Academic lectures for students of medical schools – 3rd Year updated 2004 - 2015

GENERAL PATHOPHYSIOLOGY

Hypoxia

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Definitions, terms

- **Hypoxia** = fall of oxygen in tissues that compromise aerobic metabolism to metabolic needs leading to anaerobic switch, triggering local and systemic compensations or adaptations (small variations in tissue & arterial oxygen concentrations can be part of the normal physiology)

!! Direct tissue measurement of O_2 is rare (tissue needle oxymetry, cutaneous probes in neonates). Capillary oxyhemoglobin saturation together with pulse rate is provided by oximeters (finger, ear); Deeper tissue oxygenation can be estimated through NIRS, near-infrared spectroscopy.

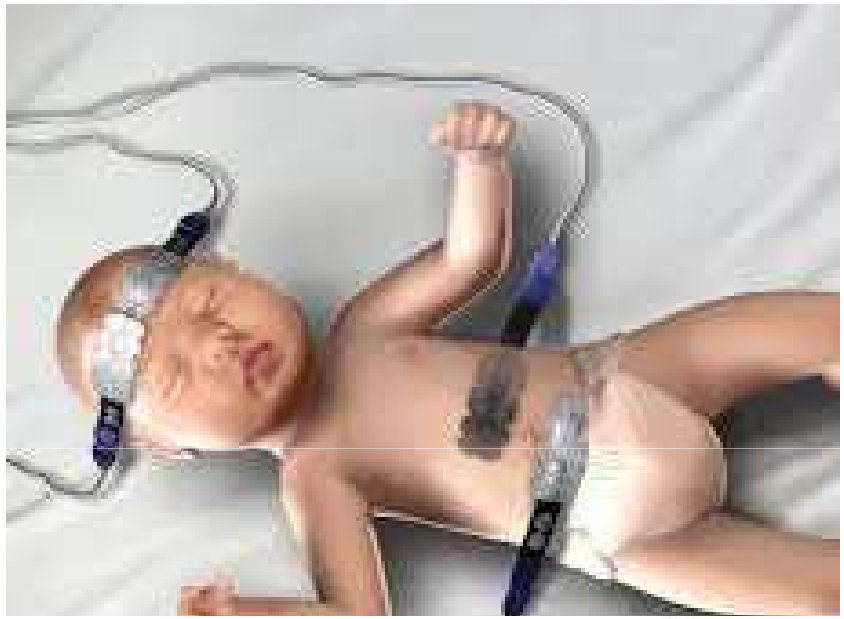
- **Focal (local) hypoxia** = restricted to an organ, tissue, body part; in within one organ it denotes sekective area (e.g; focal brain hypoxia),
- **Global (generalized) hypoxia** = effect is overall, unselective, unrestricted (e.g. global brain hypoxia);

! Distinct focal\global effects can be seen in ischemic hypoxia = **ischemia**

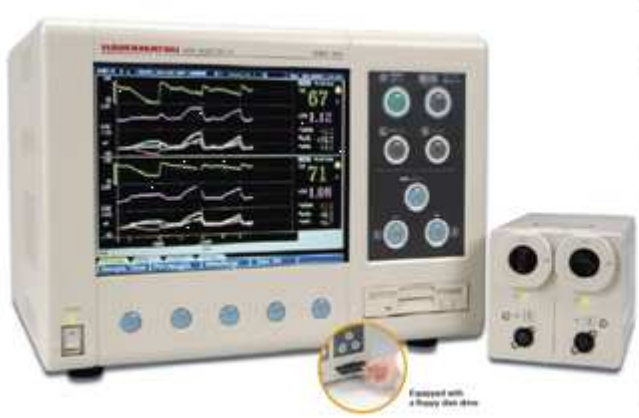
- **Anoxia** = lack of oxygen (refers rather exterior gas breathing conditions; in within the body or tissues total lakof O2 is rare)
- **Hypoxemia** = lack of O_2 in blood (arterial); hypoxia may occur w/o hypoxemia

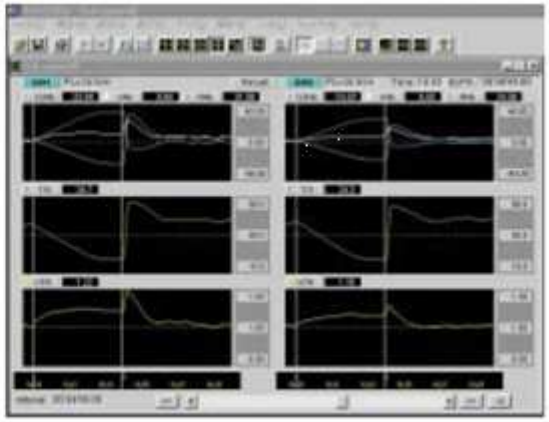
Regional deep – tissue oximetry

INVOS® Cerebral/Somatic Oximeter



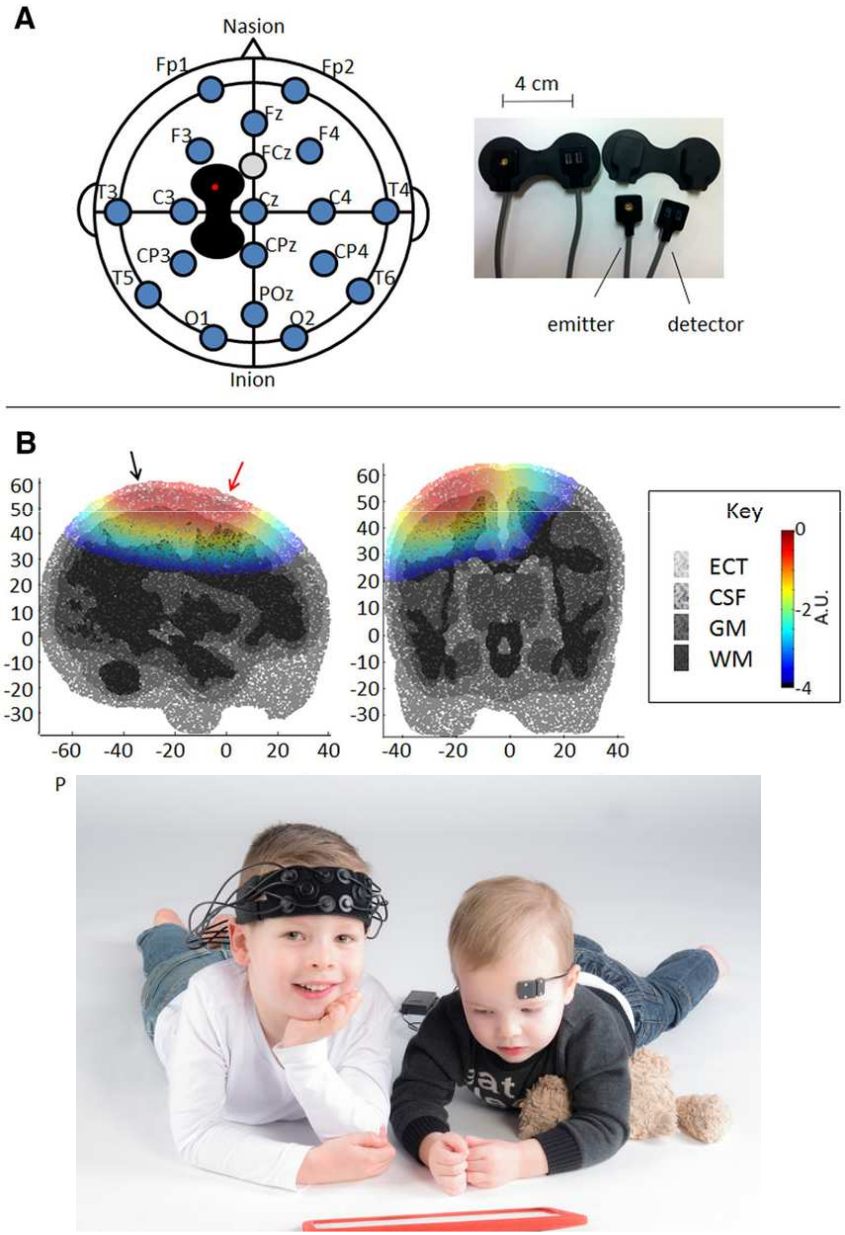
Masimo O3 Regional Cerebral Oxim

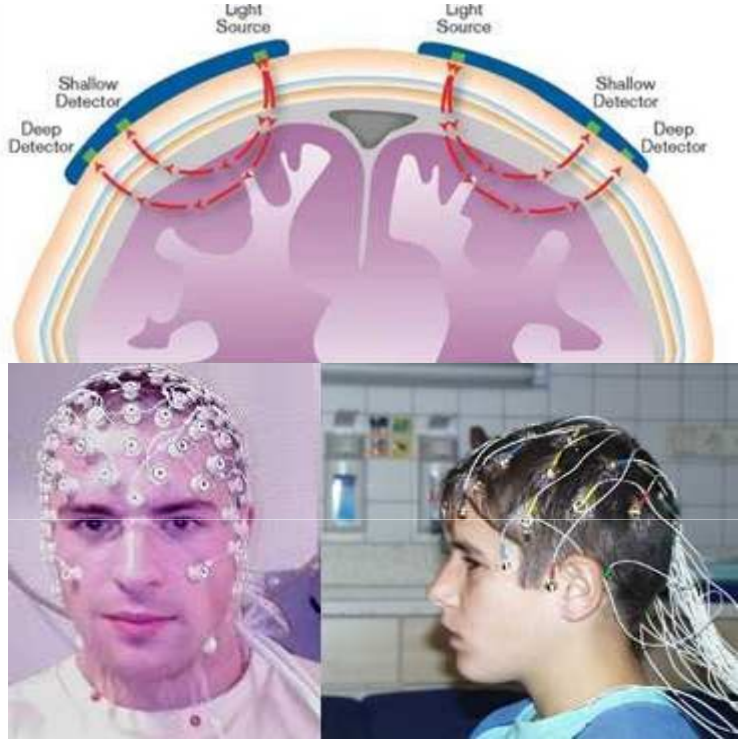




Hamamatsu NIRO monitor (NIRO-200)

Funcional fNIRS + quantitative EEG (qEEG) + (fNRM) in monitoring of cognitive processing





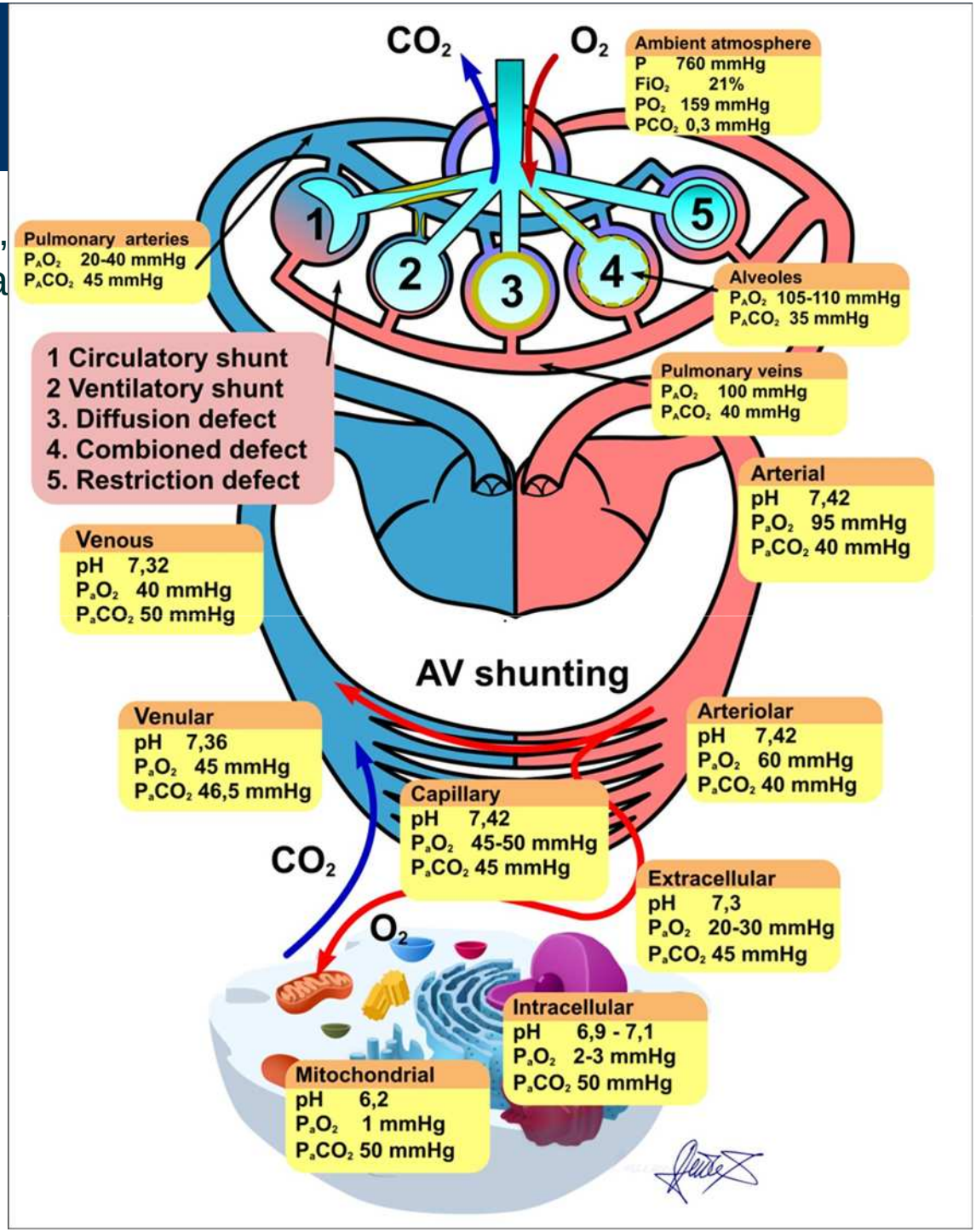
- NIRS measuring level of oxygenatiion in various brain structures indicates the intensity of metabolism and indirectly areas involved in specific tasks.
- aEEG or qEEG mapping may help in combination of data

Partial oxygen levels

- P_{atm} (sea level) = 760 mmHg (torr), 101,325 kPa = 1 atm = 1.01325 ba =14.696 ps
- $P_{atm}O_2$ = 20,93%= 159 mmHg ambient air O_2 pressure differ
- P_AO_2 = 105-112 mmHg (alveolar) lowered by partial pressure of water vapours at 37ºC (- 47 mm Hg) is the water vapor]) and CO2

P_aO_2 = 95 -100 mmHg (arterial) part of O_2 diffuses through vessels

- P_kO_2 = 50-60 mmHg (capillary) mixtured blood O_2
- $P_{exc}O_2$ = 30-40 mmHg (interstitial)
- $P_{inc}O_2$ = 10 mmHg (intracell.)
- $P_{mit}O_2$ = 3 mmHg (mitochon.)
- $P_{vn}O_2$ = 45-50 mmHg (venular)
- P_vO_2 = 38-43 mmHg (venous)



Physiological principles

1. O_2 diffuses into the red blood cell

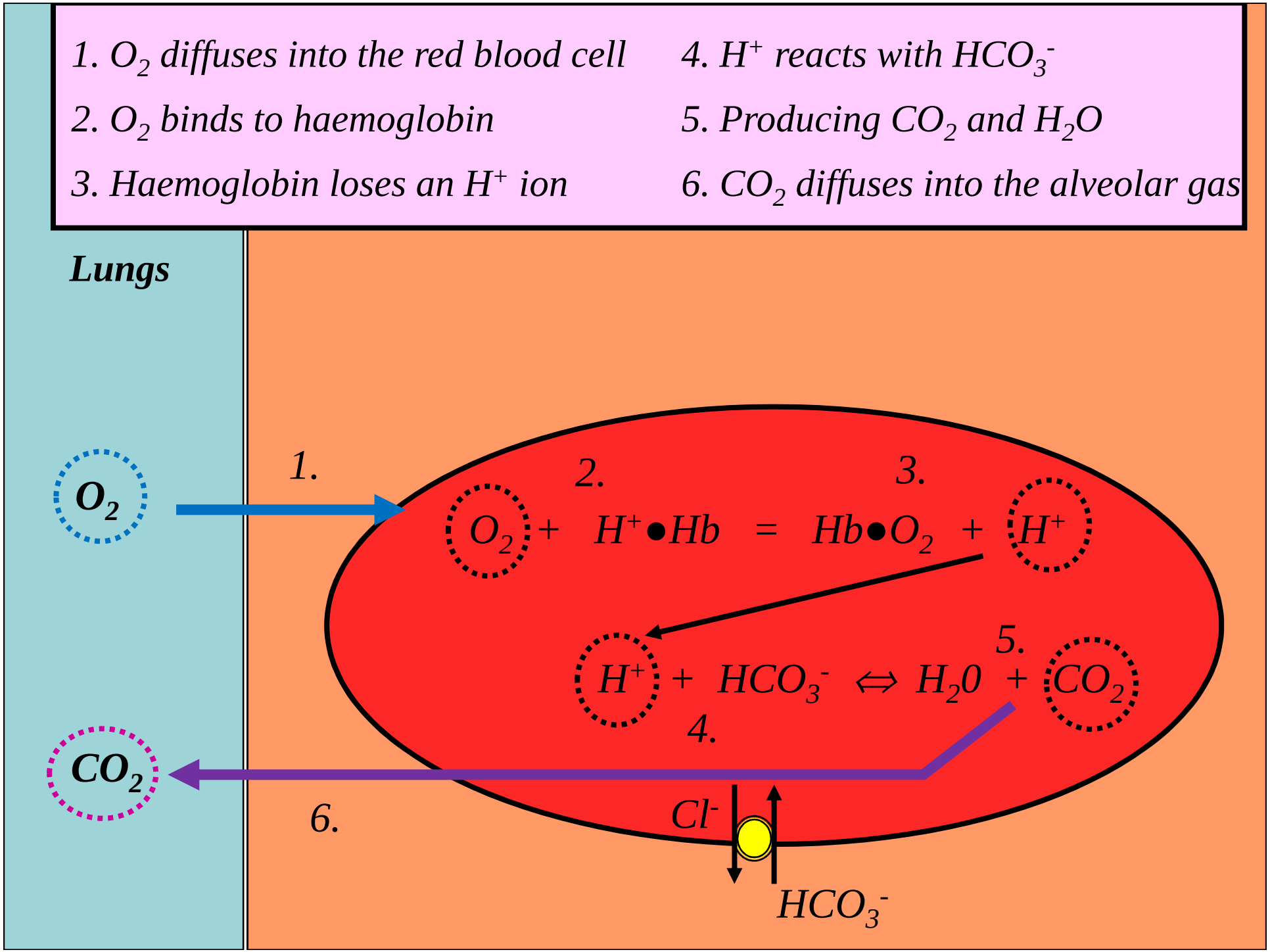
2. O_2 binds to haemoglobin

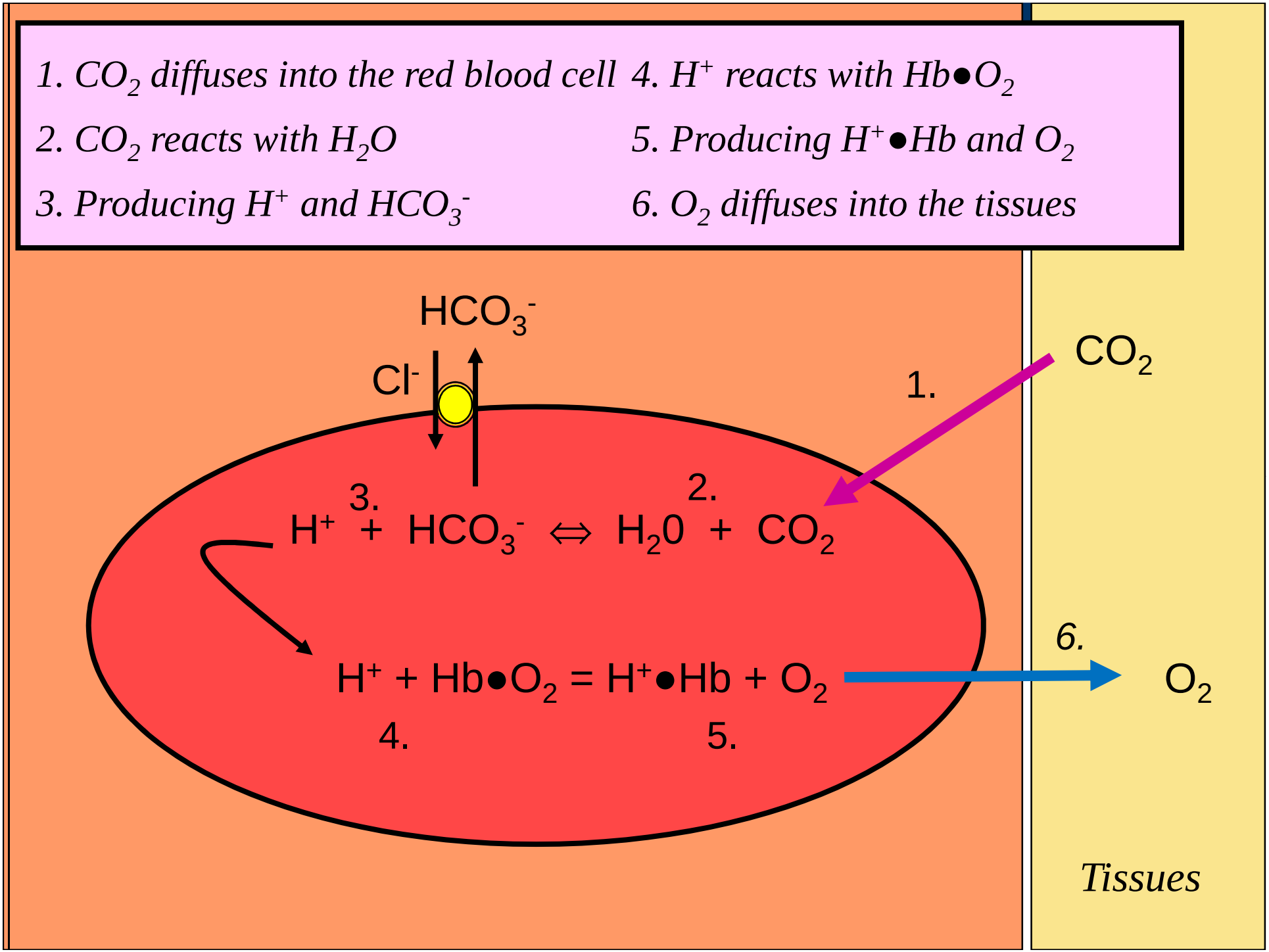
3. Haemoglobin loses an H^+ ion

4. H^+ reacts with HCO_3^-

5. Producing CO_2 and H_2O

6. CO_2 diffuses into the alveolar gas




1. CO_2 diffuses into the red blood cell
2. CO_2 reacts with H_2O
3. Producing H^+ and HCO_3^-
4. H^+ reacts with $Hb\bullet O_2$
5. Producing $H^+\bullet Hb$ and O_2
6. O_2 diffuses into the tissues
HCO_3^-
Cl^-
CO_2
1.
3.
2.
$H^+ + HCO_3^- \Leftrightarrow H_20 + CO_2$
$H^+ + Hb\bullet O_2 = H^+\bullet Hb + O_2$
4.
5.
6.
O_2
Tissues

Types of hypoxia

Hypoxic hypoxia

low oxygen intake into blood (from outside to alveoli)

Stagnation hypoxia

blood return to the lungs

Hemic hypoxia

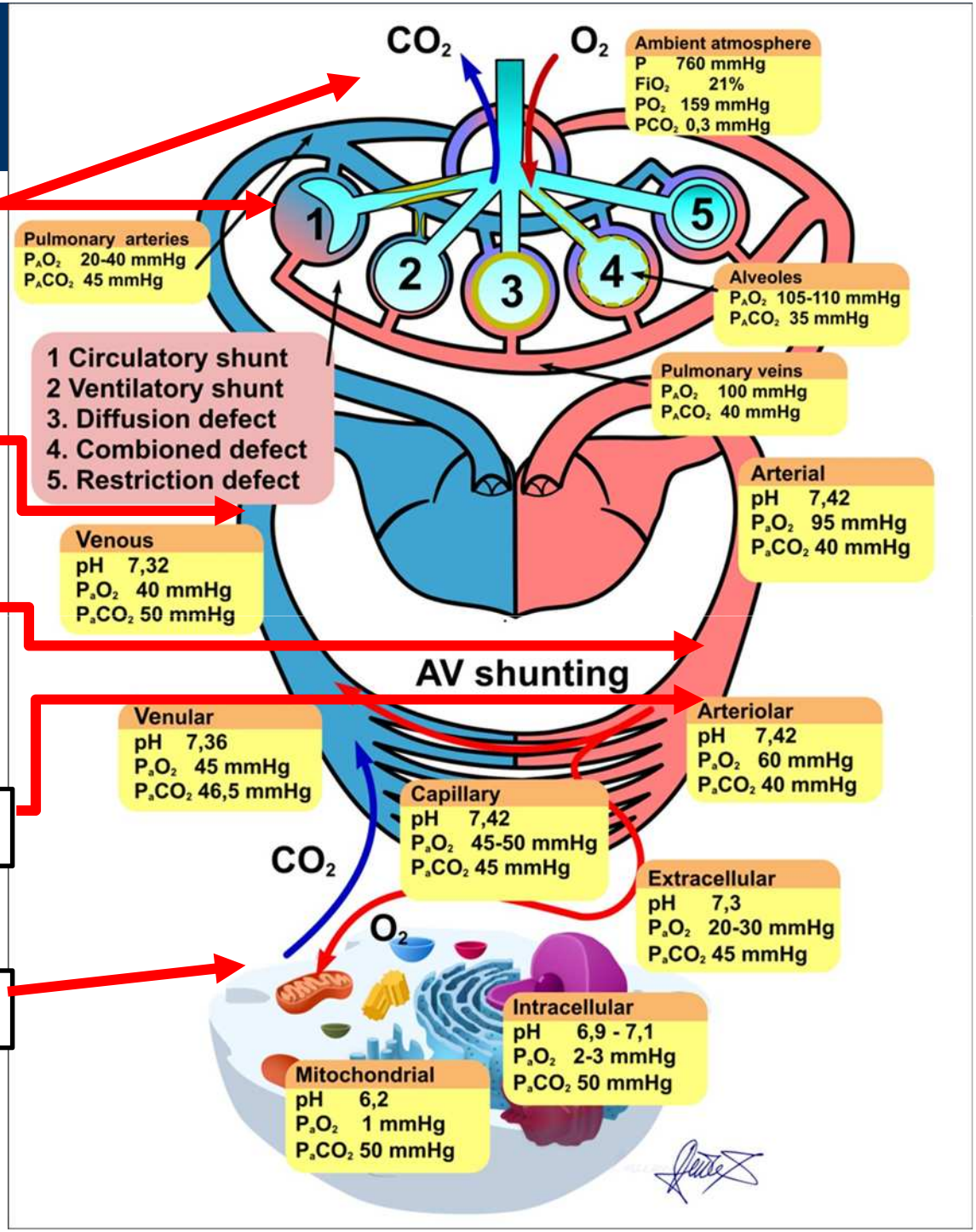
blood carying capacity for oxygen

Ischemic hypoxia

blood supply into tissues

Histotoxic hypoxia

tissue utilisation of oxygen



Differential diagnostics of hypoxia

TYPE OF HYPOXIA	$[O_2]_a$ (vol %)	$[O_2]_v$ (vol %)	C.O. (l/min)	$\dot{V}O_2$ (ml/min)
Normoxia	20	15	5	250
Stagnant	Normal	↓	⇊	Normal
Hypoxic	⇊	↓	↑	Normal
Anemic	⇊	↓	Normal or ↑	Normal
Histotoxic	Normal	↑	Normal	⇊

FiO2 %	Symptoms of ambient hypoxic hypoxia
16-21 %	little changes
13-16%	Tachypnoea, hyperpnoea, tachycardia, euphoria, headache
10-13 %	Altered judgement, confusion, muscular fatigue
6-10 %	Nausea, vomiting, lethargy, air hunger, severe incoordination
< 6 %	Gasping, seisures, stupor, coma, death

TYPES OF HYPOXIA – HYPOXIC HYPOXiA

Def.: low arterial pO2 when oxygen carrying capacity of blood and rate of blood flow to tissues are normal or elevated;

Characteristics: **1. ⇩ arterial pO_2 (PaO_2) , 2. ⇩ arterial O_2 content**
3. ⇩arterial % O_2 ⇩ S_aO2 4. ⇩ arterio-venous pO2 difference (P_{a-v} O_2)

Etio:

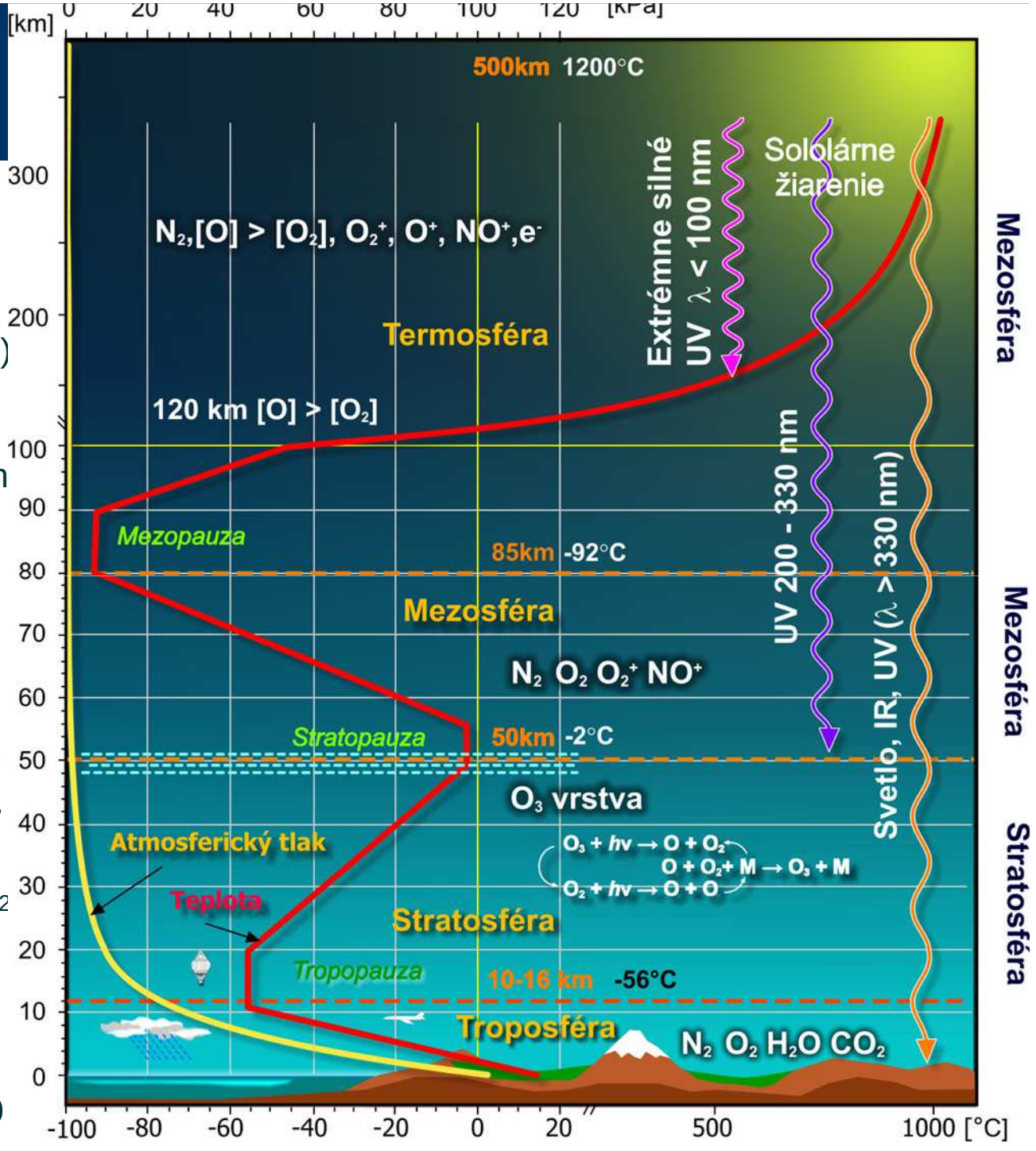
- **External-** low pO2 in a breathing gas (air or artefitial gas mixtures)
  - Mountaining - high altitude, acute decompression (planes, etc.), diving with closed-circuit rebreather systems,
  - preterm birth in neonates - suffocation in birth channel

Path:

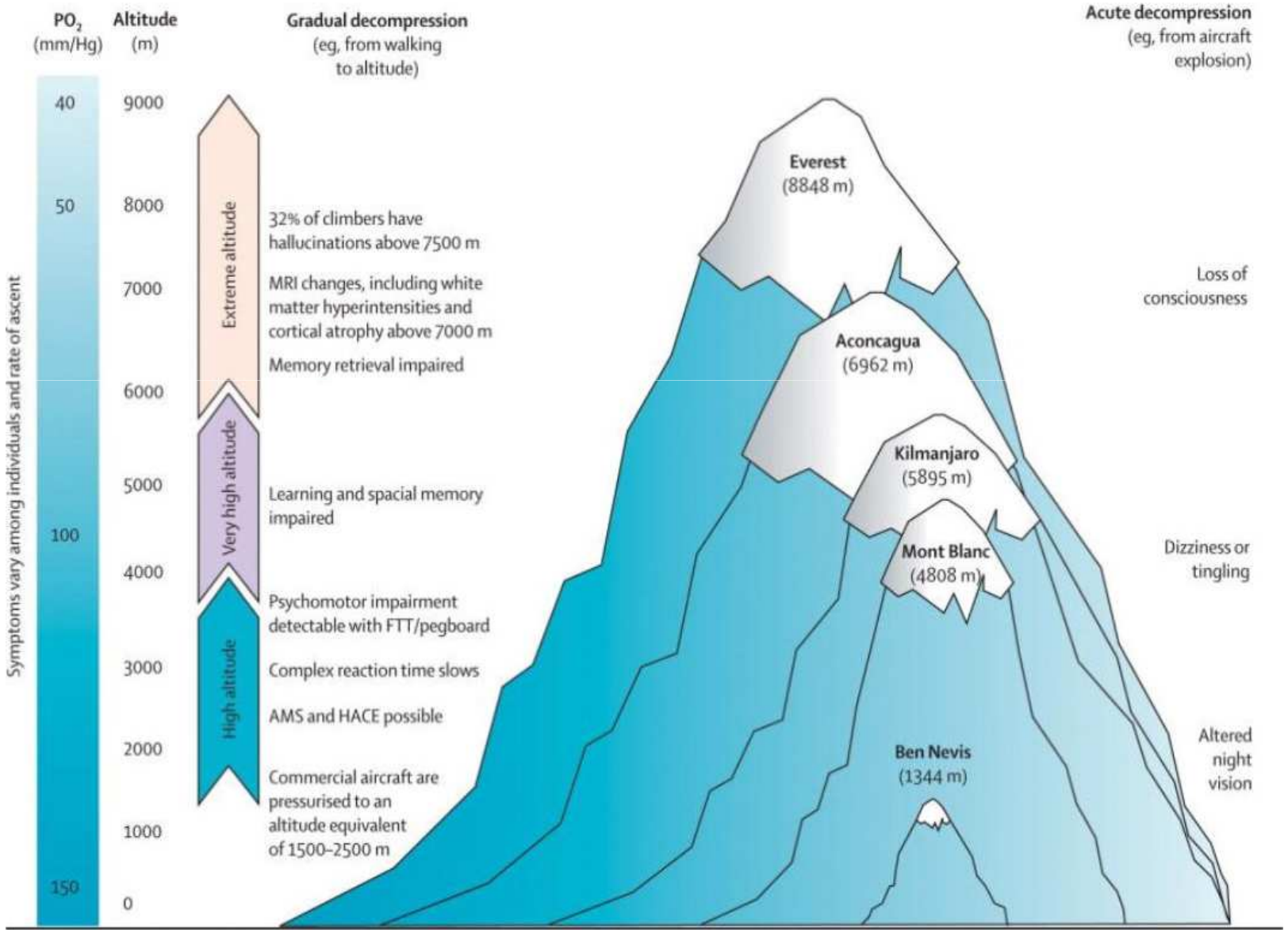
- **Internal –** from the upper airways down to pulmonary capillary
- Decreased pulmonary ventilation and air distribution,
  - failure in central regul. – central hypopnoea, apnoe (sleep breath. dis., morphin, barbitur., etc.), res. rhythm dis. (coma)
  - failure in periphery: UAW obstruction – suffocation, Bronchial disease – asthma, cystic fibrosis), extrapulmon.: restricted resp. movements (fullness in abdomen, rib cage deformities, fractures, myopathy, pneumothorax, etc.)
- Defect in exchange of gases ↓ alveolar-capillary diffusion,
- Venous - arterial shunts

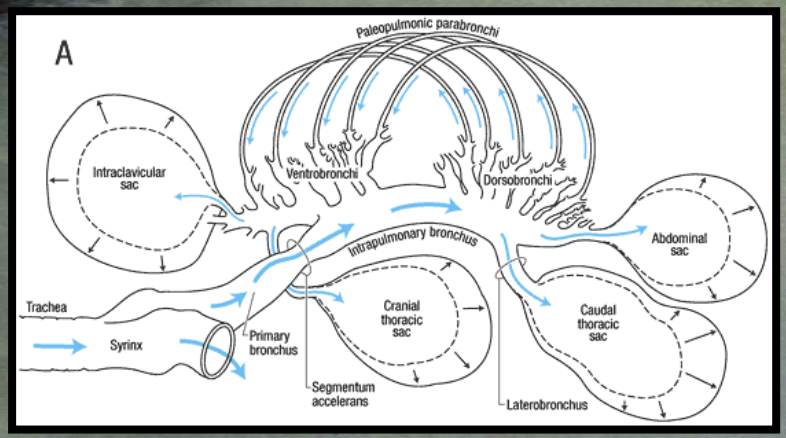
Hypoxic hypoxia

- **Atmospheric pressure** = (barometric) the pressure exerted by the weight of air in the atmosphere of Earth force (across one square centimeter) is a pressure of 10.1 N/cm2
- **decreases with distance** above the Earth's surface in an app. exponential manner
- **Normal sea level:** 760 mmHg
- In 5500 m is only 1/2 the normal, so PO_2) of moist inspired gas is (380-47) X 0.2093 = 70 (47 mm Hg is the partial pressure of water vapor at body temperature [ie, 37ºC].
- At the summit of Mount Everest (8848 m), inspired PO_2 is only 43. In spite of hypoxia associated with high altitude, approximately 15 million people live at elevations over 3050 m, and some permanent residents live higher than 4900 m in the Andes. A remarkable



Manifestation of high altitude sickness



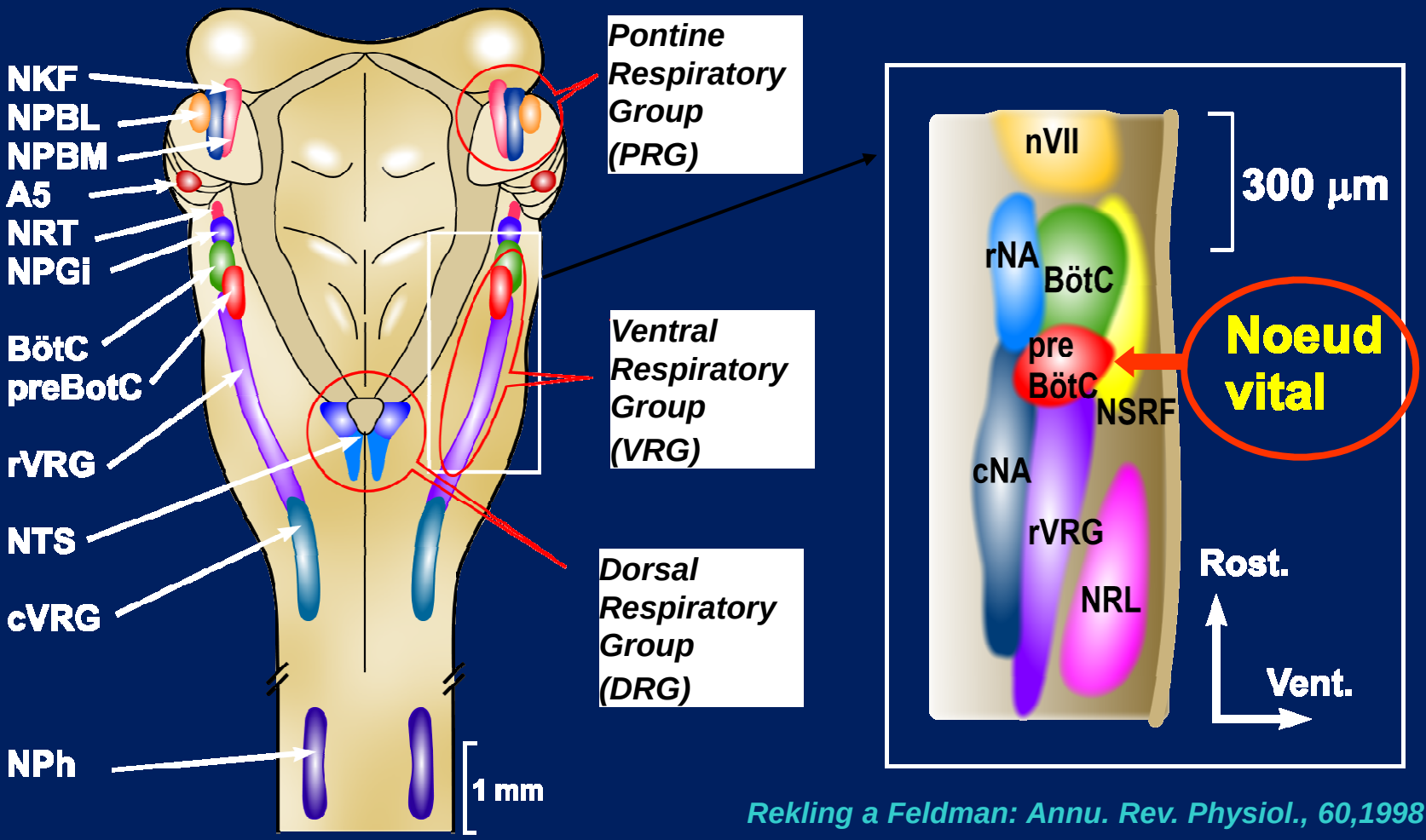


The bar headed goose migrates over Mt. Everest

"If it could be demonstrated that any complex organ existed which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down."

- Charles Darwin (Origin of Specie

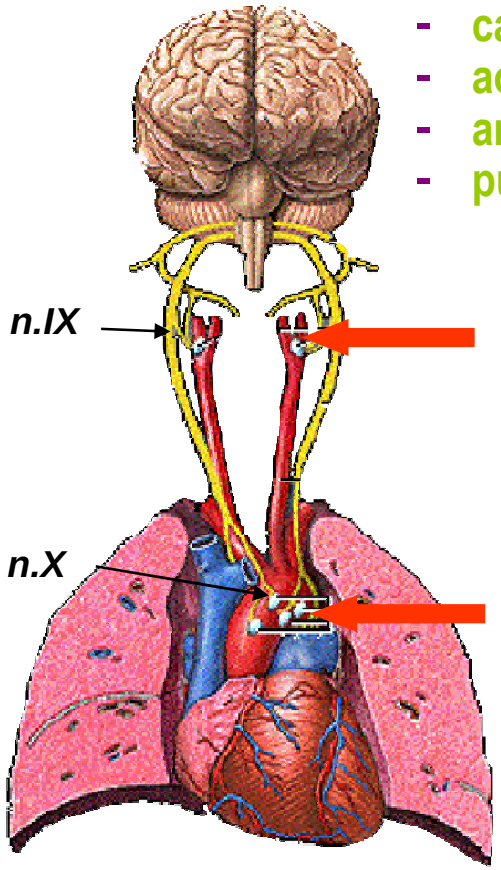
RESPIRATORY STRUCTURES



Rekling a Feldman: Annu. Rev. Physiol., 60,1998

Smith et al. 1991, 2000

PERIPHERAL O_2 – CHEMORECEPTION



- carotide receptors (pO_2, pCO_2, pH) -> n.IX -> medulla
- aortal receptors (pO_2, pCO_2) -> n.X -> medulla
- arterial O_2 sensors (pO_2, pH) -> veget. Afferents, local
- pulmonary sensors (pO_2, pH) -> n.X, local reflexes

Receptors in glomus caroticum:

- *blood flow 2 l/min/100 g*
- *stimulated when P_aO_2 <60 mmHg*
- *aditional stimulation by acidosis and hypercapnia*
- *inhibited by alkalosis and hypocapnia*

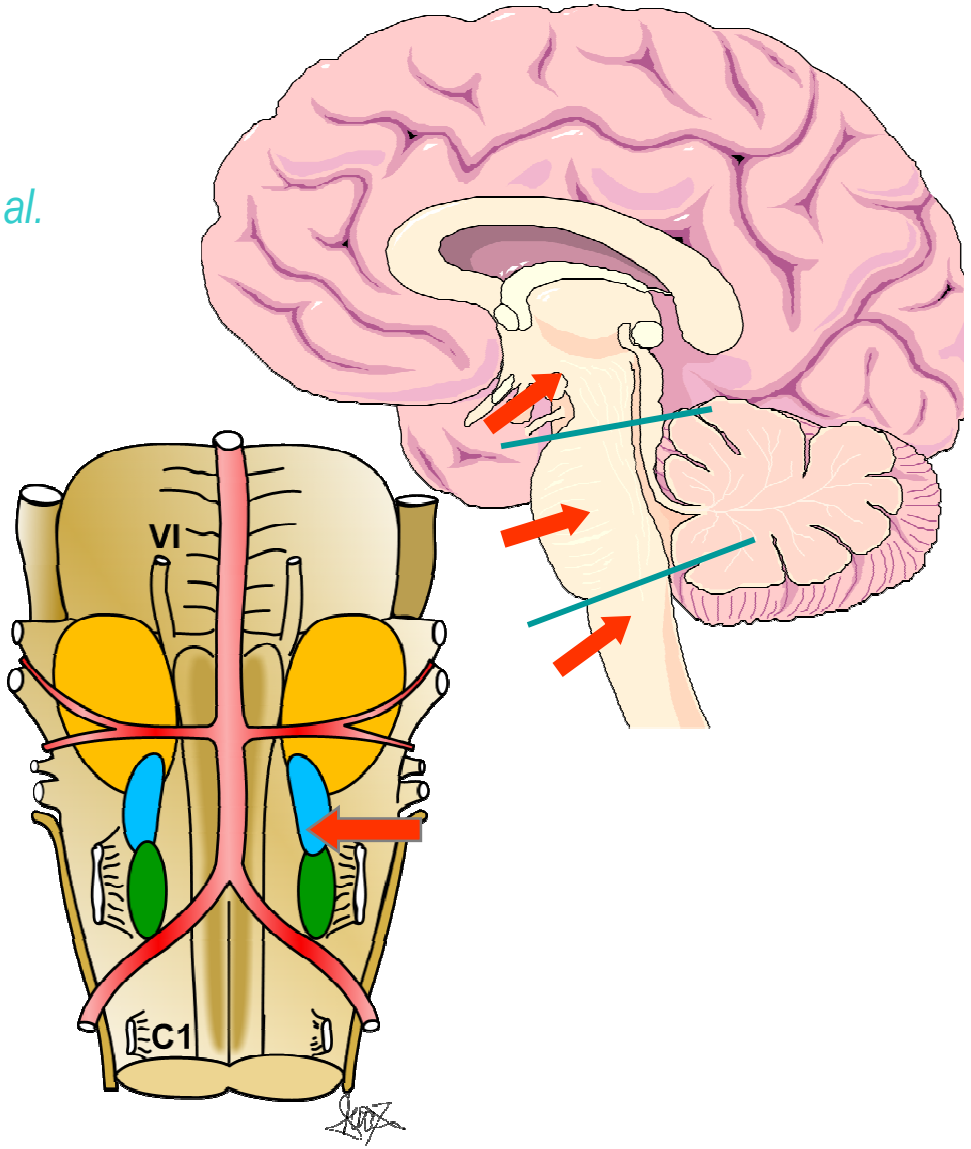
Fitzgerald a Lahiri (1986), Lahiri (1991))

Central O_2 and CO_2/pH– receptive areas

Several brain areas show **O_2- sensitivity** in respiratory stimulation:

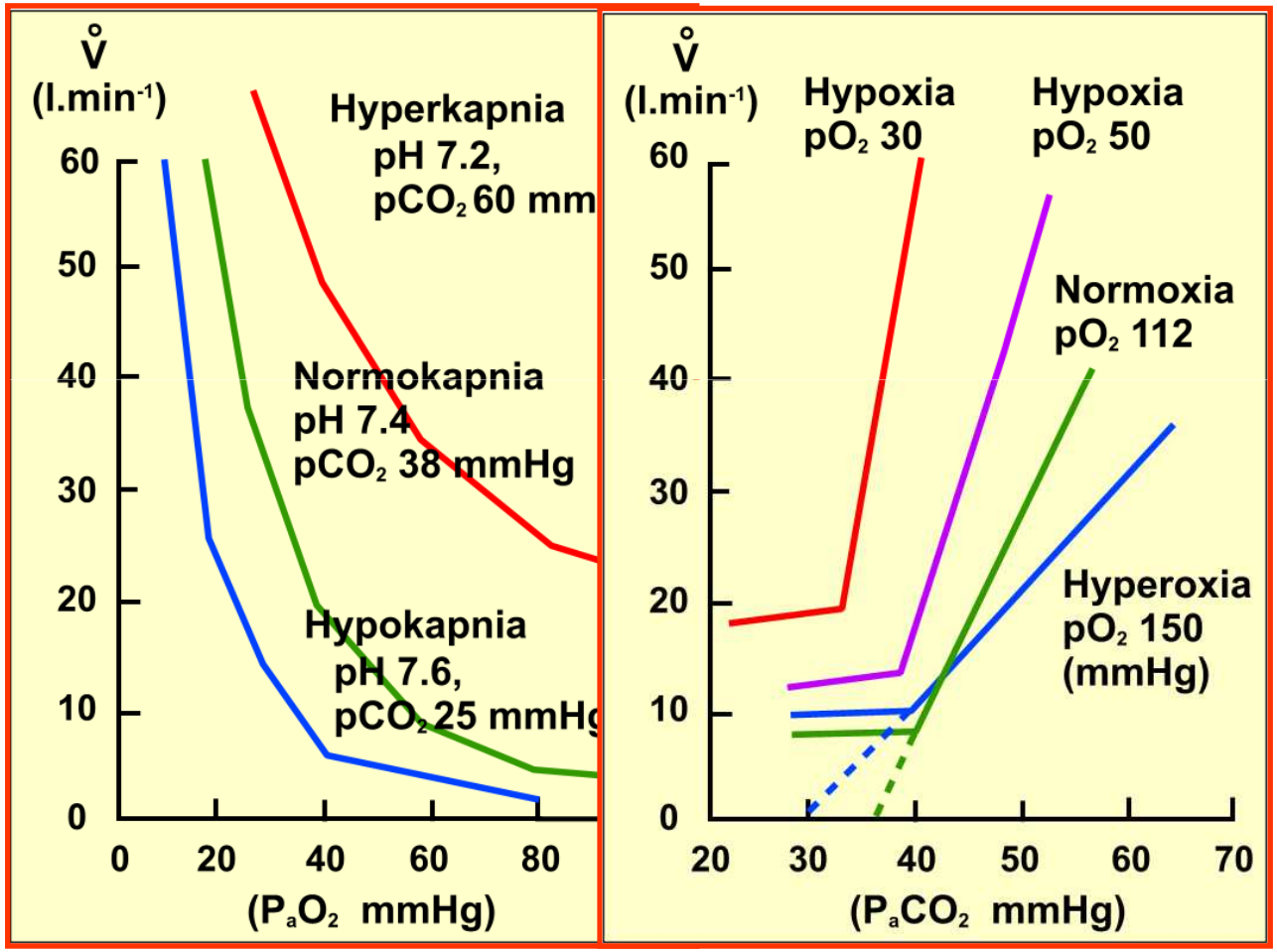
- lateral medullary reticular formation (RF) *Arita et al. (1988)*
- RF in caudal and rostral pons *St.John (1977), Edelman et. al (1991)*
- raphe nuclei *Millhorn et al. (1980,1984)*
- diencephaslic locations *Tenney a Ou (1976)*
- caudal hypothalamus *Horn a Waldrop (1997)*
- ventrolaterl reticular formation - PreBötzinger complex *Solomon et al. (200O)*

Central pH/CO_2 – sensitive structures in rostroventral medullary surface – classical central chemorecptors

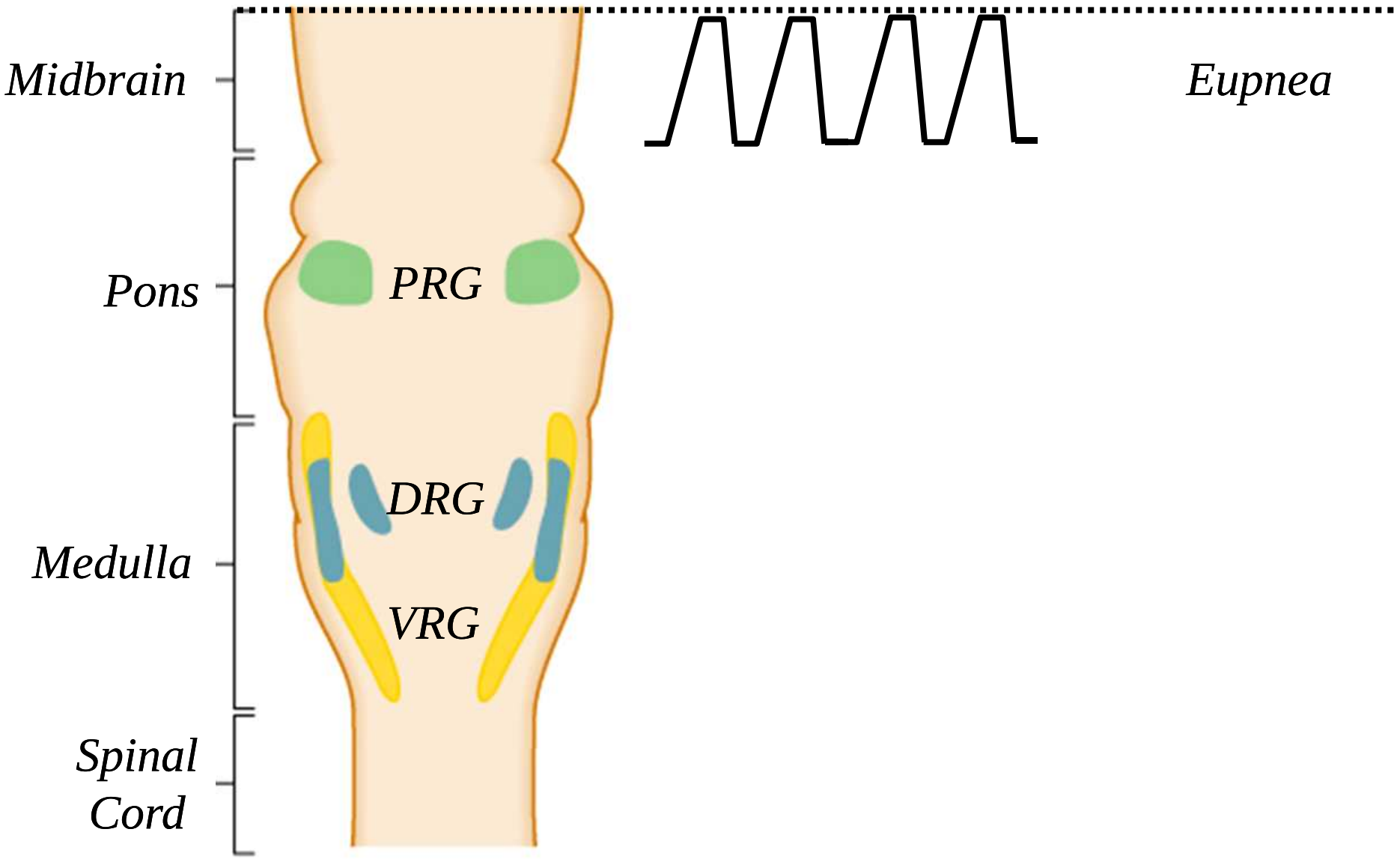


pH/CO_2 – sensitive chemoreception

CO_2 ➡ O_2 O_2 ➡ CO_2



Central Control of Breathing



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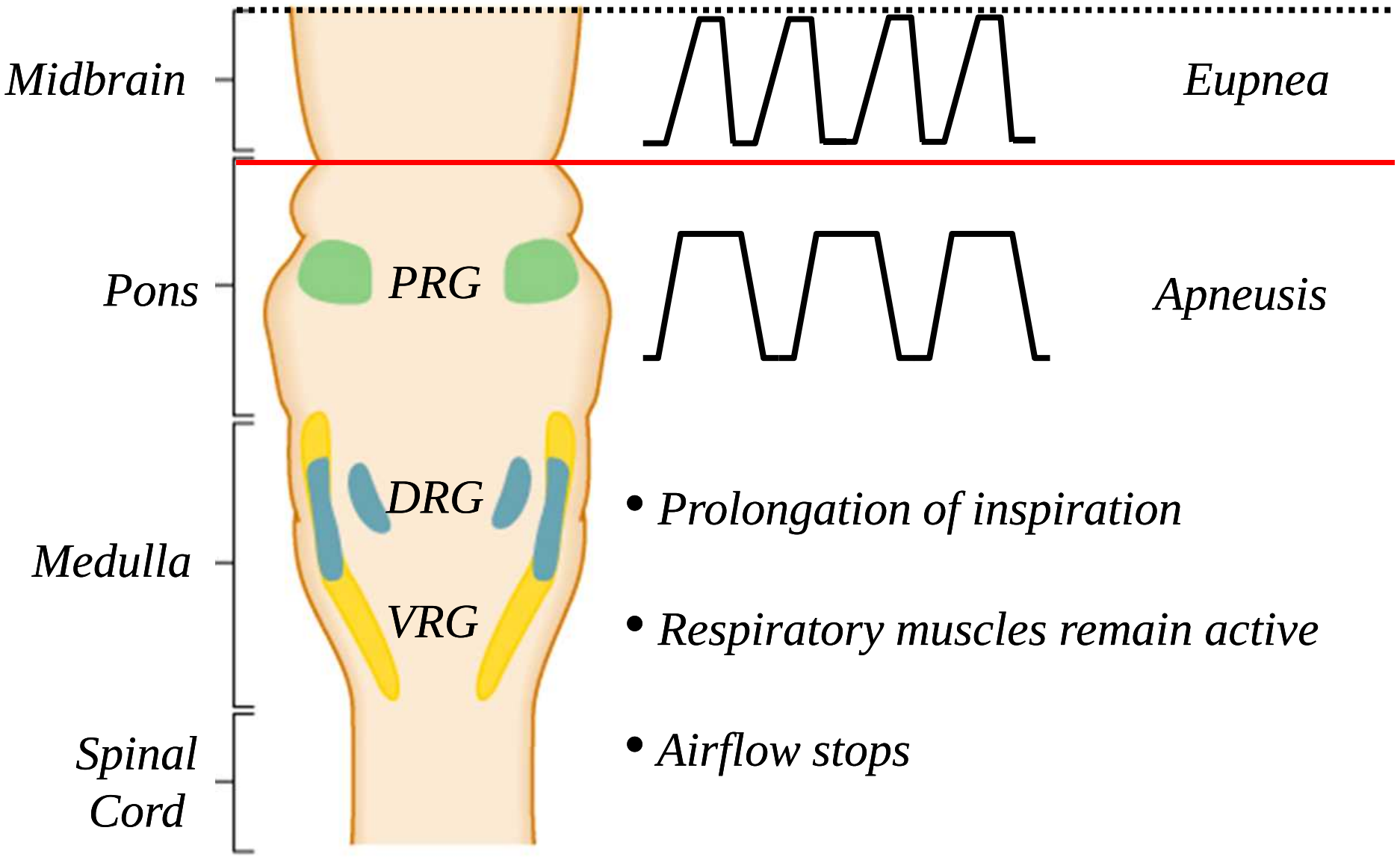
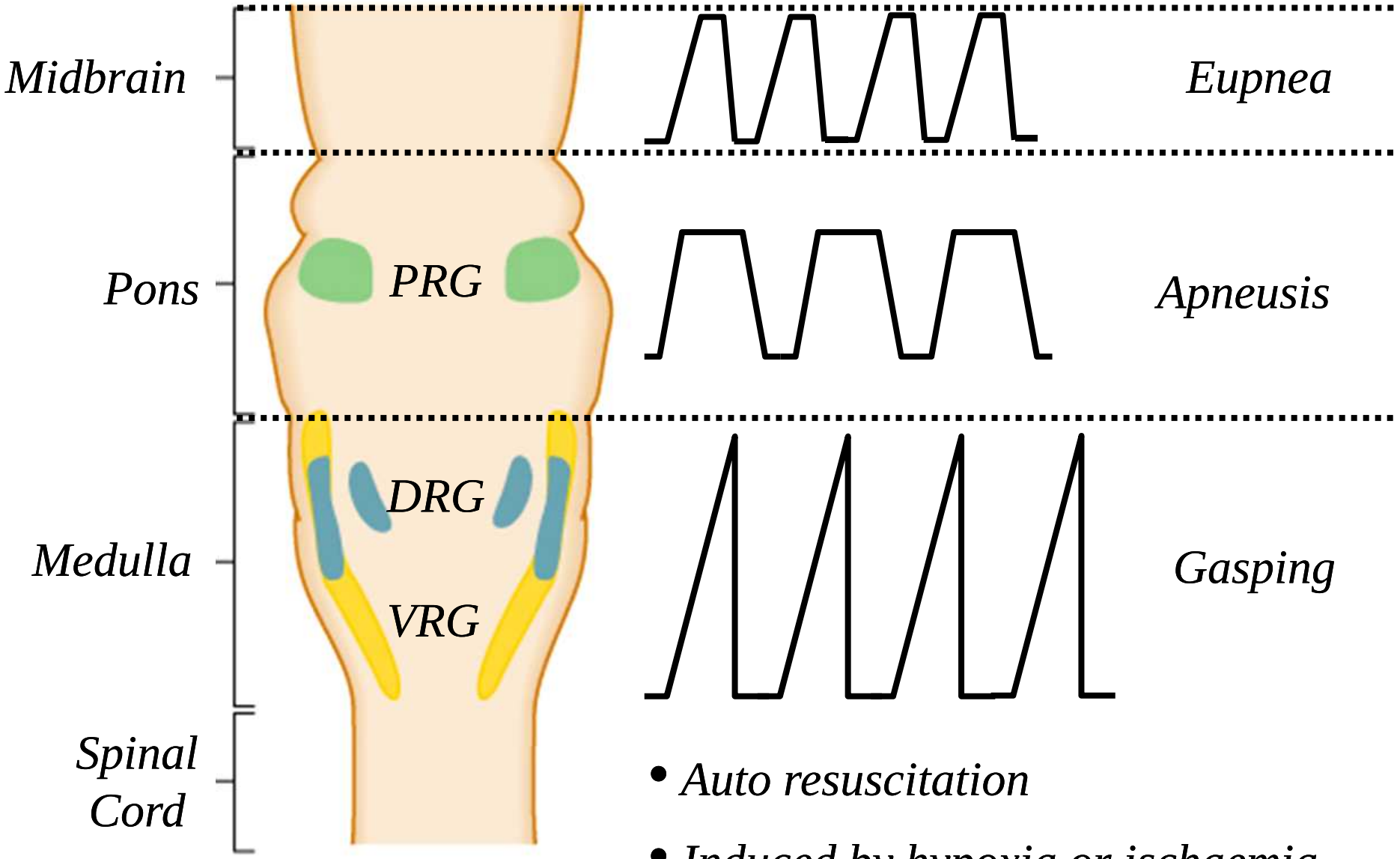


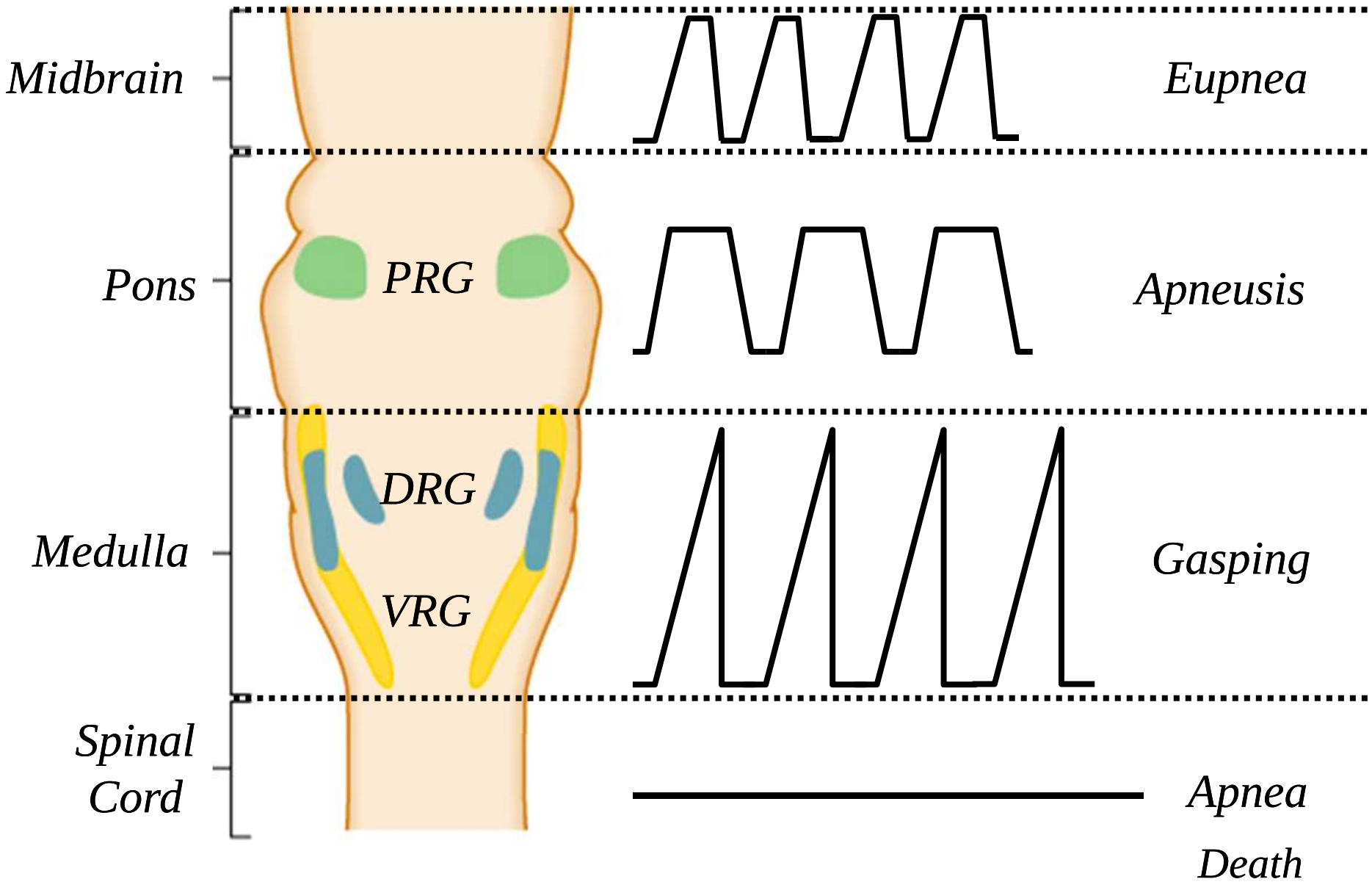
- *Prolongation of inspiration*
- *Respiratory muscles remain active*
- *Airflow stops*

Central Control of Breathing

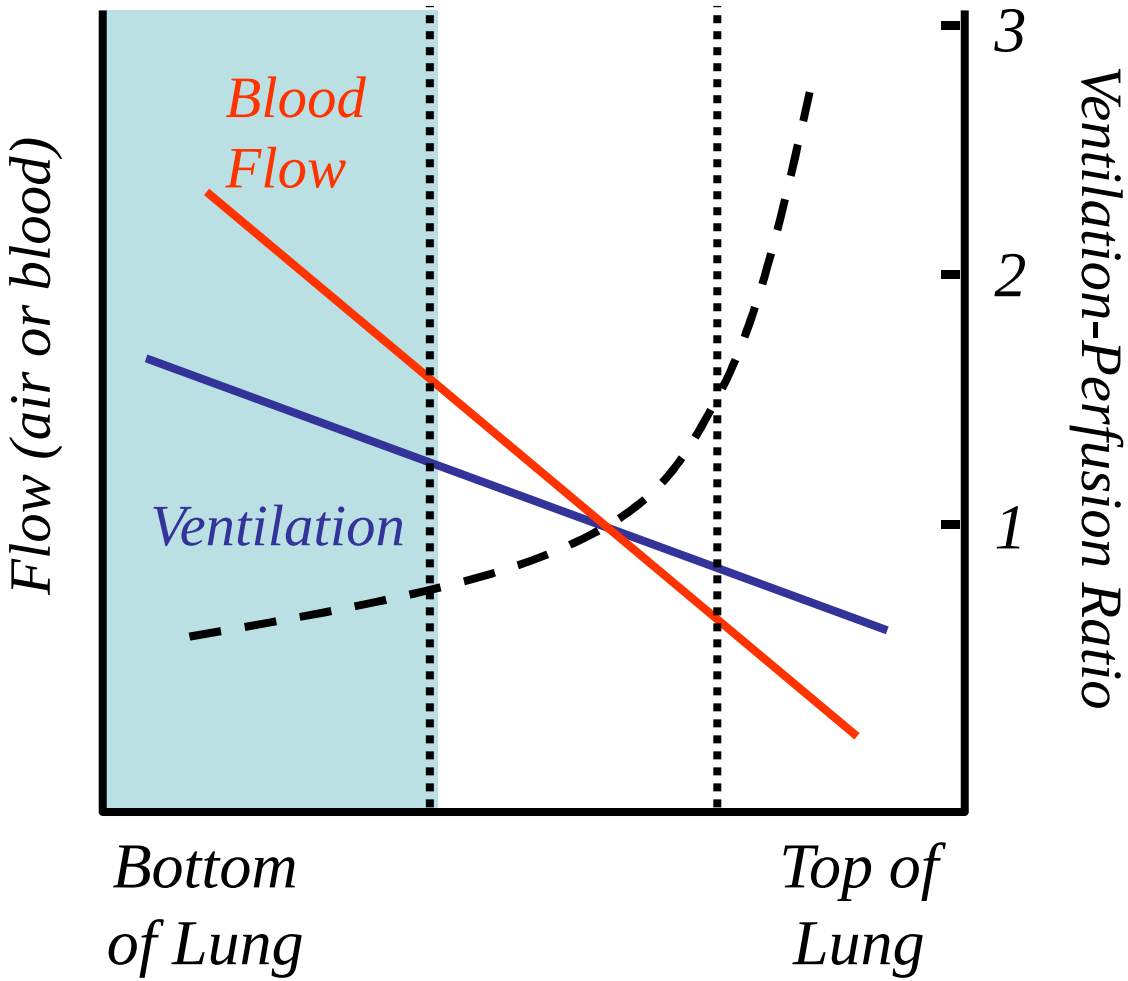


- *Auto resuscitation*
- *Induced by hypoxia or ischaemia*

Central Control of Breathing



Regional Differences in Blood Flow and Ventilation



At the bottom of the lung

Ventilation < Blood Flow

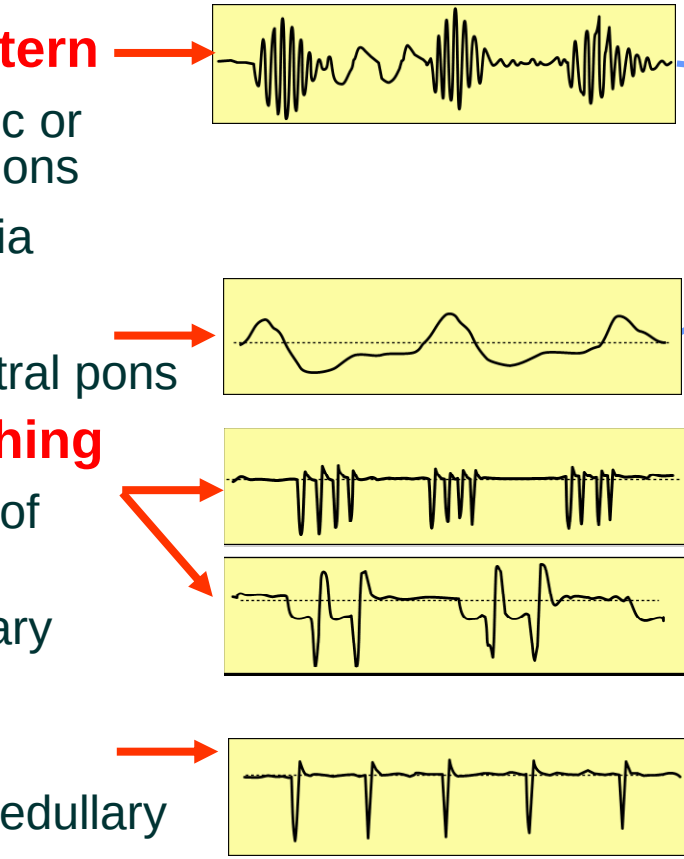
$\dot{V}_A/\dot{Q} < 1$

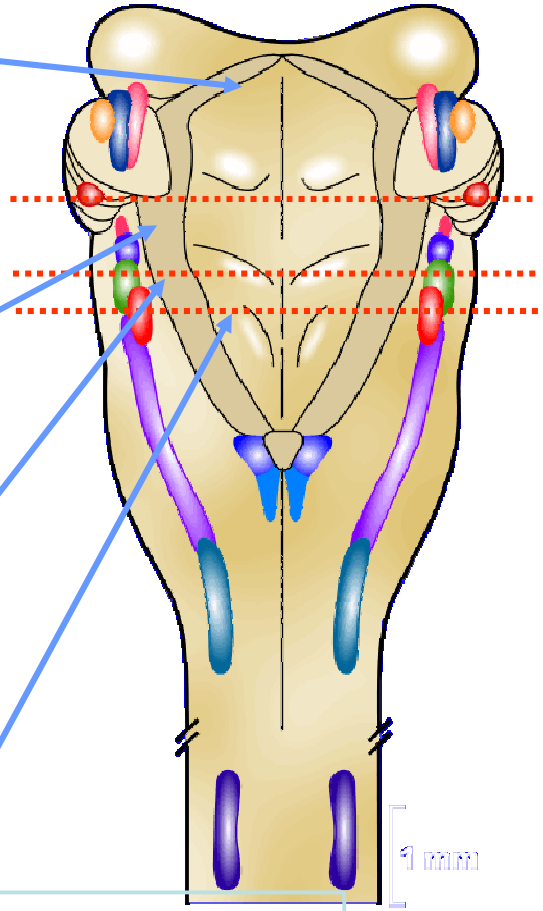
Not all of the blood gets oxygenated

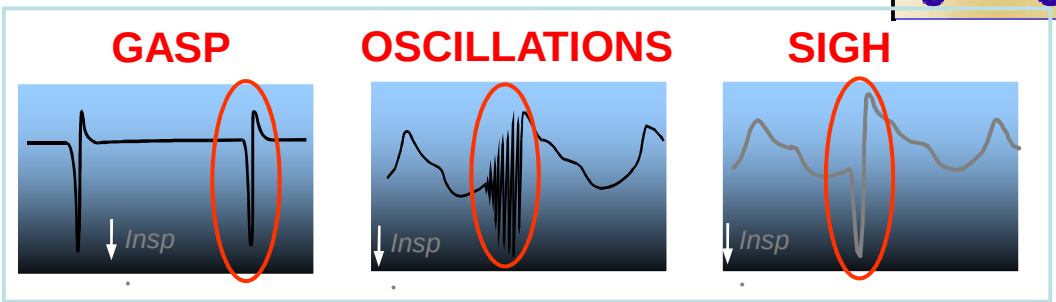
"Physiologic Shunt"

NON-EUPNOIC RHYTHMS

- **Cheyne-Stokes pattern**
  - Diffuse diencephalic or mesencephalic lesions
  - Global brain hypoxia
- **Apneusis**
  - Damage within rostral pons
- **Biot (cluster) breathing**
  - Hypoxia, ischemia of caudal pons
  - High ponto-medullary transsection
- **Gasping**
  - Defects in ponto-medullary border
  - Hypoxic brainstem
  - damage







Respiratory diseases

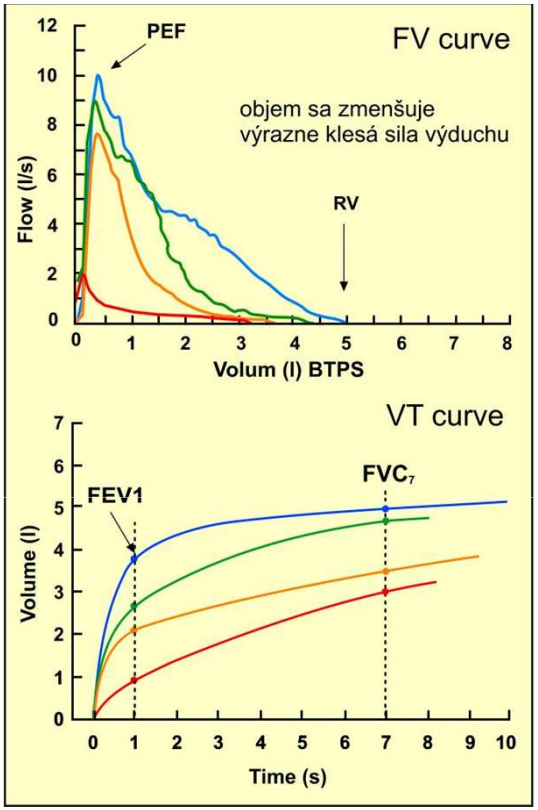
Obstructive diseases (OPD)

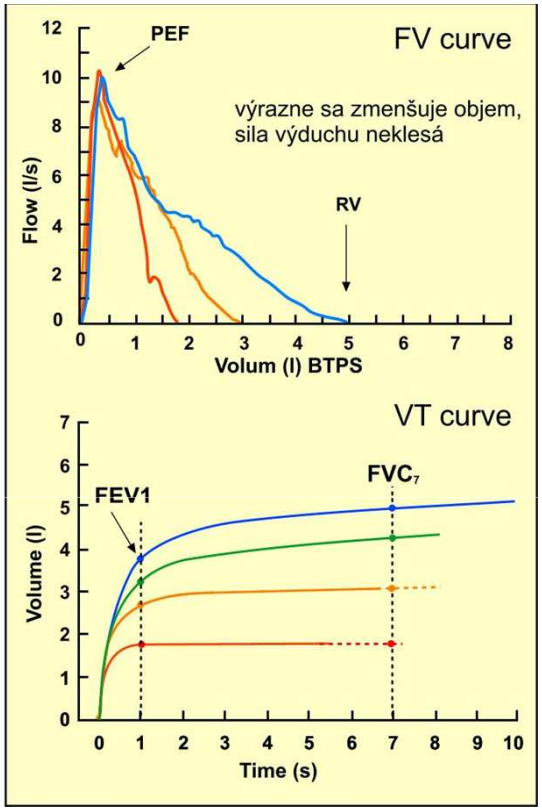
- restricted expiratory force
- ↓ FEV_1 ↑ compliance, elasticity
  - Chronic bronchitis
  - Emphysema
  - Asthma
  - Bronchiectasia
  - Cystic fibrosis
  - Athelectasia (not pure OPD)

Restrictive diseases (RPD)

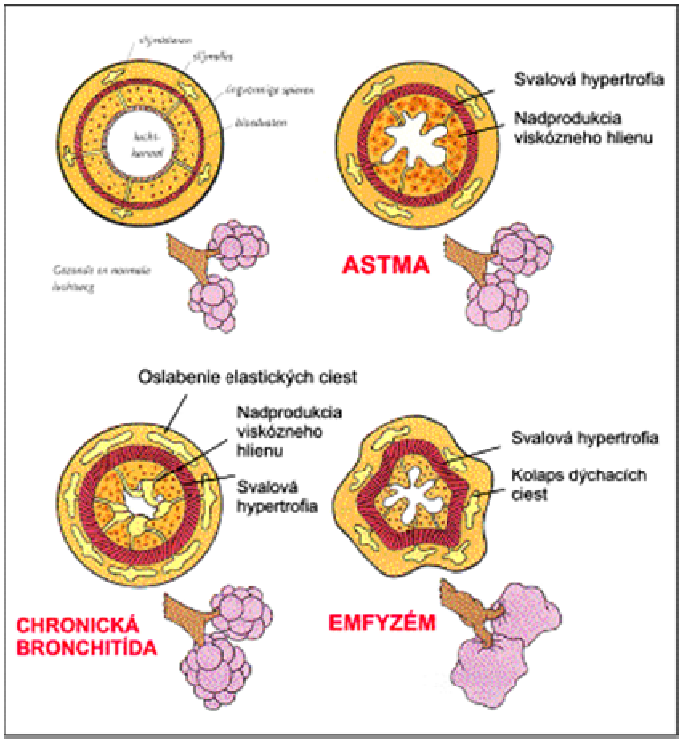
- reduced inspiratory + expiratory volumes
- ↓ VC ↓ compliance, elasticity
  - Interstitial diseases: pneumonia
  - Fibrosis of lungs –pneumoconiosis, asbestosis, silicosis, beryliosis, farmers lungs
  - Restriction to breathing: pneumothorax, ribcage malformities, fracture, obesity

Hypoxic hypoxia – Intrapulmonary causes



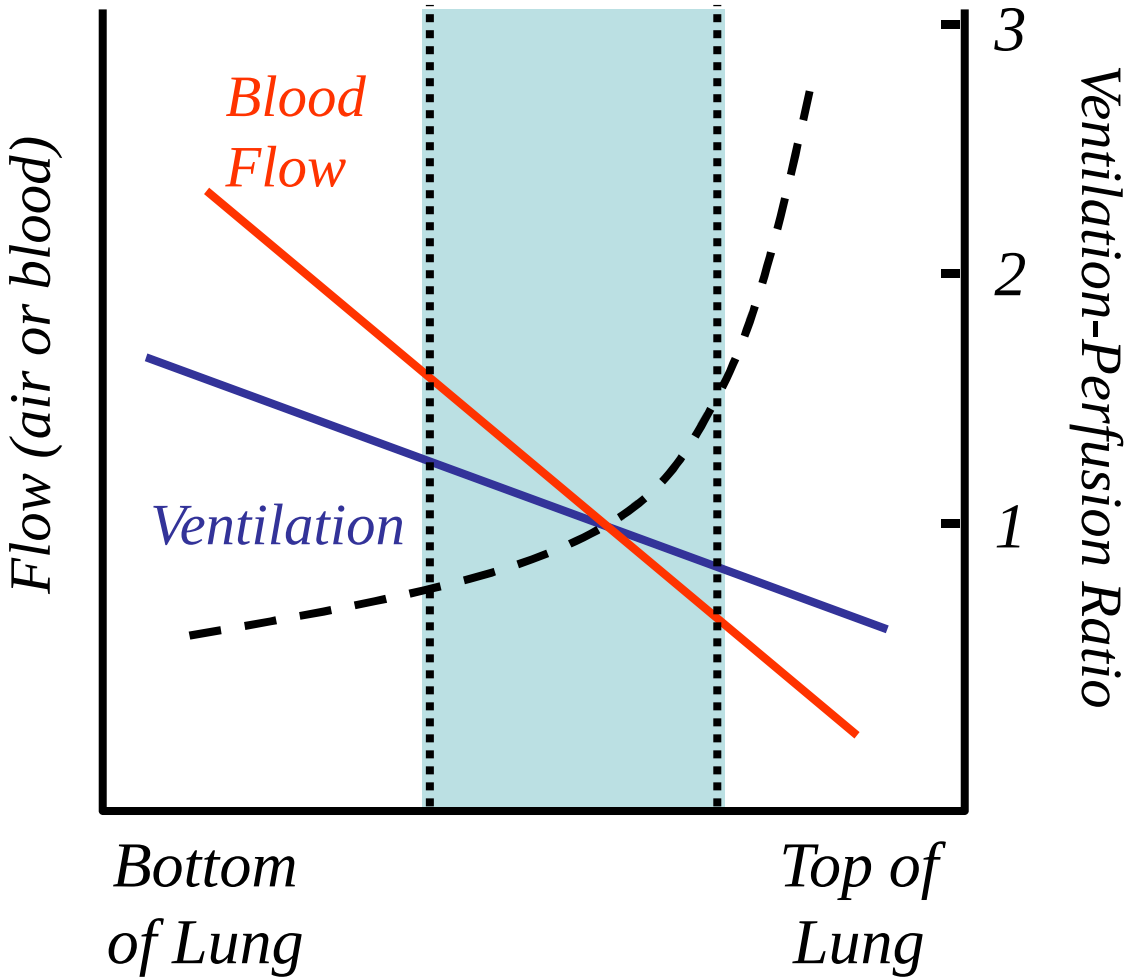


- **obstructions (acute , chronic)** related to pathways UAW, LAW; → decreased gas flow + exchange or impared air distribution, →non- ventilated areas
- **impaired diffusion** → alveolar-capillary pathway ; → alveolar edema, interstitial edema
- **restrictions** → limited volume/ time capacity (chest cage defects, fracture, pneumothorax, muscle weakness; pulmonary tissue limitations, parenchyme stiffness)



- Hyperplasia, metaplasia of mucous layer
- Hyperproduction of mucus
- Inflammation – cell infiltrates
- Thikening of muscle layer - spasms
- Airway collapsibility – air trapping; expiratory limitation

Regional Differences in Blood Flow and Ventilation

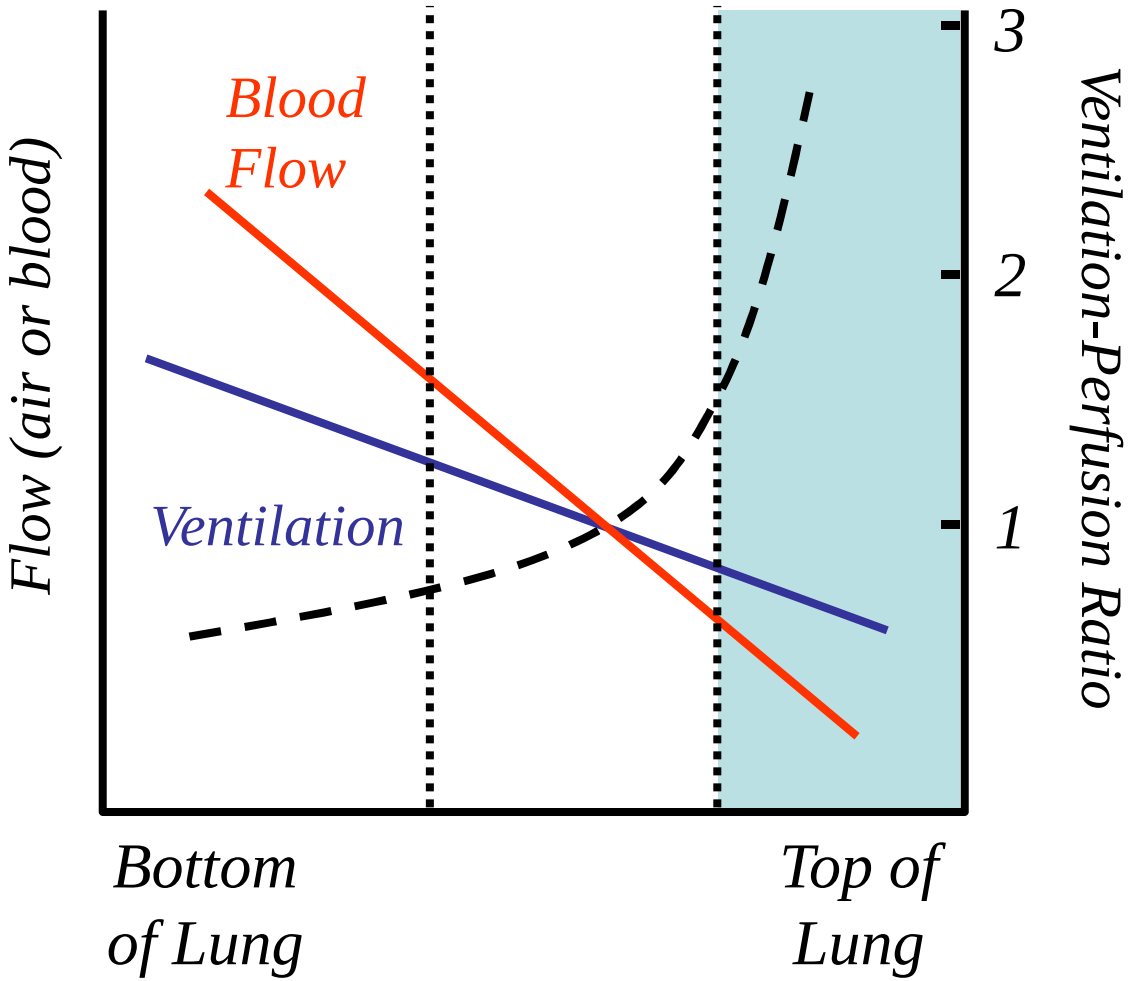


In the middle of the lung

Ventilation ≅ Blood Flow

$\dot{V}_A/\dot{Q}$ *is approximately 1*

Regional Differences in Blood Flow and Ventilation



At the top of the lung

Ventilation > Blood Flow

$\dot{V}_A/\dot{Q} > 1$

Physiologic Dead Space

TYPES OF HYPOXIA – HEMIC HYPOXIA

Def: arterial pO2 is normal but the amount of haemoglobin available to carry oxygen is reduced;

Characteristics: 1. Normal arterial pO2 ; 2. Arterial O2 content moderately reduced, SO2 reduced
3. A-V pO2 difference is normal

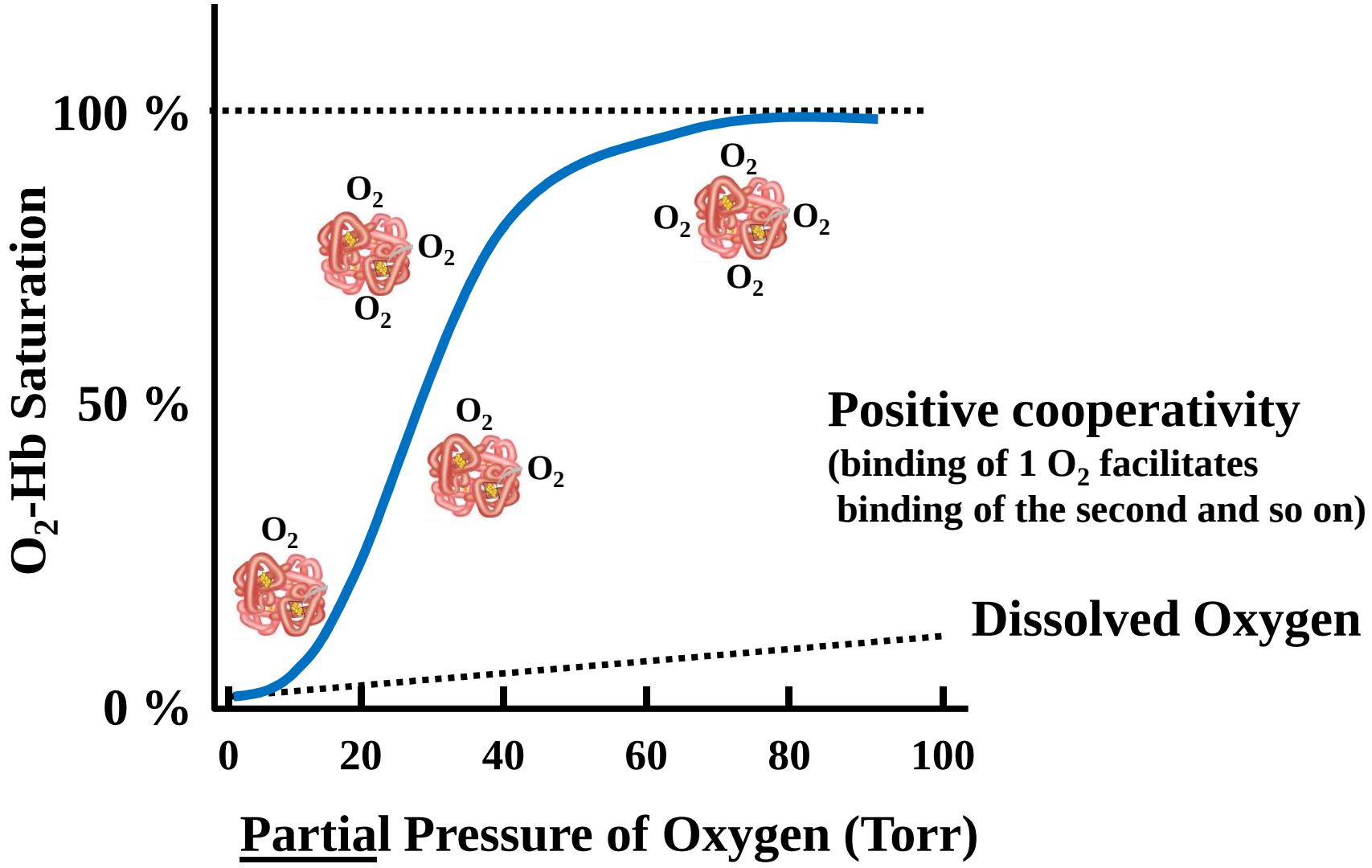
Causes:

a) Course: **Acute vs Chronic**

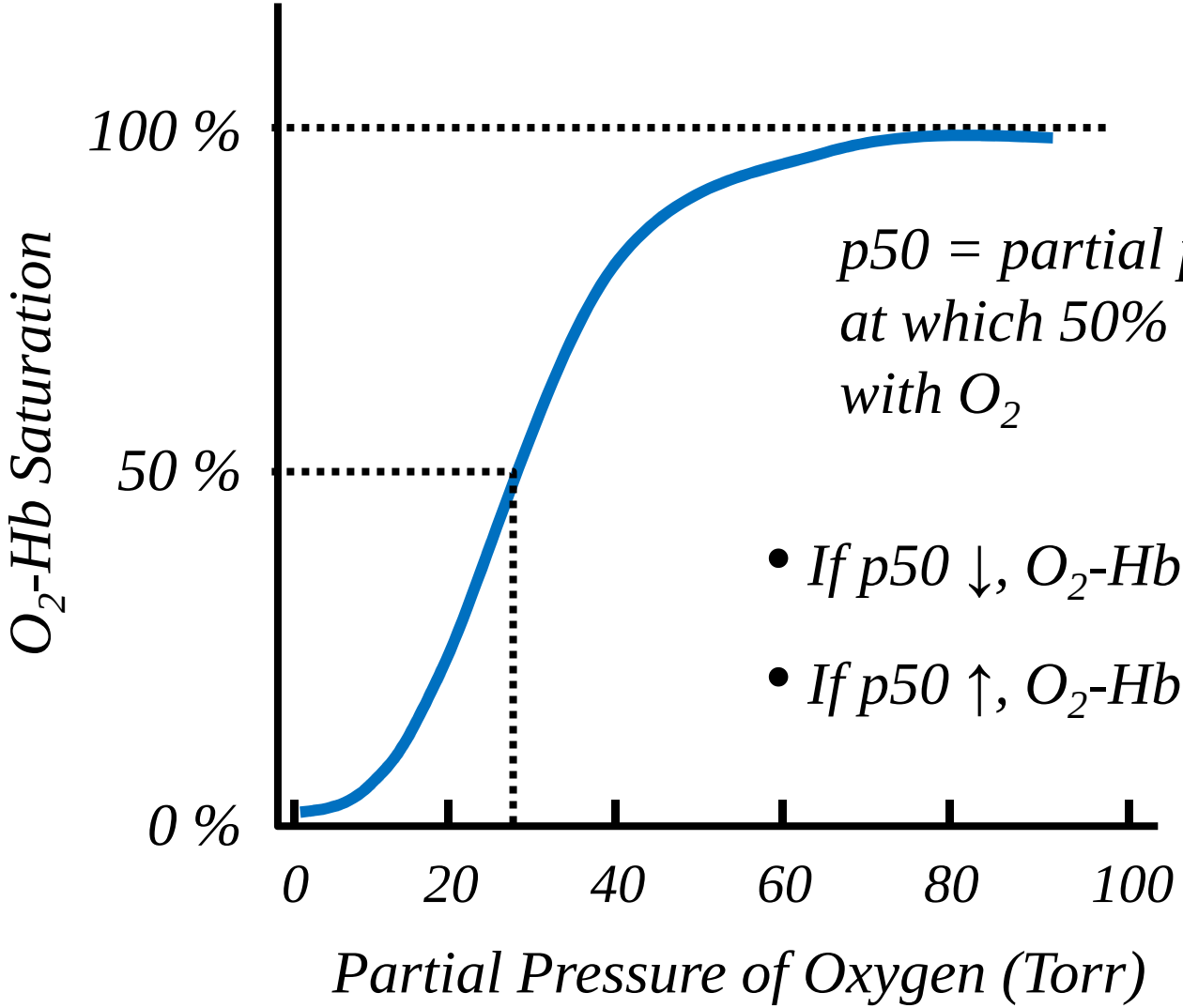
b) Reason:

- **Hemorrhage** & metabolic disorders (pH): high affinity to oxygen
- **Anemia:** sideropenic anemia (chronic bleeding), hemolytic anemia (trasfusion disord., blood donation
- **Conversion of haemoglobin** to some abnormal form
- Other: Smoking cabin contamination, engine exhaust fume Carbon Monoxide interferes with oxygen, binding to the blood
- Symptoms of hypoxia at lower altitudes, Most airlines recommend: No flight for 72 hours after donation of whole blood, No flight for 12 hours after donation of plasma

Oxygen Equilibrium (Dissociation) Curve



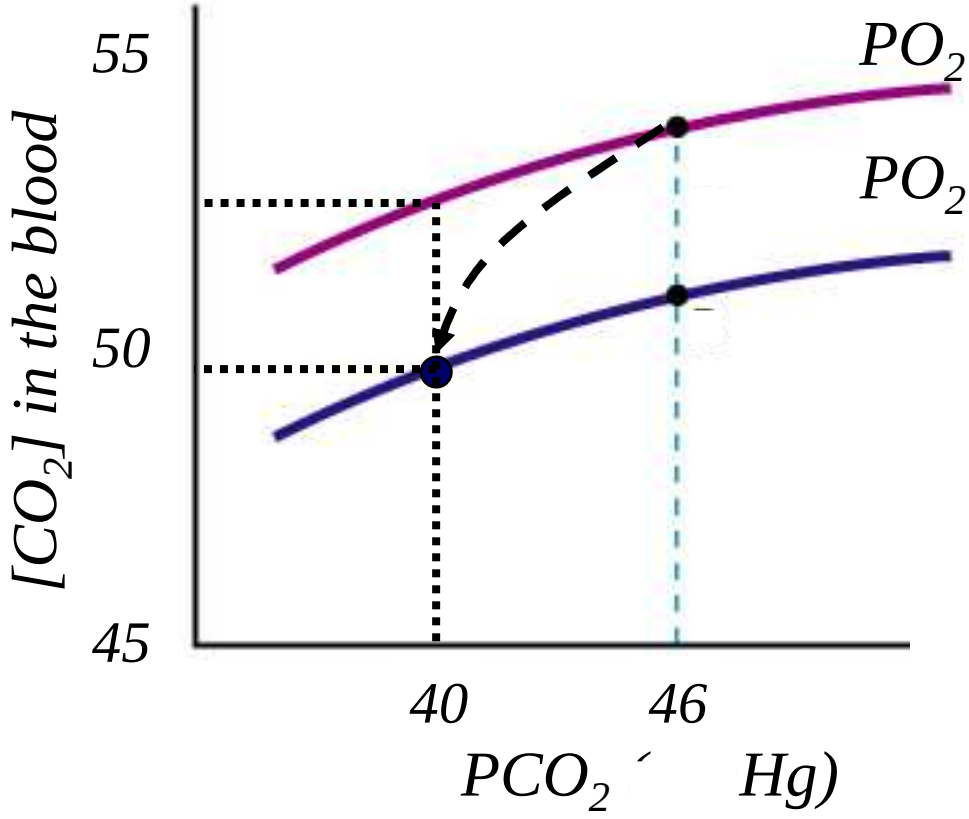
Oxygen-Hemoglobin Binding Affinity



p50 = partial pressure of O_2 at which 50% of Hb is bound with O_2

- *If p50 ↓, O_2-Hb affinity increases*
- *If p50 ↑, O_2-Hb affinity decreases*

The Haldane Effect



$PO_2 = 40\ mmHg$

$PO_2 = 100\ mmHg$

$H^+ \bullet Hb + O_2 = Hb \bullet O_2 + H^+$

Oxygenation of Hb leads to less HCO_3^- in the blood.

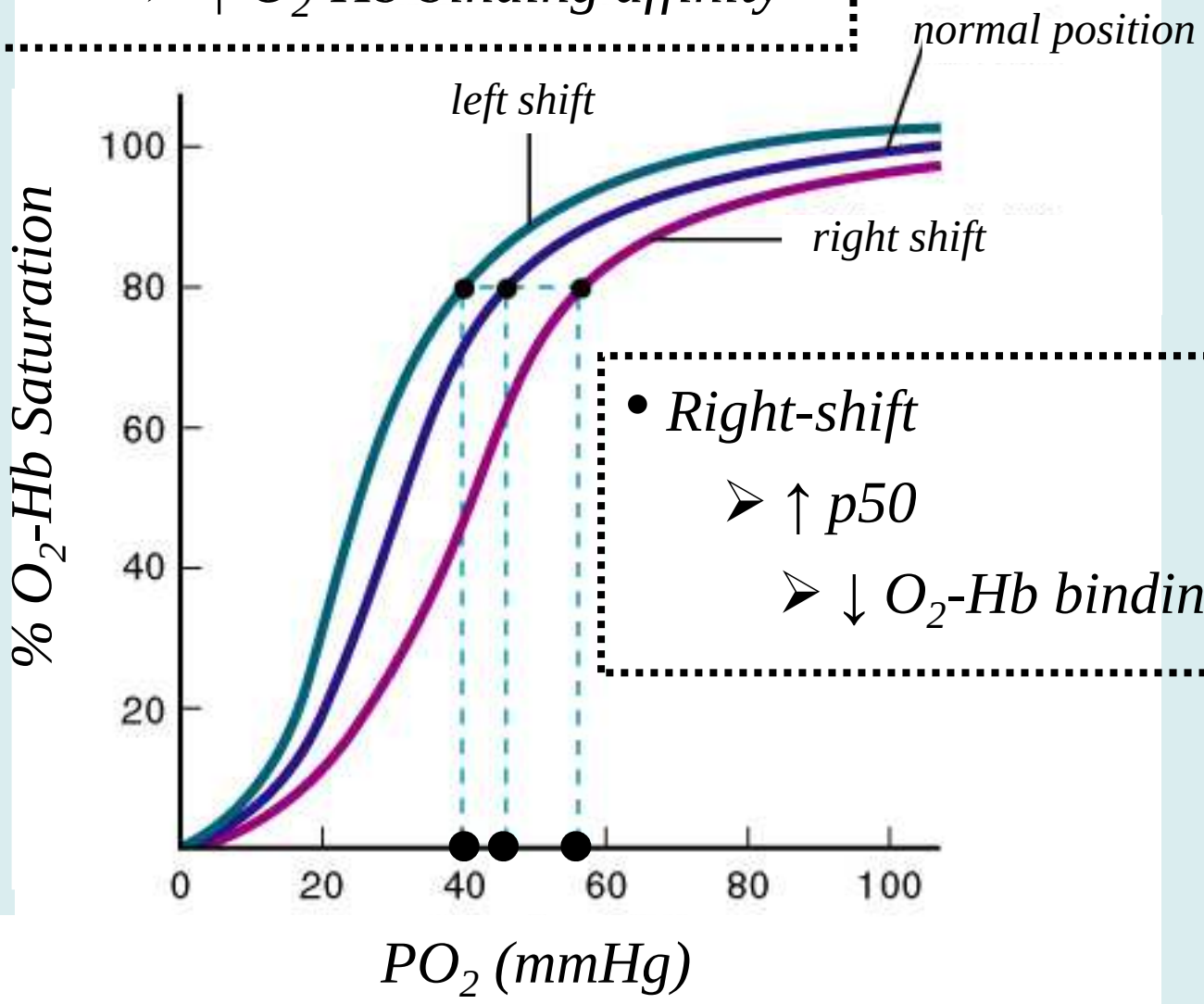
$H^+ + HCO_3^- \Leftrightarrow H_20 + CO_2$

HCO_3^- is the primary form of CO_2 in the blood

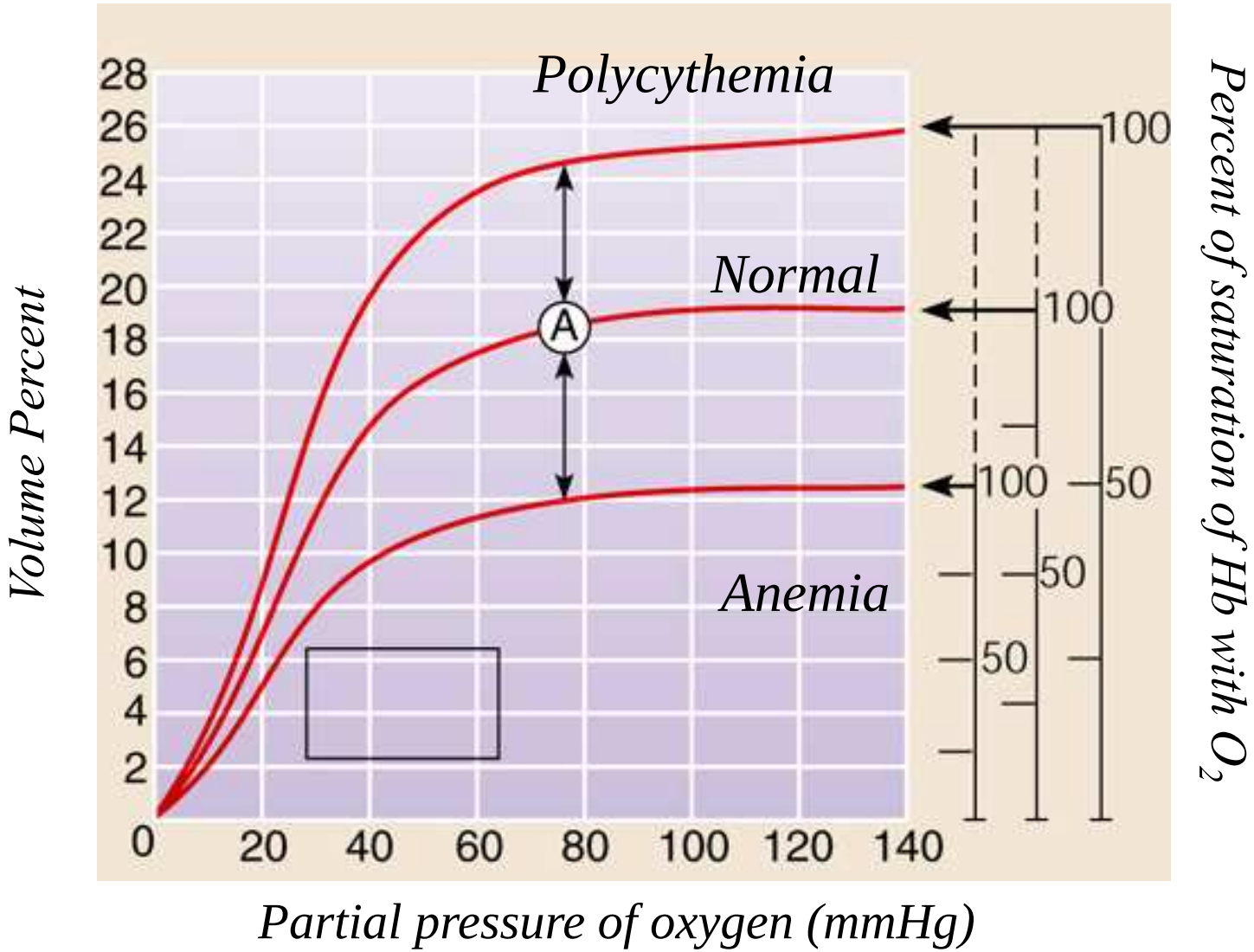
Deoxygenated blood (Hb) carries more CO_2 than oxygenated blood (Hb)

- CO_2 can bind to Hb (carbaminohaemoglobin).
- The binding of O_2 to Hb decreases the affinity of Hb for CO_2.

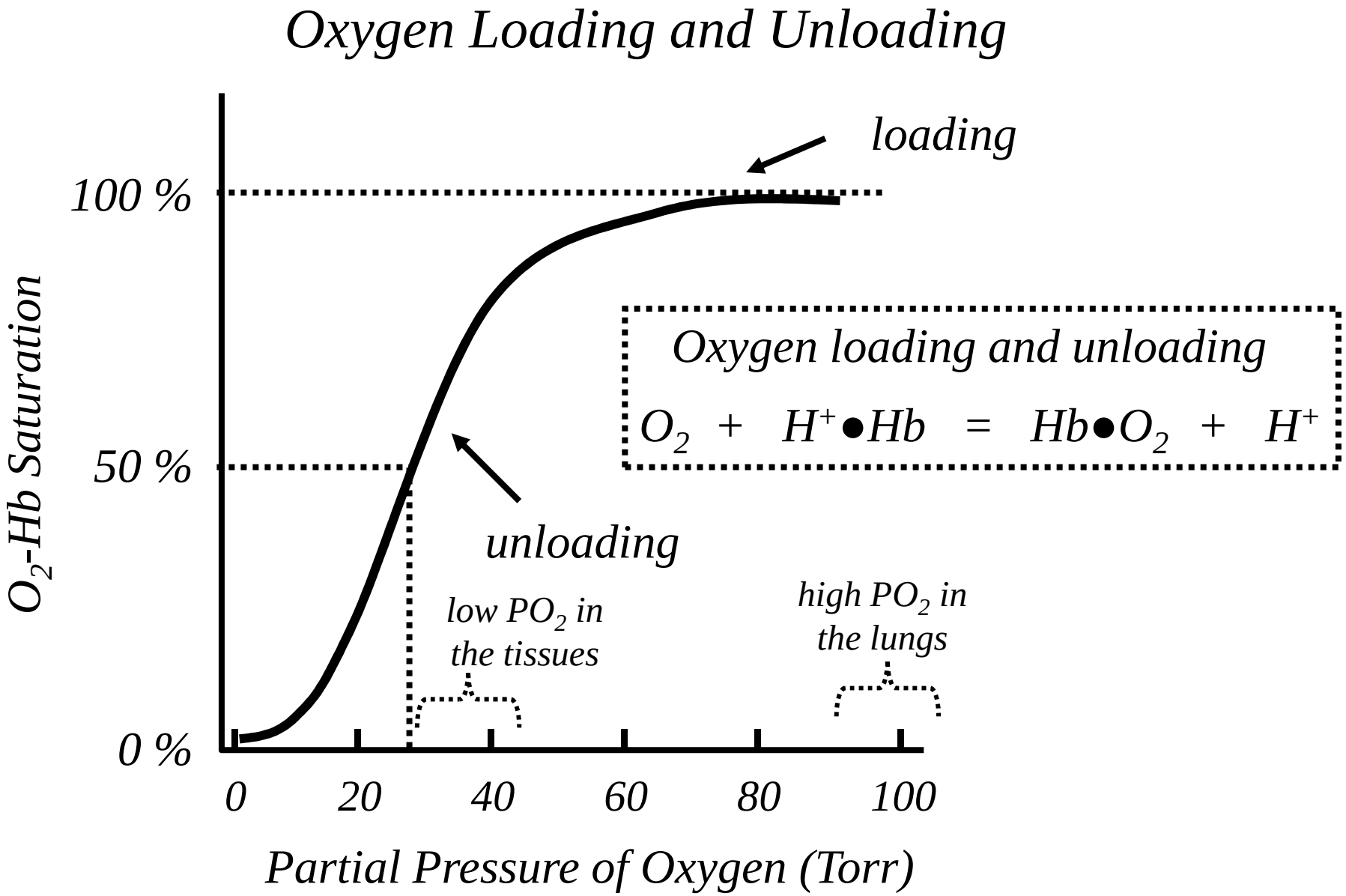
- *Left-shift*
  - ➢ *↓ p50*
    - ➢ *↑ O_2-Hb binding affinity*



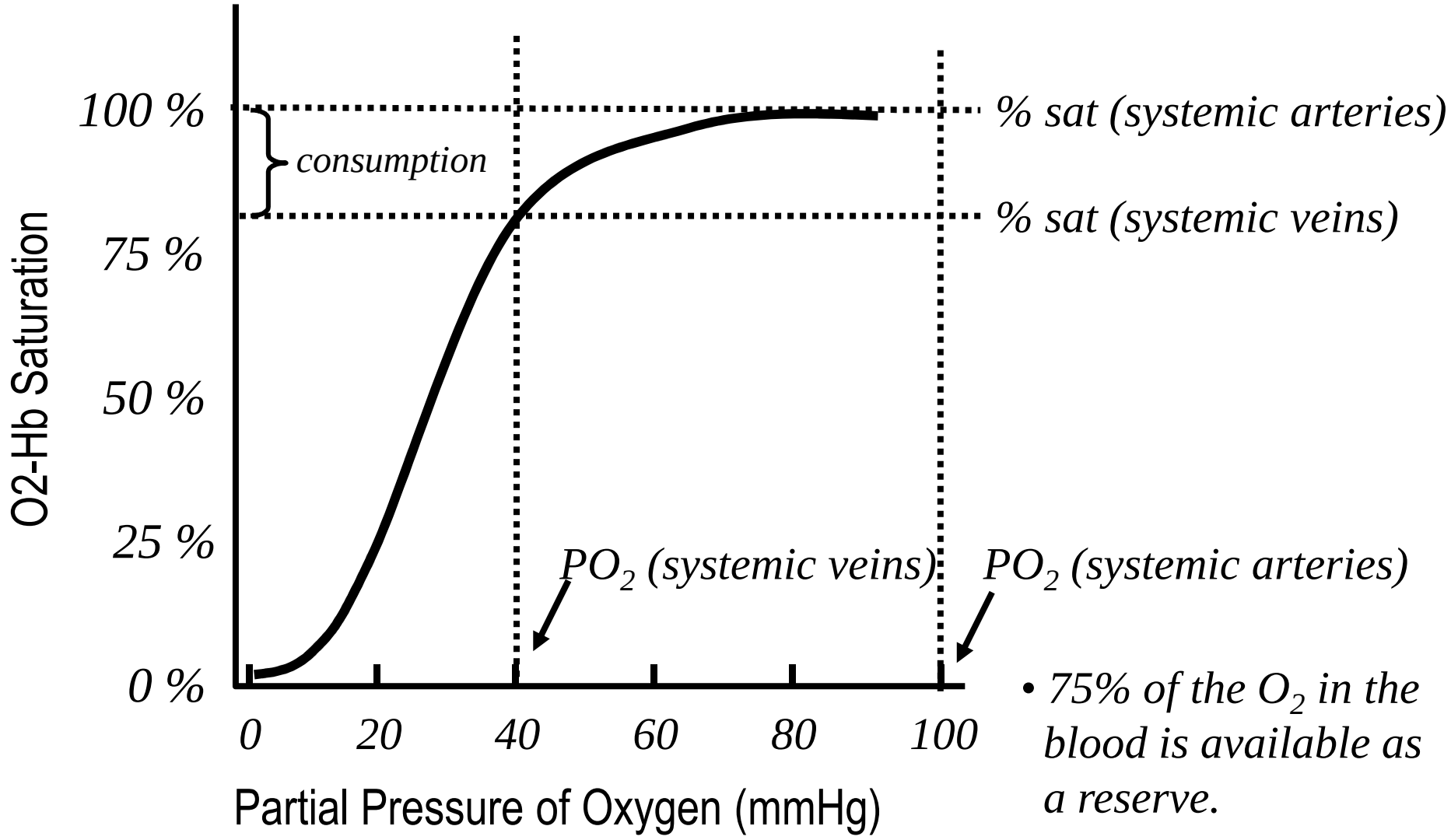
- *Right-shift*
  - ➢ *↑ p50*
    - ➢ *↓ O_2-Hb binding affinity*



In all 3 conditions the O_2-haemoglobin saturation is 100% but the total O_2 content differs

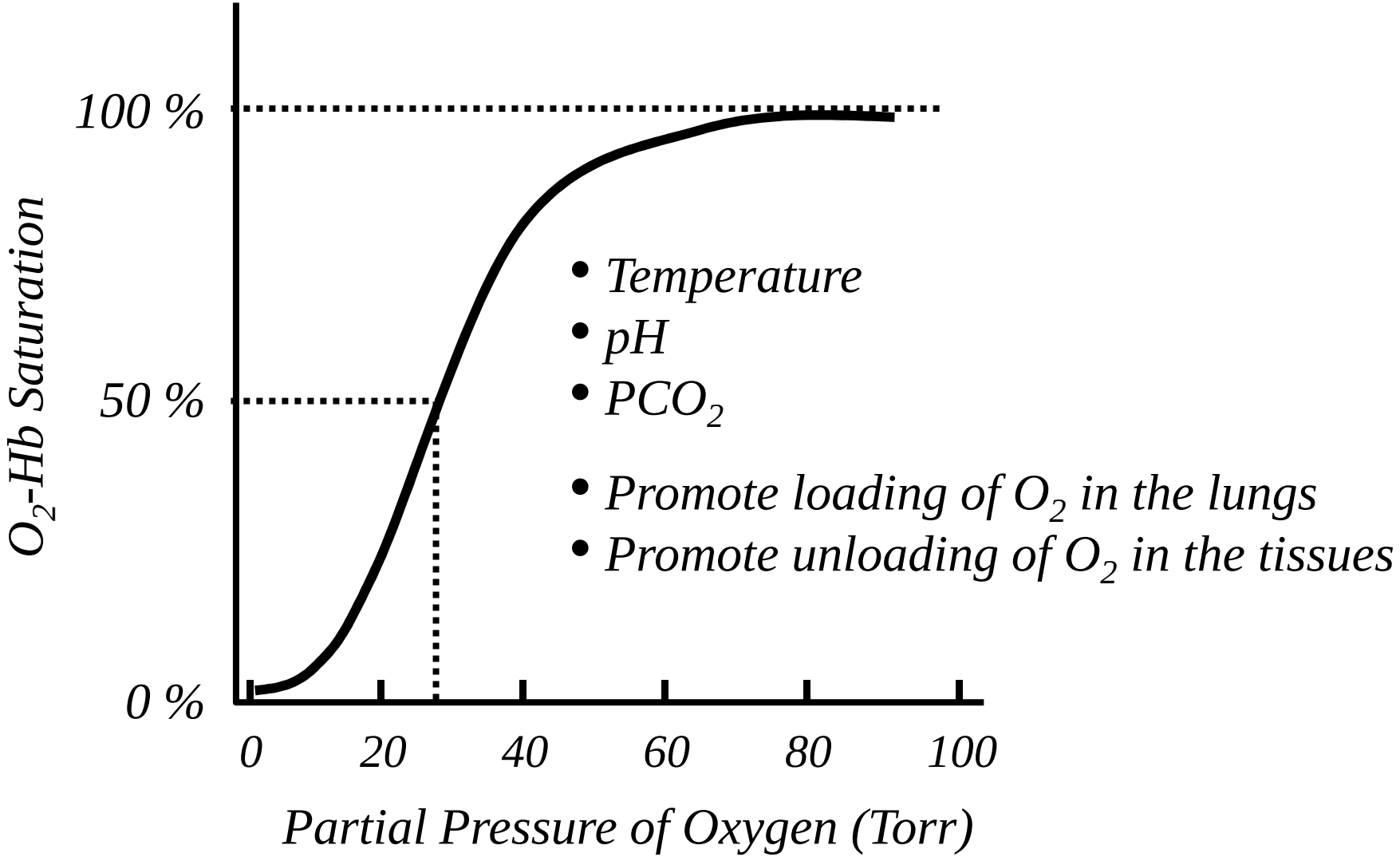

Oxygen Loading and Unloading
loading
100 %
50 %
0 %
O_2-Hb Saturation
Oxygen loading and unloading
$O_2 + H^+ \bullet Hb = Hb \bullet O_2 + H^+$
unloading
low PO_2 in the tissues
high PO_2 in the lungs
0
20
40
60
80
100
Partial Pressure of Oxygen (Torr)

Resting O_2 Consumption

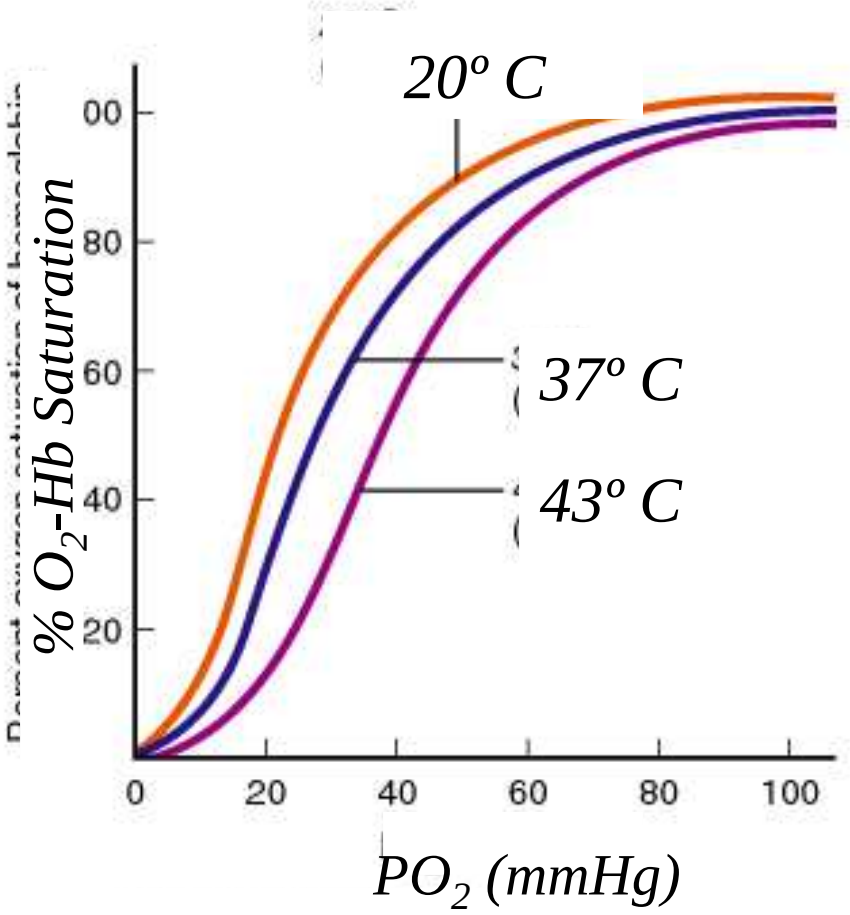


- *75% of the O_2 in the blood is available as a reserve.*

Modification of Oxygen-Hb Binding



Temperature



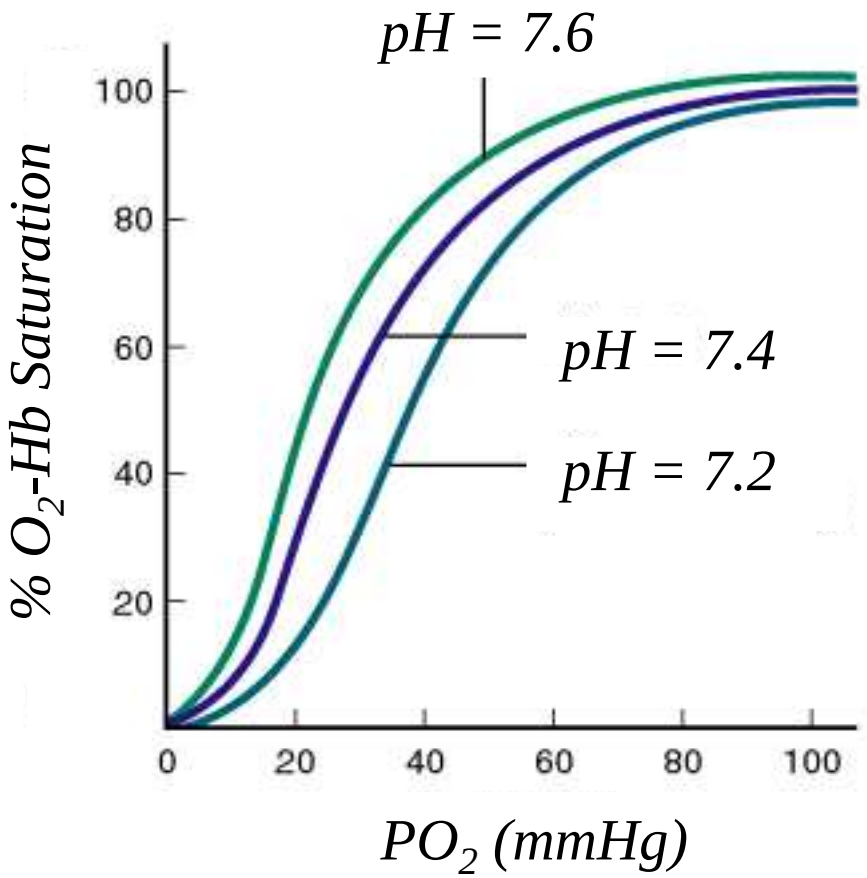
- ↓ *Temperature*
  - ↓ *p50*
    - ↑ O_2-*Hb binding affinity*

- *Temperature is elevated in metabolically active tissues (i.e., muscles)*
  - ↑ *p50:* ↓ O_2-*Hb binding affinity*
  - *Enhances* O_2 *unloading*
- *Temperature is reduced in the lungs*
  - ↓ *p50:* ↑ O_2-*Hb binding affinity*
  - *Enhances* O_2 *loading*

pH

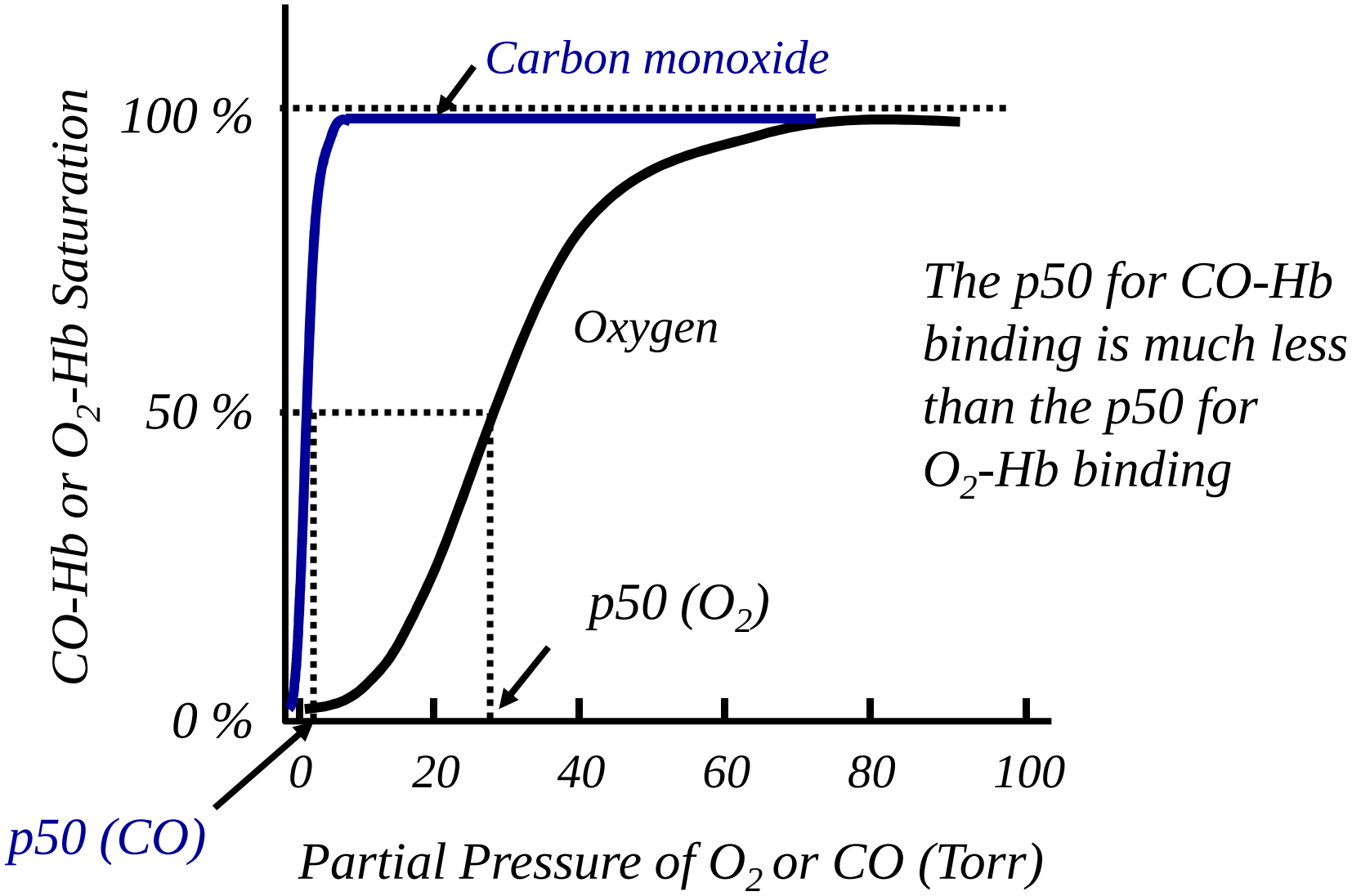
- *pH is reduced in metabolically active tissues (i.e., muscles)*
  - ➢ *↑ p50: ↓ O_2-Hb binding affinity*
  - ➢ *Enhances O_2 unloading*
- *Bohr Effect*

Carbamino Effect



- ➢ *↑ pH*
  - ➢ *↓ p50*
    - ➢ *↑ O_2-Hb binding affinity*

Carbon Monoxide (CO) Equilibrium Curves



The p50 for CO-Hb binding is much less than the p50 for O_2-Hb binding

TYPES OF HYPOXIA- CIRCULATORY HYPOXIA

Def.:Blood flow to the tissue is reduced so that adequate oxygen is not delivered to them despite normal arterial pO_2 , haemoglobin concentration and saturation.

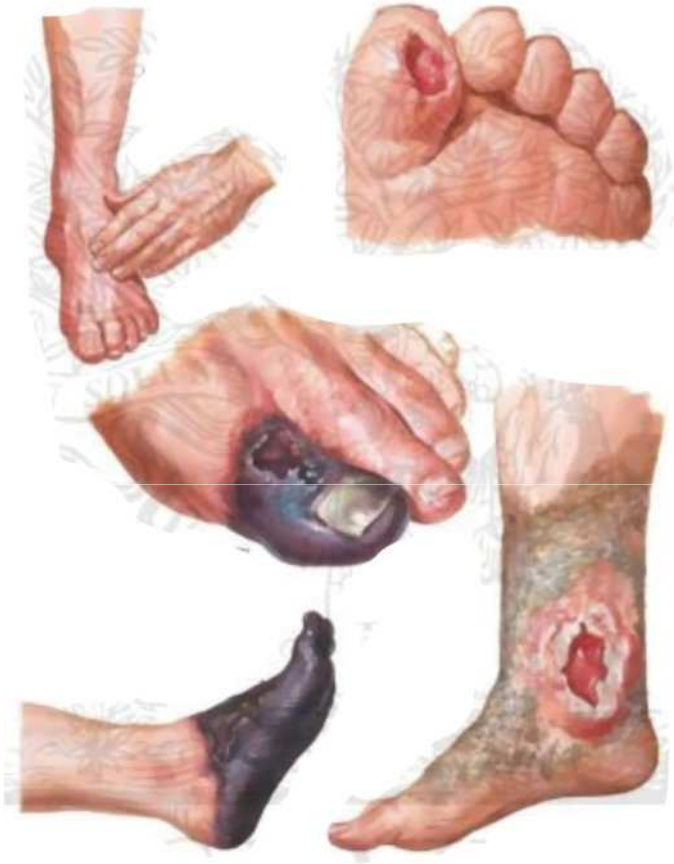
Characteristics: 1. Normal arterial pO_2 , 2. Normal arterial O_2 content,
3. Normal SaO_2 (%) saturation of Hb, 4. **A-V difference higher than normal**

Causes:

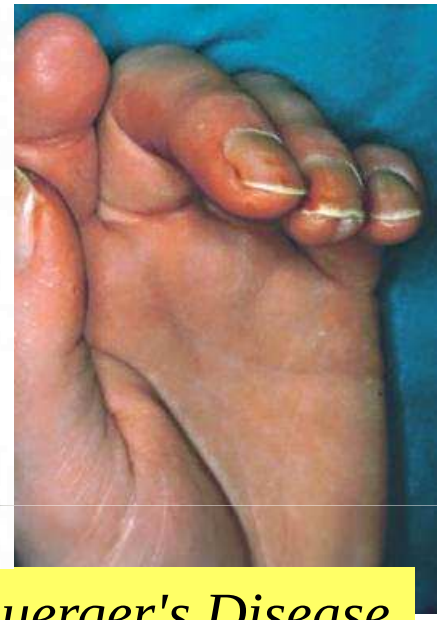
- **Ischaemic** – circulatory failure,
- Cardiac: cardiac arrest, cardiac shock, (infarction, tamponade, pulmonary embolism),
- Arterial vascular:
- a) acute: vasospasms, vasoconstriction, vasoocclusion, embolism (atheroembolism, thrombembolism, gas or fat embolism);
- b) chronic: hypertension, atherosclerosis (partial occulusion,), arterial fibrosis, thromboangiitis obliterans (Winiwanter -Buerger dis.)
- AV- shunting:

- **Venostatic** – venothrombosis, thrombophlebitis
- G forces from maneuvers (mostly aerobatic aircraft), Disease of the blood vessels, C Shock, Exposure to Cold, Sudden change in posture

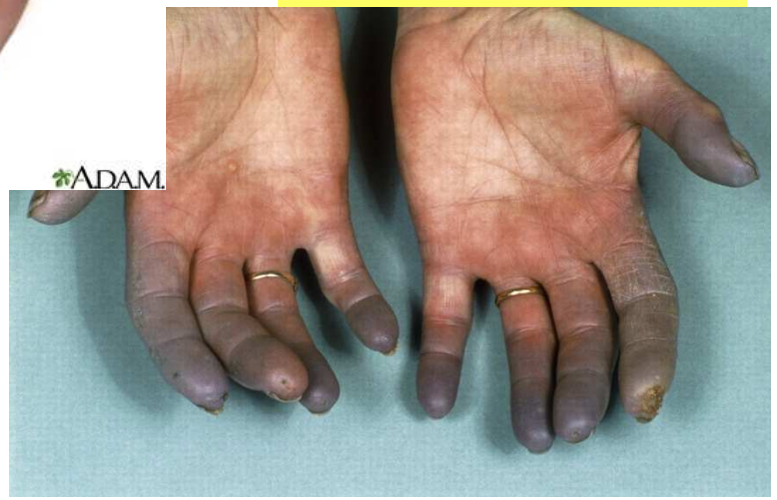
TYPES OF HYPOXIA- CIRCULATORY HYPOXIA



Diabetic macrovasculopathy



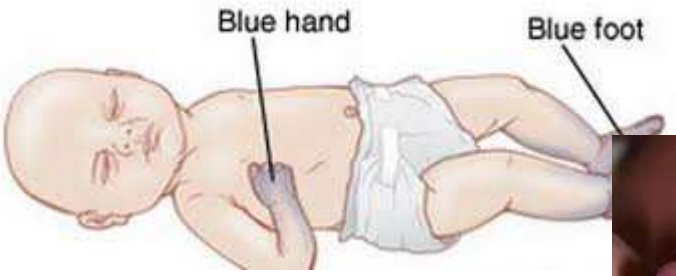
Buerger's Disease

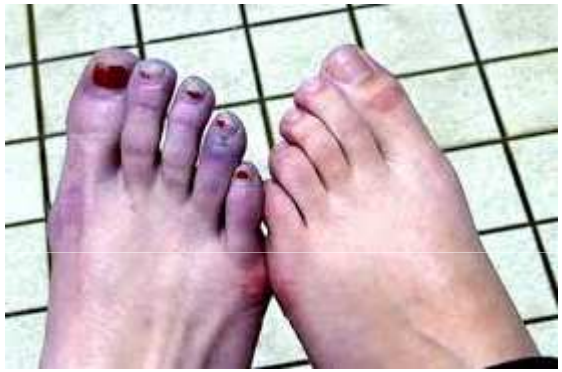


Disorders of peripheral perfusion

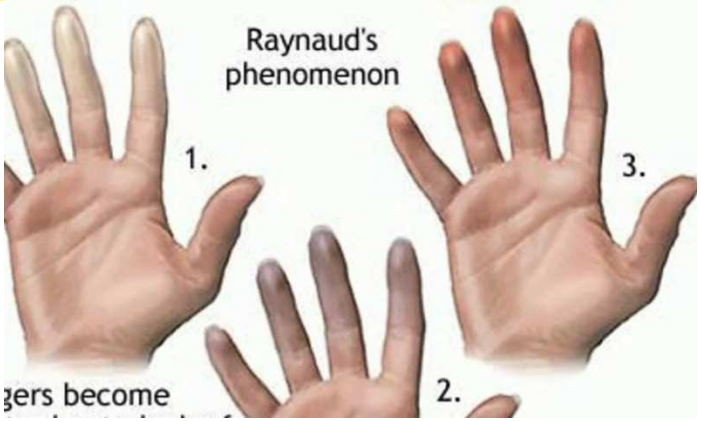
Acrocyanosis

- **Acrocyanosis** - decrease in oxygen & blood supply to the terminal parts (acral areas) of extremities due to constriction or spasm of small blood vessels caused by sympathetic nerves. Mainly, superfitial vessels near the surface of the skin are affected, mostly in hands and fingers.
  - The hands and feet turn persistently blue (cyanosis), because HHb rises locally over 50 g/l and become colder and sweaty and lack pain feeling. Pulse is normal, which rules out ischaemia.
  - Emotions and cooling the hands and worsen the symptoms etting blueish), warmth can decrease symptoms. It is benign. non-progressive, but persistent disease that is more often in women.
- **Raynaud's disease** - differs from acrocyanosis in that it causes white and red skin coloration phases, not just bluish discoloration.





Raynaud disease



TYPES OF HYPOXIA - HISTOTOXIC

Def.: Manifestation of tissue hypoxia and anaerobic metabolism (lactate acidosis) despite **normoxemia or hyperoxemia** (inhalation of oxygen), optimal systemic circulation (blood pressure), optimal perfusion (estimated by NIRS or from PaO_2 and PvO_2).

Characteristics: 1. Normal arterial pO_2 , 2. Normal arterial and venous O_2 content, 3. Normalsaturation of Hb SaO_2, 4. **A-V difference less than normal**

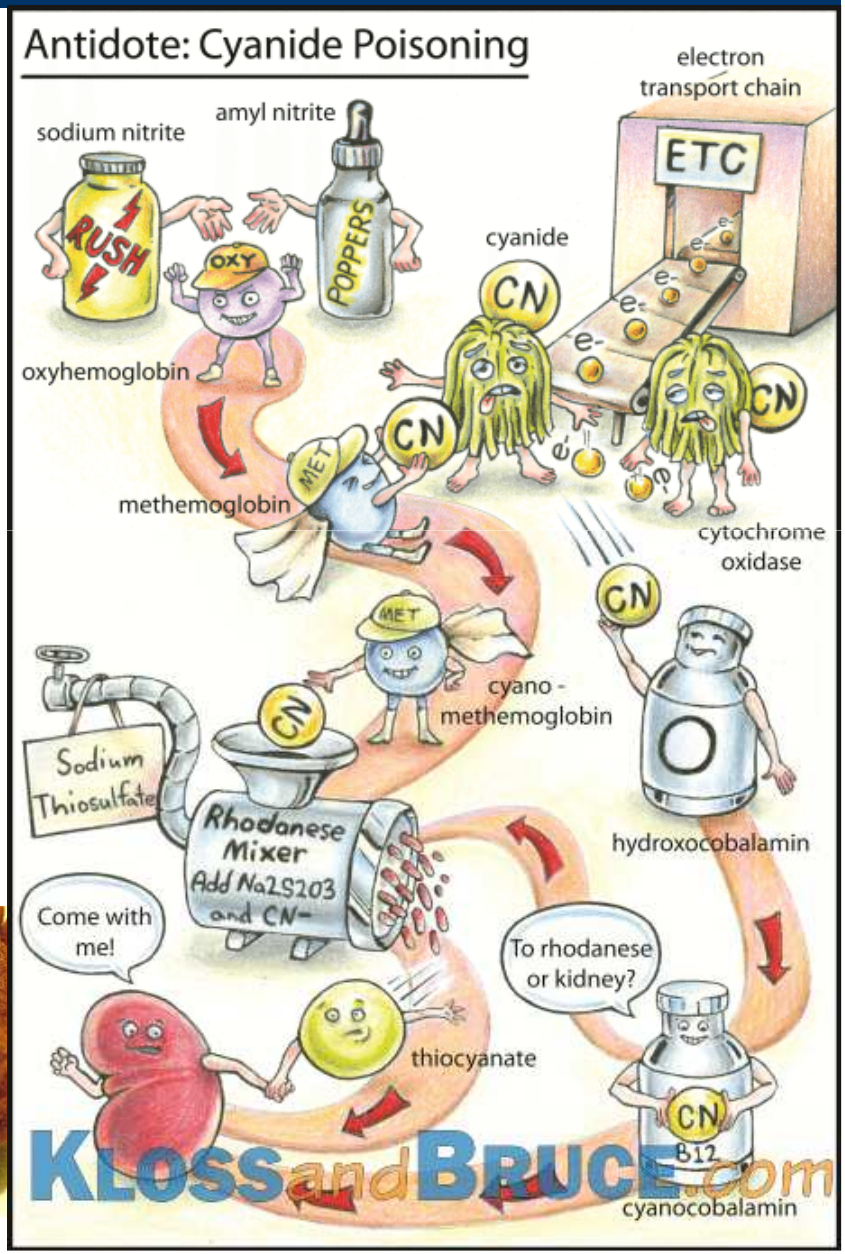
Causes: Tissues do not show extraction of O_2 from blood, while reasons are other than hemic (problem in blood itself).

- ↓ ATP production by the mitochondria due to a defect in the cellular usage of oxygen
- Defective road of oxygen to cells (rare, O_2 as gas has no barriers for diffusion through extracellular space nor cell membranes
- Mitochondrial respiratory chain defect : **Cyanate poisoning** - cytochrome inactivation (mitochondrias), **Alcohol**, Drugs: rotenone, antimycin A

TYPES OF HYPOXIA - HISTOTOXIC

Acute cyanide poisoning

- initial flushing (redness in cheeks), diaphoresis
- **Lung entry:** smoke, munition; : very fast onset,, 38% Tachycardia, cardiac arrest, 45% neurological synmptomsanxietry, agitation, confusion, bradypnoea – respiratory arrest
- **GIT entry:** Cholera-like gastrointestinal symptoms: vomiting, severe diarrhea (rice –watery, often bloody, acute distress, hypovolemic shock
- **Skin and breath may smell of bitter almonds**
- **Cyanosis doe not occur**



Manifestation of hypoxia

- Agitation or panic & anxiety due to lack of oxygen (4000m), personality change,
- Headache, hallucinations (above 7000 m)
- Nausea, vomiting, Dizziness, Hot and cold flashes
- Visual Impairment (colour vision, night vision, blurred)
- Tachycardia, tachyarrhythmias (atrial fibrillation) in predisposed
- Tachypnoe and hyperpnoe due to hypoxic compensation lead tob alkalosis
- Brain edema, pulmonary edema
- Cyanosis – manifestation of increase of reduced hemoglobin; central is typical (native persons in Ands, Himalayas – bluish people)

Manifestations in stages

- Initial stage - > 70-80 mmHg not generally aware of the effects of hypoxia, loss of night vision or color vision.
- Compensatory stage – < 70 mmHg, compensated by hyperventilation, tachycardia etc., poor judgement, drowsiness(somnolency), tiredness
- Disturbance stage - physiological compensations do not provide adequate oxygen for the tissues, impaired in flight control, handwriting, speech, coordination, cyanosis, poor judgments and difficulty with simple tasks
- Critical Stage - blackout, faint, stupor, coma

Laboratory data

Total content of oxygen in the blood (CaO2) **= 20,7%**

Tension of O_2 dissolved in the blood (PaO2) **= 100 mmHg** [100 x 0.003] = 0.3%

- O2 carried in the blood physically = 1,5% of the total content

- O2 carried bound in haemoglobin = 19,2 % of the total content

Normal arterial content of oxygen:

C_aO_2 = [O_2 sat x 1.39 x Hb content %] + [PaO_2 x 0.003]

C_aO_2 = [0.98 x 1.39 x 15] + [100 x 0.003] = **20,7 vol.%**

Data: O_2 sat % = 0,98; Hb content 150 g/l = 15 %, PaO2 = 100mmHg]

Normal mixed venous content: **15 vol %**

Arterial – venous difference: (A-V) **5 vol %**

Hypoxic hypoxia: P_aO_2=50mmHg, other data are normal

C_aO_2 = [1.39 x 0.85 x 15] = [**50** x 0.003] = **18.0 vol%**

Anemic hypoxia: Hb% = 10%, other data are normal

C_aO_2 = [1.39 x 0.98 x **10**] + [100 x 0.003] = **14.2 vol.%**

Laboratory data

SvO2 - True mixed venous oxygen saturation

ScvO2 - Central venous oxygen saturation

- **Low ScvO2**
  - **Increased need for oxygen** in the tissues (hyperthermia, shivering, or exercise) ;
  - **Decreased delivery of oxygen to the tissues** (shock, anaemia, decreased cardiac output, systemic hypoxia).
- **Very high $ScvO_2$**
  - **Decreased demands of tissues for O2** (hypothermia or when under the effects of a muscle relaxant)
  - **Tisseas are unable to extract the oxygen** (cyanide poisoning, anything else that interferes with mitochondrial function).

Normal conditions: critical oxygen extraction ratio (ER_{O2}) = 70%, corresponding to an SvO_2 of around 30%.

Critically ill population: critical ER_{O2} = 60%; SvO2 of around 40%.