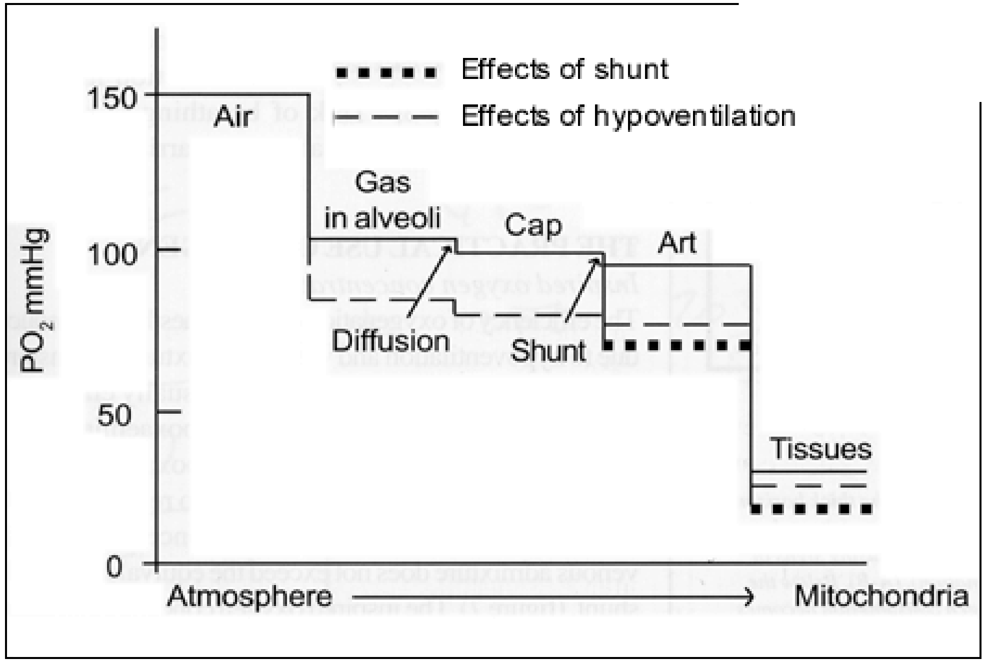
MOVEMENT OF O_2 DOWN CONCENTRATION GRADIENT



OXYGEN CASCADE

•Oxygen moves down the concentration gradient from a relatively high levels in air to that in the cell

•The PO2reaches the lowest level (4-20 mmHg) in the mitochondria



•This decrease in PO2 from air to the mitochondrion is known as the OXYGEN CASCADE

KEY STEPS IN OXYGEN CASCADE

- Uptake in the lungs
- Carrying capacity of blood
- Delivery to capillaries
- Delivery to interstitium
- Delivery to individual cells
- Cellular use of oxygen

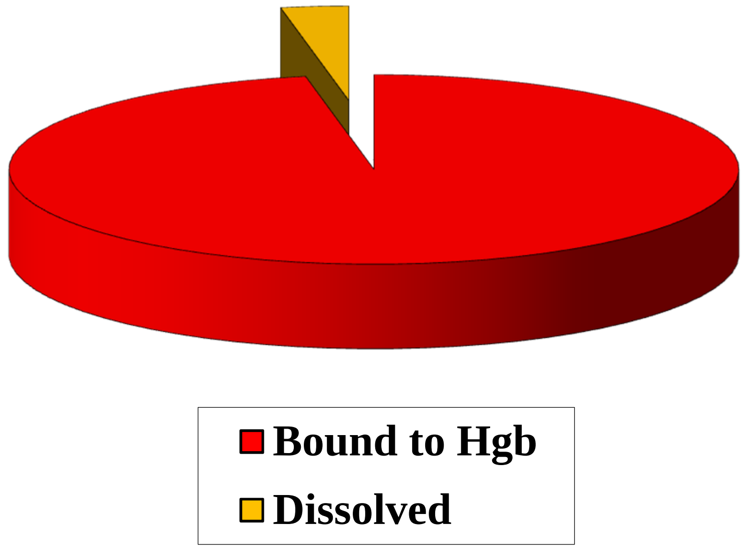
DETERMINANTS OF PaO_2

- Inspired O_2 concentration & barometric pressure
- Alveolar ventilation
- V/Q distribution & matching
- O_2 diffusion from alveoli to pul capillaries

Oxygen Transport

Carried in bld in 2 forms:

1. by red blood cells
   - ✓ Bound to Hb
   - ✓ 97-98%



2. Dissolved O_2 in plasma
   - ✓ Obeys Henry's law

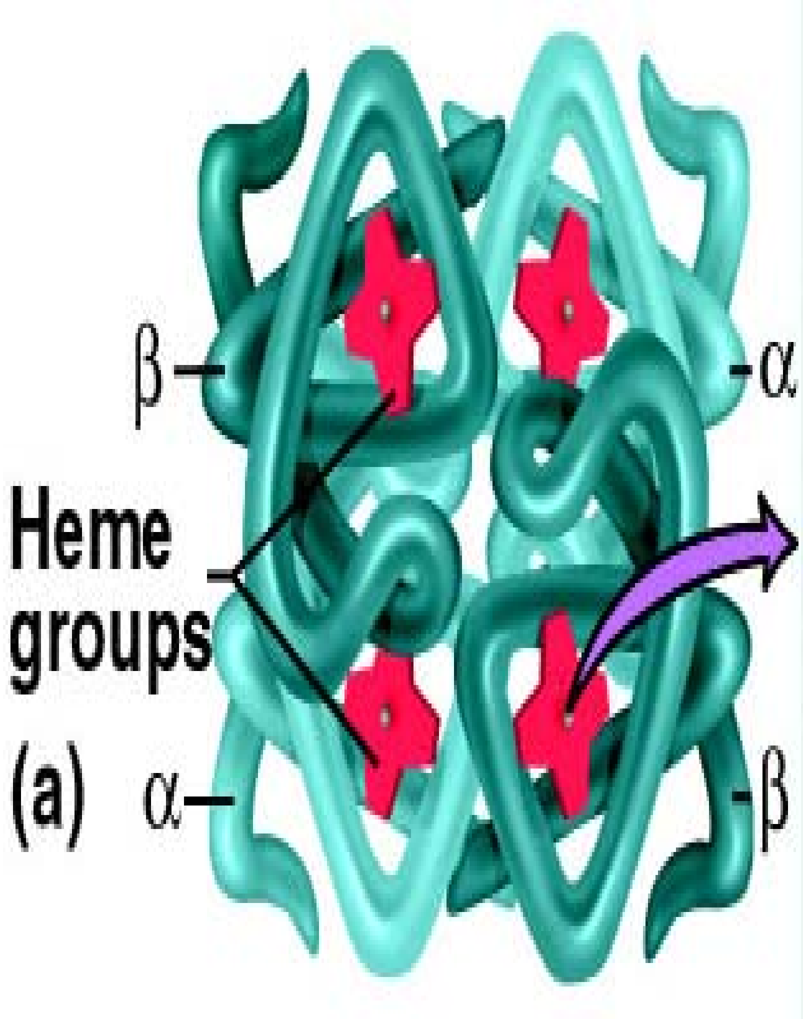
$$PO2 \times \alpha = O2 \text{ conc in sol}$$

α = Solubility Coefficient (0.003mL/100mL/mmHg at 37C)

   - ✓ Low capacity to carry O_2

Hemoglobin

- Fe porphyrin compound
- Normal adult = HbA = $\alpha 2\beta 2$
- Hb F= $\alpha 2\gamma 2$
- The γ chains ↑ hb affinity to O2
- Each gm of Hb can carry up to 1.34ml of O_2, theoretically up to 1.39 ml/gm



Molecular weight of hemoglobin is 64,000

CHEMICAL BINDING OF HEMOGLOBIN & OXYGEN

- Hemoglobin combines **reversibly** with O_2

- Association and dissociation of Hb & O_2 occurs within milliseconds
  - Critically fast reaction important for O_2 exchange
  - Very loose coordination bonds between Fe^{2+} and O_2, easily reversible

- Oxygen carried in molecular state (O2) not ionic O^{2-}

Oxygen Saturation & Capacity

- Up to four oxygen molecules can bind to one hemoglobin (Hb)
- Ratio of oxygen bound to Hb compared to total amount that can be bound is **Oxygen Saturation**
- Maximal amount of O_2 bound to Hb is defined as the **Oxygen Capacity**

O_2 Content in blood (CaO_2)

- 97-98% Carried in Combination With Hb
- 2-3% Dissolved in Plasma

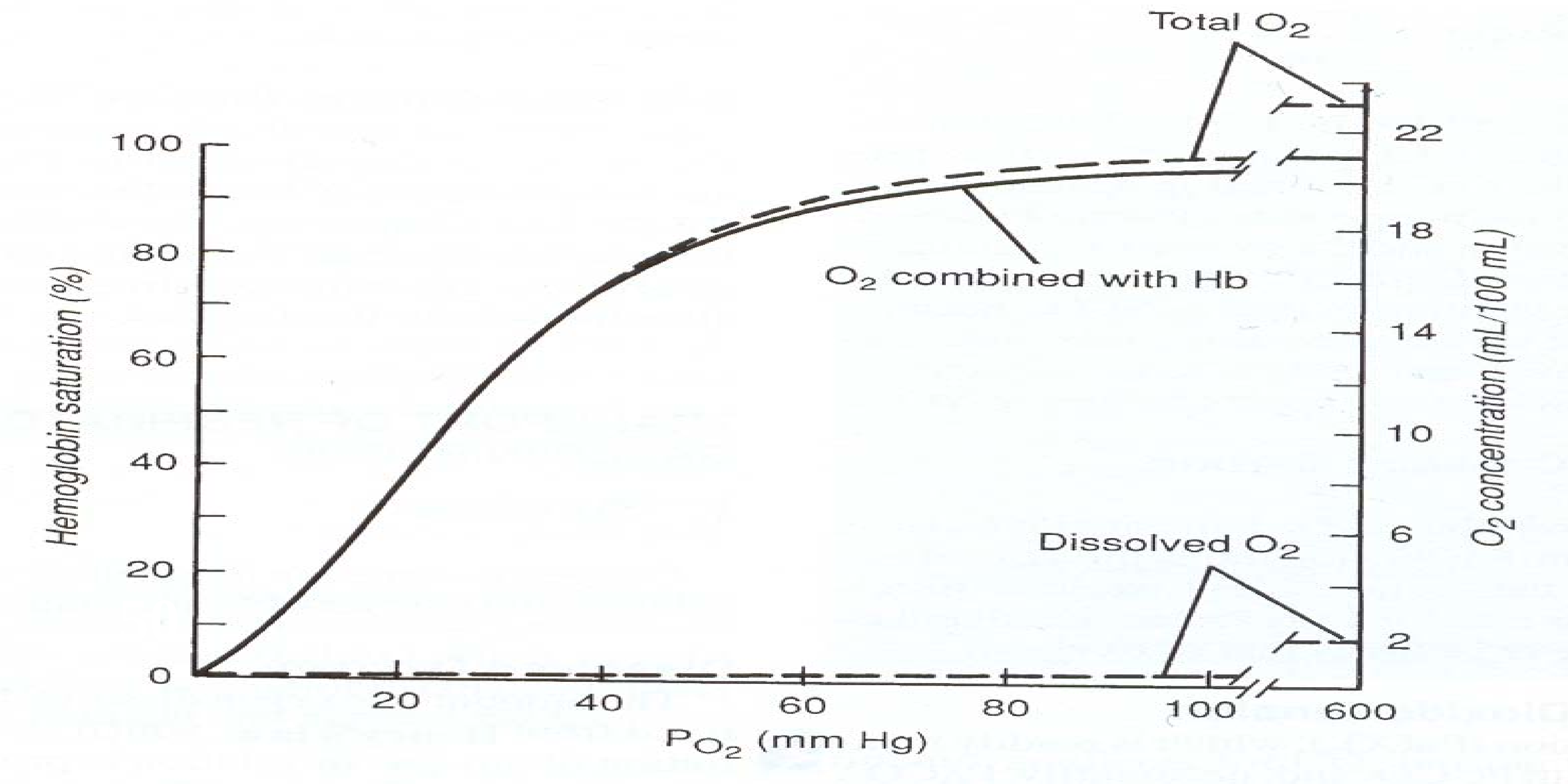
O_2 CONTENT -

The sum of O_2 carried on Hb and dissolved in plasma

$$\mathbf{CaO_2\ (ml/dL) = (SaO_2 \times Hb \times 1.34) + (PO_2 \times 0.003)}$$

- O_2 content in 100 ml blood (in normal adult with Hb 15 gm/dl) ~ 20 ml/dl

(19.4 ml as OxyHb + 0.3 ml in plasma)



If the PAO2 is ↑ed significantly (by breathing 100% oxygen) then a small amount of extra oxygen will dissolve in the plasma (at a rate of 0.003 ml O2/100ml of blood /mmHg PO2) but there will normally be no significant increase in the amount carried by haemoglobin

Venous O2 content (CvO2)

$CvO_2 = (SvO_2 \times Hb \times 1.34) + (PvO_2 \times 0.003)$

– (normally-15ml/dl)

- mixed venous saturation (SvO2) measured in the pul A represents the pooled venous saturation from all organs.
- SvO2 influenced by changes in both DO2 and VO2
- Normally, the SvO2 is about 75%, however, clinically an SvO2 of about 65% is acceptable

Arterial-Venous Difference

- The arterial-venous oxygen content difference is the difference between the CaO_2 and the CvO_2.
- The normal $C(a\text{-}v)_{O2}$: 5 vol%.

Factors that increase the C(a-v)O2:	Factors that decrease the C(a-v)O2:
• decreased cardiac output • increased O2consumption • exercise • seizures • shivering • increased temp	• increased cardiac output • skeletal relaxation (drugs) • peripheral shunting • poisons • decreased temp

O2 DELIVERY

DO_2 (ml/min) = Q x CaO_2 x 10

$DO_2 = Q \times Hb \times SaO_2 \times 1.34 \times 10$

(multiplier of 10 is used to convert CaO_2 from ml/dl to ml/L)

N- 900-1,100 ml/min

- Decreased oxygen delivery occurs when there is:
  - ↓ed cardiac output
  - ↓ed hemoglobin concentration
  - ↓ed blood oxygenation

O2 CONSUMPTION

- The amount of oxygen extracted by the peripheral tissues during the period of one minute is called oxygen consumption or V_{O2}. (N- 200-300ml/min)

$$\mathbf{V_{O2} = Q \times (CaO2 - CvO2) \times 10}$$
$$= Q \times 1.34 \times Hb \times (SaO2 - SvO2) \times 10$$

- O2 consumption is commonly indexed by the patients body surface area (BSA) and calculated by:
  - V_{O2} / BSA
  - Normal V_{O2} index is between 110 – 160ml/min/m^2

OXYGEN EXTRACTION RATIO

- The oxygen extraction ratio (O_2ER) is the amount of oxygen extracted by the peripheral tissues divided by the amount of O2 delivered to the peripheral cells.
- Index of efficiency of O2 transport
- aka: Oxygen coefficient ratio & Oxygen utilization ratio
  - $O_2ER = VO2 / DO2$
  - When SaO2 ~1 :

    O2ER ~ SaO2-SvO2
  - Normally ~ 25% but ↑ to 70-80% during maximal exercise in well trained athletes

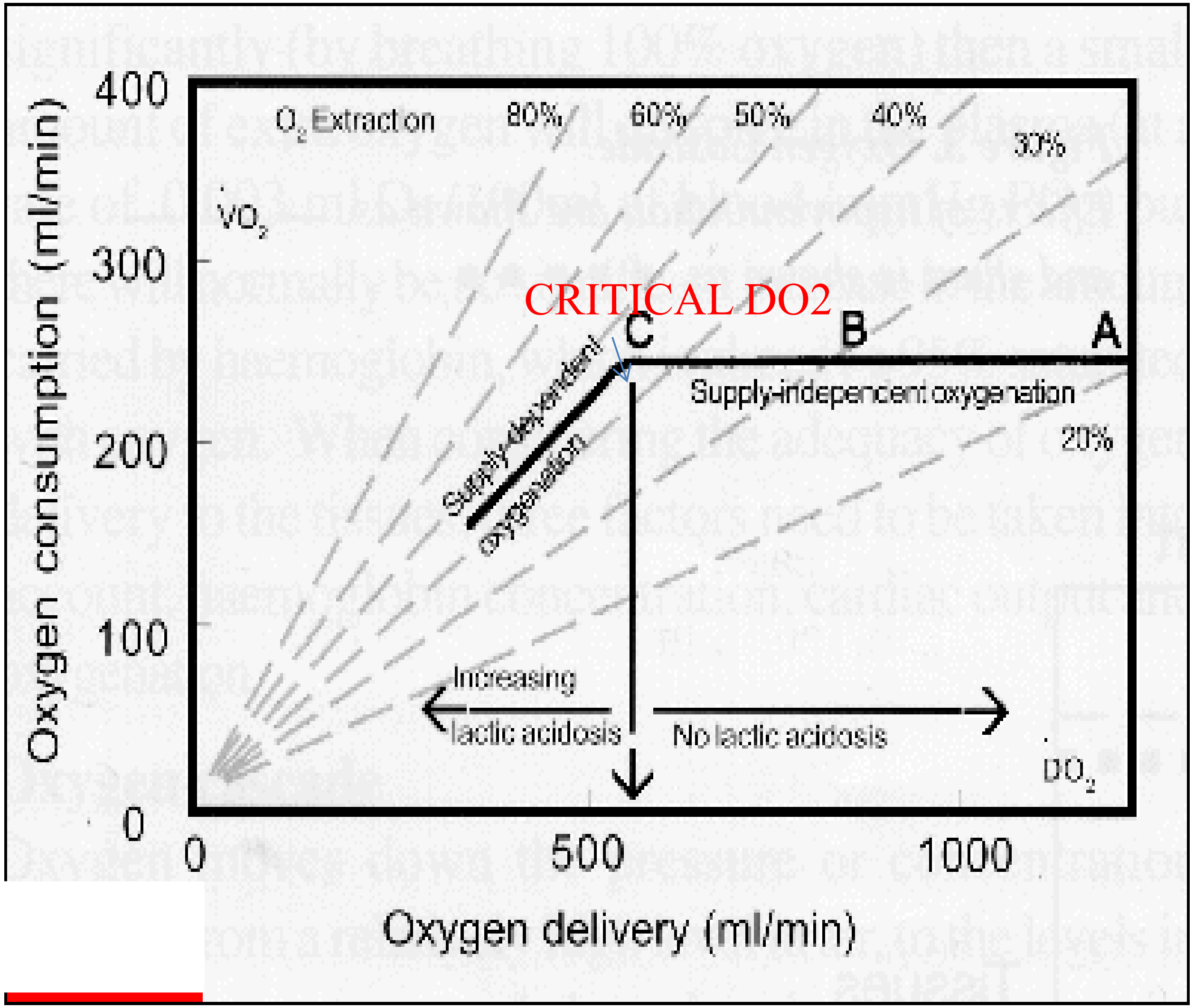
Factors that affect O_2ER

- **Increased with**:
  - Decreased CO
  - Increased VO_2
    - Exercise
    - Seizures
    - Shivering
    - Hyperthermia
  - Anemia
  - Low PaO_2

- **Decreased with**:
  - Increased Cardiac Output
  - Skeletal Muscle Relaxation
  - Peripheral Shunting
  - Certain Poisons
  - Hypothermia
  - Increased Hemoglobin
  - Increased PaO_2

- In general, DO2 >> VO2
- When oxygen consumption is high (exercise) the ↑ed O2 requirement is usually provided by an ↑ed CO

- Alternatively, if oxygen delivery falls relative to oxygen consumption the tissues extract more oxygen from the hb (the saturation of mixed venous blood falls below 70%) (a-b)



A reduction below point 'c' in figure cannot be compensated for by an increased oxygen extraction and results in anaerobic metabolism and lactic acidosis.

O2 DIFFUSION FROM INTERSTITIUM TO CELLS

Intracellular PO2 < Interstitial fluid PO2

- O2 constantly utilized by the cells
- Cellular metabolic rate determines overall O2 consumption

N PcO2 ~ 5-40 mm Hg (average 23 mmHg)

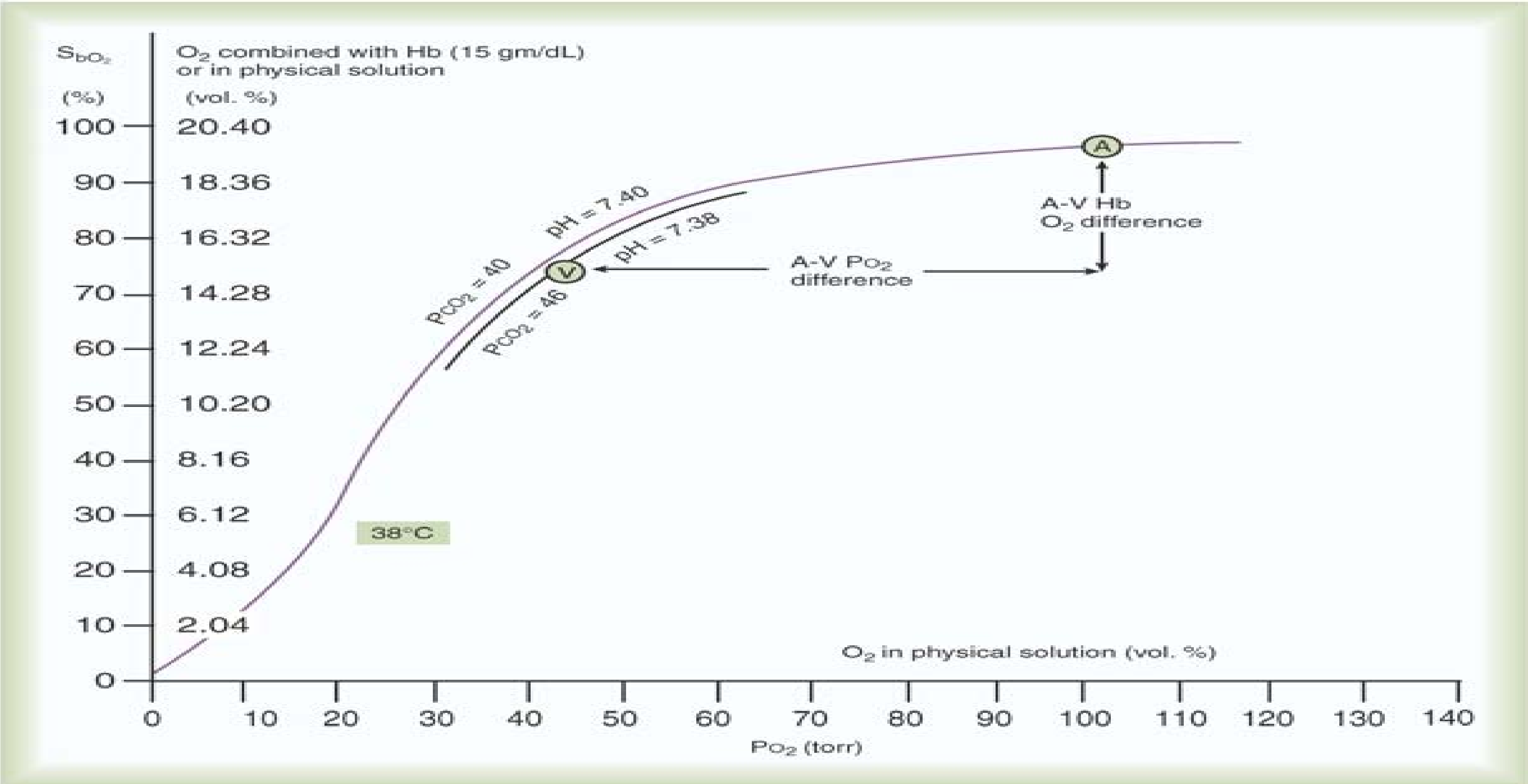
N intracellular req for optimal maintenance of metabolic pathways ~ 3 mm Hg

Pasteur point –

- critical mitochondrial PO_2 below which aerobic metabolism cannot occur
- 0.15 – 0.3 kPa = 1.4 – 2.3mmHg

Oxygen Dissociation Curve

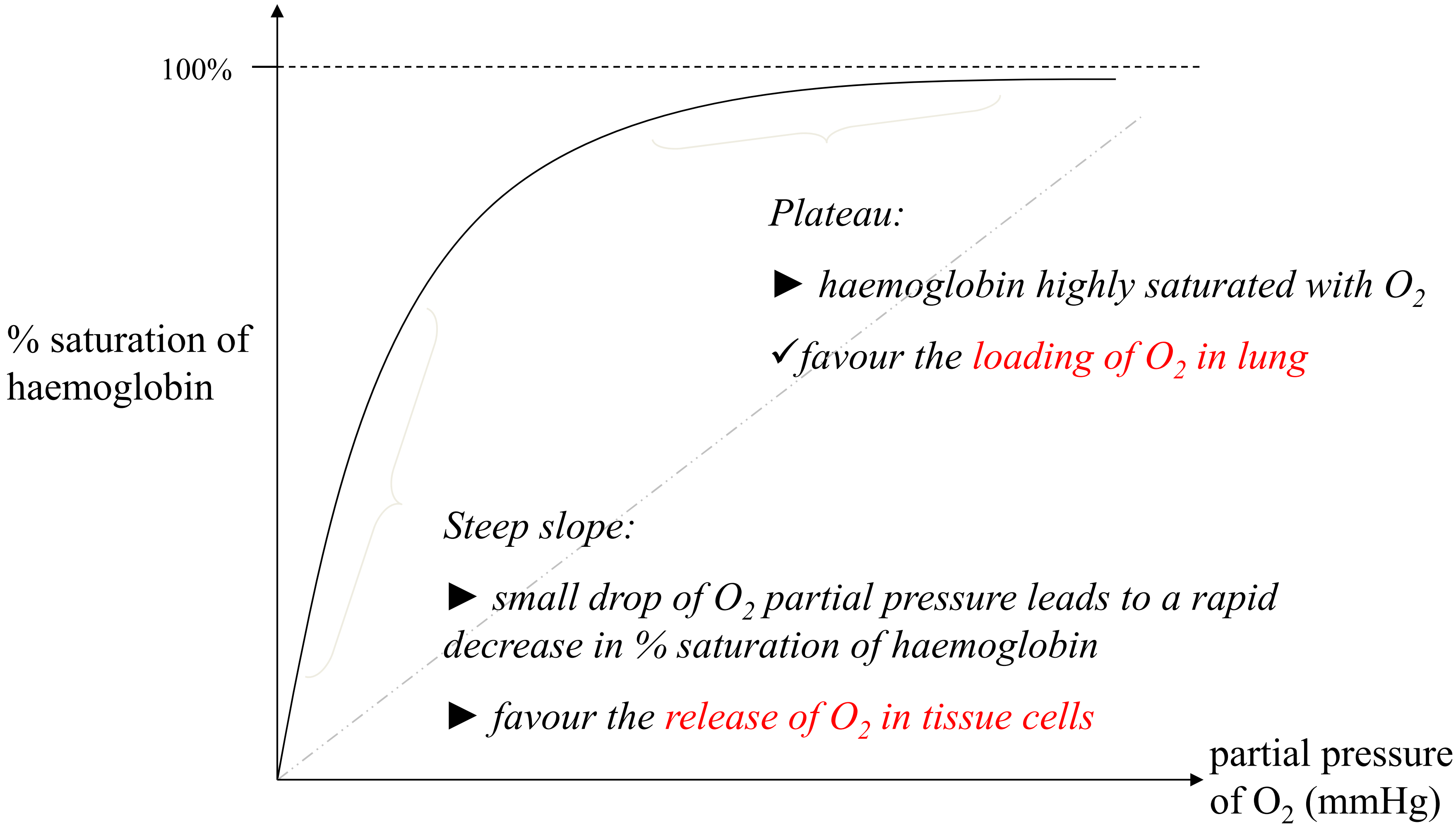
The relationship between the partial pressure of oxygen and the saturation of oxygen.



OXYGEN DISSOCIATION CURVE

- Sigmoid Shaped
- The amount of oxygen that is saturated on the hemoglobin (SO_2) is dependent on the amount dissolved (PO_2).
- Amount of O_2 carried by Hb rises rapidly upto PO_2 of 60mmHg but above that curve becomes flatter
- When Hb takes up small amount of O_2 – relaxed state favours – additional uptake
- Combination Of 1st Heme with O_2 increases affinity of 2nd Heme and so on

Significance of the S-shape curve



Steep Portion of Curve

- "Dissociation Portion" of curve.
- Between 10 and 60 mm Hg.
- Small increases in PO_2 yield large increases in SO_2.
- At the tissue capillary, blood comes in contact with reduced tissue PO_2 and oxygen diffuses from the capillary to the tissue.

Flat Portion of Curve

- "Association Portion" of curve.
- Greater than 60 mm Hg.
- Large increases in PO_2 yield small increases in SO_2.
- At the pulmonary capillary, blood comes in contact with increased alveolar PO_2 and oxygen diffuses from the alveolus to the capillary. As the PO_2 rises, oxygen binds with the hemoglobin (increasing SO_2).
- Very little rise in oxygen saturation above 100 mm Hg of PaO_2.

Rules of Thumb of the Oxyhemoglobin Curve

PO_2	SO_2
27	50
40	75
60	90
250	100

PO_2	SO_2
40	70
50	80
60	90

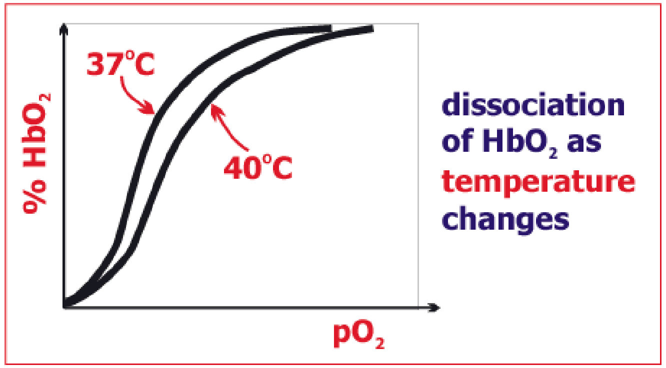
P_{50}

- The partial pressure of oxygen in the blood at which the haemoglobin is 50% saturated, is known as the P50.
- The P50 is a conventional measure of haemoglobin affinity for oxygen
- Normal P_{50} value is 26.7 mm Hg
- As P_{50} increases/decreases, we say the “curve has shifted”.
  - P_{50} less than 27: Shift to the left.
  - P_{50} greater than 27: Shift to the right.

Factors affecting Dissociation

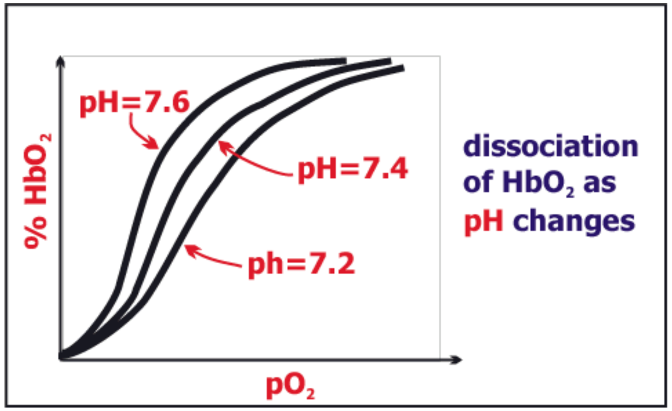
BLOOD TEMPERATURE

- increased blood temperature
- reduces haemoglobin affinity for O_2



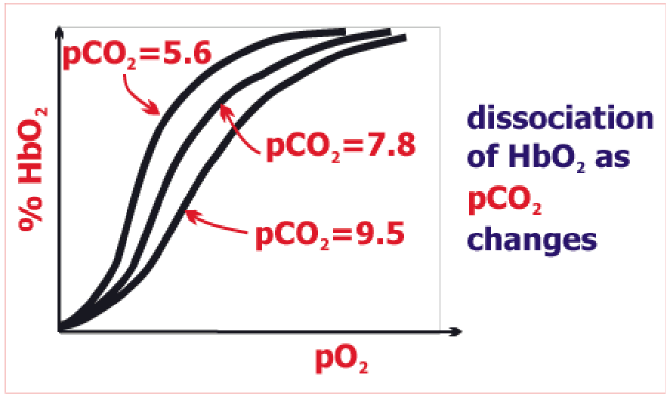
BLOOD Ph

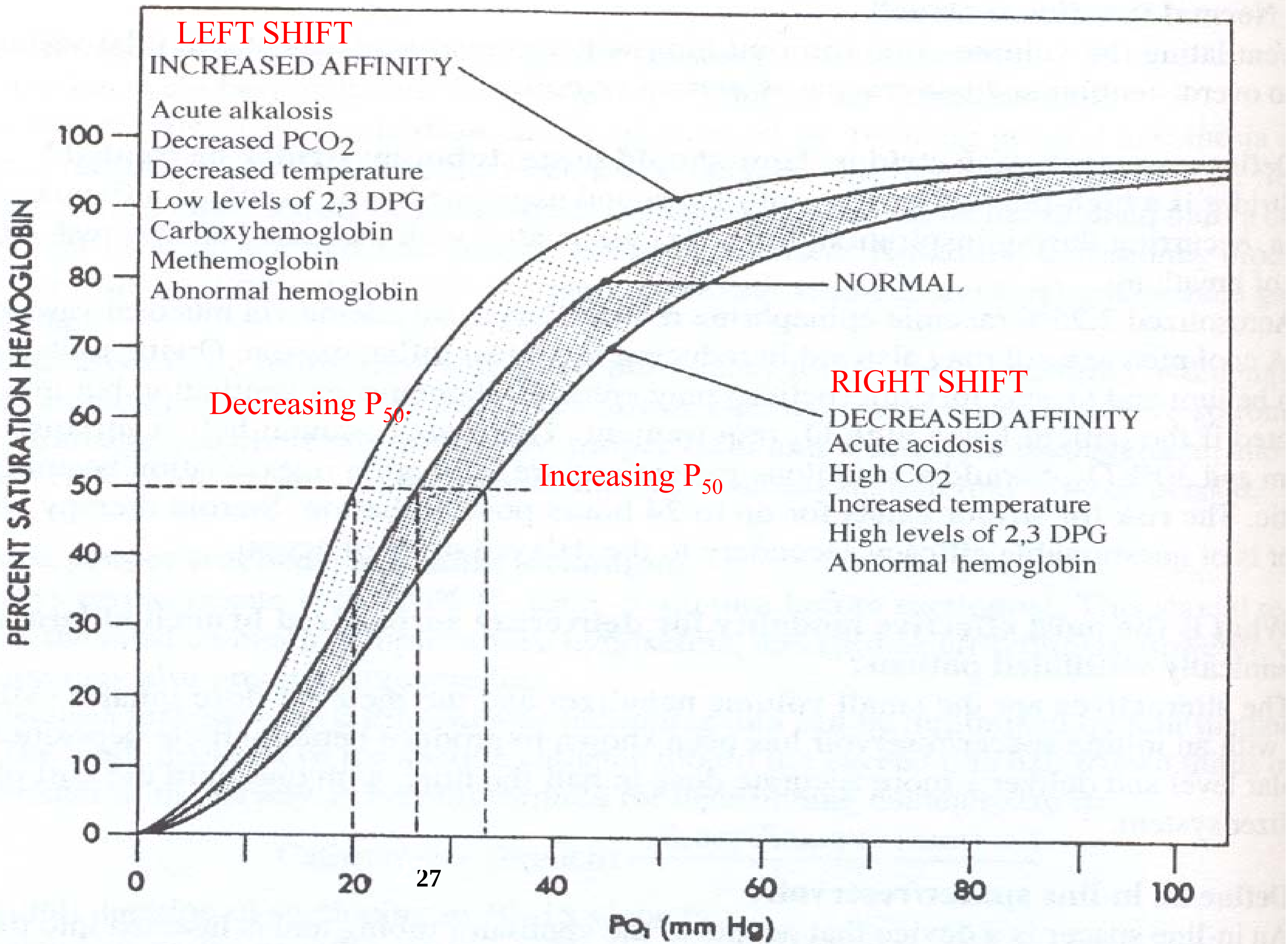
- **lowering** of **blood pH** (making blood more acidic)
- caused by presence of H^+ ions from lactic acid or carbonic acid
- **reduces affinity of Hb for O_2**



CARBON DIOXIDE CONCENTRATION

- the **higher CO_2 concentration** in tissue
- the **less the affinity of Hb for O_2**

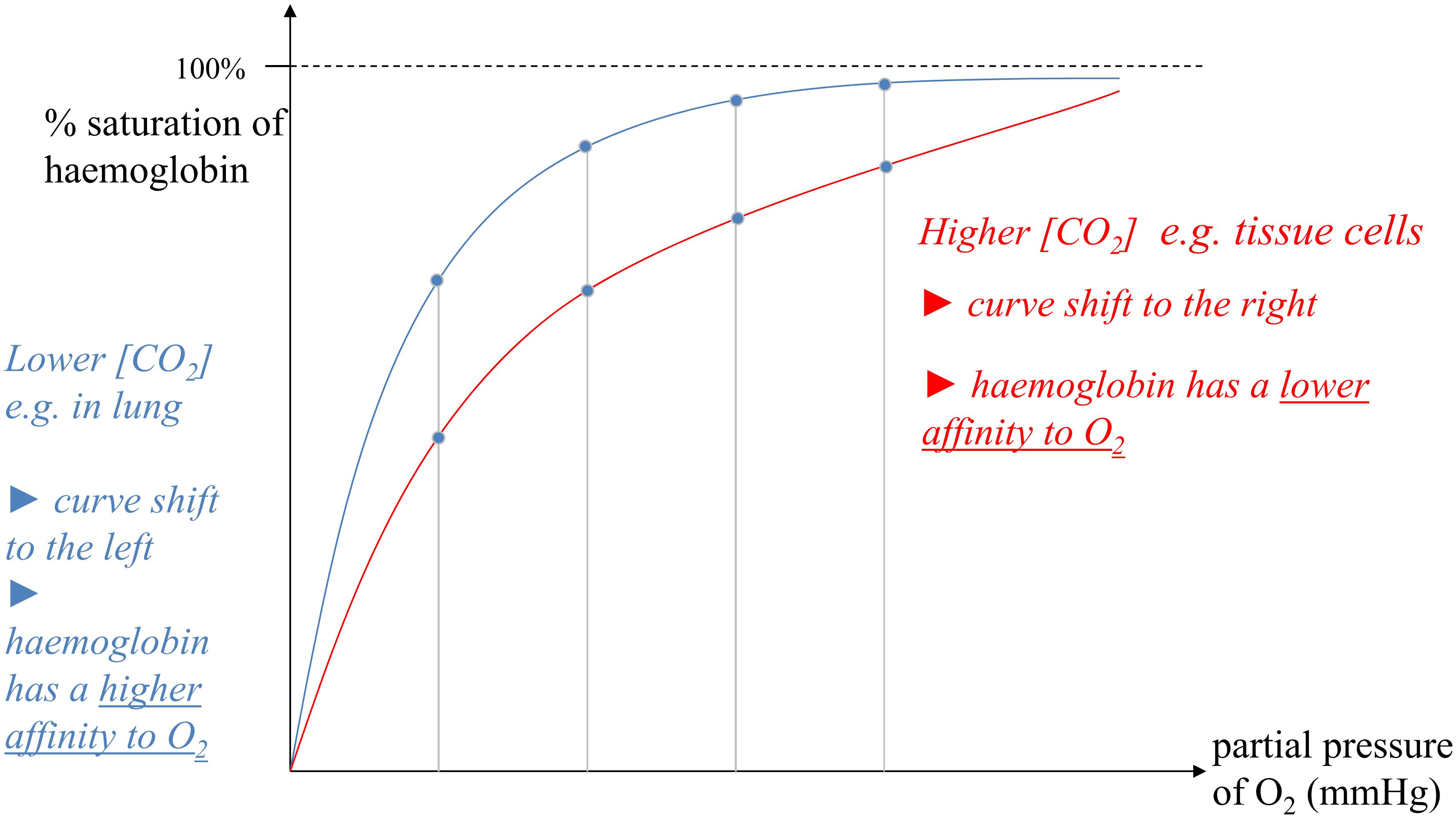



LEFT SHIFT
INCREASED AFFINITY
Acute alkalosis
Decreased PCO_2
Decreased temperature
Low levels of 2,3 DPG
Carboxyhemoglobin
Methemoglobin
Abnormal hemoglobin
NORMAL
RIGHT SHIFT
DECREASED AFFINITY
Acute acidosis
High CO_2
Increased temperature
High levels of 2,3 DPG
Abnormal hemoglobin
Decreasing P_{50}
Increasing P_{50}
PERCENT SATURATION HEMOGLOBIN
0
10
20
30
40
50
60
70
80
90
100
0
20
27
40
60
80
100
PO_2 (mm Hg)

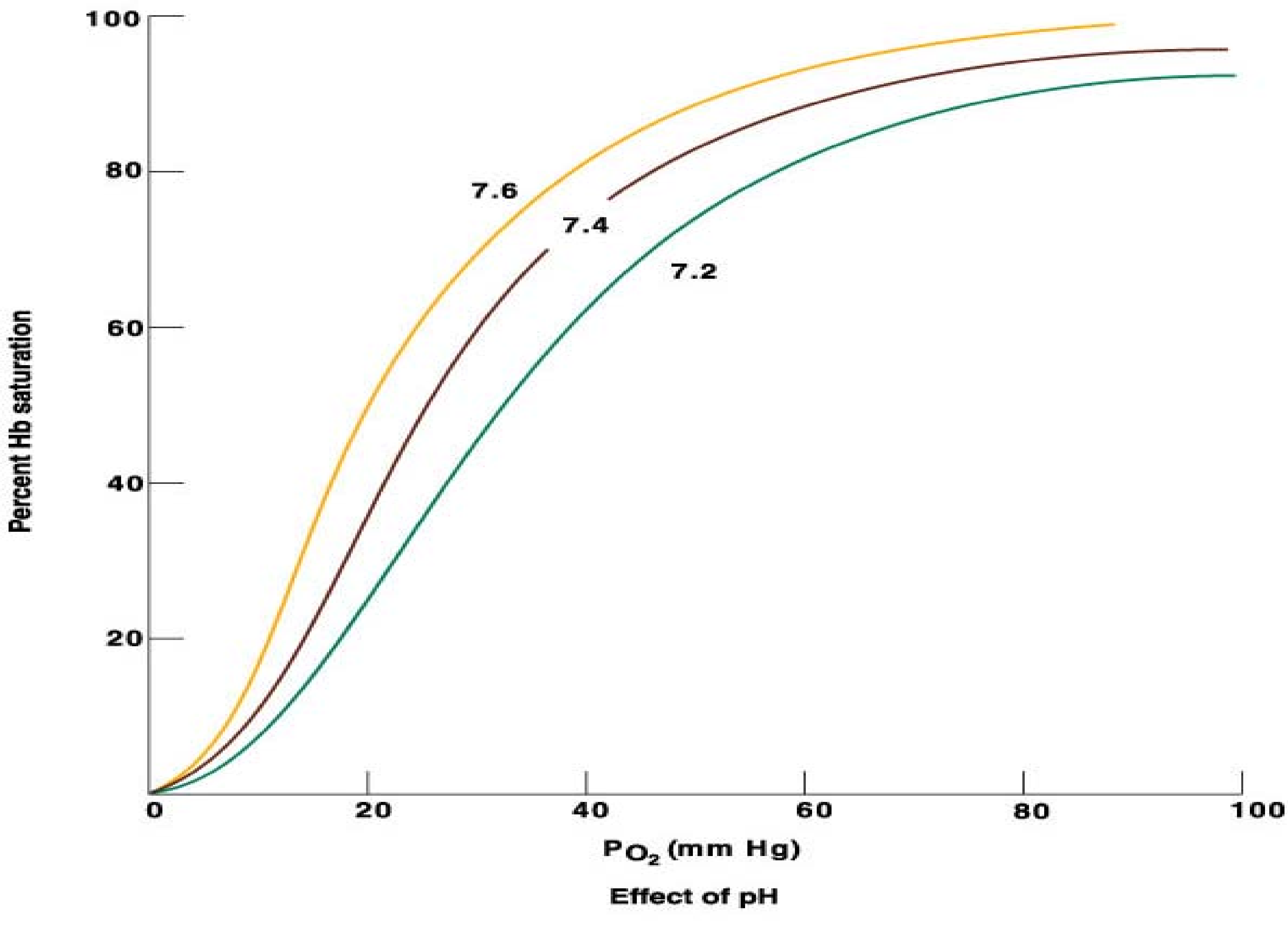
Bohr Effect

- By Christian Bohr in 1904
- The effect of CO_2 on the OHDC is known as the **Bohr Effect**
- High P_{CO_2} levels and low pH decrease affinity of hemoglobin for oxygen (a right-ward shift).
- This occurs at the tissues where a high level of P_{CO_2} and acidemia contribute to the unloading of oxygen.

Bohr effect – the effect of $[CO_2]$ on haemoglobin



pH & pO_2: BOHR EFFECT



IMPLICATIONS OF BOHR EFECT

- Enhance oxygenation of blood in lungs and to enhance release of O_2 in the tissues
- In lungs, CO_2 diffuses out of the blood (H+ conc ↓ due to ↓ in H_2CO_3 conc) → Shift of O_2-Hb curve to left → ↑ O_2 bound to Hb → ↑ O_2 transport to tissues.

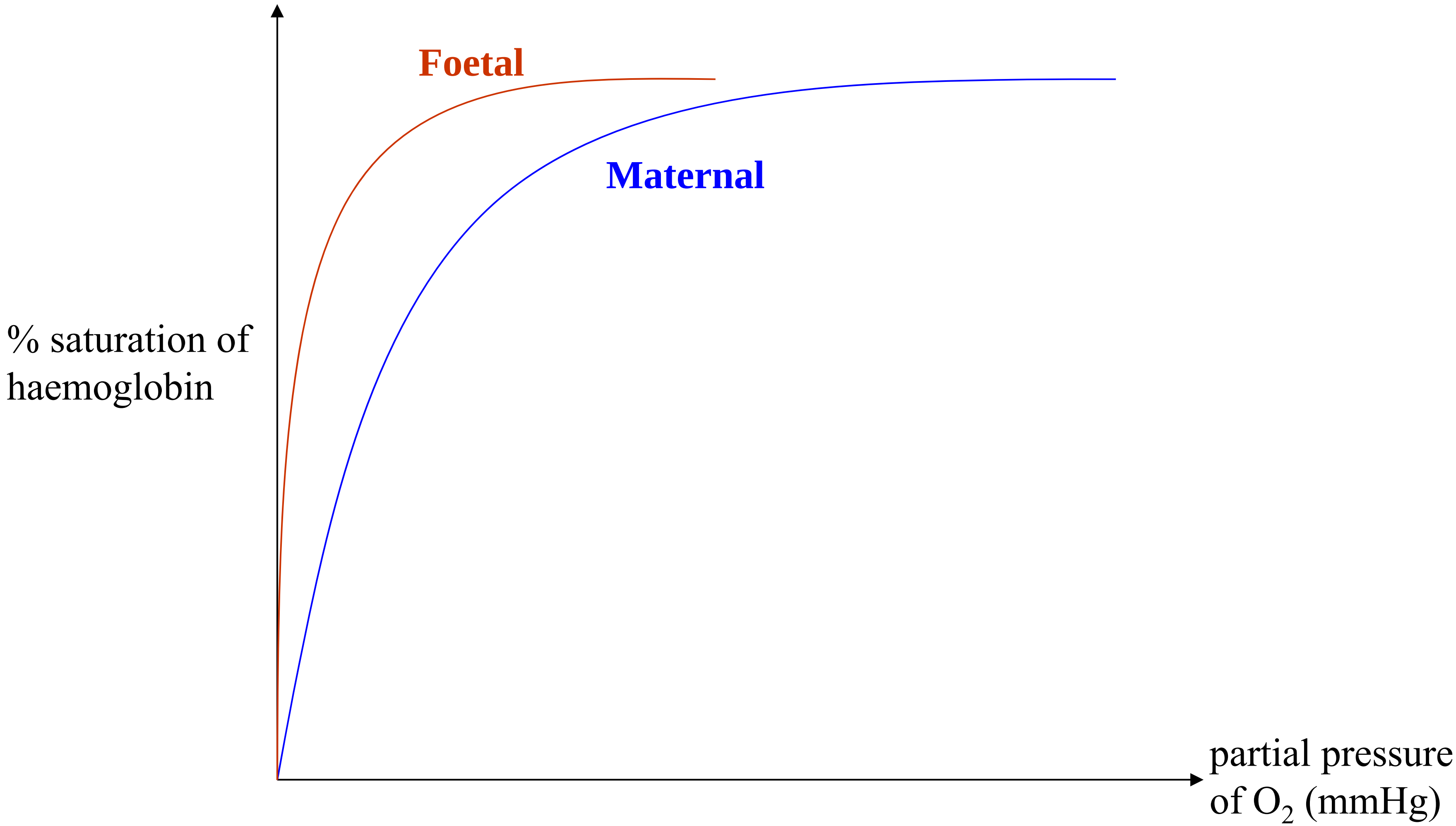
- In tissue capillaries, ↑ CO_2 and ↑ H+ → greater release of O_2 due to less avid binding of O_2 to Hb.

DOUBLE BOHR EFFECT

- Reciprocal changes in acid - base balance that occur in maternal & fetal blood in transit through the placenta

FETAL BLOOD	MATERNAL BLOOD
➢ Loss of CO_2	Gain of CO_2
➢ Rise in pH	Fall in pH
➢ Leftward shift of ODC	Rightward shift of ODC

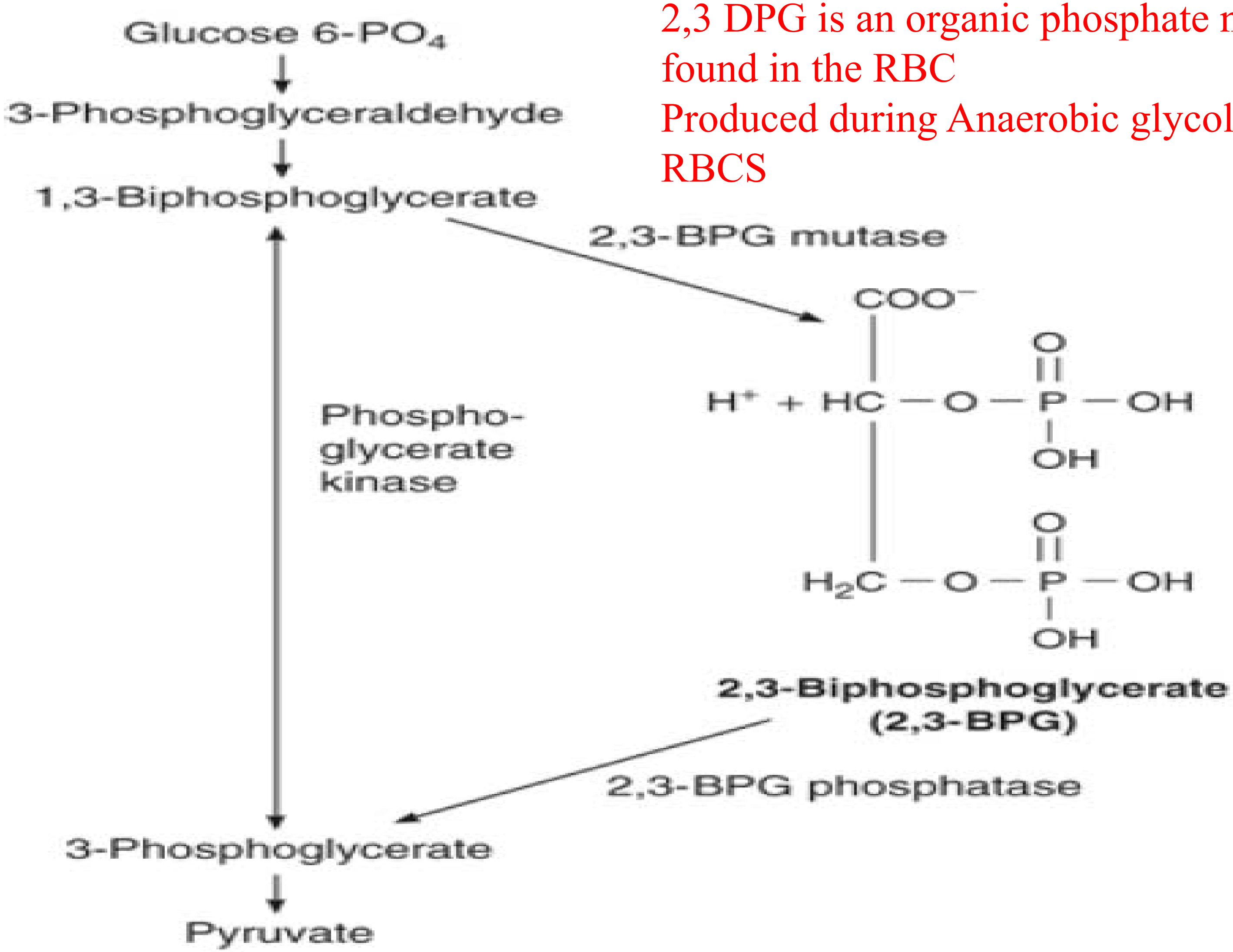
Oxygen dissociation curve:
Foetal VS Maternal



*→ **Foetal haemoglobin has higher affinity to O_2 so as obtain O_2 from maternal blood in the placenta.***

ROLE OF 2,3 DPG(diphosphoglycerate)

2,3 DPG is an organic phosphate normally found in the RBC
Produced during Anaerobic glycolysis in RBCS



2,3 DPG

- Tendency to bind to β chains of Hb and thereby decrease the affinity of Hemoglobin for oxygen.
- $HbO2 + 2,3\ DPG \rightarrow Hb\text{-}2,3\ DPG + O_2$

- It promotes a rightward shift and enhances oxygen unloading at the tissues.
- This shift is longer in duration than that due to $[H^+]$, P_{CO_2} or temperature.

  – A doubling of DPG will result in a 10 torr increase in P_{50}.

2,3 DPG

- The levels increase with
  - Cellular hypoxia.
  - Anemia
  - Hypoxemia secondary to COPD
  - Congenital Heart Disease
  - Ascent to high altitudes
- The levels decrease with
  - Septic Shock
  - Acidemia
  - Stored blood
    - No DPG after 2 weeks of storage.

EFFECTS OF 2,3-BPG ON STORED BLOOD

- In banked blood , the 2,3-BPG level falls and the ability of this blood to release O_2 to the tissues is reduced.

- less if blood is stored in citrate–phosphate–dextrose solution than acid–citrate–dextrose solution.

Effects of anemia & CO on the oxyhemoglobin dissociation curve

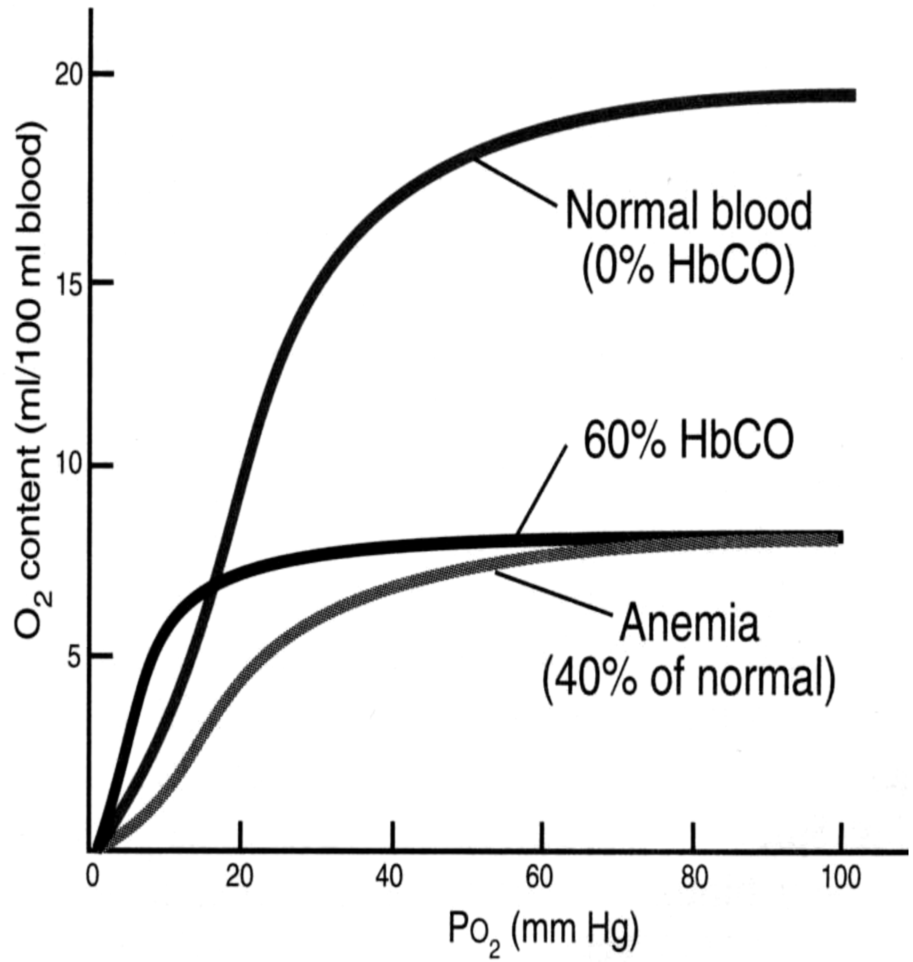
Anemia

- ↓OCC of blood & O_2 content;
- SaO_2 remains normal

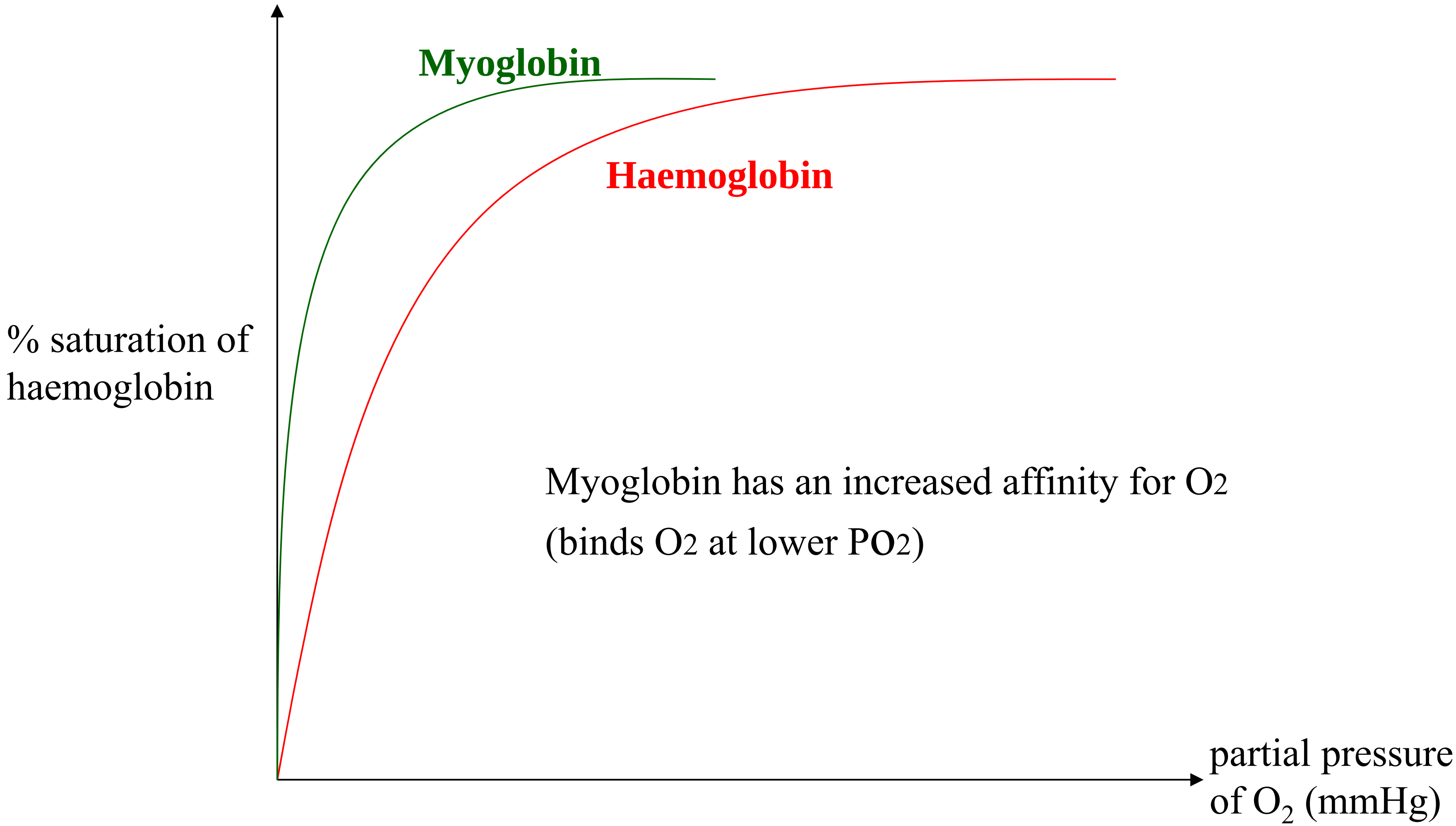
Carbon Monoxide [CO]

- affinity of Hb for CO is 250 fold relative to O_2 competes with O_2 binding
- L shift- interfere with O_2 unloading at tissues
- severe tissue hypoxia
- sigmoidal HbO2 curve becomes hyperbolic

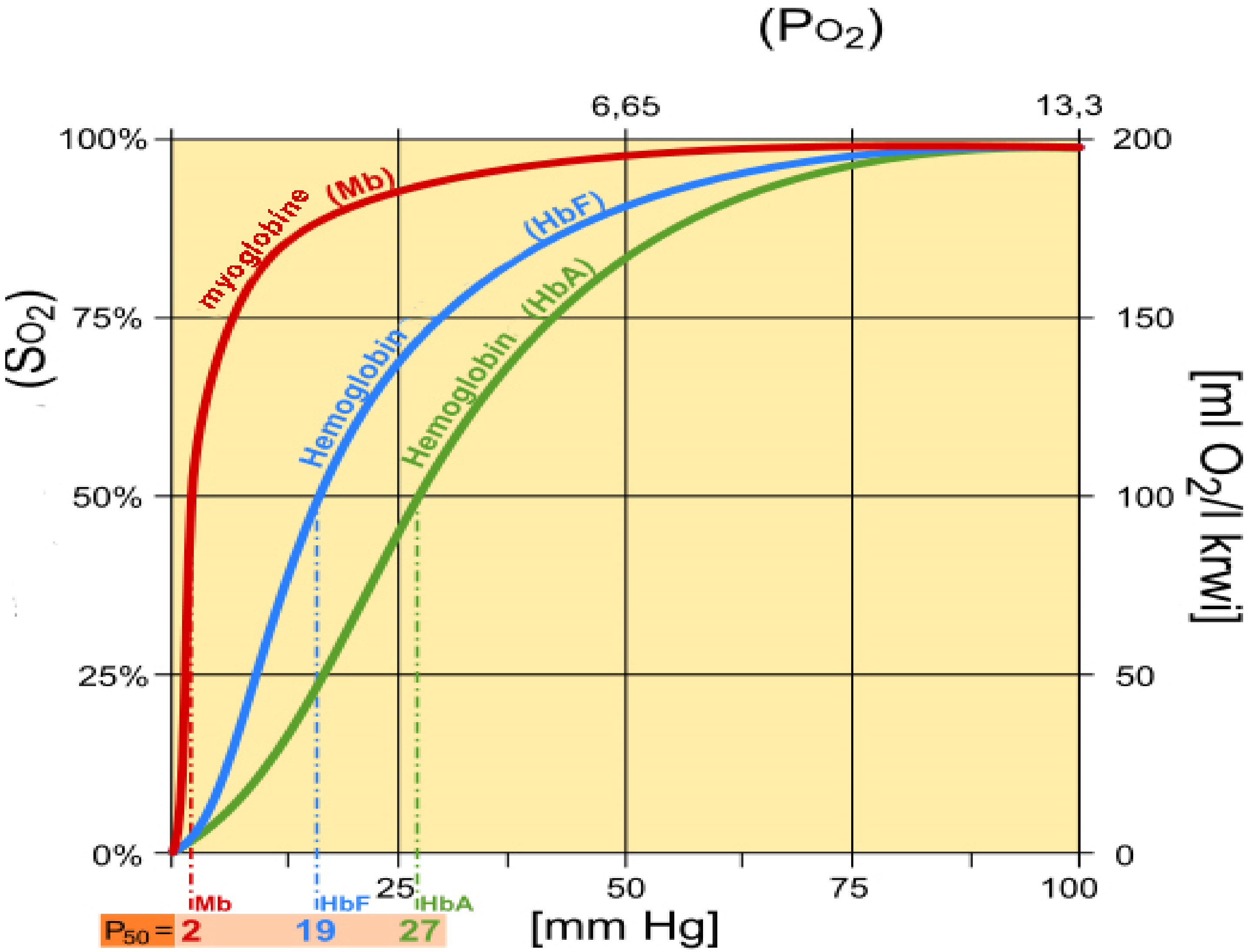
CHANGE THE SHAPE OF OHDC



Oxygen dissociation curve: Haemoglobin VS Myoglobin



→ Myoglobin stores O_2 in muscles and release it only when the O_2 partial pressure is very low.



(Po2)
6,65
13,3
100%
75%
50%
25%
0%
200
150
100
50
0
(So2)
[ml O2/l krwi]
myoglobine (Mb)
Hemoglobin (HbF)
Hemoglobin (HbA)
25
50
75
100
iMb
iHbF
iHbA
[mm Hg]
P50 = 2 19 27

O2 DELIVERY DURING EXERCISE

- During strenuous exercise VO2 may ↑ to 20 times N
- Blood also remains in the capillary for <1/2 N time due to ↑ C.O.

O2 Sat not affected

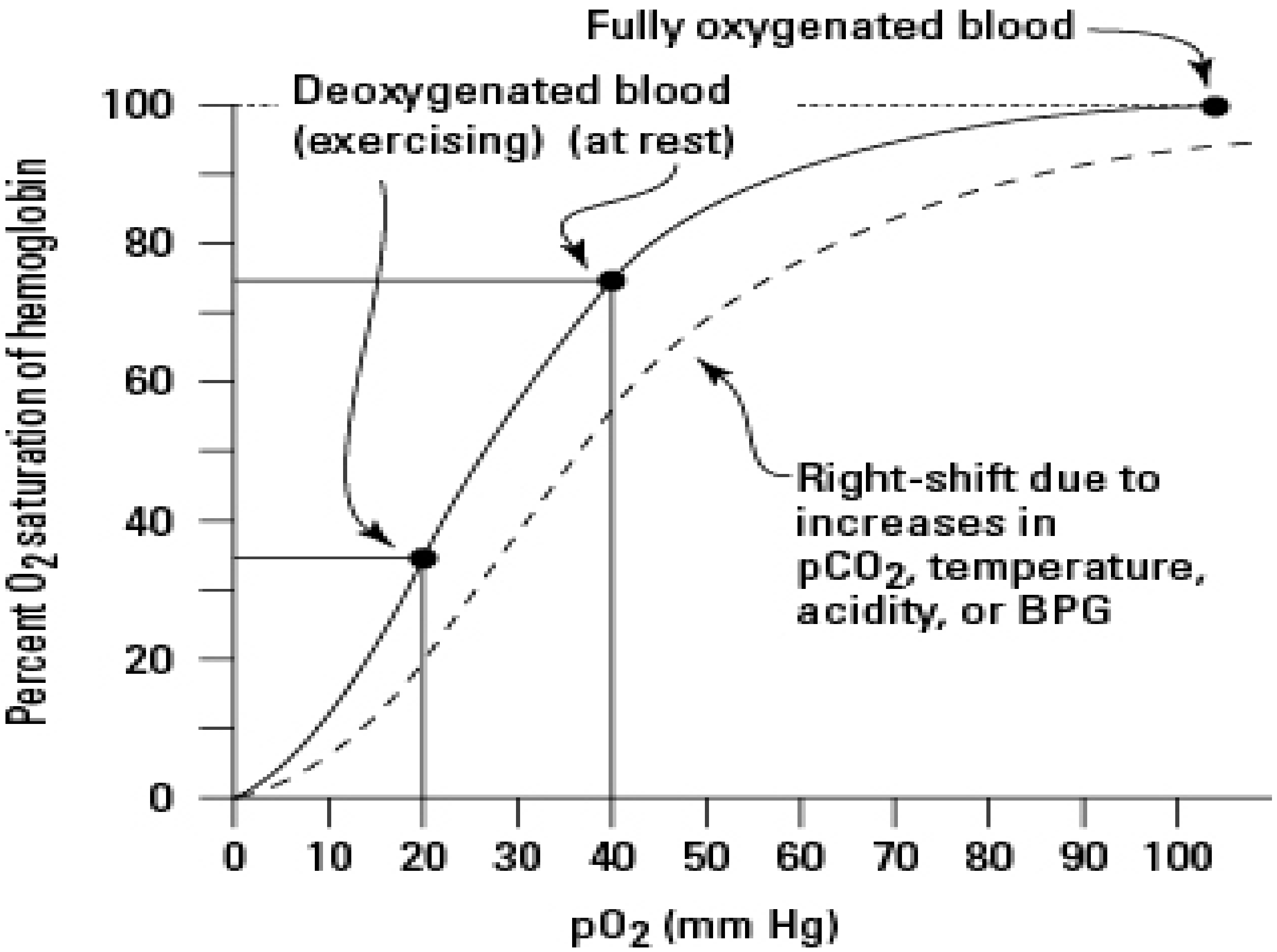
- Blood fully sat in first 1/3 of N time available to pass through pul circulation

- Diffusion capacity ↑ upto 3 fold since:

1. Additional capillaries open up → ↑ no of capillaries participating in diffusion process
2. Dilatation of both alveoli and capillaries → ↓ alveolo-capillary distance
3. Improved V/Q ratio in upper part of lungs due to ↑ blood flow to upper part of lungs

Shift of O2-Hb dissociation curve to right because of:

1. ↑ CO_2 released from exercising muscles
2. ↑ H^+ ions → ↓ pH
3. ↑ Temp
4. Release of phospates → ↑ 2,3 - DPG



Fully oxygenated blood
Deoxygenated blood
(exercising) (at rest)
Right-shift due to increases in pCO_2, temperature, acidity, or BPG
Percent O_2 saturation of hemoglobin
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80 90 100
pO_2 (mm Hg)

OXYGEN DELIVERY IN CRITICAL ILLNESS

- Tissue hypoxia is due to disordered regional distribution of blood flow
- often caused by capillary microthrombosis after endothelial damage and neutrophil activation rather than by arterial hypoxaemia

OXYGEN STORES

- o2 stores are limited to lung and blood.
- The amount of O2 in the lung is dependent on the FRC and the alveolar concentration of oxygen.
- Breathing 100% oxygen causes a large increase in the total stores as the FRC fills with oxygen
- This is the reason why pre-oxygenation is so effective.

THE EFFECTS OF ANAESTHESIA

- **The normal protective response to hypoxia is reduced by anaesthetic drugs and this effect extends into the post-operative period.**

- **Following induction** of anaesthesia : FRC ↓
- V/Q mismatch is ↑ed
- Atelectasis develops rapidly
- This 'venous admixture' increases from N 1% to around 10% following induction of anaesthesia.

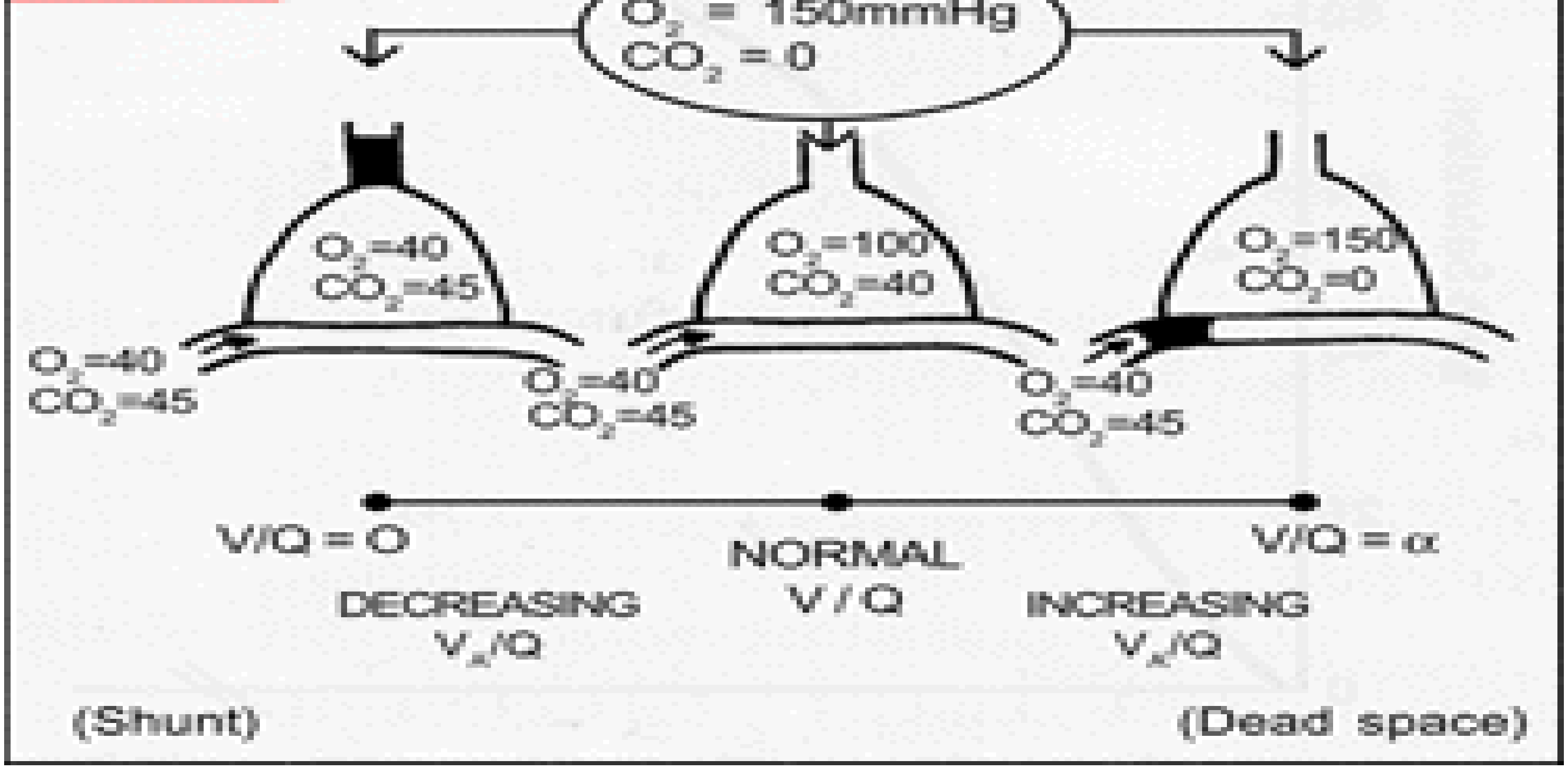
THE EFFECTS OF ANAESTHESIA

- Volatile anaesthetic agents suppress hypoxic pulmonary vasoconstriction.
- Many anaesthetic agents depress CO and therefore ↓ O2 delivery.
- Anaesthesia causes a 15% ↓ in metabolic rate and therefore a **reduction in oxygen requirements**.
- Artificial ventilation causes a further 6% ↓ in oxygen requirements as the work of breathing is removed.

Pulmonary Shunting

- PERFUSION WITHOUT VENTILATION.
- Pulmonary shunt is that portion of the cardiac output that enters the left side of the heart without coming in contact with an alveolus.
  - "True" Shunt – No contact
    - Anatomic shunts (Thebesian, Pleural, Bronchial)
    - Cardiac anomalies
  - "Shunt-Like" (Relative) Shunt
    - *Some* ventilation, but not enough to allow for complete equilibration between alveolar gas and perfusion.
- Shunts are refractory to oxygen therapy.

Fig1



O2 = 150mmHg
CO2 = 0
O2=40
CO2=45
O2=100
CO2=40
O2=150
CO2=0
O2=40
CO2=45
O2=40
CO2=45
O2=40
CO2=45
V/Q = O
NORMAL
V / Q
V/Q = α
DECREASING
VA/Q
INCREASING
VA/Q
(Shunt)
(Dead space)

Venous Admixture

- Venous admixture is the mixing of shunted, non-reoxygenated blood with reoxygenated blood distal to the alveoli
- resulting in a reduction in:
  - PaO_2
  - SaO_2
- Normal Shunt: 3 to 5%
- Shunts above 15% are associated with significant hypoxemia

CO_2 TRANSPORT

INTRODUCTION TO PHSYIOLOGY OF CO2 TRANSPORT

- end-product of aerobic metabolism.
  - production averages 200 ml/min in resting adult
  - During exercise this amount may increase 6x
- Produced almost entirely in the mitochondria.
- Importance of co2 elimination lies in the fact that -Ventilatory control system is more responsive to PaCO2 changes.

- Carbon dioxide is transported in the blood from the tissue to the lungs in 3 ways:

(i) dissolved in solution;

(ii) buffered with water as carbonic acid;

(iii) bound to proteins, particularly haemoglobin.

- Approximately 75% of carbon dioxide is transport in the red blood cell and 25% in the plasma attributable to
  - lack of carbonic anhydrase in plasma
  - plasma plays little role in buffering and combination with plasma proteins is poor.

Dissolved carbon dioxide

- Carbon dioxide is 20 times more soluble than oxygen;
- obeys HENRY'S LAW, which states that the number of molecules in solution is proportional to the partial pressure at the liquid surface.

$$PCO_2 \times \alpha = CO_2 \text{ conc in sol}$$

$$\alpha = \text{Solubility Coefficient}$$

Value dependant upon temp (inversely proportional) → more temp lesser amount of CO_2 dissolved.

- The carbon dioxide solubility coefficient is 0.69 ml/L/mm Hg at 37C.

- At rest, contribution of dissolved CO_2 to total A-V CO_2 conc diff only ~10%. In absolute terms only 0.3 ml of CO_2/dL transported in dissolved form

- During heavy exercise contribution of dissolved CO_2 can ↑ 7 fold → ~1/3 of total CO_2 exchange

CO_2 BOUND AS HCO_3

- Dissolved CO_2 in blood reacts with water to form Carbonic Acid
  - $CO_2 + H_2O \Leftrightarrow H_2CO_3$

Carbonic acid dissociates into H+ & HCO_3

$H_2CO_3 \Leftrightarrow H + HCO_3$

↓

When conc of these ions inc in RBCs, HCO_3 diffuses out

↓

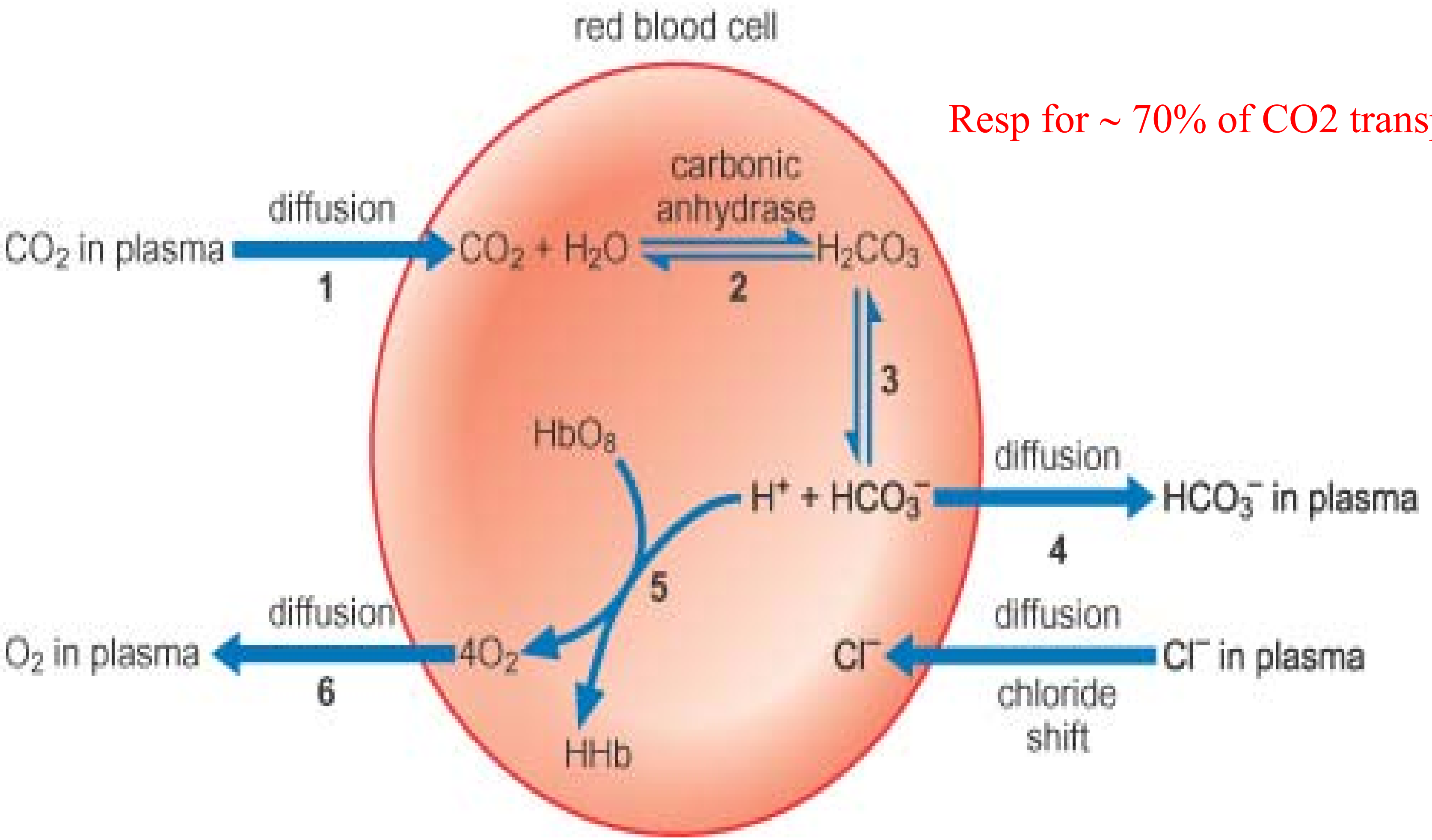
but H+ can't easily do this because cell memb is relatively impermeable to cations.

↓

Thus to maintain electrical neutrality, Cl- ions move into cell from plasma [CHLORIDE SHIFT] *Band 3 HCO_3/Cl carrier protein in RBC memb*

Movement of gases at tissue level

Resp for ~ 70% of CO2 transport



- Most of H+ combine with Hb because reduced Hb is less acidic so better proton acceptor
- This fact that deoxygenation of the blood inc its ability to carry CO2 is known as HALDANE EFFECT.

- As a result of the shift of chloride ions into the red cell and the buffering of hydrogen ions onto reduced haemoglobin, the **intercellular osmolarity increases slightly** an →→ water enters causing the cell to swel →→ **an increase in mean corpuscular volume (MCV**)..
- Hematocrit of venous blood is 3%>arterial
- Venous RBC are more fragile
- Cl content of RBCs V>A

CO_2 BOUND AS CARBAMATE

- 15-25% of total CO_2 transport
- CO_2 reacts directly with terminal amine group of Hb to form the carbaminoHb (Hgb.CO)
- Reversible RX
- Amount of CO_2 bound as carbamate to Hb or plasma proteins depends on:

  1) O_2 Sat of Hb

  2) H^+ conc
- During passage of blood through muscle & tissues, O_2 Sat and H^+ conc change considerably, in particular during exercise.

Reduction of Hb (↓ oxygenation of heme)

↓

↑ basicity of Hb

TISSUES

↓

↑ H^+ binding to reduced Hb

↓

↑ dissociation of H_2CO_3

↓

↑ carriage of CO_2 as HCO_3

Oxygenation of Hb

↓

↑ acidity of Hb

↓

↓ tendency to combine with CO_2 to form Hgb.CO

↓

Displacement of CO_2 from Hb

↓ H^+ binding to Hb

↓

↑ Release of H^+ from Hb

↓

↑ formation of H_2CO_3

↓

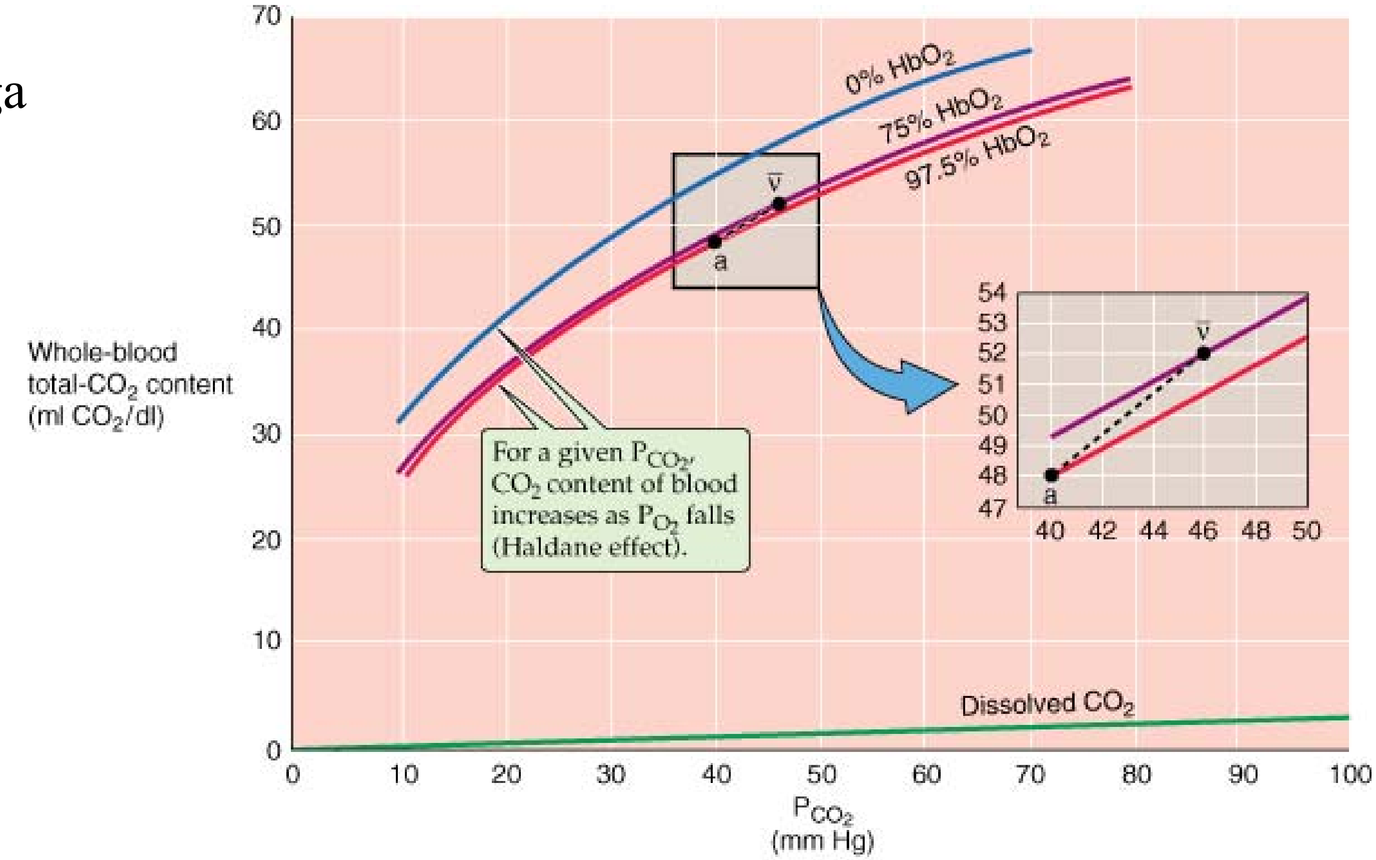
↑ **release of CO_2**

LUNGS

CO2 DISSOCIATION CURVE

- Total CO2 carriage in the blood depends on the three blood-ga parameters:
  - PCO2
  - Plasma pH
  - PO2

Carbon dioxide dissociation curves relate PaCO2 to the amount of carbon dioxide carried in blood



CARBON DIOXIDE DISSOCIATION CURVE

- carbamino hb is much affected by the state of oxygenation of hb, less so by the PCO2.
- **Lower the saturation of Hb with O2 , larger the CO2 conc for a given PaCO2**
- CO2 curve is shifted to right by increase in SpO2

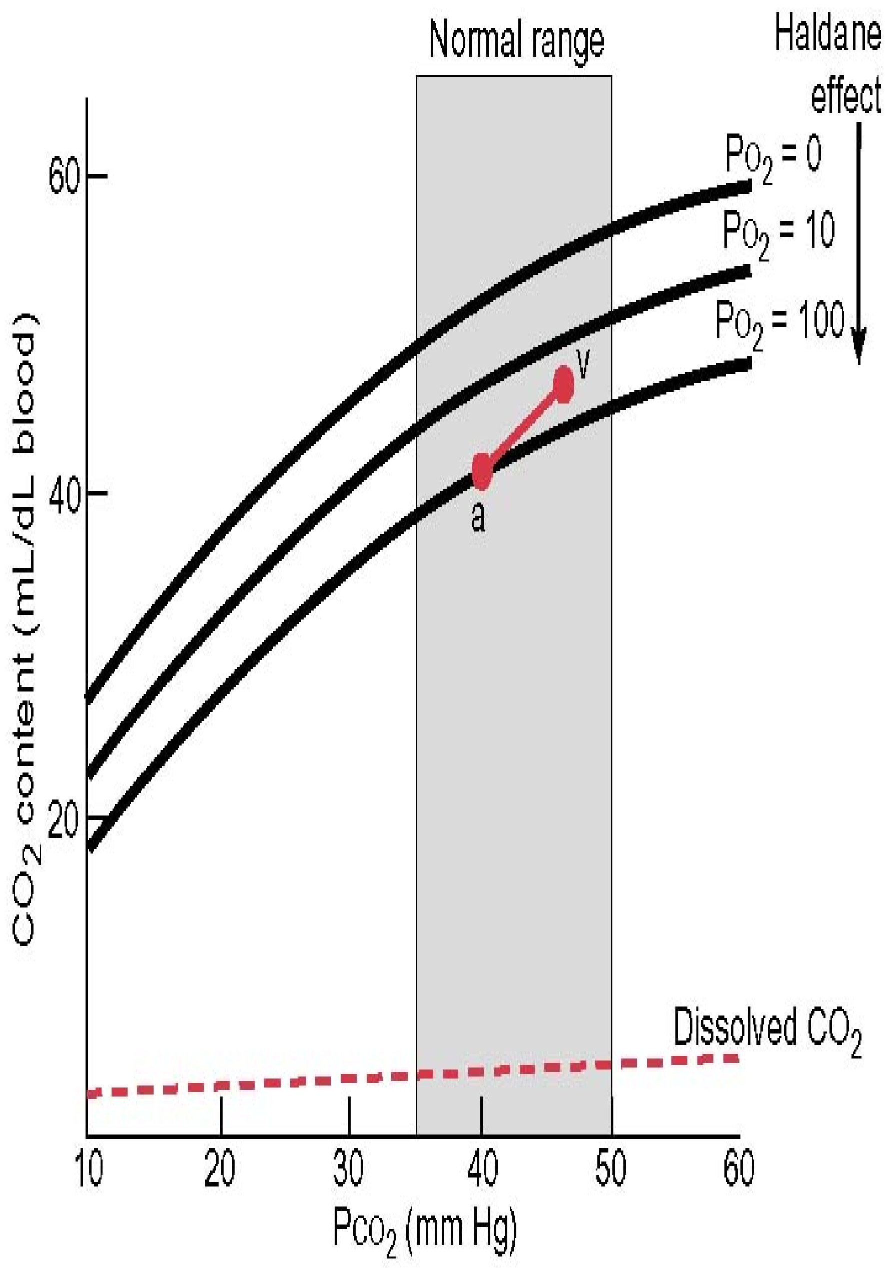
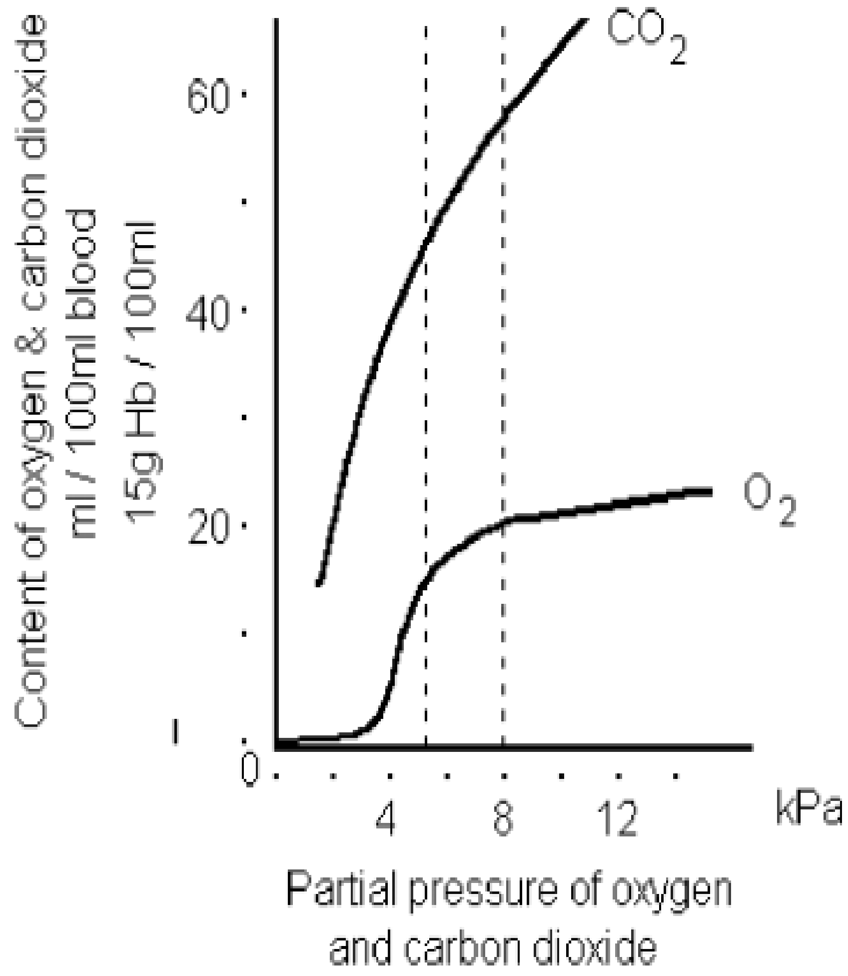
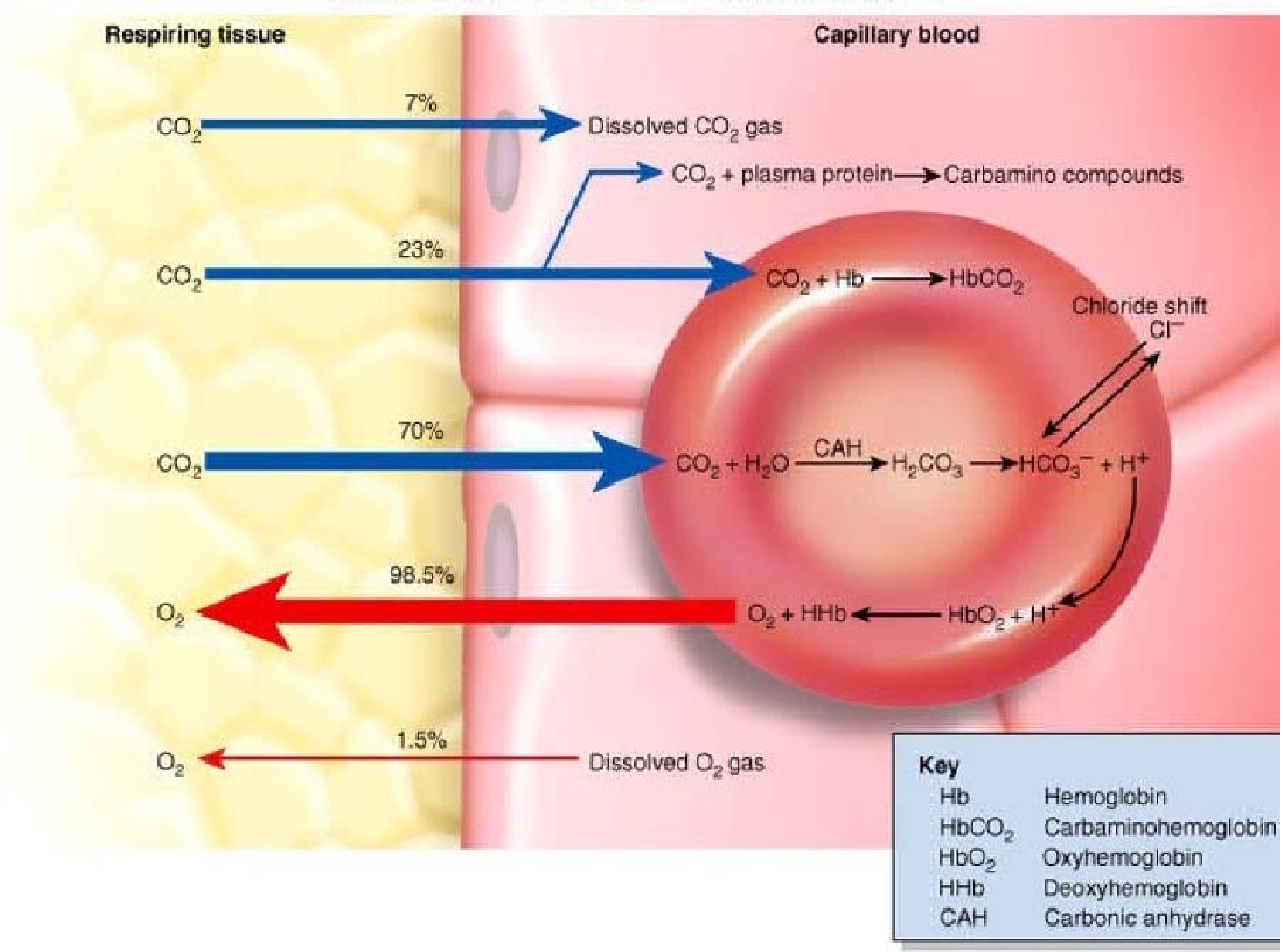


Figure 21.10 Effect of O_2 on the carbon dioxide equilibrium curve.

- CO2 content rises throughout the increase in partial pressure.
- O2content rises more steeply until a point at which the hb is fully saturated. After that, the increase is small because of the small increased amount in solution.
- *Consequently, the CO2 curve is more linear than the O2Hb dissociation curve.*



- Graph illustrates the difference between the content in blood of oxygen and carbon dioxide with change in partial pressure.



Respiring tissue
Capillary blood
7%
CO_2
Dissolved CO_2 gas
CO_2 + plasma protein → Carbamino compounds
23%
CO_2
CO_2 + Hb → $HbCO_2$
Chloride shift
Cl^-
70%
CO_2
CAH
$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+$
98.5%
O_2
O_2 + HHb ← $HbO_2 + H^+$
1.5%
O_2
Dissolved O_2 gas
Key
Hb Hemoglobin
$HbCO_2$ Carbaminohemoglobin
HbO_2 Oxyhemoglobin
HHb Deoxyhemoglobin
CAH Carbonic anhydrase

THANK YOU

O2 DELIVERY FROM LUNGS TO TISSUES

- Major function of circulation to transport O2 from lungs to peripheral tissues at a rate that satisfies overall oxygen consumption.
- Under normal resting conditions -DO2 >> VO2