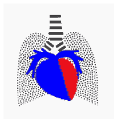
O_2 & CO_2 transport in the blood

vaclav.hampl@lf2.cuni.cz

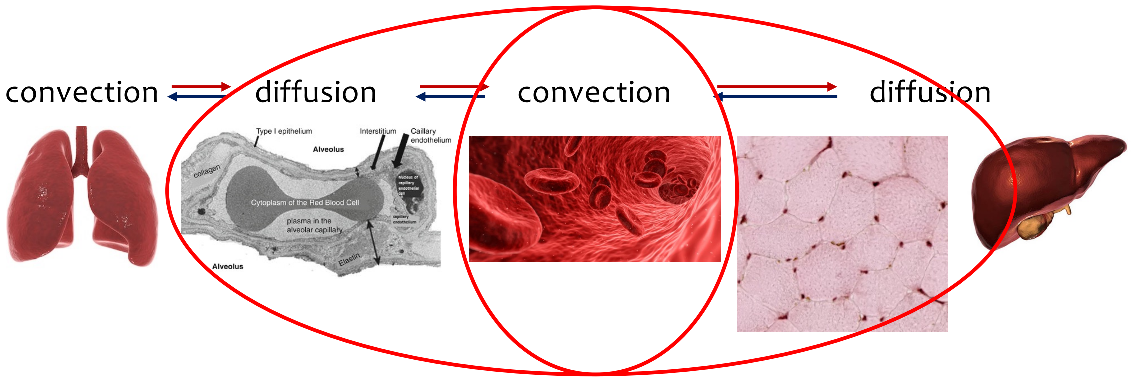
http://fyziologie.lf2.cuni.cz/en
http://vh.cuni.cz

CHARLES UNIVERSITY
Second Faculty of Medicine



1

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



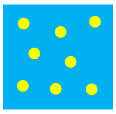
2

Diffusion in gases

Fick's first law (1855): $J = -\mathbf{D} / RT \times \mathbf{\Delta P} / \mathbf{\Delta x}$

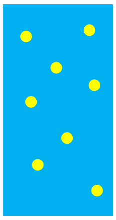
- liquids: Δ concentration ($C_2 - C_1$)
- gases: **compressibility**

8 mol / 1 L
@ P = 1



P = 1 → P = 1/2

(PxV=const.)



8 mol / 2 L
@ P = 1/2
i.e. 4 mol / L

Adolf Eugen Fick
1829-1901

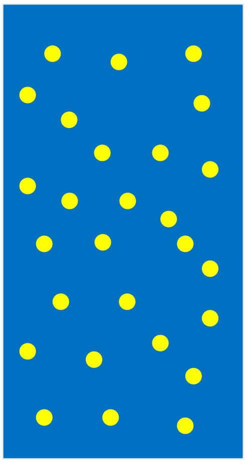
i.e. for gases, concentration without pressure info not very useful

→ hence partial pressure (C x P)

3

Concentration & partial pressure

O_2 molecules in air



Dry air: 21% is O_2

F_{O2} = 0.21

$[O_2]$ = 210 ml/l

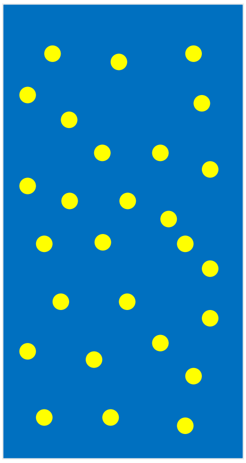
As P_B ~ 760 mmHg

P_{O2} = 0.21 x 760 mmHg
= 160 mmHg

4

Effect of water vapor

37°C

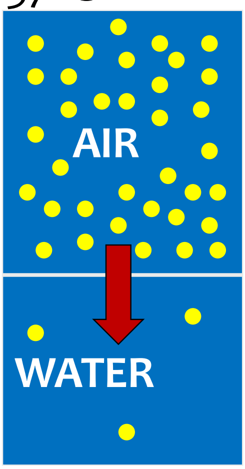


P_B ~ 760 mmHg
P_{H_2O} = 47 mmHg (at 37°C)
P_{DRY} = 713 mmHg
P_{O_2} = 0.21 x 713 mmHg
= 150 mmHg

5

O_2 in solution

37°C



37°C

After equilibration:
AIR: P_{O_2} = 150 mmHg
WATER: P_{O_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)

6

O_2 transport in solution during exercise

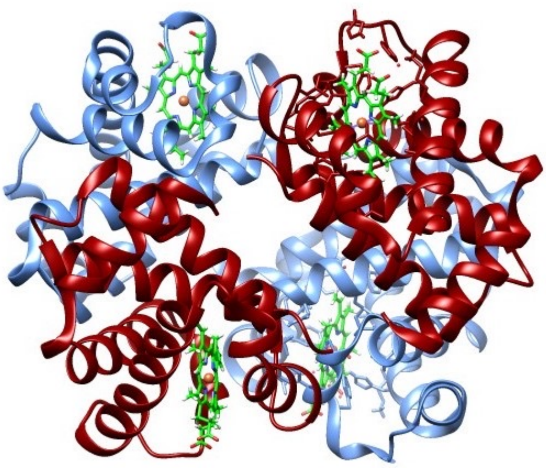
- solubility = 0.003 ml/(dl.mmHg)
- P_{O2} in arterial blood = 100 mmHg
- $[O_2]$ = 3 ml/l
- cardiac output = 30 l/min
- maximum O_2 available = 90 ml/min

But O_2 requirement is 3000 ml/min!

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

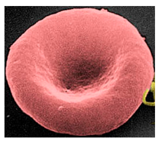
7

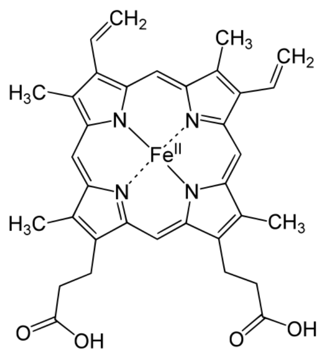
Hemoglobin (Hb)



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 porphyrine ring)

8

CO_2 transport in the blood

2 compartments:

- plasma
- RBC

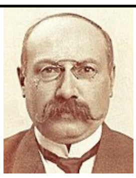
3 mechanisms:

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

plasma → dissolved: ~4%
RBC → dissolved: ~ 4%
plasma → HCO_3^-: ~5%
RBC → HCO_3^-: ~ 65%
plasma → carbamino: ~2%
RBC → carbamino: ~20% (Hb)

9

CO_2 transport as HCO_3^-



Hartog Jakob Hamburger (1859-1924)

CO_2

plasma

RBC

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

carboanhydrase

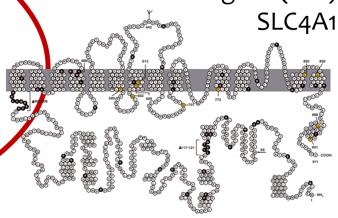
$HHb \leftrightarrow H^+ + Hb^-$

Cl^-

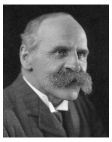
chloride shift

(Hamburger phenomenon)

solute carrier family 4 member 1
band 3 anion transport protein
anion exchanger 1 (AE1)
SLC4A1

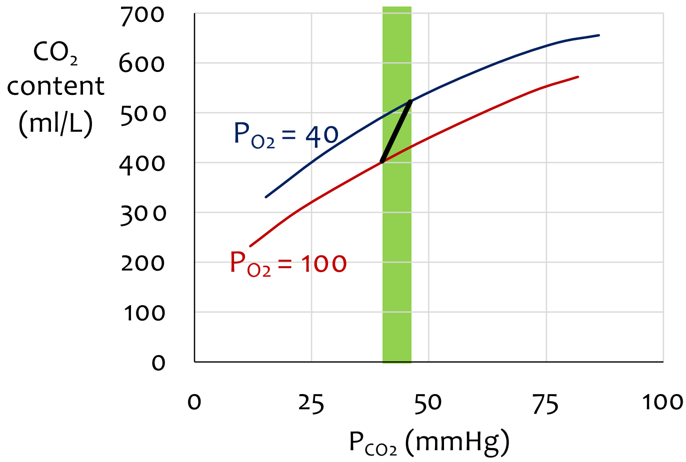


10



John Scott Haldane
(1860-1936)

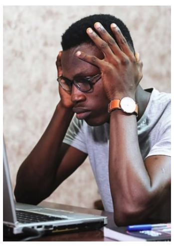
CO_2 transport as carbaminoHb: Haldane effect

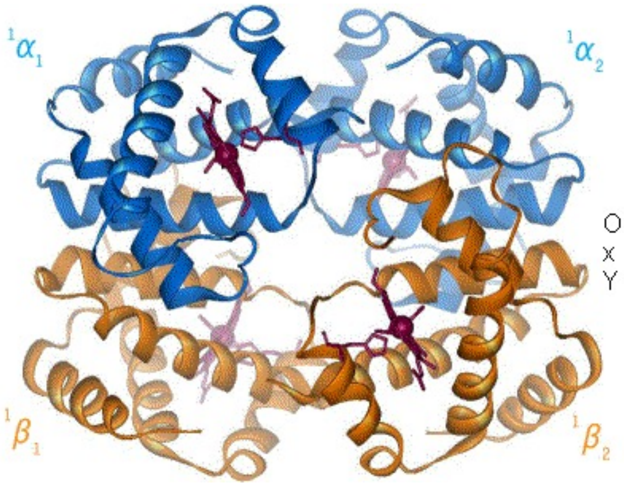


11

O_2 transport: 2 Hb conformation states

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

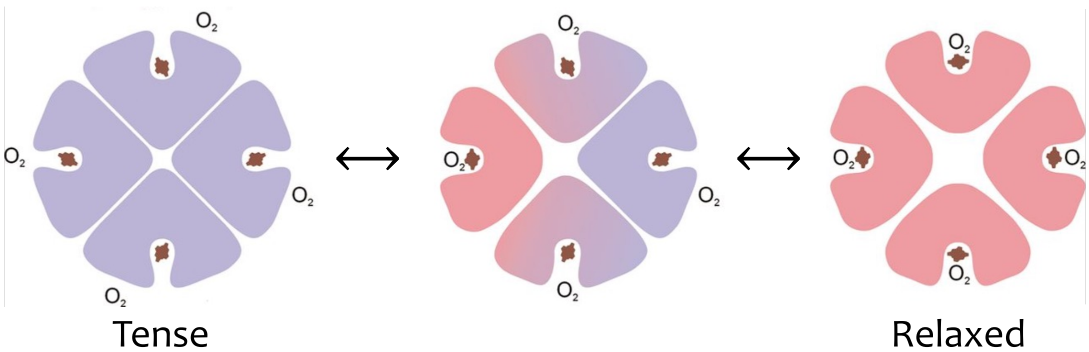




NH_3 groups protonation ⟶ + charge ⟶ ionic interactions with near COOH groups

12

T → R transition (Hb "breathing motions")

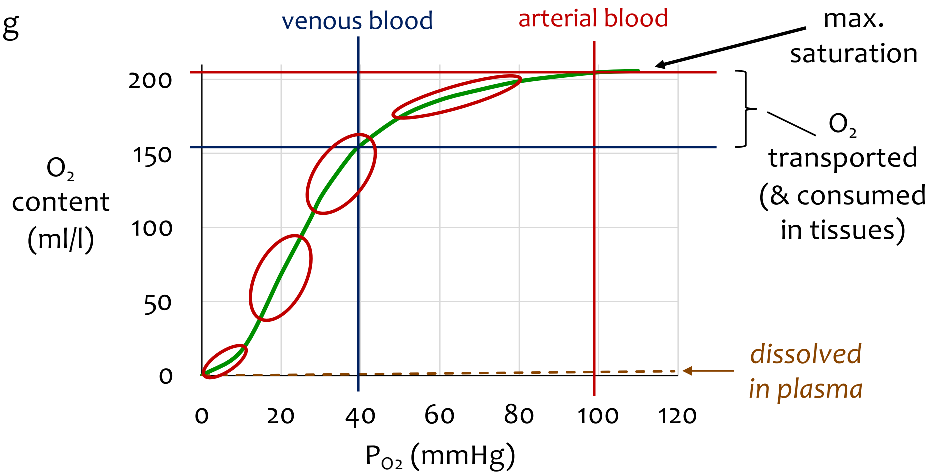


co-operative O_2 binding

13

O_2 transport in the blood: Hb-O_2 binding curve

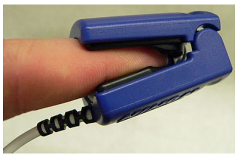
co-operative O_2 binding



14

Pulse oxymetry

16

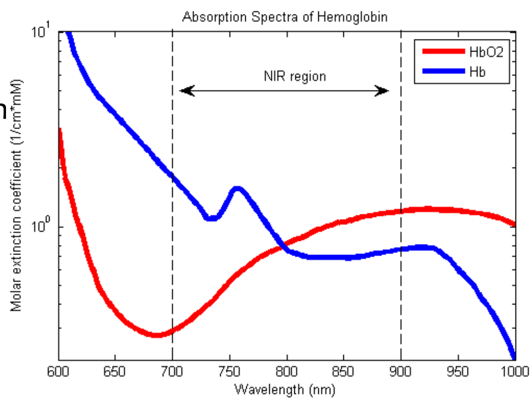


Pulse oxymetry (peripheral SO_2)

- safe, convenient, noninvasive, inexpensive, useful in ICU
- not always identical to arterial SaO_2
  - correlates pretty well
- 2 wavelengths of light through a thin body part to a photodetector
- measures the absorbance at each of the wavelengths
- pulsatile + non-pulsatile component
- ⇒ measures S_{O_2}, not $[O_2]$ nor P_{O_2}

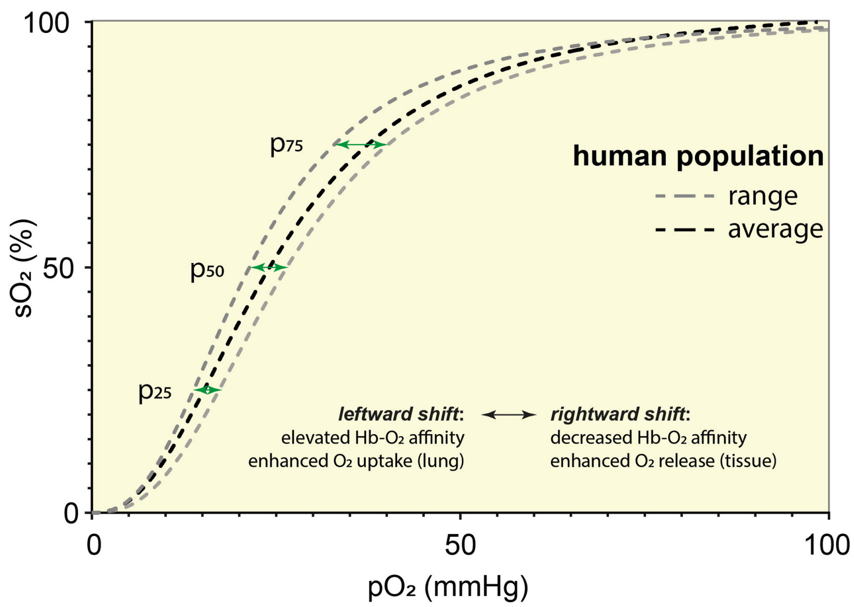
  < 93% → !

  < 90% → !!!



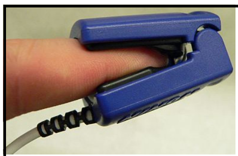
17

ODC

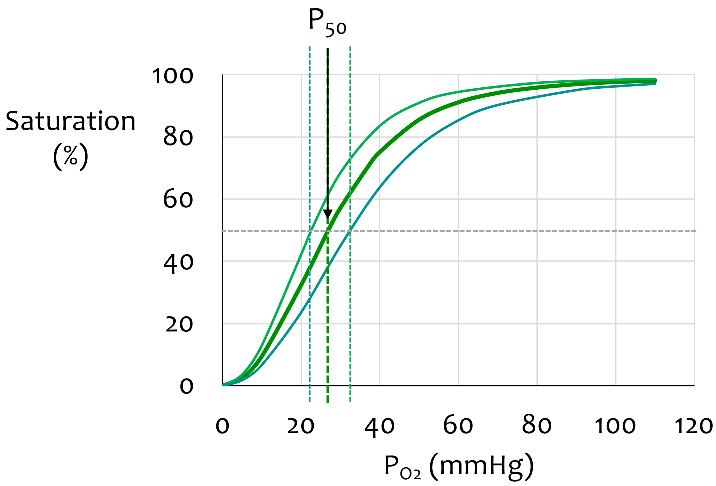


Kulow & Fähling: Acta Physiol 2021

18



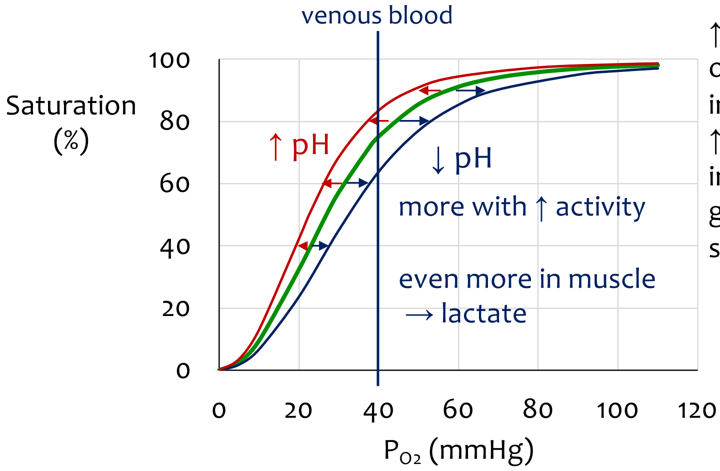
O_2 transport in the blood: Hb-O_2 binding curve



19

Christian Bohr
1904

H^+ → ↓ Hb-O_2 affinity: <u>Bohr effect</u>

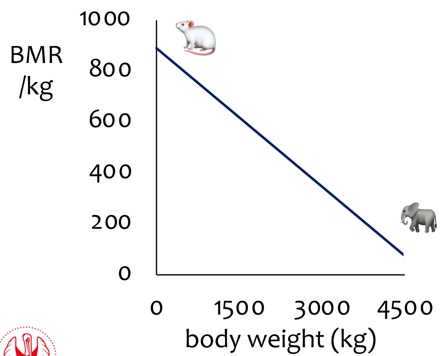


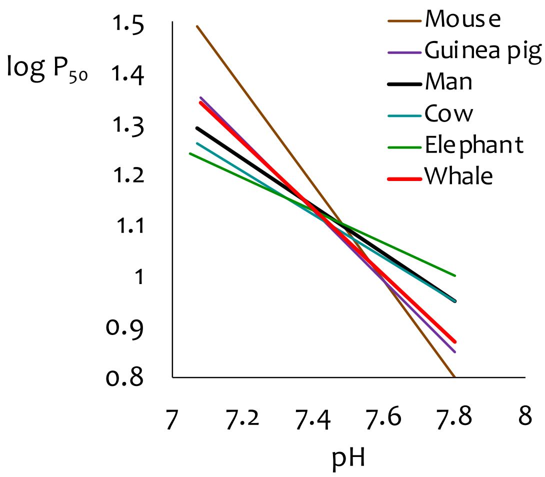
↑ H^+ → ↑ protonation of α & β chains in T state →
↑ + charge → ↑ ionic interactions w/ COOH groups nearby → stabilization of T state

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

20

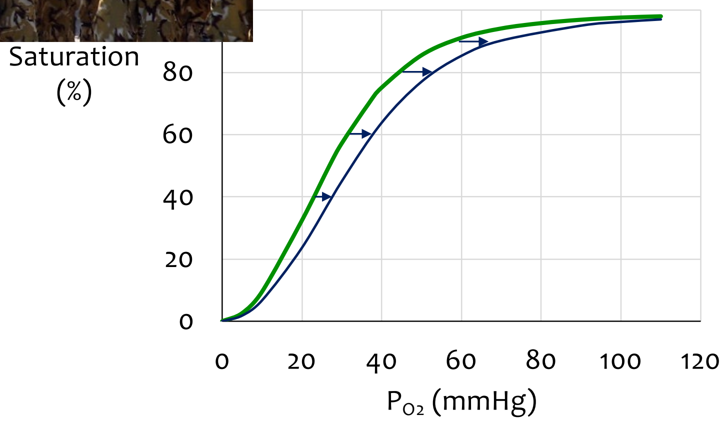
Bohr effect stronger in smaller mammals





21

CADETs – look right!

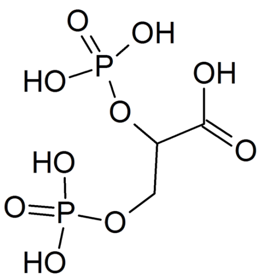


CO_2
Acidity
DPG (2,3-BPG)
Exercise
Temperature

supported by Cl^- shift: ↑[Cl^-] ⟶ ↑P50

22

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

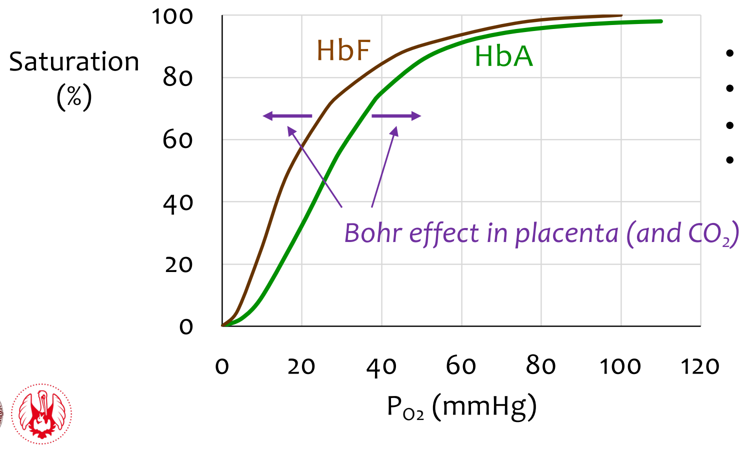


- intermediate of glycolysis in RBC (~ 5 mM)
- rapidly consumed at normal P_{O_2}, accumulates at ↓P_{O_2}
- binds preferentially to β chains
- at ~9 Å, it fits in the deoxyHb form (11 Å pocket), not in the oxyHb form (5 Å)

24

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

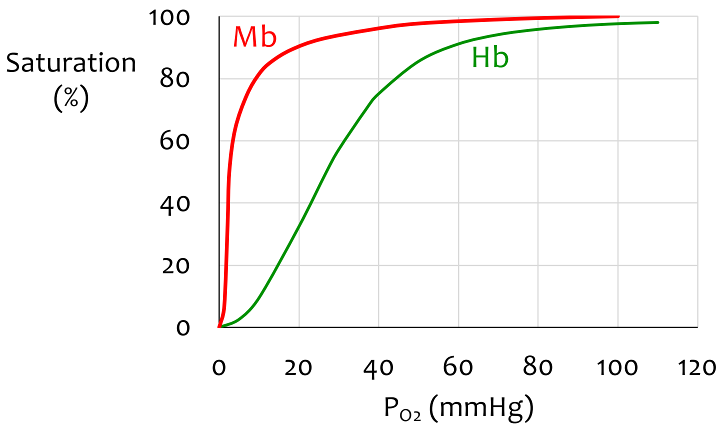


- from wk 6: embryonic Hb (incl. F)
- F dominates from 3[rd] mo
- A from wk 40
- at * 50-95% F
- A dominates from 6[th] mo

25

Myoglobin (Mb)

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



26

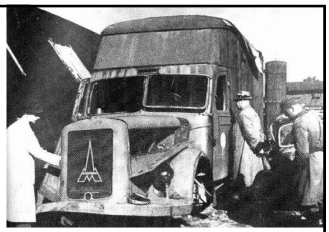
Dyshemoglobinemia

Hb forms that cannot transport O2: O_2:

1) **Competition with O_2 for Fe**: carboxy-Hb (carbonyl-Hb; CO-Hb)
   - Fe affinity for CO ~240x higher than for O_2
2) **Oxidation Fe^{2+}** → Fe^{3+} : metHb
3) **Non-competitive blockade** of O_2 binding to Fe: sulf-Hb
   (S irreversibly binds the pyrrole nucleus of heme, interferes with O_2 binding) - H2S, sulfonamides, sumatriptan,...
4) **Hemoglobinopathies** - globin mutations affect O_2 binding (very rare; they mostly affect RBC viability and properties - thalassemia, sickle cell anemia) - ↑P_{50} (Chesapeake) nebo ↓P_{50} (Beth Israel)

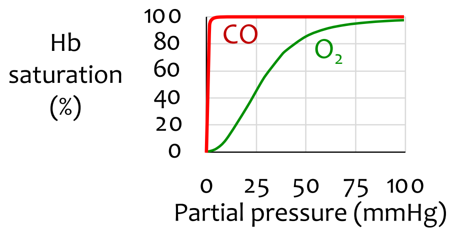
27

CO-Hb (CO poisoning)

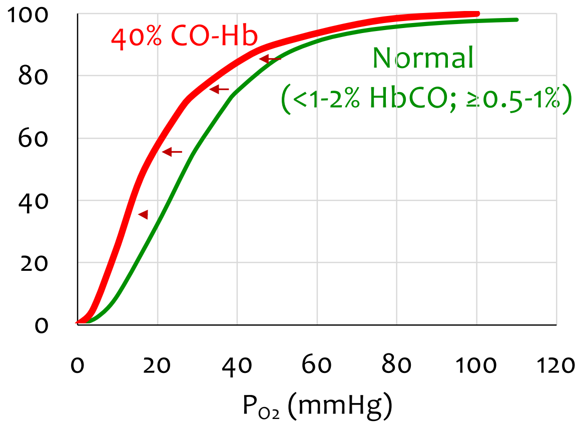


- fires, exhaust fumes, smoking, pollution, heating, volcanoes, ...
- endogenous - heme metabolism (mostly Hb): heme → biliverdin + Fe + CO (heme oxygenase)
- normally 0.5-2% of total Hb is CO-Hb (city ≤5%)
- smoking ≤10– max 15%, newborns ≤12%
- ≤2.5% OK, >15% problem, >30% life threatening
- 85% of CO bound to Hb (most abundant), the rest Mb, CytC oxidase (inhibition), NADPH reductase
- CO-Hb half-life normally ~5 hrs (~80-90 min at 100% O_2)

28



CO-Hb (CO poisoning)

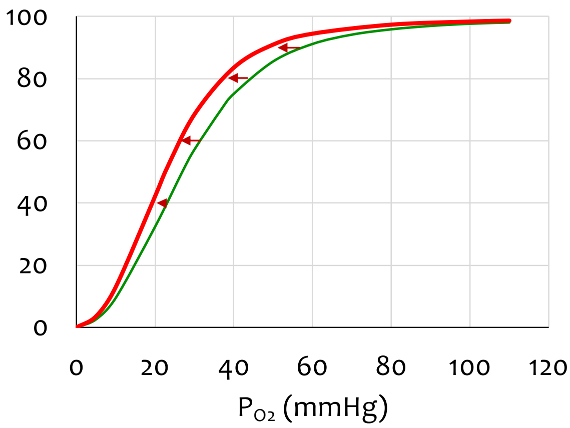


- 240x higher affinity to heme Fe
- + greater effect on cooperativity (when P_{O2} decreases, CO-Hb releases O_2 less readily- shift to L)
- prevents carbaminoHb formation → acidosis

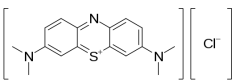
29

Methemoglobinemia

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



Therapy:
metylene blue
Fe^{3+} → Fe^{2+}



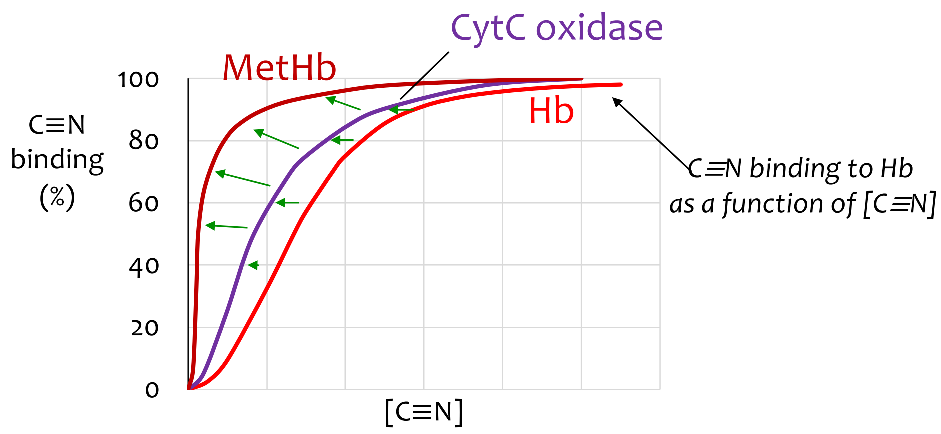
- normally 1-2%
- smokers more
- >5-7% hazard

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

31

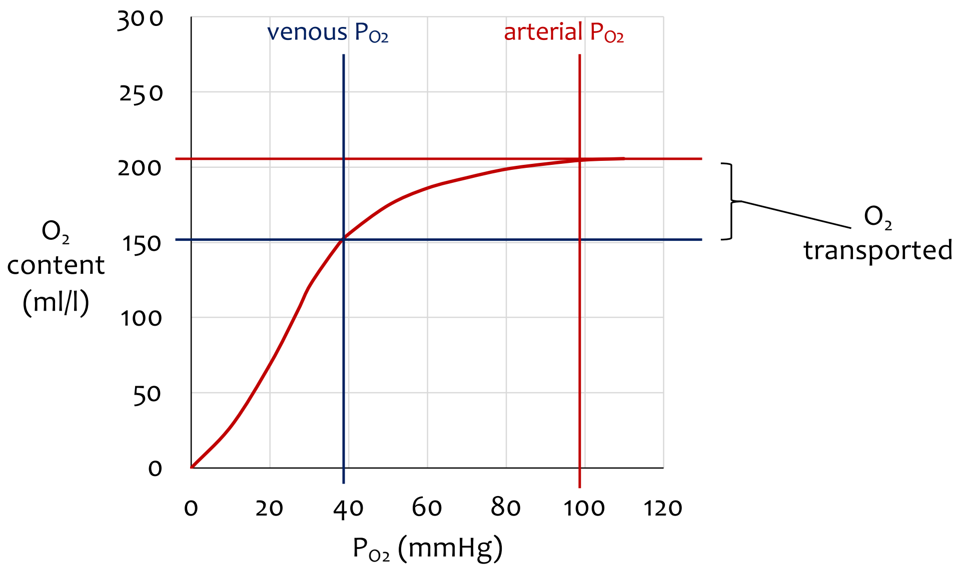
When is methemoglobinemia good?

Cyanide poisoning



32

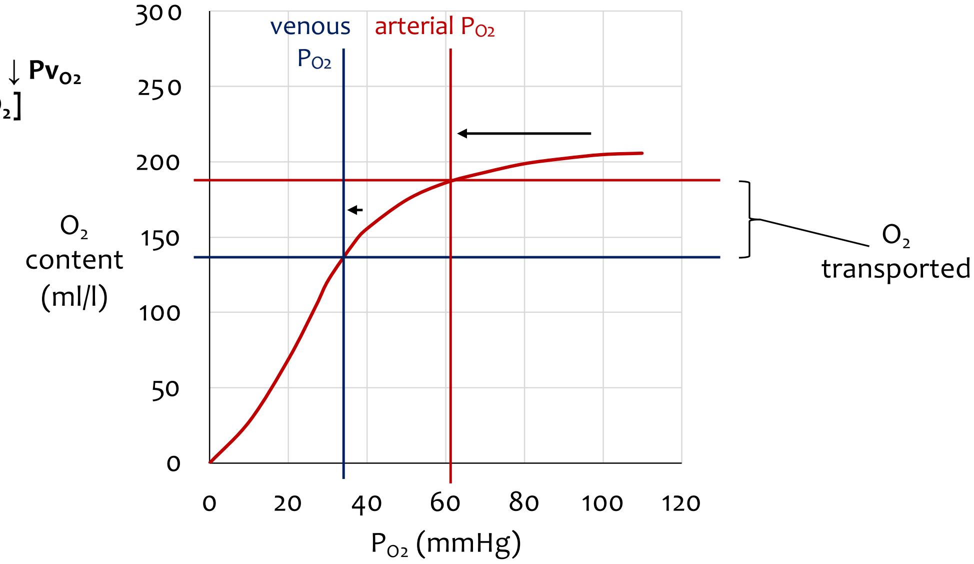
Types of hypoxia



33

Types of hypoxia: hypoxic

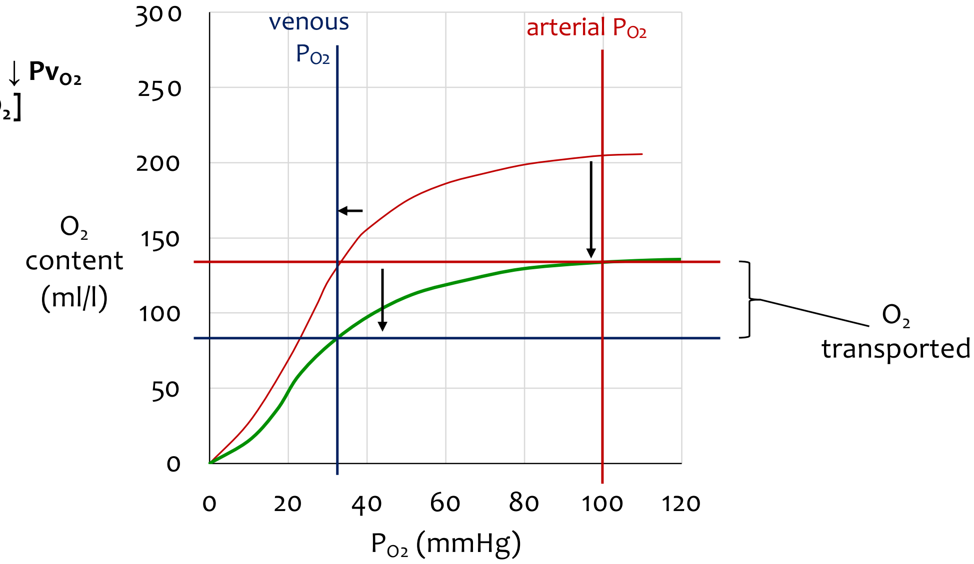
↓↓ Pa_{O_2} + ↓ Pv_{O_2}
= ΔA-V [O_2]



34

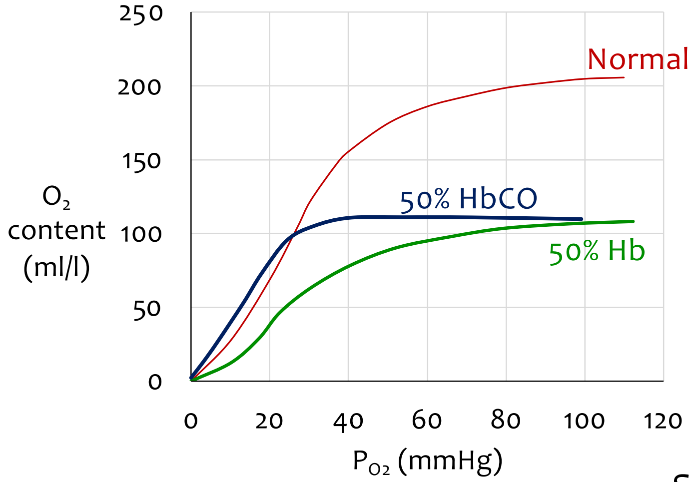
Types of hypoxia: anemic

= Pa_{O_2} + ↓↓ Pv_{O_2}
= ΔA-V [O_2]



35

CO poisoning



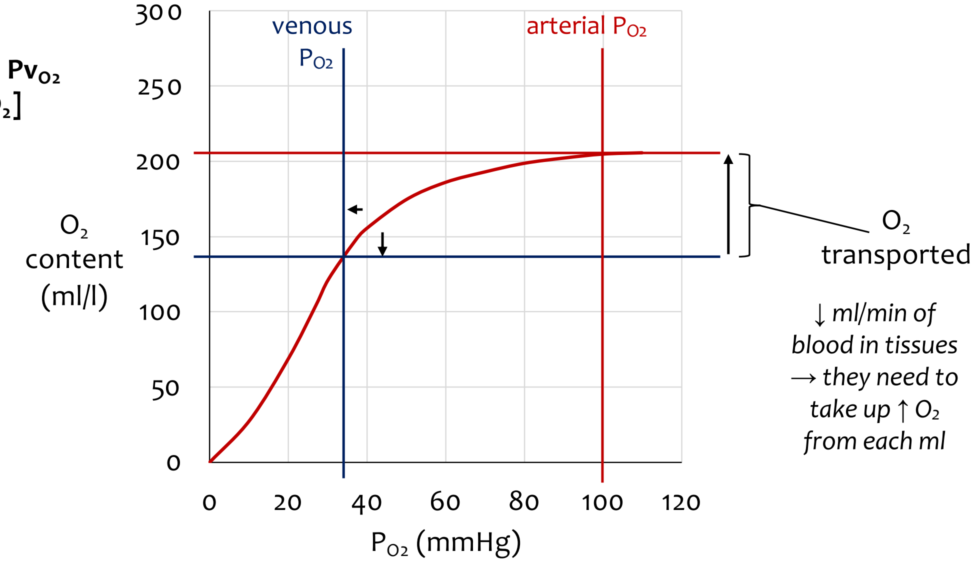
Similarly metHb

36

Types of hypoxia: ischemic (stagnant)

= Pa_{O_2} + ↓ Pv_{O_2}

↑ ΔA-V [O_2]

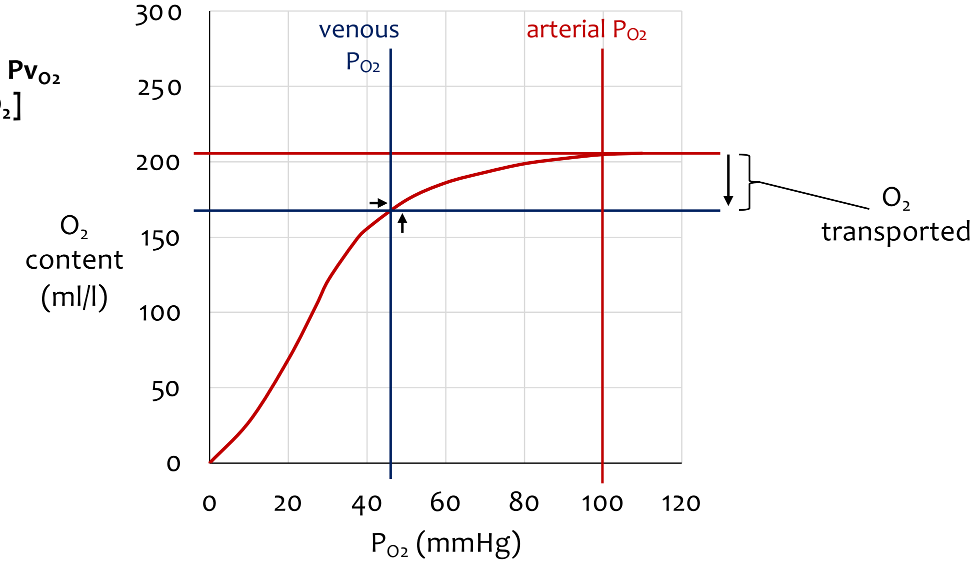


↓ ml/min of blood in tissues → they need to take up ↑ O_2 from each ml

37

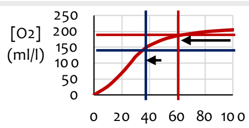
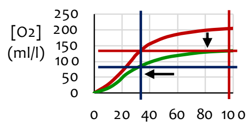
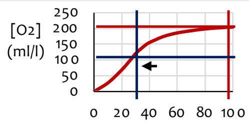
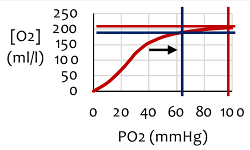
Types of hypoxia: histotoxic

= Pa_{O_2} + ↑ Pv_{O_2}
↓ ΔA-V [O_2]



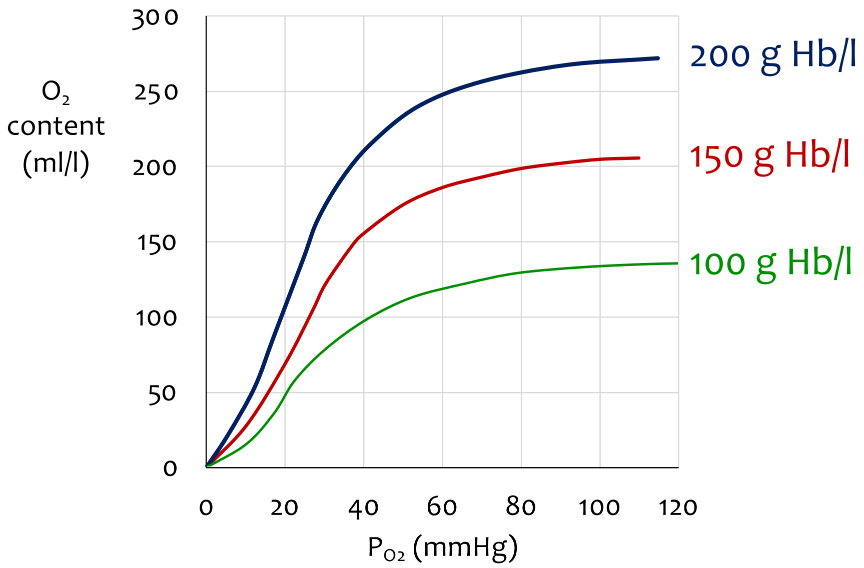
38

4 types of hypoxia

	Pa_{O_2}	ΔA-V [O_2]	Pv_{O_2}	
hypoxic	↓↓	=	↓	
anemic	=	=	↓↓	
ischemic	=	↑	↓	
histotoxic	=	↓	↑	

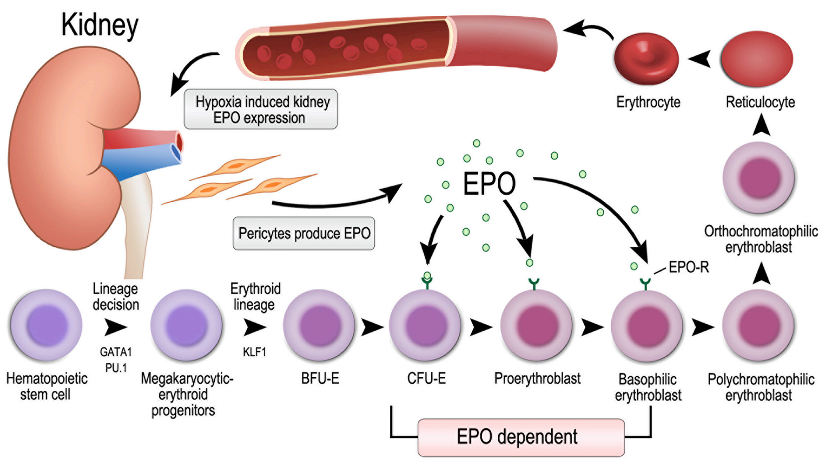
39

Compensation



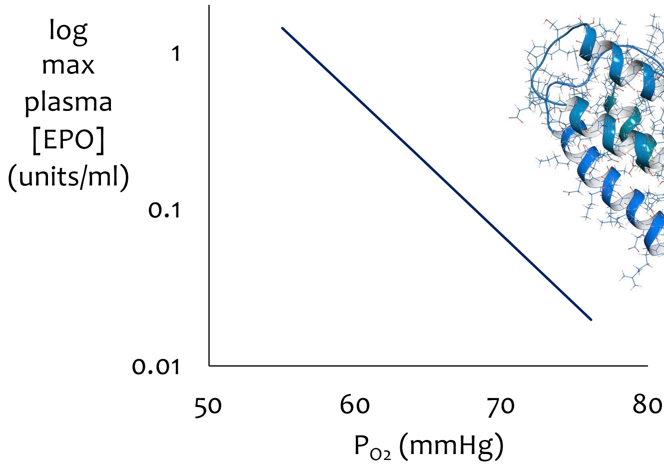
40

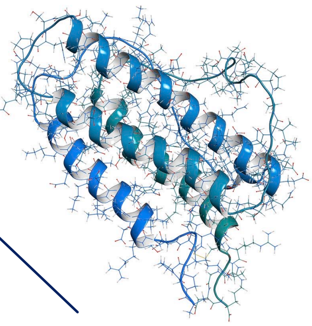
Erythropoietin controls RBC development



41

Erythropoietin release controlled by hypoxia





42

Hypoxia-inducible factors (HIF 1-3)

Constitutively: HIFα HIFβ

Normoxia:

Hypoxia:

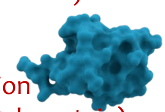
O_2-dependent

HIFα prolyl hydroxylases (PHD1-3)

hydroxylation (at conserved prolines)

VHLE3 ubiquitin ligase

ubiquitination (ubiquitin=small regul. protein)

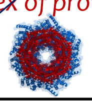


proteasome (complex of proteases)

rapid degradation

HIFαβ

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



Originally (1991): HIF-1
2020 (kidney): HIF-2

43

44