O_2 & CO_2 transport in the blood

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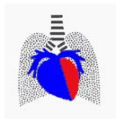

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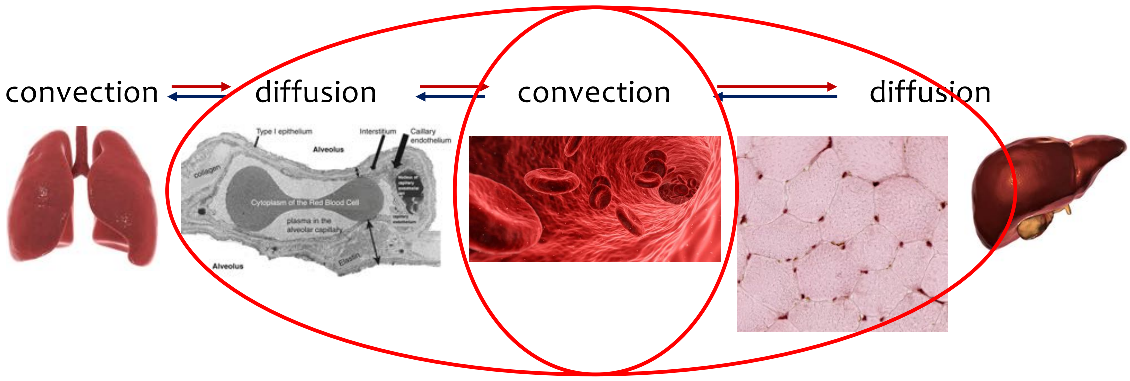
Transport of O_2 & CO_2 („blood gases“) in the body



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Diffusion

- Fick's first law (1855): J=-**D**/RTx**ΔP**/ **Δx**

  - large surfaces
  - short distances
  - large differences in partial pressures

  - CO_2 20x faster than O2

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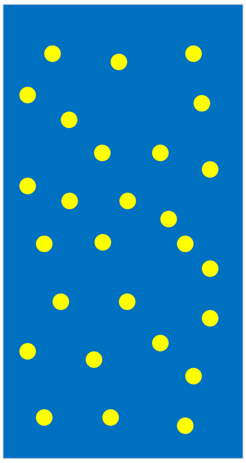
Concentration & partial pressure

O_2 molecules in air



Dry air: 21% is O_2

FO_2 = 0.21

$[O_2]$ = 210 ml/l

As P_B ~ 760 mmHg

PO_2 = 0.21 x 760 mmHg

= 160 mmHg

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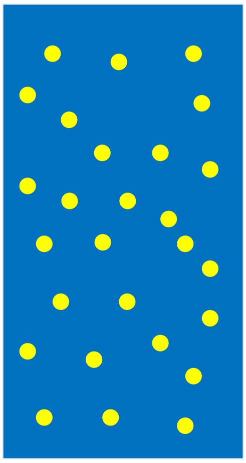
Effect of water vapor

37°C



P_B ~ 760 mmHg
P_{H_2O} = 47 mmHg (at 37°C)
P_{DRY} = 713 mmHg
PO_2 = 0.21 x 713 mmHg
= 150 mmHg

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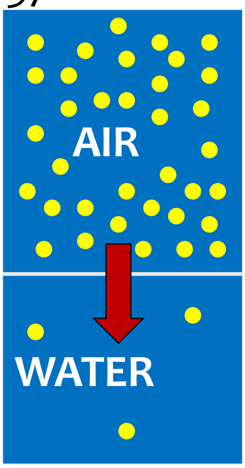
O_2 in physical solution

37°C



37°C

After equilibration:
AIR: PO_2 = 150 mmHg
WATER: PO_2 = 150 mmHg

AIR: $[O_2]$ = 210 ml/l
WATER: $[O_2]$ = 4.5 ml/l

O_2 solubility
= 4.5 / 150 = 0.003 ml/(dl.mmHg)

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O_2 transport in solution during exercise

- solubility = 0.003 ml/(dl.mmHg)
- PO_2 in arterial blood = 100 mmHg
- $[O_2]$ = 3 ml/l
- cardiac output = 30 l/min
- maximum O_2 available = 90 ml/min

But O_2 requirement is 3000 ml/min!

CO_2 similarly (solubility 0.067 ml/(dl.mmHg))

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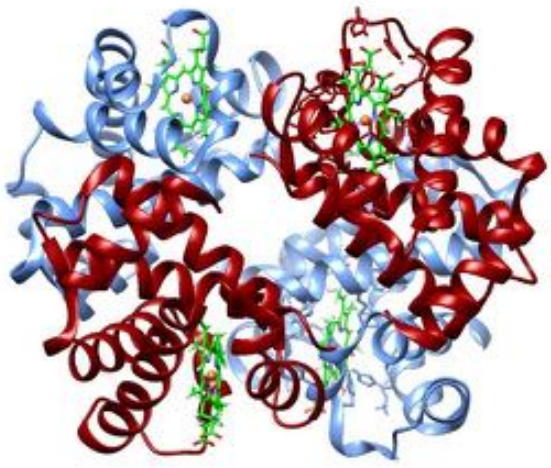
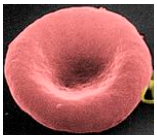
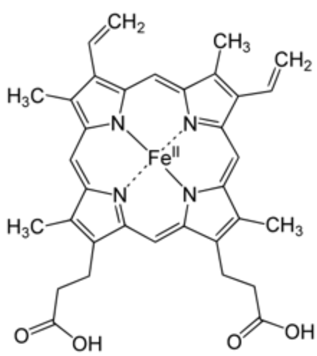
Hemoglobin (Hb)



oxyHb A: $\alpha_2\beta_2$

- both CO_2 & O_2 transport
  - NH_2 groups of N-terminal *val*
  - *heme Fe^{2+}*
- RBC (35% of it)





- 4 globins + 4 hemes (Fe^{2+} in porphyrin ring)

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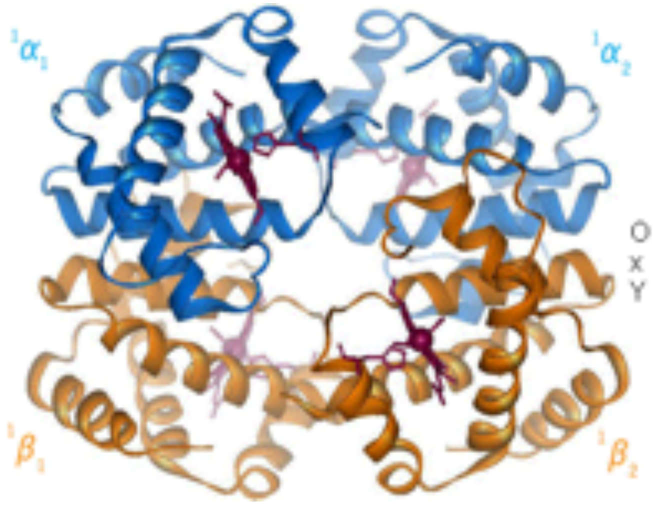
2 Hb conformation states

- **R** (relaxed):
  - high O_2 affinity
  - stabilized by ↑pH
- **T** (tense)
  - low O_2 affinity
  - stabilized by CO_2 & H^+



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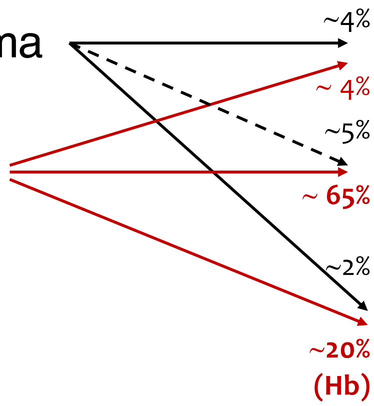
CO_2 transport in the blood

2 compartments:

- plasma
- RBC



3 mechanisms:

- dissolved (~8%)
  solubility > O_2 (22x)
- as HCO_3^- (~70%)
- as carbamino protein complexes ($R\text{-}NH_2 + CO_2$)

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CO_2 transport as HCO_3^-

Carboanhydrase in RBC:

$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$

Free H^+ quickly buffered by Hb

($\downarrow$pH $\rightarrow$ $\downarrow$ transport as HCO_3^-)

Part of HCO_3^- diffuses from RBC x Cl^- in

(electroneutrality, osmotic =): chloride shift

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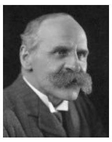
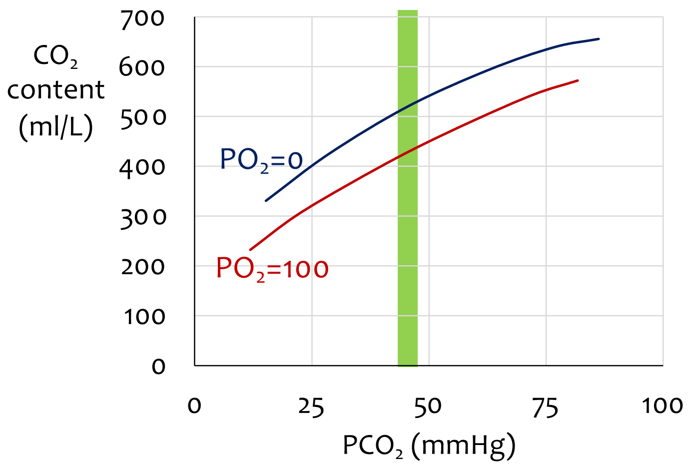


John Scott Haldane
(1860-1936)

CO_2 transport as carbaminoHb: Haldane effect

CO_2 + NH_2 groups of N-terminal *val* of deoxyHb α & β chains
$\rightarrow$ 1 Hb molecule transports up to 4 CO_2 molecules



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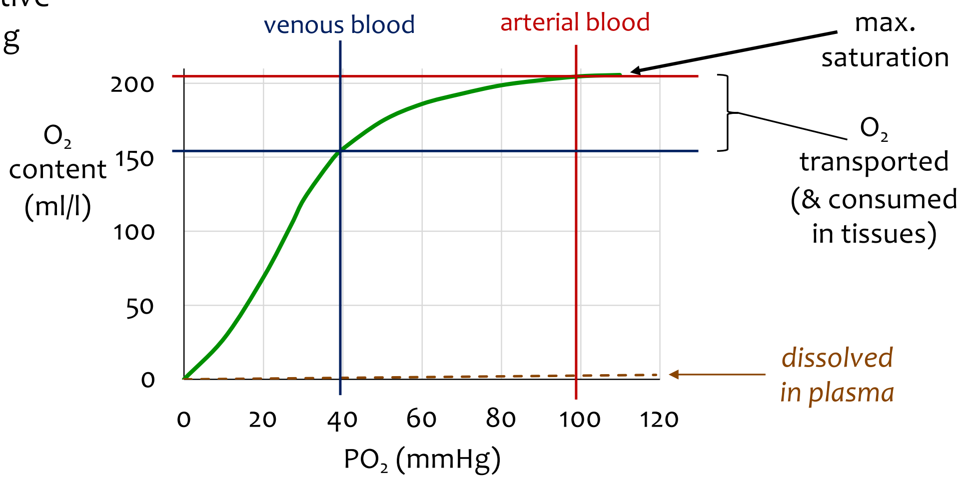
O_2 transport in the blood: Hb-O_2 saturation curve

co-operative O_2 binding



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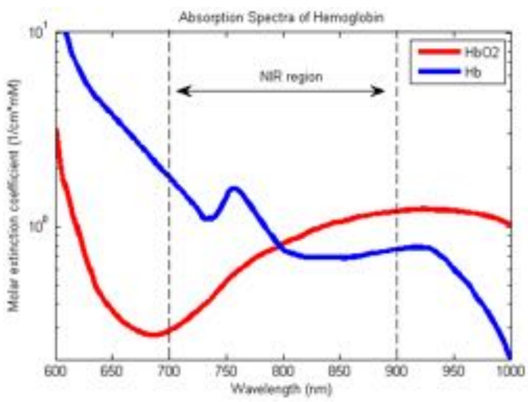
Pulse oxymetry (peripheral SO_2)

- safe, convenient, noninvasive, inexpensive, useful in ICU
- not always identical to arterial SaO_2
- correlated well enough

- 2 wavelengths of light through a thin body part to a photodetector
- measures the absorbance at each of the wavelengths

- ⇒ measures SO_2, not $[O_2]$



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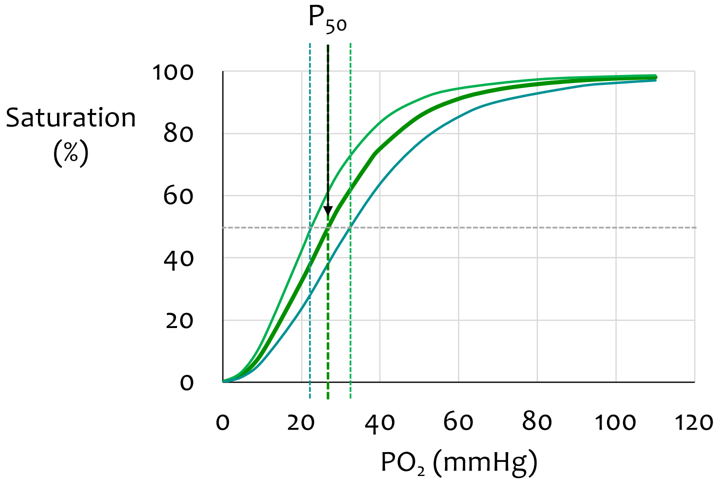
O_2 transport in the blood: Hb-O_2 saturation curve



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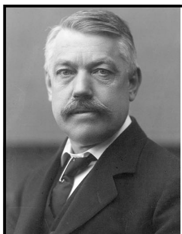
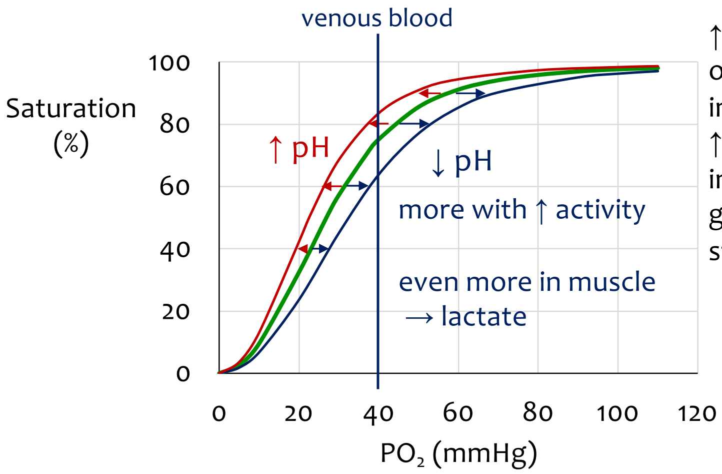


Christian Bohr
1904

$H^+ \rightarrow \downarrow$ Hb-O_2 affinity: Bohr effect



↑ H^+→ ↑ protonation of α & β chains in T state→
↑ + charge → ↑ ionic interactions w/ COOH groups nearby → stabilization of T state

CO_2 similar but smaller effect (via R-NH_2+CO_2) (~Haldane effect) + effect on pH

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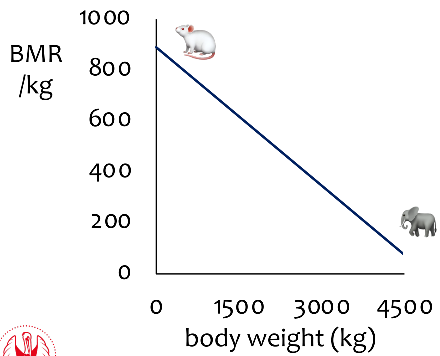
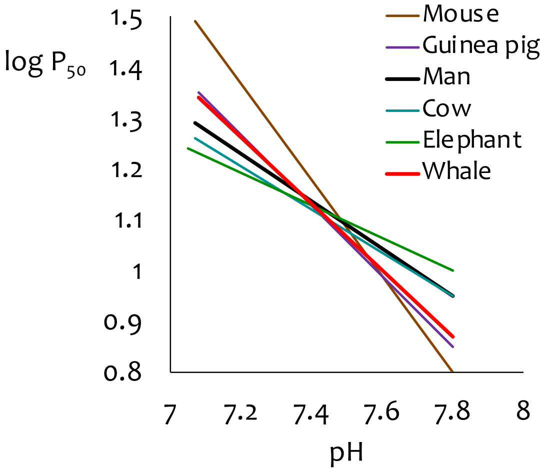
Bohr effect stronger in smaller mammals





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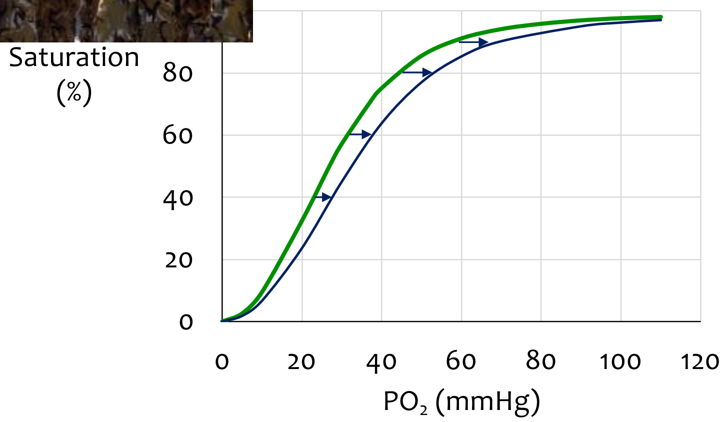
CADETs – look right!



CO_2
Acidity
DPG (2,3-BPG)
Exercise
Temperature

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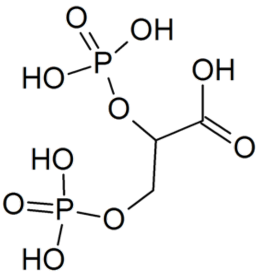
2,3-bisphosphoglycerate (2,3-BPG) (2,3-diphosphoglycerate, 2,3-DPG)



- intermediate of glycolysis in RBC (~ 5 mM)
- rapidly consumed at normal PO_2, accumulates at ↓PO_2
- binds preferentially to β chains
- at ~9 Å, it fits in the deoxyHb form (11 Å pocket), not in the oxyHb form (5 Å)

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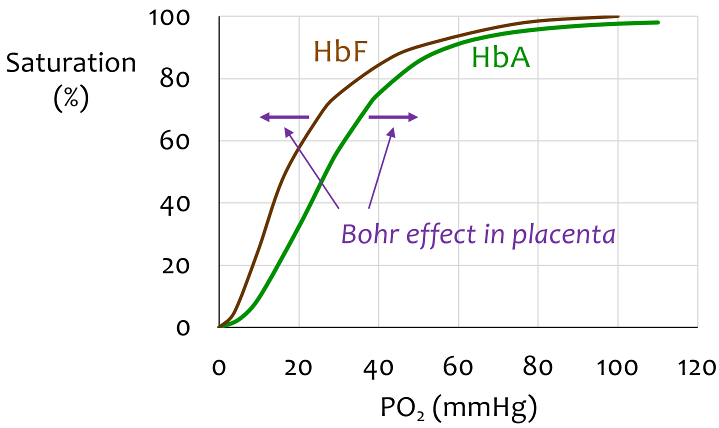
Fetal Hb (Hb F: $\alpha_2\gamma_2$)

- BPG binding: γ<α< β
- γ has less + charges that attract the - charges on BPG
- ↑ BPG formation in placenta



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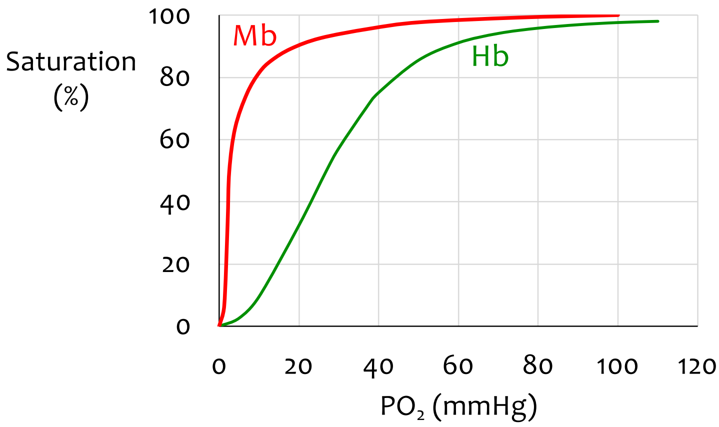
Myoglobin (Mb)

1 chain → no cooperative O_2 binding ("all or nothing")



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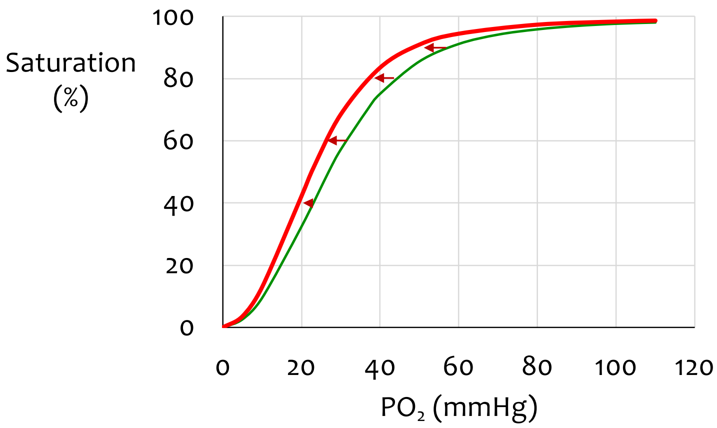
Methemoglobinemia

- Fe^{2+} in heme oxidized to Fe^{3+} (NO & its donors, CO, C≡N)
- Fe^{3+} impairs Hb cooperativity → ↓ O_2 unloading in tissues (~Mb)



- normally 1-2%
- >5-7% hazard
- smokers <10%

Correction:
NADH **metHb reductase** (cytochrome-b5 reductase)

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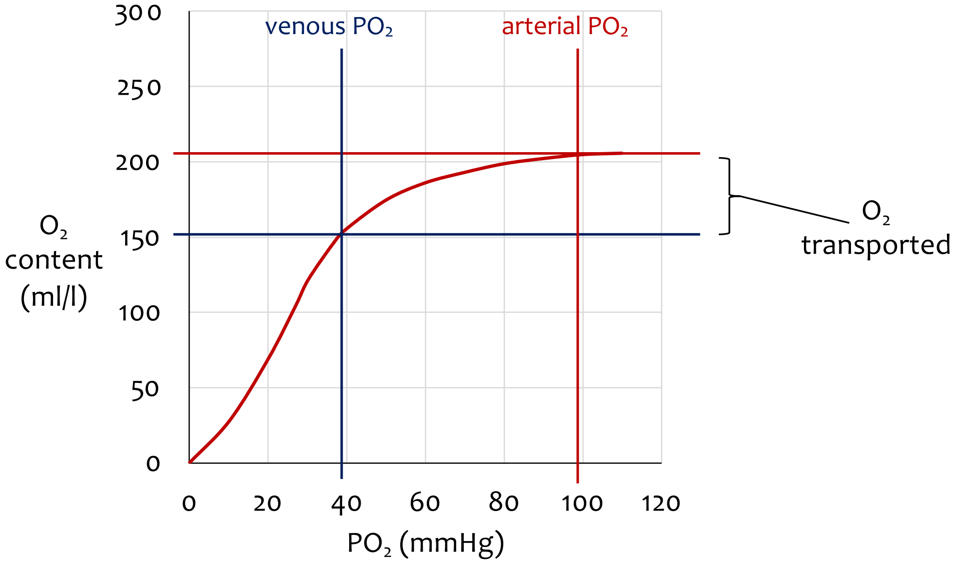
Types of hypoxia



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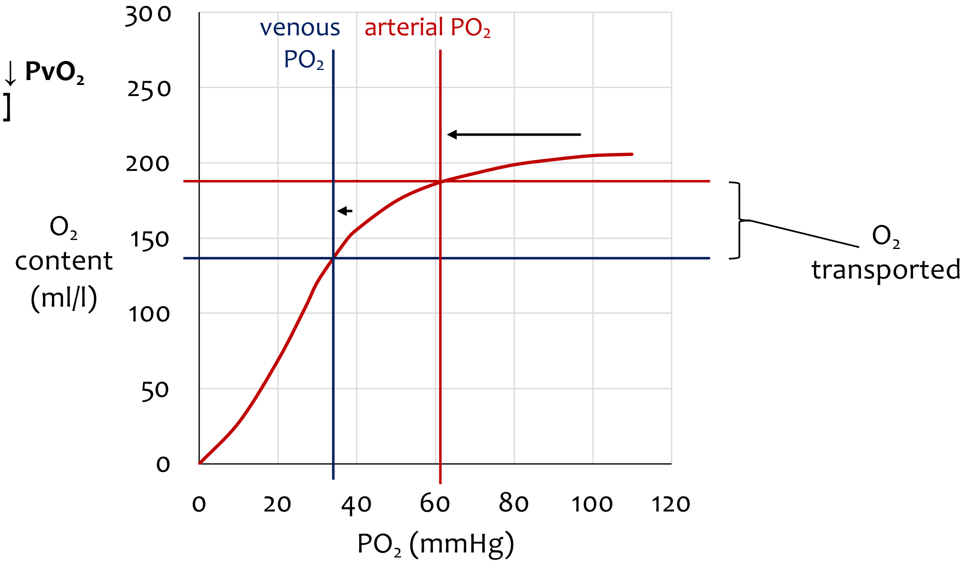
Types of hypoxia: hypoxic

↓↓ PaO_2 + ↓ PvO_2 = ΔA-V [O_2]



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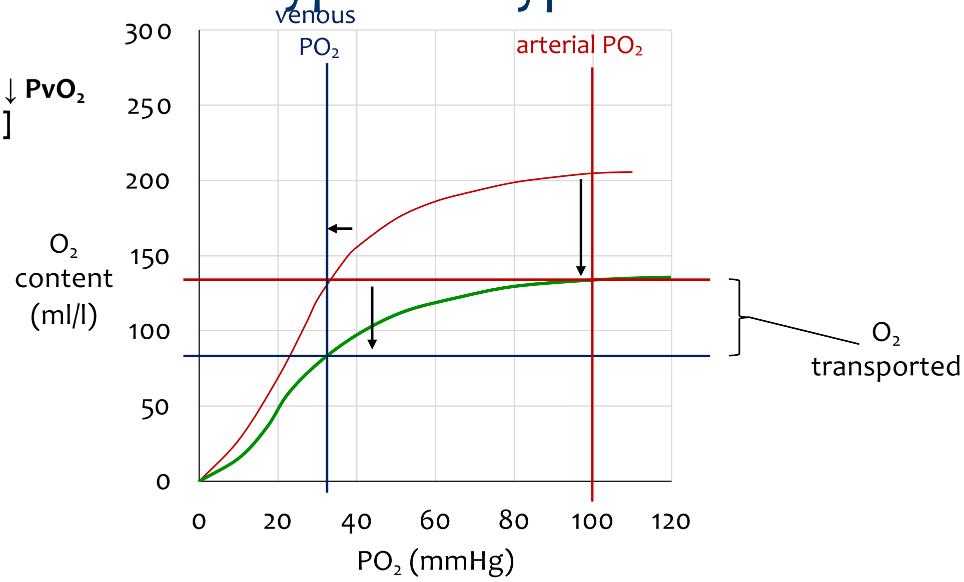
Types of hypoxia: anemic

= PaO_2 + ↓↓ PvO_2
= ΔA-V [O_2]



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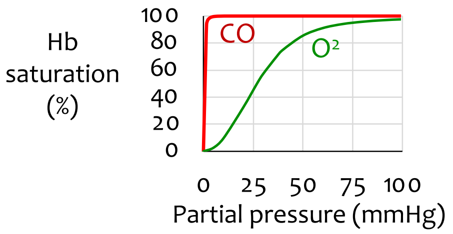
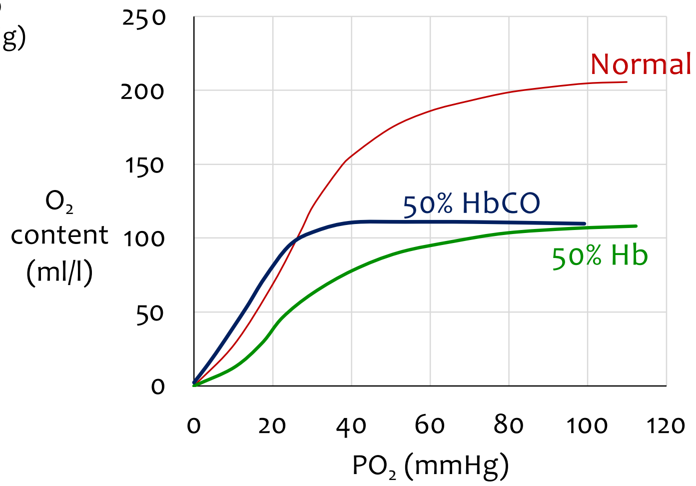
CO poisoning





CO binds to O_2's site

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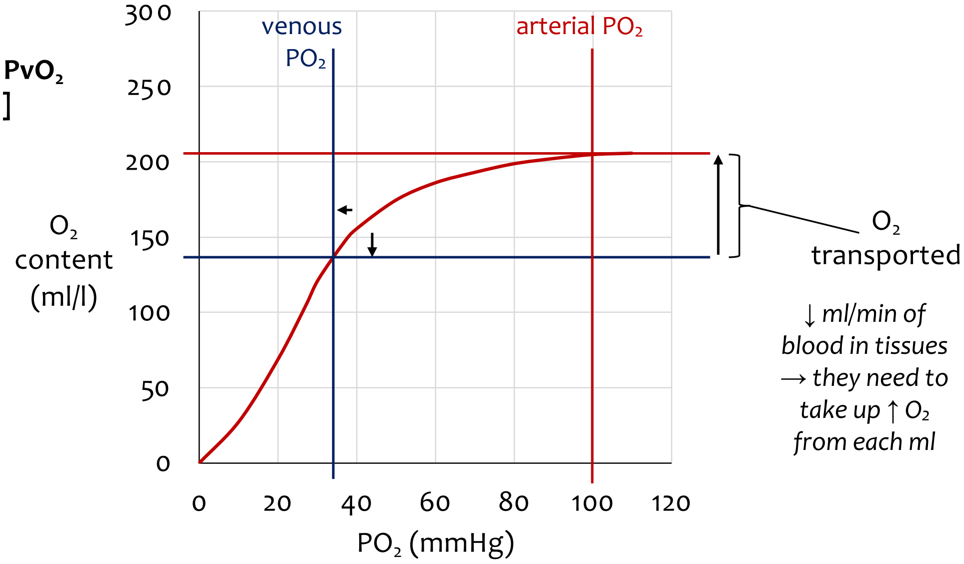
Types of hypoxia: ischemic (stagnant)

= PaO_2 + ↓ PvO_2
↑ ΔA-V [O_2]



↓ ml/min of blood in tissues → they need to take up ↑ O_2 from each ml

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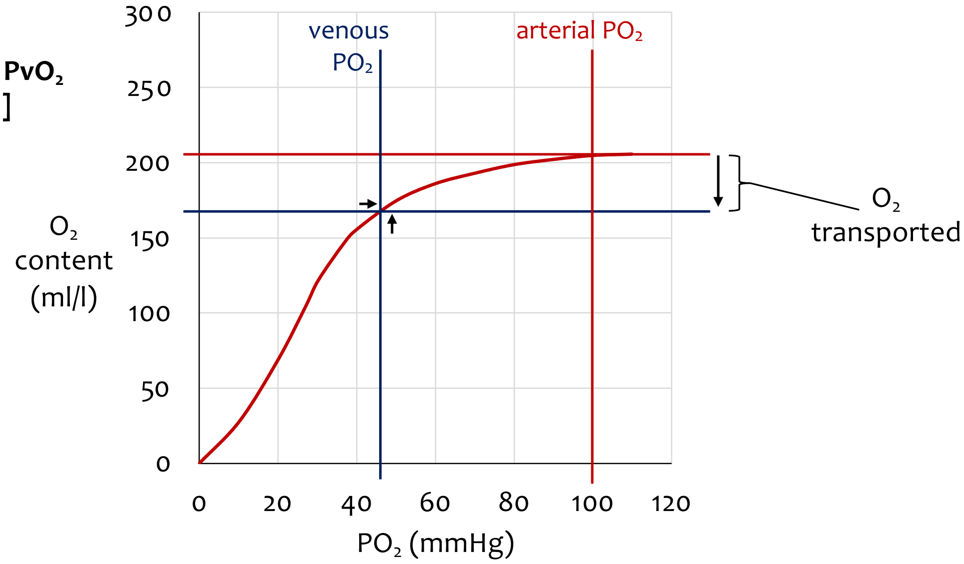
Types of hypoxia: histotoxic

= PaO_2 + ↑ PvO_2
↓ ΔA-V [O_2]



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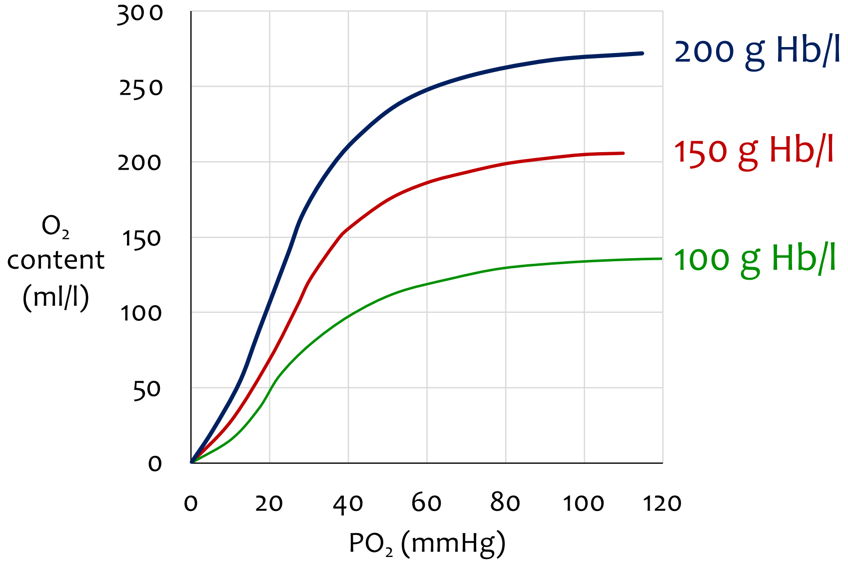
Compensation



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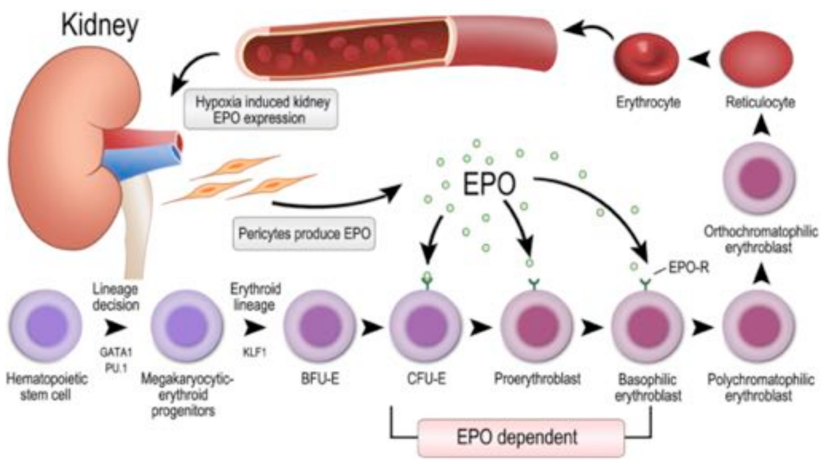
Erythropoietin controls RBC development



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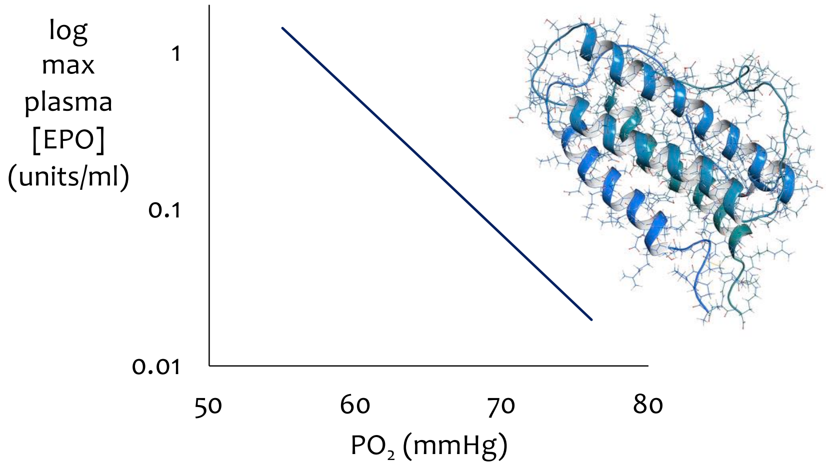
Erythropoietin release controlled by hypoxia



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Hypoxia-inducible factors (HIF 1-3)

Constitutively: HIFα HIFβ

Normoxia:

Hypoxia:

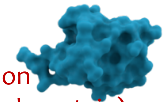
O_2-dependent

HIFα prolyl hydroxylases (PHD1-3)

hydroxylation (at conserved prolines)

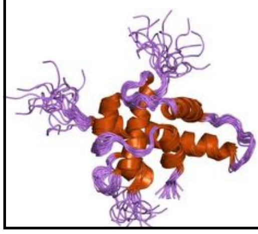
VHLE3 ubiquitin ligase

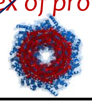
ubiquitination (ubiquitin=small regul. protein)



proteasome (complex of proteases)

rapid degradation





HIFαβ

↑ gene transcription (EPO, VEGF, glycolysis,...)

Originally (1995): HIF-1
2020 (kidney): HIF-2

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