HYPOXIA, ISCHAEMIA, CYANOSIS

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https://sarasotavascular.com/wp-content/uploads/2024/11/lower.jpg, https://physiopedia-images.s3.us-east-va.perf.cloud.ovh.us/thumb/9/9b/Peripheral_Cyanosis.jpg/300px-Peripheral_Cyanosis.jpg

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HYPOXIA

GENERAL DEFINITIONS

- Hypoxia
  - Lack of oxygen in tissues
- Hypoxemia
  - Drop of oxygen amount in blood
  - p_aO_2 <8 kPa (60 mmHg) or SpO_2 <90 %
- Hypercapnia
  - p_aCO_2 >5.8 kPa (>45 mmHg)
    - Some sources state value of P_aCO_2 >6.3 kPa (approximately 47.2 mmHg)
- Hypocapnia
  - p_aCO_2 <4.8 kPa (<35 mmHg)

HYPOXIA CLASSIFICATION

- Hypoxic
  - Decreased amount of O_2 in inhaled air
  - Disorders of breathing
- Anemic/Hypoxemic
  - Disturbances in blood oxygen transport
- Circulatory
  - Disorders of circulation
- Histotoxic
  - Inability to utilise oxygen in cells

- Fulminant
- Acute
- Chronic

- Localized
- Generalized

HYPOXIC HYPOXIA

- Drop in oxygen tension in pulmonary capillaries

1. „There is nothing to breathe“
   - Low pressure of air e.g. high altitude
   - Low concentration of O_2 and high CO_2 in some areas (e.g. wine cellar)
2. „There is nothing to breathe with“
   - Disorders and diseases of respiratory system and/or respiration

„THERE IS NOTHING TO BREATHE“

- Low pressure of air and oxygen
- Hypoxic breathing gas
  - From rebreather, life-support system or anesthetic machine

- Mountain sickness (high-altitude sickness)
  - Acute
  - Chronic

HIGH ALTITUDE AND HYPOXIA

- High altitude - >1500 metres above sea level (asl)
  - High – 1500–3500 metres asl
    - Rapid ascent to 2500 metres – drop in blood saturation (S_aO_2), p_aO_2 drop to 7.3-10 kPa (55–75 mmHg)
    - Mild AMS may be manifested
  - Very high – 3500–5500 metres asl
    - Requires acclimatisation, dangerous during climbing
    - S_aO_2 75–85 %, p_aO_2 5.3–8 kPa (40–60 mmHg)
    - Dangerous hypoxia may occur during sleep or exercise
  - Extreme high – 5500–8850 metres asl
    - Progressive deterioration of bodily function counters acclimatisation
    - Rapid descent means severe disease or death
    - Severe hypocapnia and hypoxia, S_aO_2 58–75 %, p_aO_2 3.7–5.3 kPa (28–40 mmHg)

ADAPTATION TO HYPOXIA – TIBET VS. ANDES

Tibetans

- Strengthening of HVR
- Loss-of-function mutations in
  - PHD2 gene – intense HVR (breathing more air units per time)
  - HIF2α - decreased pulmonary artery pressure
- Normal or low Hb concentration prevent thrombotic events
- Reentry HAPE almost always excluded

Andeans

- Hb concentration altitude dependent
- Remodelling of pulmonary arteries (thicker muscular part)
- Higher blood viscosity – risk for CMS
- Can suffer from AMS if ascended/reascended suddenly
- HVR attenuated
- Reentry HAPE possible

HVR – hypoxic ventilatory response, HAPE – high-altitude pulmonary edema

Andeans (Peru)



Tibetans (PR China)



https://cdn.shopify.com/s/files/1/0891/1098/files/traditional-dress_11c35f4b-c839-48a5-9f4b-bfdecd956454_1024x1024.jpg?8086517366377391217
https://www.travelchinatibet.com/data/upload/ueditor/20170216/58a48a8b85e33.jpg

RESPIRATORY ADAPTATION TO HIGH ALTITUDE

- Hypoxic ventilatory response (HVR)
  - Immediate hyperventilation partially effective – drop in p_aCO_2 attenuated respiratory center
  - HIF-1α – oxygen-sensitive transcription factor
    - Cellular response to hypoxia
    - Maintains glycolysis, angiogenesis and erythropoiesis
    - Probable role in central adaptation – respiratory center sensitivity to hypoxia
  - Ventilation rises for seven days
    - Bicarbonate excretion by kidneys to counter respiratory alkalosis

PULMONARY RESPONSE TO HIGH ALTITUDE

- Hypoxic pulmonary vasoconstrictor response (HPVR)
  - V/Q ratio (ventilation/perfusion) temporarily improved
  - Redistribution of blood to less perfused but better ventilated lung areas

  - Increase in pulmonary arterial blood pressure
  - HIF-1α
    - Protein secretion, inflammatory cytokines and leukocytes in bronchi increased
    - Matrix-metalloproteinase 9 upregulated
    - Isthmin 1 (ISM1) upregulated
    - Microvascular permeability increased

CIRCULATION AND HEMOPOIETIC RESPONSE IN HIGH ALTITUDE

- Mild increase in cerebral circulation

- Increased diuresis and plasma volume depletion – haemoconcentration
- Increased secretion of erythropoietin by kidney
  - Chronic adaptation, important in CMS
  - Hb saturation affected
    - Hypoxia (decreasing) vs. RAL, increased 2,3-diphosphogylcerate (DPG) in Ery (increasing)
    - Goal is to keep saturation of Hb in pulmonary arteries

HIGH ALTITUDE SICKNESS

- Acute mountain disease (AMS)
- High altitude cerebral edema (HACE)
- High altitude pulmonary edema (HAPE)

ACUTE MOUNTAIN SICKNESS (AMS)

- Occurs in minutes to hours
- Altitude above 2500 metres asl (sometimes >2000 metres)
- Main symptom – headache
  - GIT symptoms – nausea, vomiting, diarrhea
  - Fatigue
  - Dizziness/light-headedness
- Lake Louise Questionnaire Score, Lake Louise Symptom Score and AMS Clinical Function Score for assesment of severity
  - Recommended to do after 6 hours to exclude travel symptoms or effect of acuta hypoxia via vagal responses
  - Symptoms persisting >3 days – other diagnose for consideration

LAKE LOUISE QUESTIONNAIRE SCORE (AMS)

Symptoms	Score
Headache	0—None at all 1—A mild headache 2—Moderate headache 3—Severe headache, incapacitating
Gastrointestinal symptoms	0—Good appetite 1—Poor appetite or nausea 2—Moderate nausea or vomiting 3—Severe nausea and vomiting, incapacitating
Fatigue and/or weakness	0—Not tired or weak 1—Mild fatigue/weakness 2—Moderate fatigue/weakness 3—Severe fatigue/weakness, incapacitating
Dizziness/light-headedness	0—No dizziness/light-headedness 1—Mild dizziness/light-headedness 2—Moderate dizziness/light-headedness 3—Severe dizziness/light-headedness, incapacitating

Based on LLQS score, AMS is classified as follows:

- Mild: 3–5 points
- Moderate: 6–9 points
- Severe: 10–12 points

https://www.researchgate.net/publication/362314681/figure/tbl1/AS:11841337158860 82@1659330886129/Lake-Louise-Questionnaire-Score-for-diagnosis-of-AMS.png

LAKE LOUISE CLINICAL SCORE

Parameter	0	1	2	3	4
Mental status	Normal	Lethargy/lassitude	Disoriented/confused	Difficult to rouse/unconscious	-
Ataxia (heel-toe)	Normal	Maneuvres to balance	Steps off line	Falls down	Unable to stand for the test
Peripheral edema	None	One location	≥2 locations	-	-

If symptoms (from LLQS) + clinical sings ≥5 -> consider AMS

According to: https://scielo.org.za/img/revistas/samj/v107n7/08f02.jpg

AMS CLINICAL FUNCTION SCORE

- Influence of AMS on activities performance

Value	Influence on activities	Necessity of evacutation
0	None	No
1	Slight reduction	No, symptoms not forcing activities change
2	Moderate reduction	Cease ascent, patient eligible for descent
3	Severe reduction	Yes

HIGH ALTITUDE PULMONARY EDEMA (HAPE)

- Occur within 1 – 3 days after reaching new altitude (after 4+ days unlikely)
- Pathomechanism
  - Hydrostatic oedema due to HPVR
    - Caused by hypoventilation, alveolar hypoxia, increased sympathetic activity, decreased NO production
    - Increase in pulmonary arterial pressure
    - Inflammatory cytokines as secondary factors
    - Microvascular permeability developed
- Gradual ascent at maximal speed 600 metres/day (+additional day after every 600 – 1200 metres) decrease the risk
  - After AMS/HACE or HAPE only maximum 300 metres/day recommended

Table 3. Diagnostic criteria for HAPE.

A. At least two of these symptoms:	• Dyspnea • Cough • Asthenia • Reduced physical performance • Chest tightness • Congestion
B. At least two of these symptoms:	• Crackles • Whistles • Tachypnea • Tachycardia

https://www.mdpi.com/2077-0383/11/14/3937

HIGH ALTITUDE CEREBRAL OEDEMA (HACE)

- Develops within 3–5 days after ascending to 2750 metres asl
  - With higher altitudes the risk increases, often emerges suddenly
- Symptoms

Main symptoms	Typical symptoms	Rare symptoms
Clouding of senses	Truncal ataxia*	Papilledema
Lethargy (to coma)		Retinal hemorrhage
Ataxia		Cranial nerve palsy
		Abnormal reflexes
		Focal neurological deficits

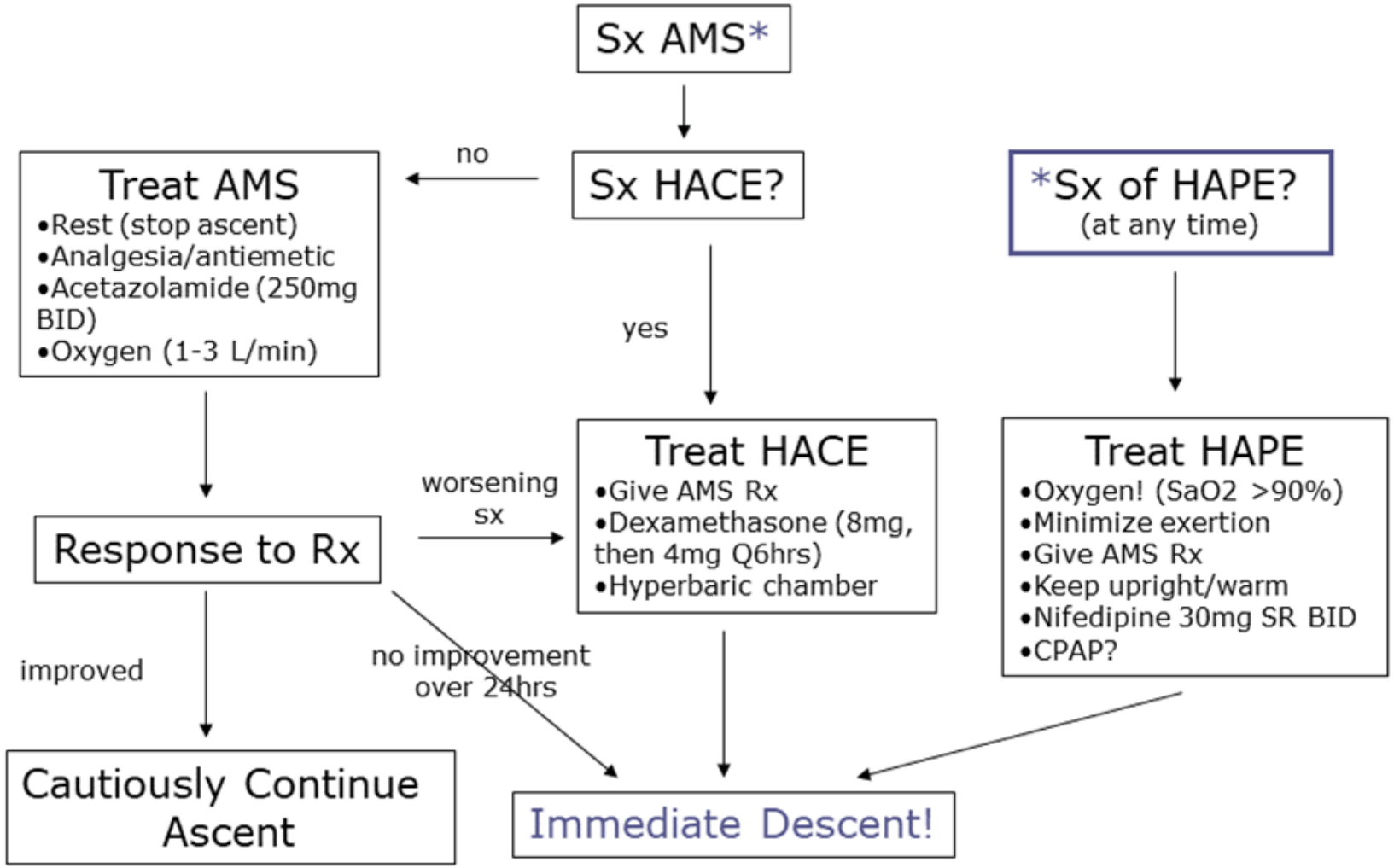
Truncal ataxia – absence of coordination between the trunk and upper or lower limbs

HIGH ALTITUDE CEREBRAL OEDEMA (HACE)

- Pathomechanism
  - Capillary permeability and increased hydrostatic pressure
  - Neurotransmitters altered – cognitive deficit and mood changes
    - Serotonin decreases
    - Dopamine increases – post-synaptic receptors and signal transduction changes impair its effect
    - Acetylcholine decreases – probable cause of fatigue
  - Nitric oxide and inflammatory mediators may alter blood-brain barrier permeability
  - Vasogenic oedema – grey matter more vulnerable
- Death due to cerebral herniation

DIAGNOSTICS CRITERIA FOR HACE AND SYMPTOMS

1. AMS + ataxia/decreased level of consciousness
2. Ataxia + decreased level of consciousness (without AMS)



https://s3.ap-southeast-2.amazonaws.com/wikem.cf.bucket/images/Altitude_flow_sheet.png

„THERE IS NOTHING TO BREATHE WITH“

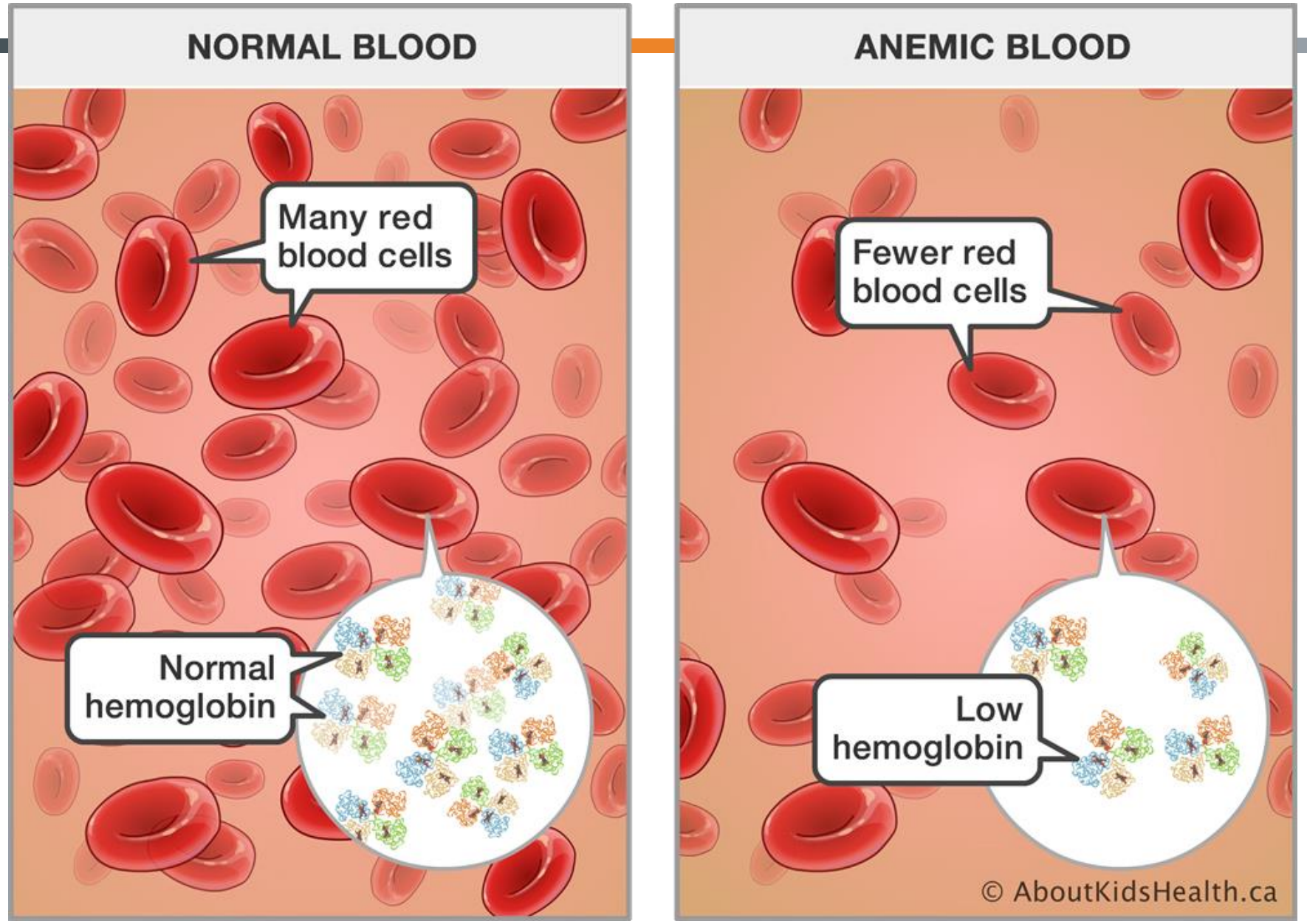
- Airway obstruction
  - Choking, drowning
  - COPD
  - Neuromuscular diseases
  - Interstitial lung disease
- Hypoventilation of lungs
  - Fatigue
  - Excessive work of breathing
  - Barbiturate posioning
  - Pneumothorax
  - Sleep apnea syndrome
- Thoracic alterations
  - Kyphoscoliosis
- Pulmonary hypoxia
  - Enough oxygen in inhaled air (e.g. chronic bronchitis)

PULMONARY HYPOXIA (HYPOXIC HYPOXIA)

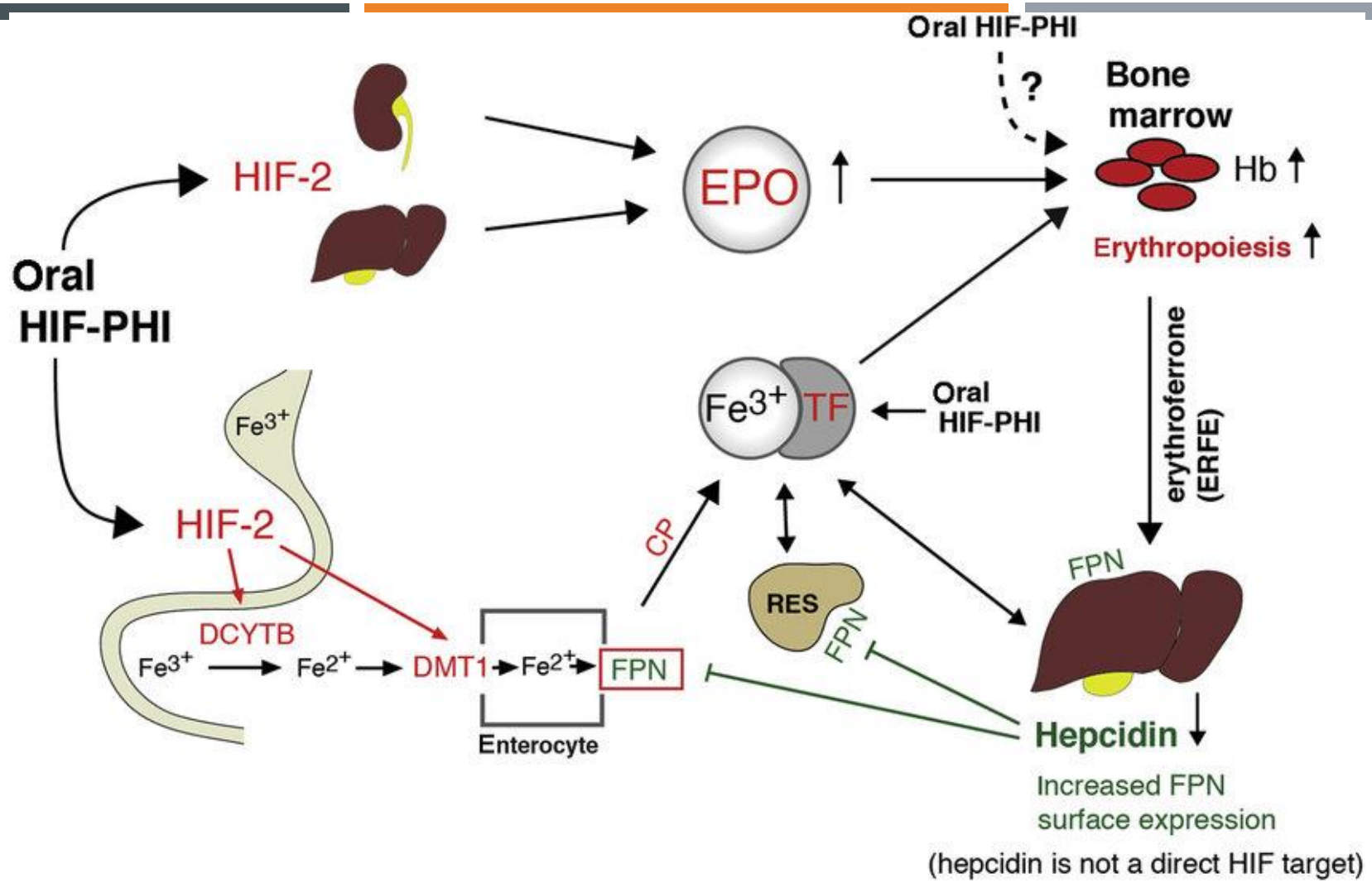
- V/Q mismatch
  - Reduced – bronchitis, obstructive respiratory disease, mucus, pulmonary edema
  - Increased – impaired perfusion
- Pulmonary shunt
  - Right-to-left shunts – intracardiac shunts, pulmonary arteriovenous malformations, fistulas, hepatopulmonary syndrome or physiological shunting (via non-ventilated alveoli)
- Impaired diffusion
  - Thickening of alveolo-capillary membrane
    - Interstitial lung diseases – pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis
    - Connective tissue disorders

ANAEMIC HYPOXIA

- Lack of a sufficient amount of oxygen transporter
- Causes
  - Loss of erythrocytes
    - Haemorrhages
    - Aplastic anaemia (may be induced by chemotherapy as well)
  - Haemoglobin affected
    - Iron deficiency anaemia
    - Megaloblastic and pernicious anaemia
    - Sideroblastic anaemia
    - CO poisoning
    - Methemoglobinemia (nitrites e.g.)



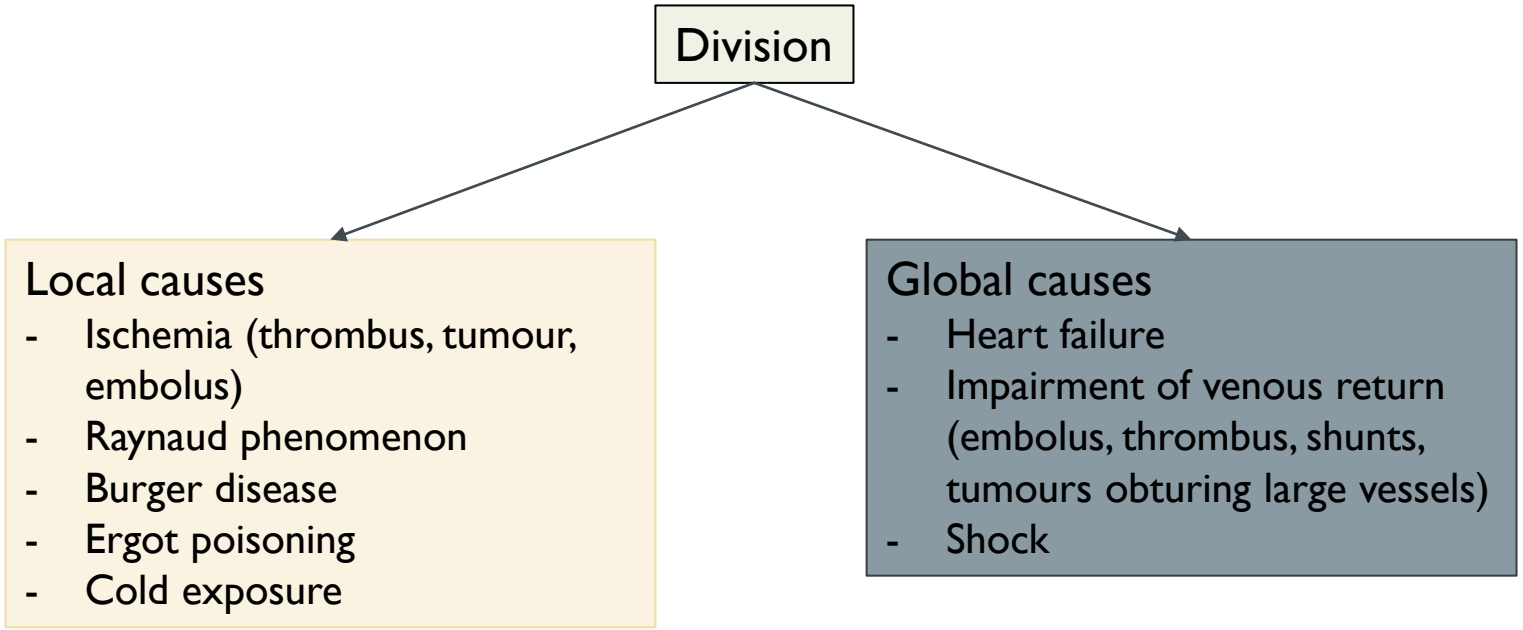
https://assets.aboutkidshealth.ca/akhassets/Anemia_MED_ILL_EN.png?RenditionID=19



https://www.researchgate.net/publication/350185321/figure/fig1/AS:1004531466895360@1616510373111/Overview-of-hypoxia-inducible-factor-HIF-regulation-of-erythropoiesis-Reprinted-from.jpg

CIRCULATORY HYPOXIA

- Blood flow is abnormally low in circulation
- Increased O_2 extraction in tissues -> $\downarrow p_vO_2$ (<5.3 kPa)
- Cyanosis may emerge (reduced Hb >50 g/l) -> local/global



HISTOTOXIC HYPOXIA

- Inhibition of utilisation of oxygen in mitochondria
- Decreased O_2 extraction by tissues -> p_vO_2 almost equal to p_aO_2

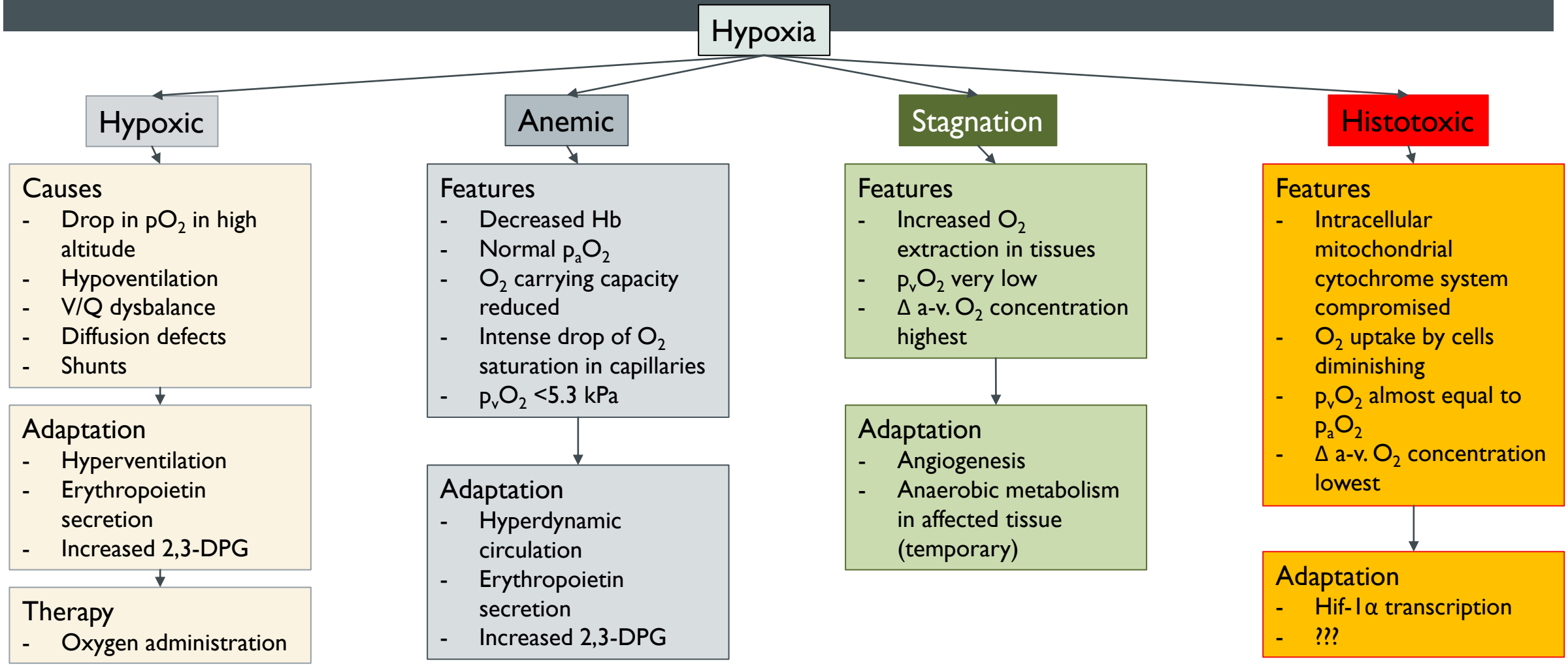
Cause	Mechanism	Interesting facts
Cyanide poisoning	Cytochrome c oxidase inhibition	
Rotenone	Mitochondrial complex I inhibition	Used as pesticide, piscicide and insecticide
Antimycin A	Cytochrome c reductase inhibition	Used as piscicide Fungus-growing (Attini tribe) ants live in symbiosis with Streptomyces bacteria to inhibit pathological fungi growth (Escovopsis genus)
Methanol poisoning	Cytochrome c inhibition	Formic acid as active metabolite May lead to respiratory arrest



Attini tribe ants – „inventors of agriculture“

https://2.bp.blogspot.com/-RAMFb-yO0YA/Uab-ACeAoDI/AAAAAAAAJww/_Lf61yfBnUE/w1200-h630-p-k-no-nu/Trachymyrmex+septentrionalis.jpg

HYPOXIA SUMMARY



According to: https://d45jl3w9libvn.cloudfront.net/jaypee/static/books/9789351529293/Chapters/images/210-1.jpg

SIGNS AND SYMPTOMS OF HYPOXIA

- **Main signs**
  - cyanosis – concentration of reduced Hb ≥ 50 g/l
    - central
    - Local/peripheral
  - dyspnea

- Brain
  - Euphoria, depression or irritation, memory disorders, insomnia or sleepiness, brain edema
- Heart
  - Disorders of heart rhythm
- Lungs
  - Lung edema
- Kidneys
  - Renal insufficiency, activation of renin-angiotensin-aldosterone system, increased production of erythropoietin
- Muscles
  - pain

HYPOXIA VERSUS ISCHEMIA

Characteristics	HYPOXIA	ISCHEMIA
Definition	Oxygen saturation below 90%	Interrupted blood flow
Causes	Respiratory failure and certain medical conditions Can be environmental (high altitude sickness)	Blood clot or spasms of blood vessels
Substance that becomes limited	Oxygen	Oxygen and all nutrients
Testing	Pulse oximeter, then X-rays and CT scans	Physical exam, then X-rays and CT scans
Treatment	Supplemental oxygen by nasal cannula, face mask, mechanical ventilator	Medication, clot-busting drugs, angioplasty, surgery
Part of body affected	Systemic, all organs of the body	Often localized to one organ or tissue
Complications	Cyanosis, brain death	Organ failure, gangrene, peritonitis, death

DifferenceBetween.net

https://3ba1f5b2.rocketcdn.me/wp-content/uploads/2018/04/Hypoxia-VERSUS-Ischemia.jpg

ISCHEMIA

HYPOXIC-REPERFUSION INJURY

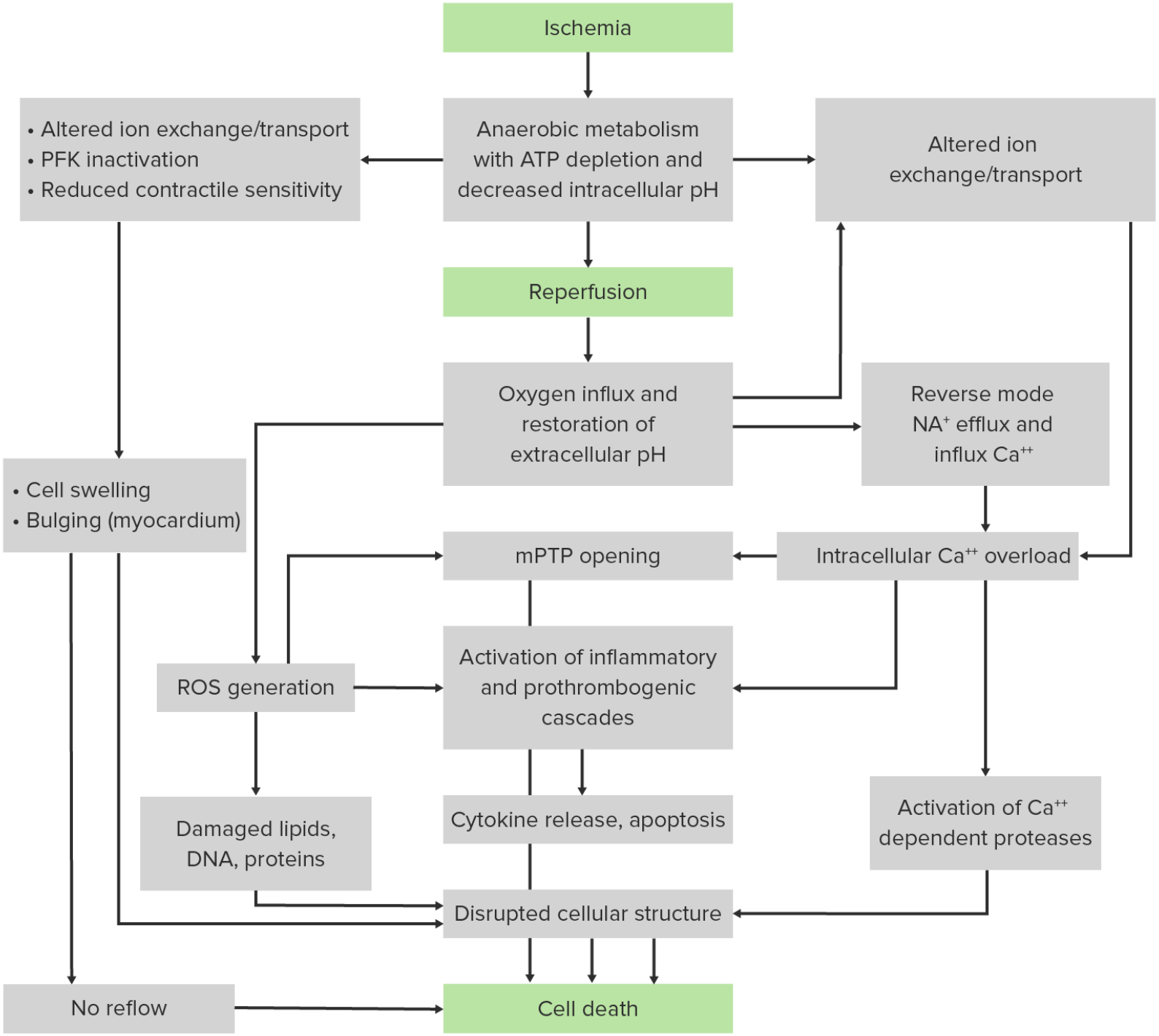
ISCHAEMIA – MOLECULAR EVENTS

1. Ischaemia -> tissue hypoxia
   - Glycogen breakdown via anaerobic glycolysis -> 2 ATPs
   - Pyruvate -> Lactic acid -> cellular acidosis -> ATP production hindered
2. ATP sequential breakdown
   - ATP -> ADP -> AMP -> inosine monophosphate (IMP) -> hypoxanthine -> xanthine
3. ATP-dependent ion pumps dysfunction
   - Na^+/K^+-ATPase
     - Na^+ influx -> osmotic water drawing into cells -> hydroponic cellular swelling
     - K^+ efflux -> hyperkalaemia imminent, membrane potential disruptions
   - Ca^{2+}
     - Ca^{2+} into cells
     - Mitochondrial Ca^{2+} into cytosol -> calpain activated -> xanthine dehydrogenase converted to xanthine oxidase

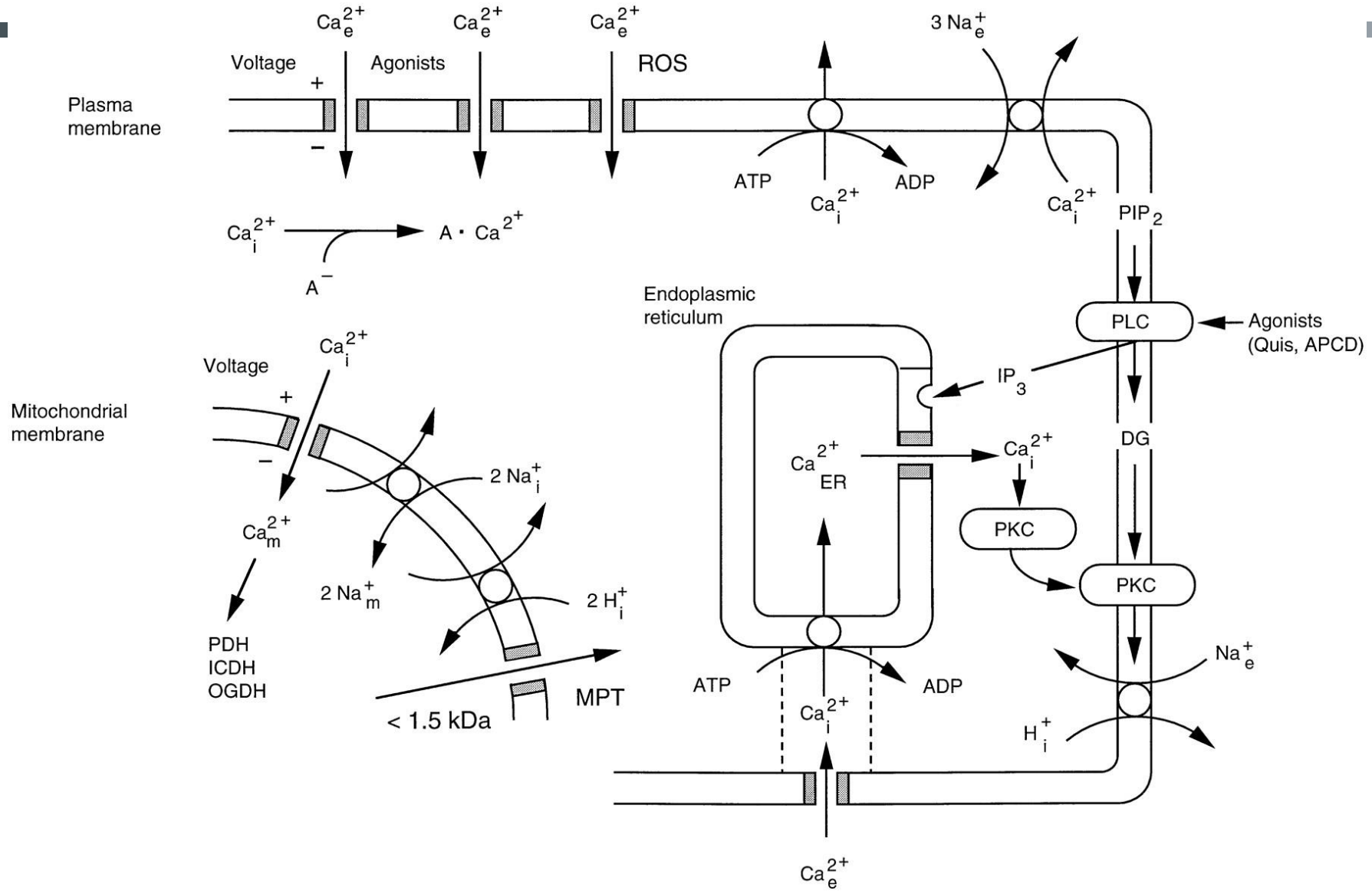
ISCHAEMIA – MOLECULAR EVENTS

4. Phospholipases activated
   - Membrane lipids degraded
     - ↑Fatty acids in circulation
     - ↑Eicosanoids production -> neutrophiles attracted
5. Intracellular Ca^{2+} overload
   - Ca^{2+} into cells -> if cellular Ca^{2+} over10 µmol/l -> ryanodine receptors on ER/SR activated
   - Reduced Ca^{2+} efflux
   - ER decreases uptake of Ca^{2+}
   - ER/SR-mitochondrial transport of Ca^{2+}
6. Cellular edema
   - Ion dysbalance leads to accumulation of fluids inside of cells
   - Vacuoles detected inside of cytoplasm
   - Macroscopic changes – organs getting more pale and enlarged

MAIN CELLULAR EVENTS IN I/R INJURY



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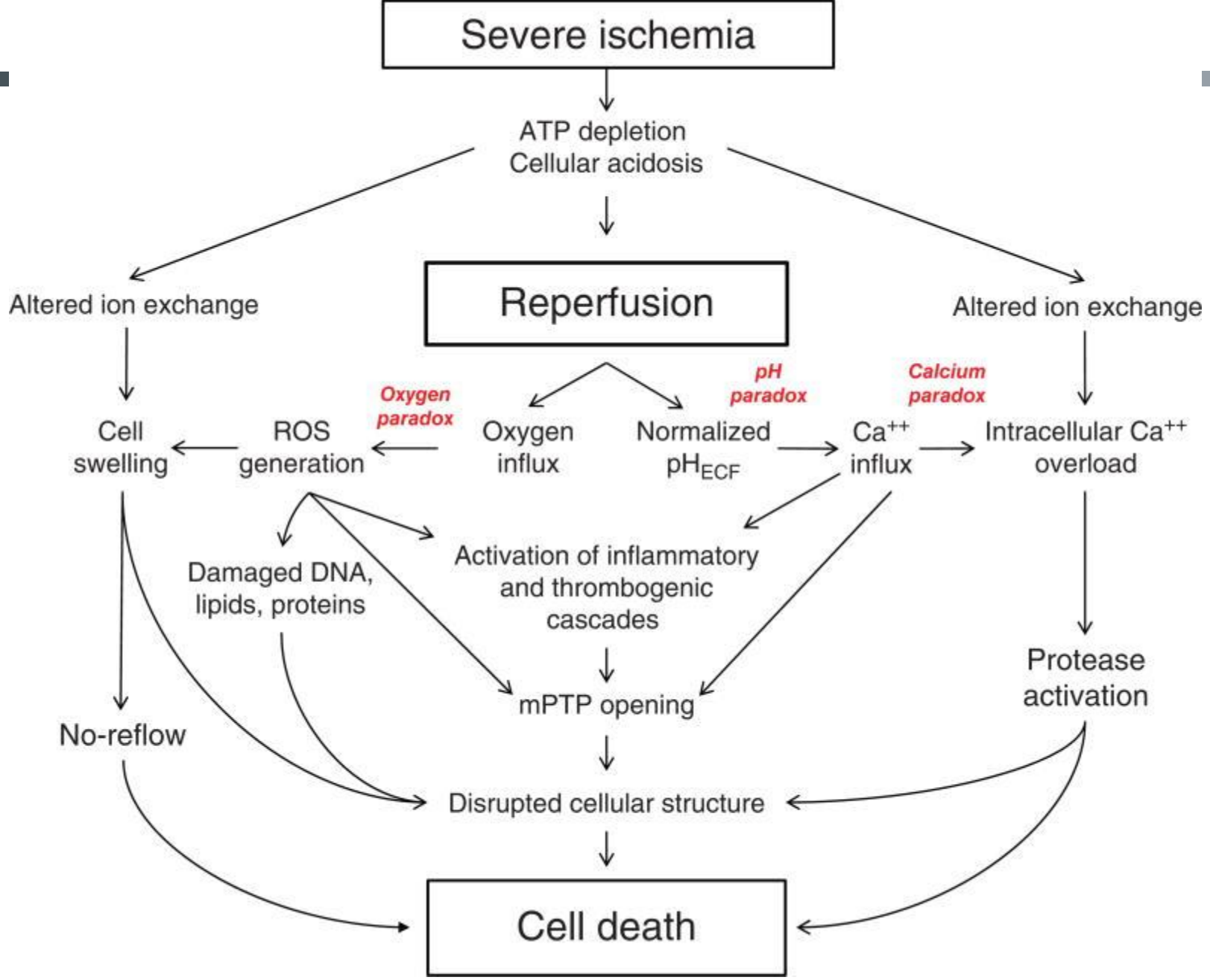


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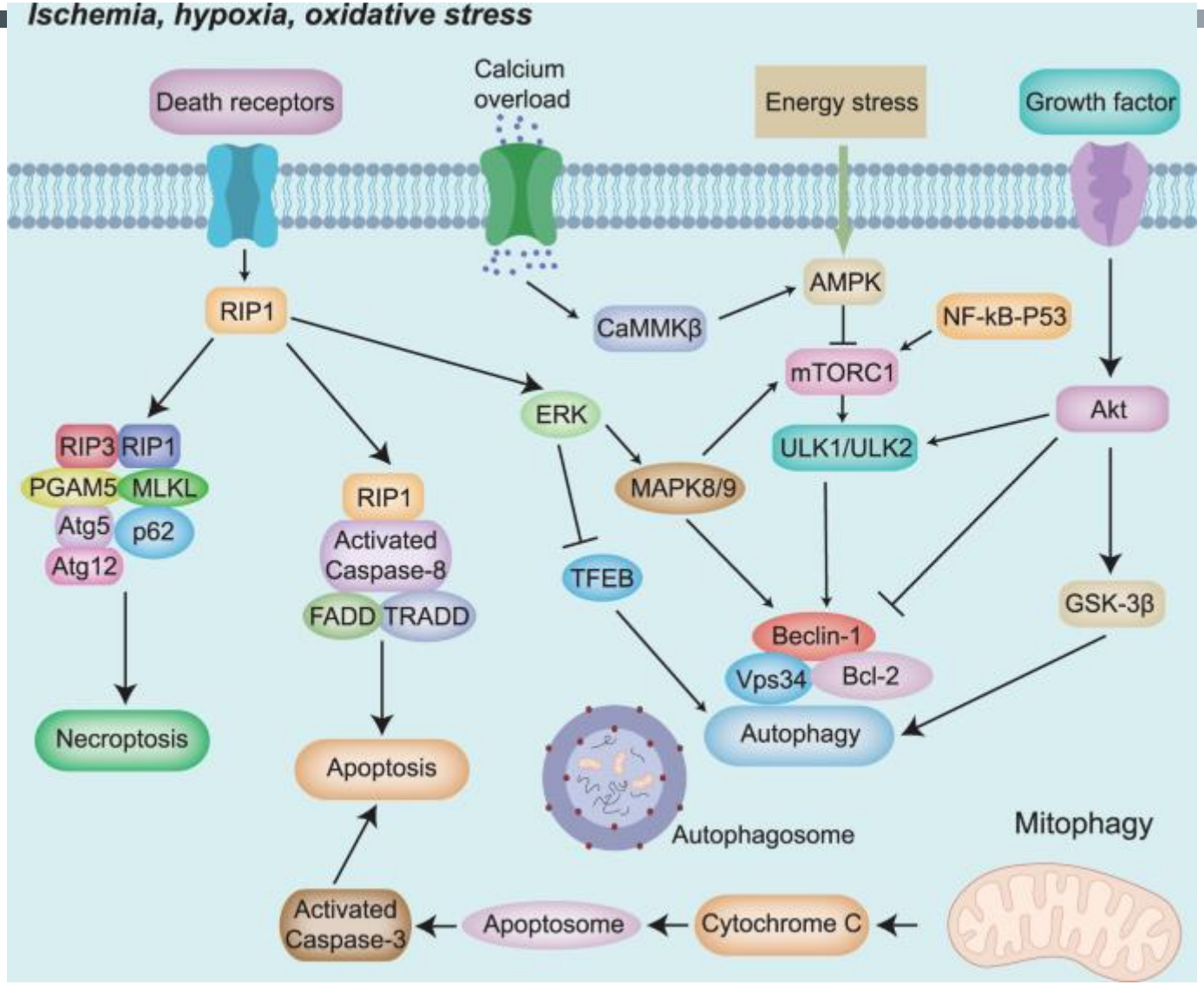
REPERFUSION INJURY HALLMARKS

- Complex and a multifactorial process

1. Generation of reactive oxygen (and nitrogen) species
2. Calcium overload
3. MPT (mitochondrial permeability transition) pores opening
4. Endothelial dysfunction
5. Appearance of prothrombogenic phenotype
6. Pronounced inflammatory response



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5648017/bin/nihms880873f1.jpg



RIP1 – receptor interacting protein 1 (part of RIPK1 (receptor interacting Ser/Thr-protein kinase)/RIP1 cascade, Atg – autophagic proteins, Akt – protein kinase B (set of three Ser/Thr-specific protein kinases)

https://media.springernature.com/lw685/springer-static/image/art%3A10.1038%2Fs41392-022-01064-1/MediaObjects/41392_2022_1064_Fig5_HTML.png

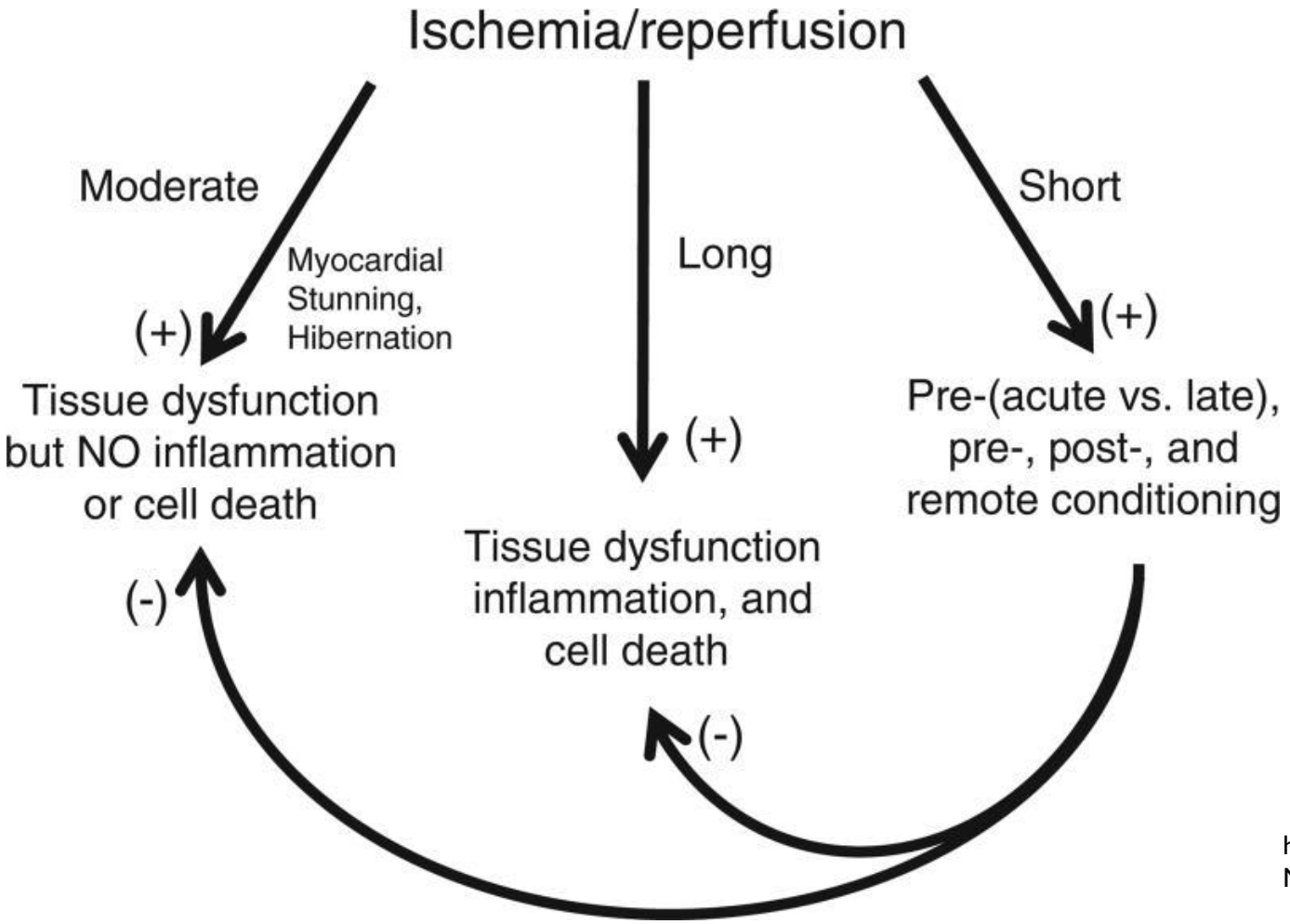
ISCHEMIA-REPERFUSION INJURY PARADOXES

1. Oxygen paradox
   - Atfer reperfusion oxygen will not turn into ATP but into ROS
   - Mostly via xanthine dehydrogenase to xanthine oxidase
2. pH paradox
   - Hydrolases activated during ischemia
   - Acidic cellular pH prevents activity of many enzymes
   - Ca^{2+}-independent
   - Rapid normalisation of cellular pH -> cellular damage increased

ISCHAEMIA-REPERFUSION INJURY PARADOXES

3. Calcium paradox
   - Ischemia
     - Lactate and acid accumulation -> Intracellular acidosis -> Na^+/H^+ antiport active -> intracellular hypernatremia -> Na^+/Ca^{2+} antiport active -> $\uparrow$intracellular Ca^{2+}
     - ATP depletion -> $\downarrow Ca^{2+}$ efflux
   - Reperfusion
     - $\uparrow$intracellular Na^+, Ca^{2+} ($\downarrow$intracellular H^+)
     - mPTP (mitochondrial permeability transition pores) opening, calpain activation, Ca^{2+}-dependent kinases activation

ISCHAEMIA TIME AND REPERFUSION OUTCOMES



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5648017/

PRECONDITIONING

- Short lasting ischemia has a protective effect (10–40 mins) when followed by reperfusion
- Classification
  - Early – 2–3 hours of protection then diminishes
    - Cell death prevention
  - Late – 3–4 days
    - Possible clinical relevance
    - Some cellular changes may occur (stunning, hibernation)
- Target goals
  - Maintain ATP storages longer
  - Prevent damaging effects of Ca^{2+} overload and ROS generation

STUNNING VS HIBERNATION OF CELLS

Stunning (myocardium)

- Reversible dysfunction of cells
- Decrease of ATP, Ca2+ overload (mediated by Ca2+-ATPase/SERCA and RyR2)
- Temporary disorder of ATP utilisation after reperfusion (may last days)
- Fully reversible

Hibernating cell (myocardium)

- Moderate ischemia
- Functions not fully restored after reperfusion
- Decreased mRNA expression, damage to contractile and cytoskeletal proteins
- ↓myocardial phosphates, ↓myofibrils response to Ca2+
- Anaerobic metabolism preferred
- Partly reversible, may result from chronic/cumulative hypoxia damage

MITOCHONDRIA ROLE IN ISCHAEMIA/REPERFUSION INJURY

Pathomechanisms of mitochondrial alteration during ischemia

- Ischemia -> uncoupling of oxidative phosphorylation -> ↓ATP -> Na^+/K^+-ATPase not working
- Ca^{2+} accumulation in mitochondria
  - Further impairment of ATP production
  - Dysregulation of mitochondrial calpains
  - More intense accumulation during reperfusion (consequence of pH correction)
  - Activation of Ca^{2+}-dependent NADH oxidase -> ROS production

Mitochondrial changes

- mPTP (mitochondrial permeability transition pores) opening
- Membrane potential loss
- Mitochondrial swelling
- Loss of cristae organisation
- Mitochondrial DNA degraded

MITOCHONDRIA ROLE IN ISCHAEMIA/REPERFUSION INJURY

- Ca^{2+} accumulation -> mPTP opening
  - Main parts
    - ANT (adenosine nucleotide translocator)
    - VDAC (voltage-dependent anion-selective channel)
    - mtCypD, hexokinase, creatine kinase, Bak, Bax, Bcl-2, Bcl-xL, benzodiazepine receptor, glycogen synthase kinase 3 beta (GSK3-β), PKCε, PKG, p53 and complement component 1Q subcomponent-binding protein (C1QBP)
  - Non-selective transport channel -> membrane potential loss
    - Formation starts from the inner membrane
  - Release of cytochrome c and procaspases into cytosol
    - Role in apoptosis

- Cytochrome c oxidase -> •NO production -> nitrosative stress (N_2O_3, $ONOO^-$)
  - Under hypoxic conditions

MITOCHONDRIA AS A FACTOR OF SURVIVAL

- Damaged mitochondria removal is crucial for cell survival
- Not all mitochondria affected equally (probably those in vicinity of ER more?)

MITOCHONDRIA AS A FACTOR OF SURVIVAL

- Based on mitochondria removal/damage
  - Apoptosis
    - Bax/Bak into outer mitochondrial membrane
    - Pro-apoptotic substances released - cytochrome c, Smac/DIABLO, Omi/HtrA2, and endonuclease-G
  - Autophagy
    - ROS -> inhibition of mTOR (mammalian target of rapamycin)
    - ↑Atg1,-13,-17 -> ↑Vps34, class III PI3K -> ↑Vps150, Atg14, Beclin-1
    - Beclin 1 is crucial in autophagosome formation
    - PARK2 (parkin) and PINK1 (phosphatase and tensin homolog induced kinase) may induce specific form -> mitophagy
      - Ubiquitin-mediated pathway -> via PINK1
      - Receptor-mediated pathway -> via BINP3-L (Bcl2 interacting protein 3 like) or FUNDC1 (FUN14 domain containing 1, active under hypoxic conditions)

MITOCHONDRIA AS A FACTOR OF SURVIVAL

- Based on mitochondria removal/damage
  - Necrosis
    - Deregulated mPTP opening -> prevailing over apoptosis
  - Necroptosis
    - TNF receptor 1 or Fas receptor
    - RIPK1, RIPK3 activated -> MLKL activated
    - Necrostatin-1 reduced TNFα effect (protective)
  - Mitochondrial permeability transition dependent regulated necrosis (MPT-RN)
    - mPTP opening
    - ROS production and $mtCa^{2+}$ overload -> swelling and rupture of mitochondria
  - Parthanatos
    - PARP1 (poly(ADPribose) polymerase 1) -> Aif released from mitochondria
    - PARP1 may activate RPIK1 (necroptosis) (connection unclear)

MITOCHONDRIAL CA2+ EFFECT

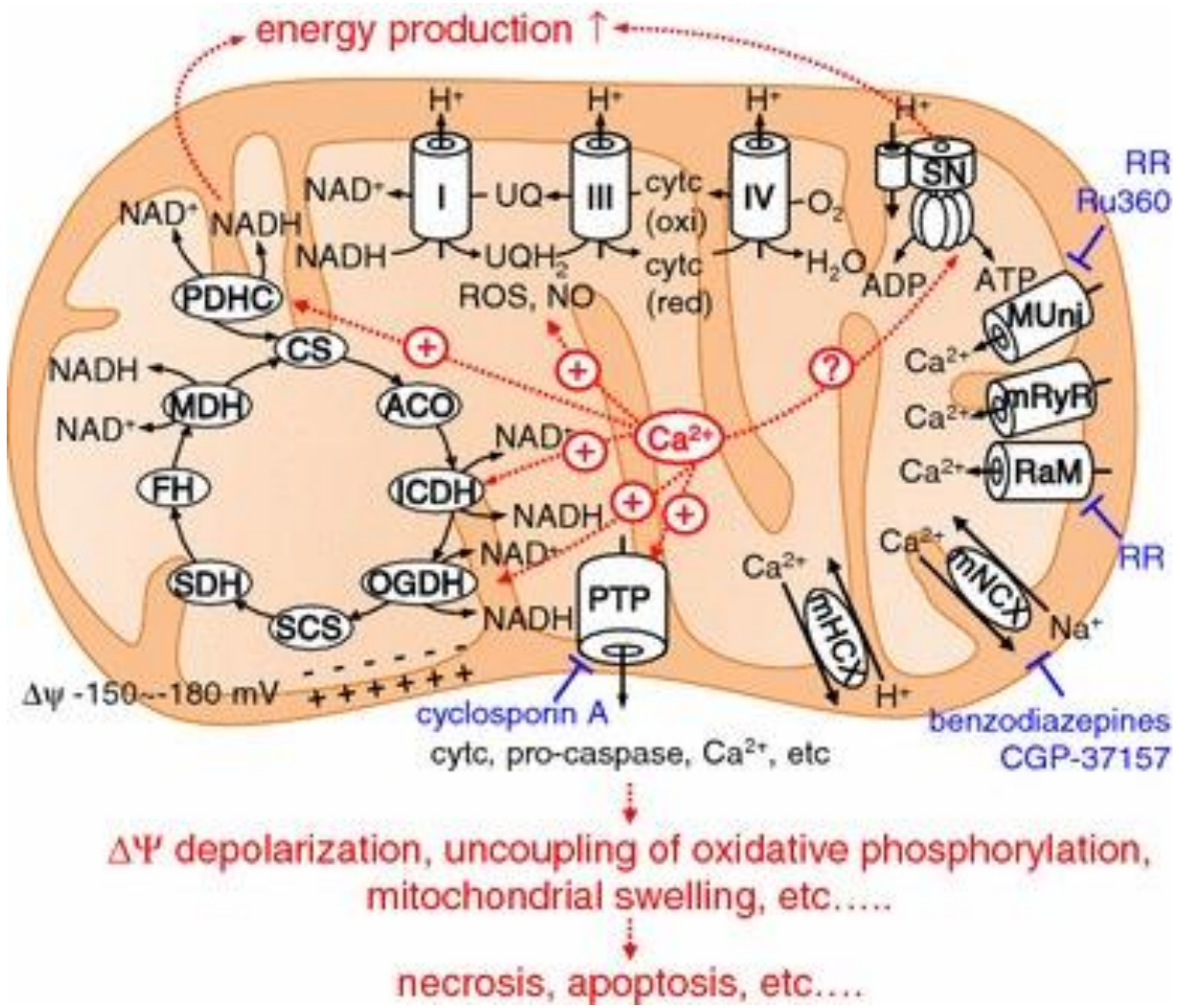
- Ca^{2+} influx into cells
  - VDCC (Ca^{2+}-voltage dependent channels)
  - CRAC (Ca^{2+}-release-activated Ca^{2+} channels) -> source of calcium paradox

- Mitochondria are in vicinity of ER/SR (endoplasmic/sarcoplasmic reticulum)
  - Via RyR (ryanodine receptors) activation
- Mitochondrial Ca^{2+} transported from ER/SR
  - Controversial -> not all mitochondrias are close to ER/SR
  - Influx
    - $mtCa^{2+}$ uniporter (MCU/CCDC190A)
  - Efflux
    - Na^{+}/Ca^{2+} antiport – responds to Na^{+} cytosolic concentration
    - H^{+}/Ca^{2+} antiport

PINK1 gene deficiency -> $\downarrow Ca^{2+}$/calmodullin domain activity -> dysfunction of Na^{+}/Ca^{2+} antiport -> $\downarrow mtCa^{2+}$ efflux (possible in autosomal recessive Parkinson disease?)

MITOCHONDRIAL CA2+ EFFECT

- Physiological
  - Activation of pyruvate dehydrogenase, oxoglutarate dehydrogenase, isocitrate dehydrogenase
    - ↑NADH/NAD^+ ratio -> stimulation of ATP production (increased energy demands)
  - Balancing of ATP production via F1-F0-ATP synthase regulation (?)
- Pathological/cell death
  - ↑mPTP opening
  - ↑Ca^{2+}-dependent NADH oxidase
    - ROS production -> cellular damage
    - Main damaging factor $ONOO^-$ (peroxynitrite radical) -> ROS, RNS (nitrosative stress)



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4276810/bin/12576_2014_326_Fig1_HTML.jpg

CYANOSIS

CYANOSIS – GENERAL OVERVIEW

- Definition
  - Reduced haemoglobin concentration increase in circulation >50 g/L (some sources state >30 g/L)
    - Ev. drop in S_aO_2 to approximately 80 %
  - Blue discoloration of body parts and areas
    - Negroid race – grey/ashy discoloration of skin possible
- Manifestation
  - Typical – rich vascularised parts and thin epidermis – lips, nose, ear lobes, oral cavity, distal parts of fingers and toes
  - Generally – each body part with visible blood vessels



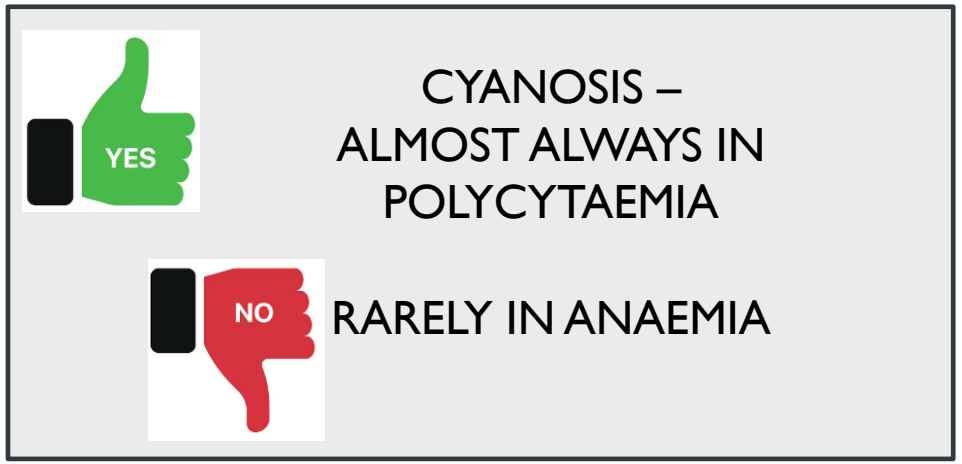
Peripheral neonatal cyanosis – blue-to-purple lips discoloration with nose and philtrum area

https://img.grepmed.com/uploads/3662/clinical-cyanosis-perioral-pediatrics-newborn-original.jpeg

HAEMOGLOBIN CONCENTRATION EFFECT IN CYANOSIS MANIFESTATION

- Absolute value of reduced (deoxygenated) haemoglobin is crucial (HbH_2)!

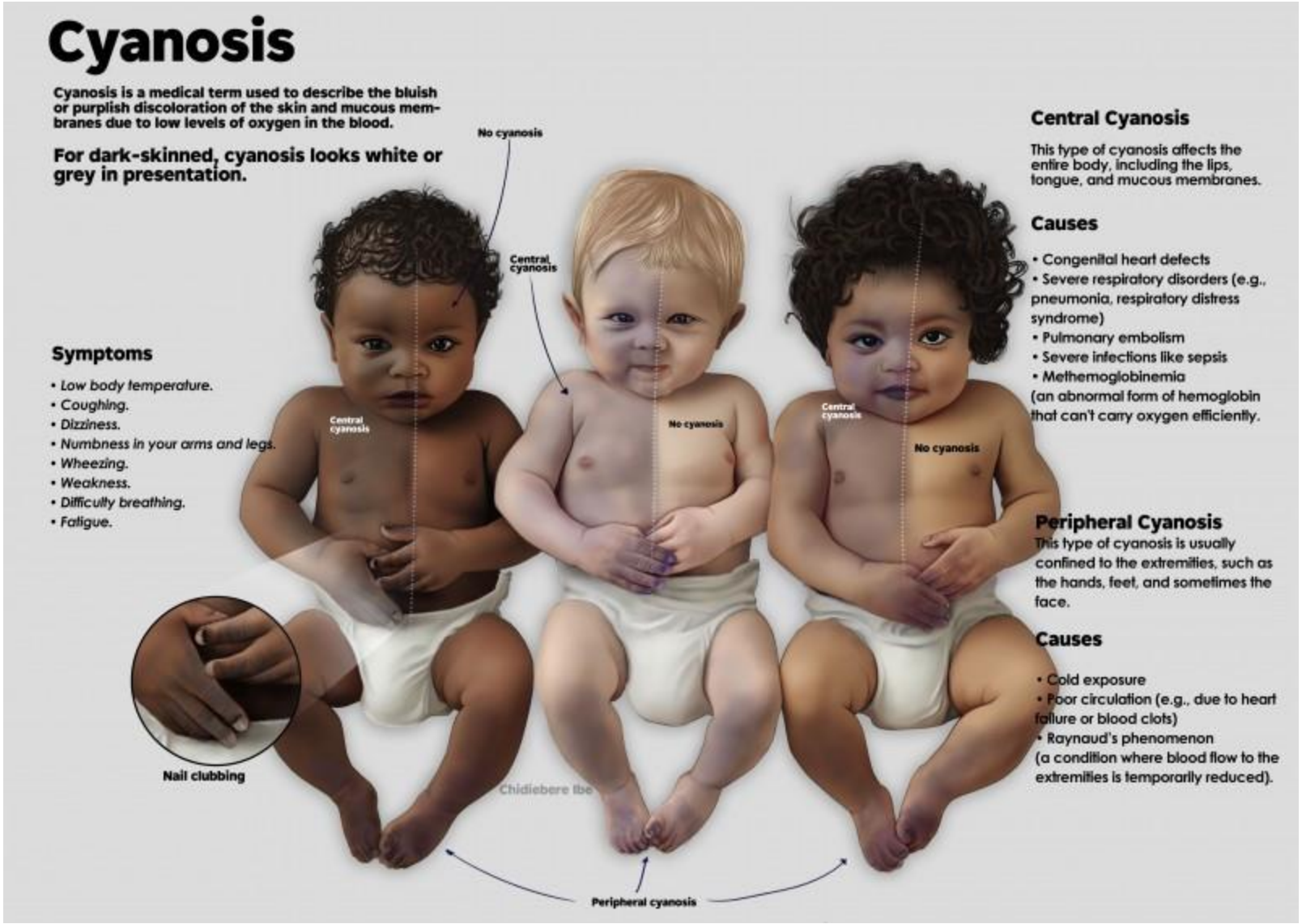
1. Polycythaemia vera; „blood doping“
   - Hb concentration = 210 g/l
   - At HbH_2 = 30 g/l -> **cyanosis manifests at S_aO_2 = 85 %**
2. Normal
   - Hb concentration = 150 g/l
   - At HbH_2 = 30 g/l -> **cyanosis manifests at S_aO_2 = 80 %**
3. Anaemia
   - Hb concentration = 100 g/l
   - At HbH_2 = 30 g/l -> **cyanosis manifests at S_aO_2 = 70 %**



CYANOSIS - CLASSIFICATION

1. Central cyanosis
   - Blue colour of body – visible on mucosae and acral parts
   - Oxygenation disorder as primary cause (Hb saturation problem), **arterial blood desaturation**
2. Peripheral cyanosis
   - Acral body parts blue colour – fingers and toes tips, lips, periorbital area
   - **Peripheral vasoconstriction** typical -> rarely affects mucosa
   - Less severe usually -> may be important in differential diagnostics!
3. Differential cyanosis (classic vs. reverse)
   - Asymmetric upper and body parts discoloration
   - **Severe cardiovascular cause** usually

PSEUDOCYANOSIS
Blue skin colour (ev. mucosa) in normal oxygenation
Causes – toxins, drugs, heavy metals, etc.



https://files.selar.co/product-images/2024/products/chidiebere-ibe1/cyanosis-illustration-selar.co-66ba8692355e7.jpg

CENTRAL VS. PERIPHERAL CYANOSIS DIFFERENCES

Parameter	Central cyanosis	Peripheral cyanosis
Mechanism	Arterial desaturation	Increased peripheral O_2 utilisation
Location	Mucosa, skin	Skin, acral party mainly (lips, nose, ears, finger tips, periorbital afrea)
Tongue	Blue	No change
Body parts temperature when touched	Warm	Cold
Clubbed (Hippocratic) fingers	Present	Absent
Polycytaemia	Yes – secondary	No
S_pO_2 – arteries	Decreased	Normal
Warmin up/massage of acral parts	No effect	Cyanosis disappears/improves
Oxygenotherapy	Cyanosis disappears (pulmonary cause; no effect otherwise)	No effect (?, some sources state positive impact)
Capillary return	<2 seconds	>2 seconds

CYANOSIS PATHOMECHANISM

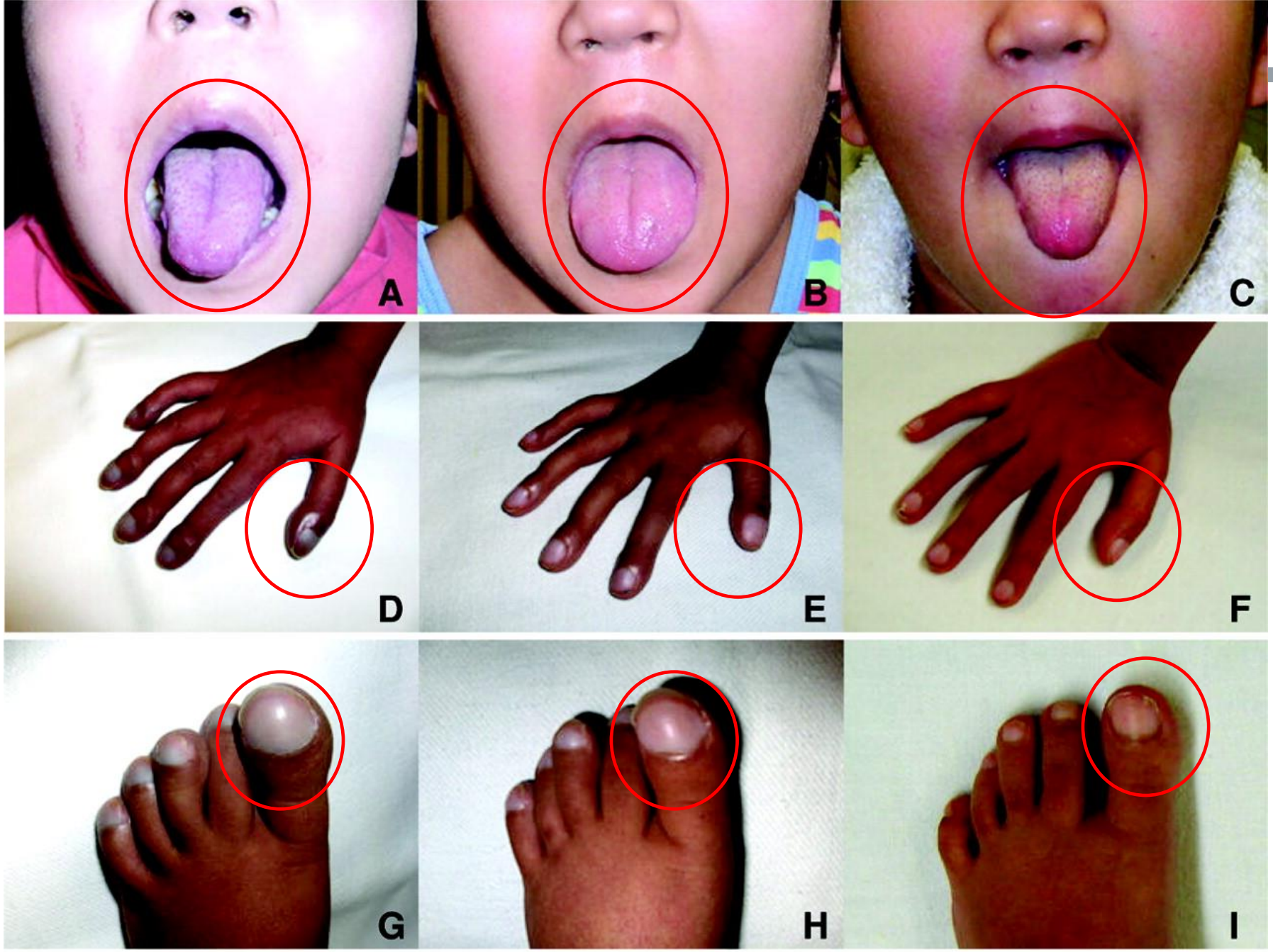
CENTRAL CYANOSIS

CENTRAL CYANOSIS – DESATURATION (DECREASED OXYGENATION)

- Causes
  - CNS damage/injury -> hypoventilation
    - Intracranial hypertension, drugs overdose/intoxication (barbiturates, heroine), generalised tonic-clonic seizures
  - Respiratory diseases and disorders
    - Pneumonia, bronchiolitis
    - Bronchospasm (bronchial asthma)
    - Pulmonary hypertension, pulmonary embolism
    - Hypoventilation conditions
    - COPD, chronic bronchitis
- Result – decreased Hb saturation in its physiological concentration (faster drop to required HbH_2 values)

CENTRAL CYANOSIS – INCREASED UTILISATION (SHUNTS)

- Causes
  - Cardiovascular
    - Right-to-left shunts (congenital heart defects) – tetralogz of Fallot, transposition of great arteries, etc.; Eisenmenger syndrome
    - Heart failure
    - Congenital and acquired valvular defects
    - Acute coronary syndrome -> myocardial infarction
- Result – deoxygenated blood recirculation/stasis during physiological saturation in respiratory system



Blallock-Tausig shunt effect in tetralogy of Fallot
(girl, 6 years, Afghanistan; tetralogy of Fallot compensated by rich collateral circulation)

https://www.ahajournals.org/cms/10.1161/CIRCULATIONAHA.108.788257/asset/c5c7cd29-39bb-4617-a153-d1b54be5dc7f/assets/graphic/2ff1.jpeg

CENTRAL CYANOSIS – HAEMOGLOBINOPATHIES AND OTHERS

- Causes
  - Haemoglobinopathies
    - Methemoglobinemia (see „pseudocyanosis“)
    - Sulfemoglobinaemia (see „pseudocyanosis“)
    - Polycythaemia vera; secondary polycythaemias
    - Congenital cyanosis – „Haemoglobin M“ disease (HbM Boston, other variants) – AD, tyrosine replaces histidine -> Fe^{2+} change to Fe^{3+} -> Fe^{3+}-phenolate complex forming -> functional Hb restoration disrupted -> fixed in „taut“ form (decreased Hb affinity to oxygen)
  - Other
    - Acute mountain sickness (>2400 m. n. m.)
    - Hypothermia (chilblains, frostbites)
    - Obstruction sleep apnoea syndrome – desaturation + polycythaemia + heart failure combination

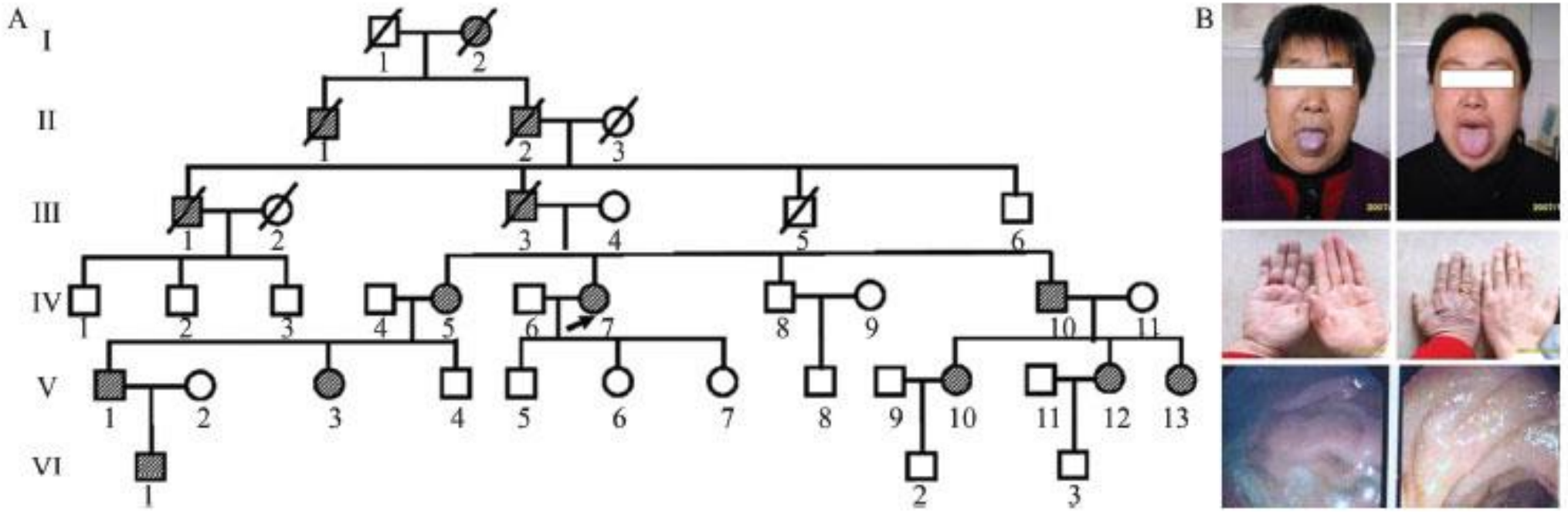


Figure 1 - (A) Family pedigree; grey-striped symbols are family members that present HB-M disease with cyanosis. (B) Proband with cyanosis (left) and one of her noncyanotic daughters (V6; right): lips, hands and stomach visualized by gastroendoscopy.

„Haemoglobin M“ disease

https://minio.scielo.br/documentstore/1678-4685/snzhsNk5qCLGxVqk8CrmTrJ/ffaf224283a23c70a7e3903e12ed0c57b54db474.jpg

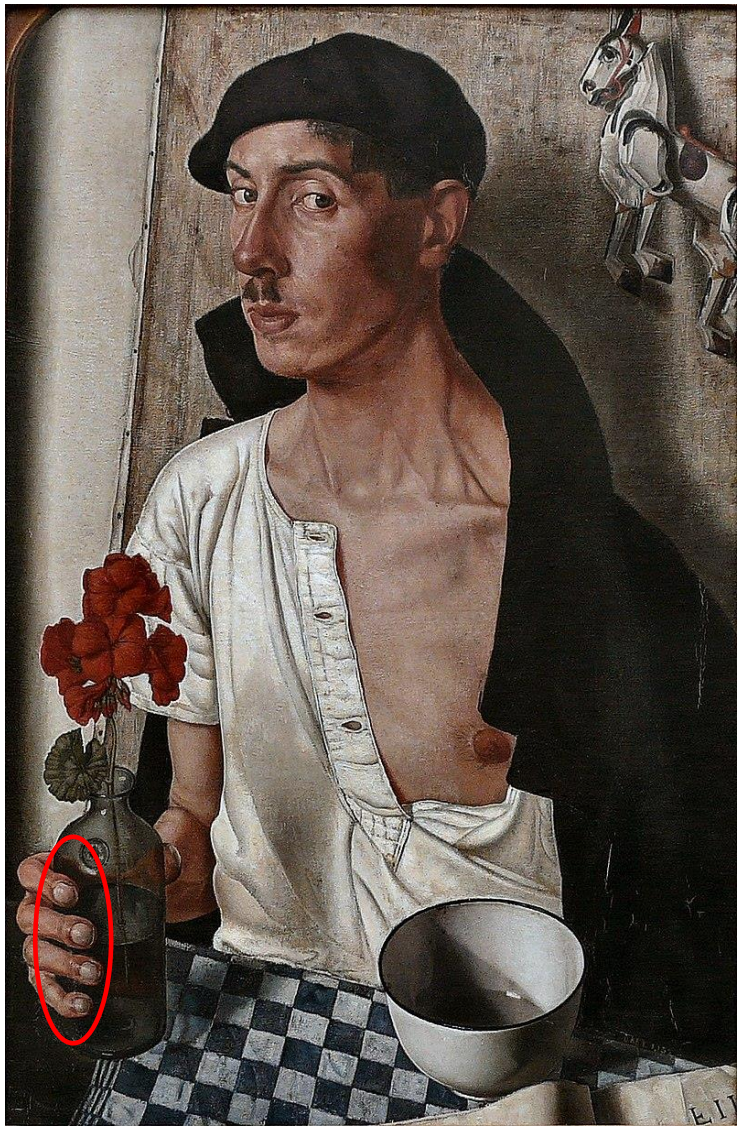
CLUBBING FINGERS PATHOPHYSIOLOGY

- Definition – fingers and toes phalanges dilation due to chronic peripheral hypoxia
- Causes
  - Common – lung tumours, cyanotic congenital heart defects, infectious endocarditis, pulmonary TBC, interstitial lung diseases, pulmonary abscess, empyema, bronchiectasis, metastases, lymphomas, inflammatory bowel diseases (IBDs), biliary cirrhosis
  - Rare – atypical malignancies spreading, asbestosis, pulmonary AV malformations, coeliac disease, active stage of chronic hepatitis, thyroid acropachy (thickening of limbs), cystic fibrosis, atrial myxoma

CLUBBING FINGERS PATHOPHYSIOLOGY

- Physiological
  - Megakaryocytes parts released into circulation -> trapping in pulmonary capillaries -> dissolution to platelets
- Pathomechanism
  - A-V circulation shunt -> megakaryocytes parts trapping on periphery
    - PDGF and VEGF release from trapped megakaryocytes and platelets -> connective tissue hypertrophy and ↑vascular permeability
    - Hypoxia -> PDGF and VEGF effect stimulation and upregulation
    - PGE_2 production -> mRNA for VEGF upregulation
    - Other factors synergy effect -> basic FGF, TGF-β1, carbonic anhydrase IX
  - Peripheral tissues growth -> nail bed -> finger phalanx





Dick Ket (1902 – 1940; dg. dextrocardia?)

https://upload.wikimedia.org/wikipedia/commons/f/f1/CongenitalHeartCase-133.jpg
https://upload.wikimedia.org/wikipedia/commons/thumb/7/7c/Dick_Ket_-_Autoportrait.jpg/800px-Dick_Ket_-_Autoportrait.jpg

CLUBBING FINGERS STAGES

1. No clubbing
   - Nail bed fluctuation and softening
2. Mild clubbing
   - Physiological Lovibond angle between nail bed and cuticula lost (physiological <160 °; clubbing >180 °)
   - Curth angle alteration (physiological approx. 180 °, clubbing <160 °)
   - No Schamroth window
3. Moderate clubbing
   - Changes visible at a glance
4. Severe clubbing
   - Whole phalanx thickening („drummer sticks“)
5. Hypertrophic osteoarthropathy
   - Joints and bones affected, wrinkled and shiny, glossy skin

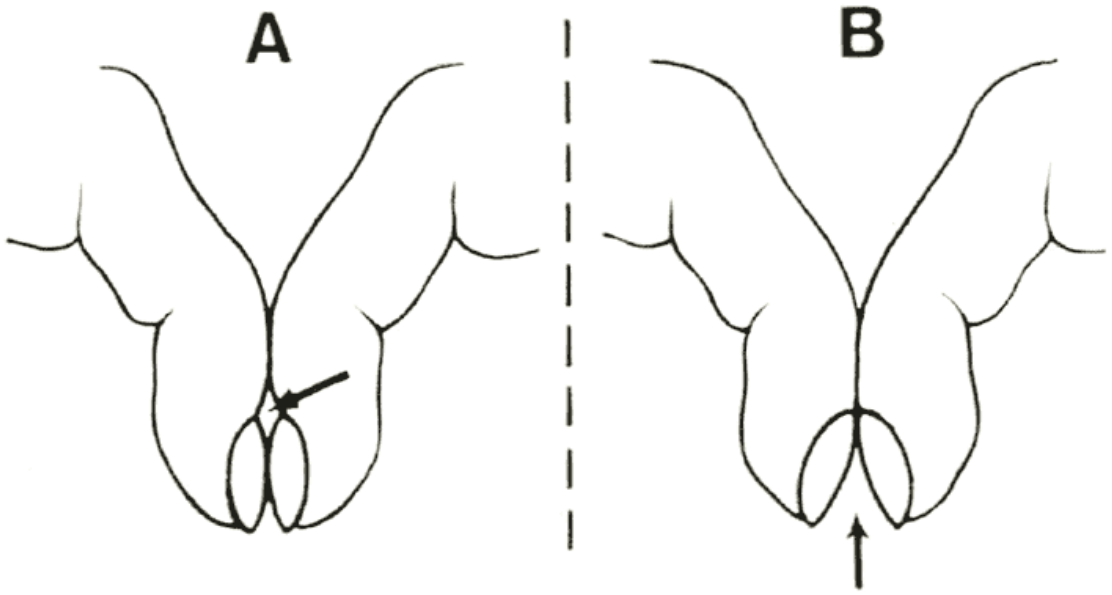
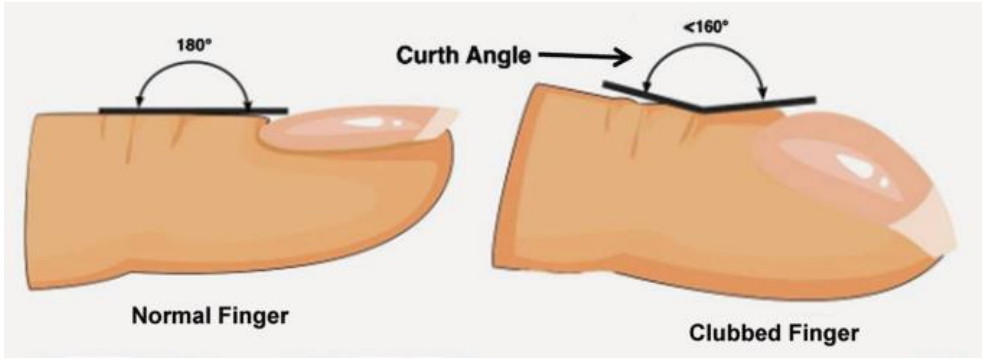
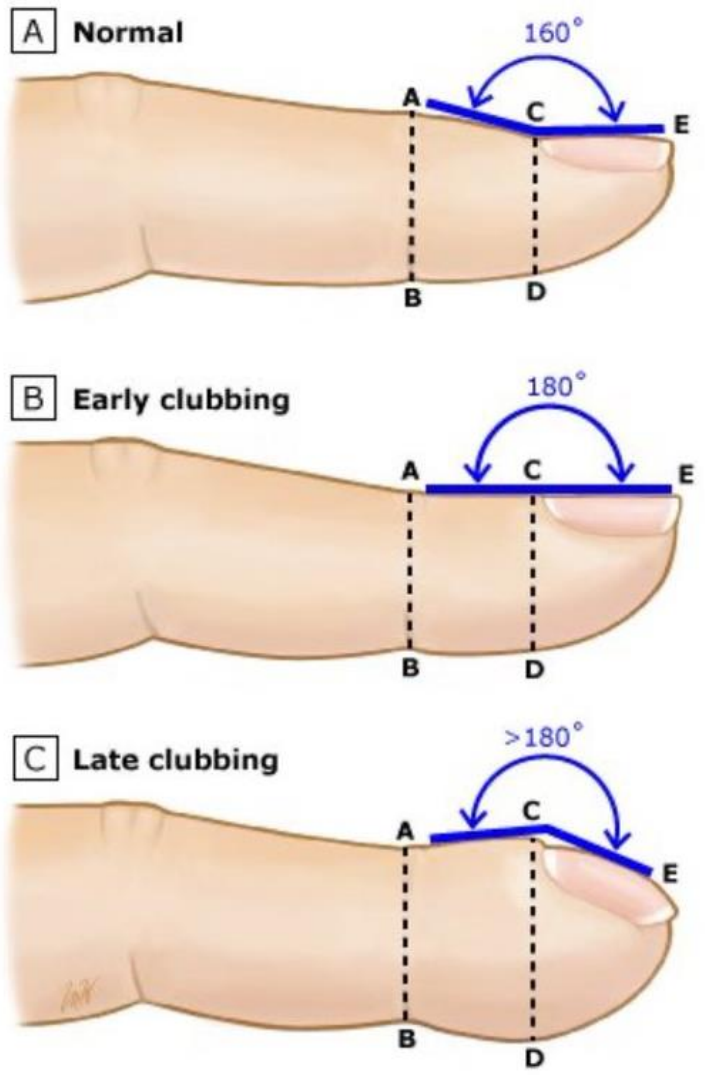


Fig. 1. Diagrams illustrating (A) normal finger contour, and (B) clubbing of the fingers.

Schamroth window



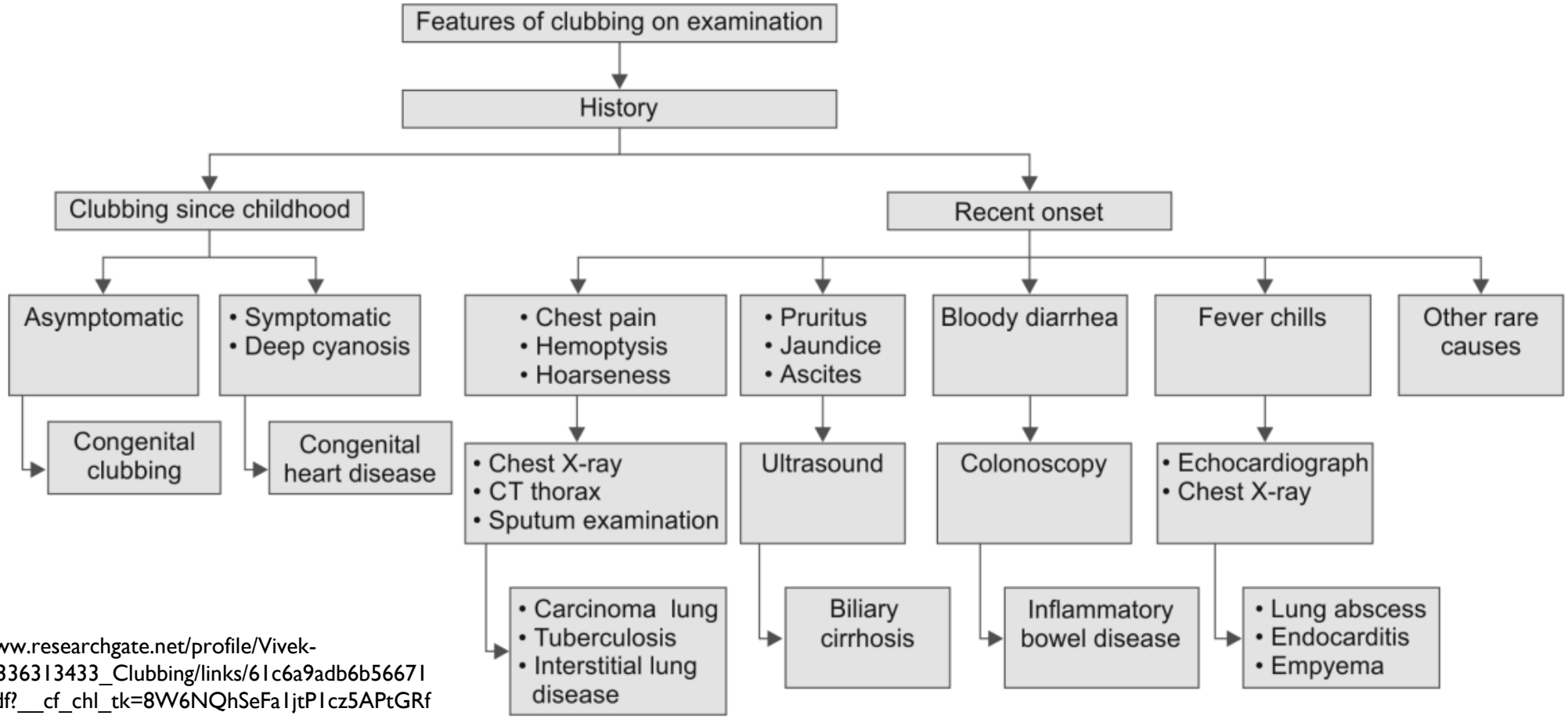
Curth angle



Lovibond angle

https://litfl.com/wp-content/uploads/2019/07/Schamroth%E2%80%99s-window.png
https://pbs.twimg.com/media/GIohfNuWYAA-_g4.jpg
https://media.springernature.com/lw685/springer-static/image/chp%3A10.1007%2F978-3-319-53811-2_9/MediaObjects/426771_1_En_9_Fig91_HTML.png

CLUBBING FINGERS CAUSE – DIFFERENTIAL DIAGNOSTICS



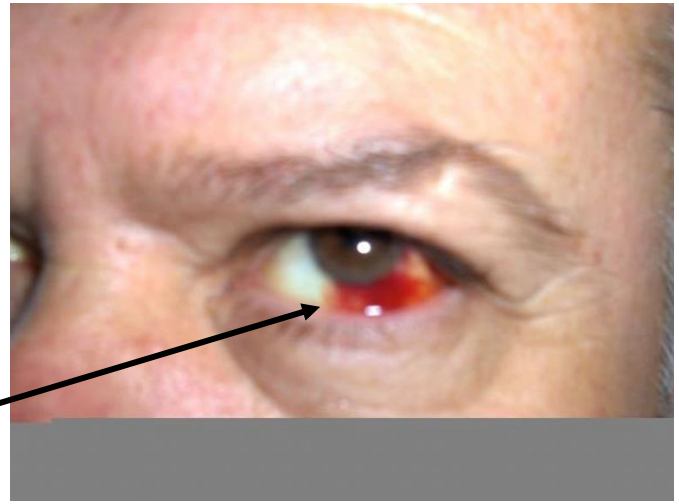
https://www.researchgate.net/profile/Vivek-Chauhan/publication/336313433_Clubbing/links/61c6a9adb6b5667157a38916/Clubbing.pdf?__cf_chl_tk=8W6NQhSeFa1jtP1cz5APtGRf6KFh7Nd.e7R_OoGQiec-1747996502-1.0.1.1-oN_yCZYBmVk2mA621.218rN6wdu3_MPeA66M1xEBfBA

„BLUE MASK“ SYNDROME (PERTHES SYNDROME, TRAUMATIC ASPHYXIA)

- Definition – severe to life-threatening condition associated with intrathoracic pressure increase and retrograde blood flow to head and neck veins (ev. upper limbs)
- Causes
  - Traumatic – car crash, trauma, „crush“ syndrome
  - Iatrogenic – positive-end-expiration-pressure artificial pulmonary ventilation (in order to prevent alveolar collapse)
- Pathophysiology
  - Injury + Valsalva manoeuvre application (breathing against closed glottis) -> air-trapping -> systemic venous circulation pressure elevation -> upper body parts veins dilation -> blood pooling/stagnation -> cyanosis
    - Lower veins are protected by valve system
- Prognosis – good (if the trigger/cause can be contained), long-term neurological consequences risk



„Blue mask syndrome“, susp. delivery trauma



Subconjunctival haemorrhage (injury impact? Retrograde pressure propagation?)



Chest injury (hemopneumothorax bilat.)

https://www.researchgate.net/publication/337162585/figure/fig53/AS:824040105189394@1573477879513/The-term-neonate-with-blue-mask-syndrome-Stagnation-cyanosis-of-the-face-Continual-aEEG.png
https://cdn.ncbi.nlm.nih.gov/pmc/blobs/974e/3047851/edcf399ea622/12245_2010_204_Fig1_HTML.jpg
https://cdn.ncbi.nlm.nih.gov/pmc/blobs/974e/3047851/6c89b55e8bf9/12245_2010_204_Fig2_HTML.jpg

PERIPHERAL CYANOSIS

PERIPHERAL CYANOSIS POSSIBLE CAUSES

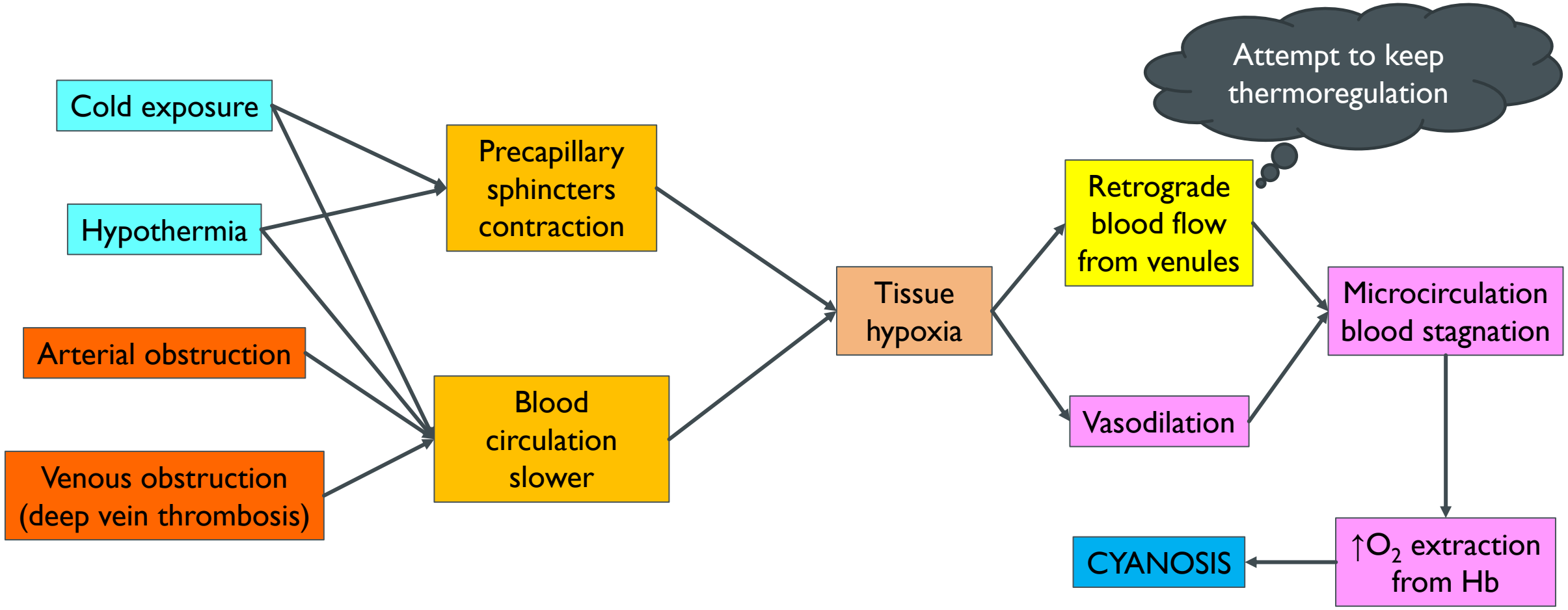
- Decreased cardiac output*
  - Secondary in shoch, heart failure*
- Local vasoconstriction
  - Cold, hypothermia, acrocyanosis, Raynaud‘s phenomenon
- Vasomotor instability
  - Microvasculopathy
  - Often associated with sex hormones concentration changes

*CENTRAL CYANOSIS CAUSES MAT TRIGGER SECONDARY PERIPHERAL CYNOSIS MANIFESTATION

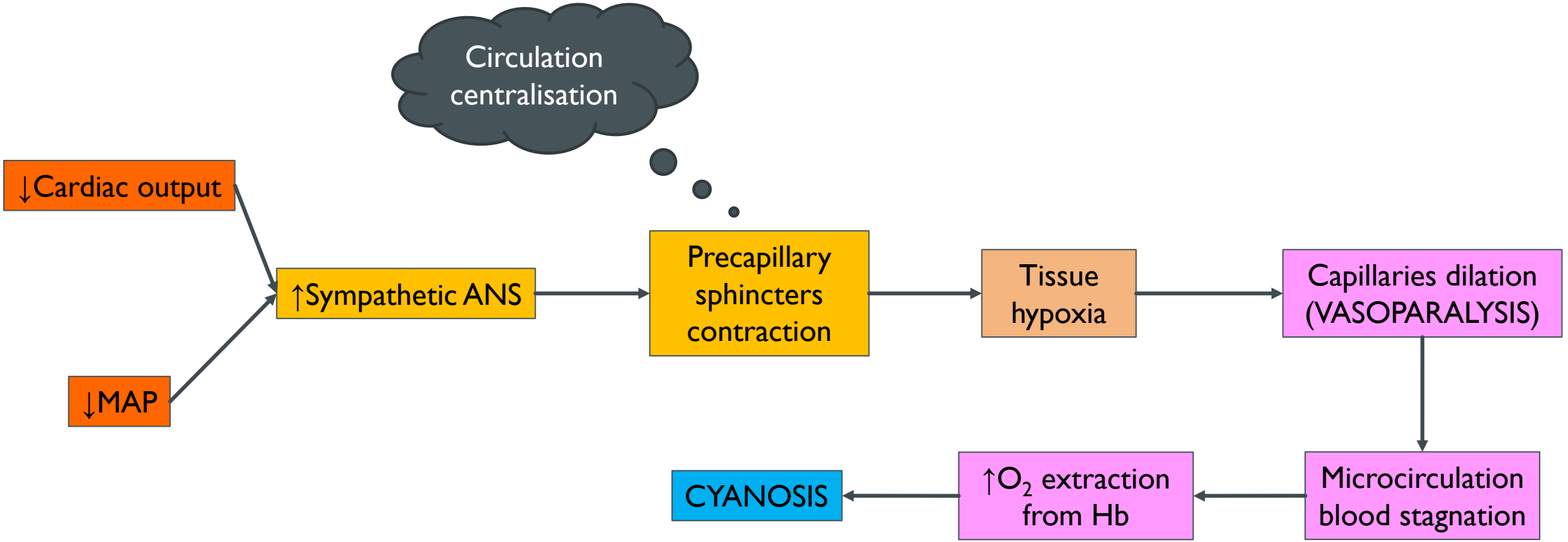
PERIPHERAL CYANOSIS POSSIBLE CAUSES

- Arterial obstruction -> regional ischaemia
  - Peripheral blood vessels affected – atherosclerosis, Berger disease (vasculitis), atheroembolism (cholesterol crystals release with subsequent small vessels blockade)
- Venous region stasis/obstruction
  - Deep vein thrombosis
- Hyperviscous blood
  - Leukaemia, multiple myeloma, polycythaemia, macroglobulinemia

PERIPHERAL CYANOSIS - STAGNATION



PERIPHERAL CYANOSIS – DECREASED PERFUSION





https://upload.wikimedia.org/wikipedia/commons/thumb/1/1a/Peripheral_Cyanosis_due_to_Ischemia.jpg/800px-Peripheral_Cyanosis_due_to_Ischemia.jpg

ACROCYANOSIS

- Definition – persistent blue or cyanotic hands colour (ev. legs, distal facial parts, etc.)
- Causes
  1. Benign (primary) – neurohumoral changes (?)
     - CAVE – cold exposure -> frostbites in acrocyanosis are painless!
  2. Severe (secondary) – infection, toxaemia, antiphospholipid syndrome, cryoglobulinemia; also as paraneoplastic syndrome
     - Often associated with central cyanosis
     - Less lesion symmetry

ACROCYANOSIS

- Pathomechanism
  - ??? -> vasospasm
    - Arteriolar contraction -> cyanosis
    - Venular dilation -> retrograde blood flow -> attempt to keep thermoregulation -> sweating
  - Serotonin effect -> worsens acrocyanosis
  - Tricyclic antidepressants in paediatric patients -> acrocyanosis more frequent
- Treatment and prognosis
  - Treatment -> symptomatic, ev. sympathectomy
  - Prognosis -> often favourable (depends also on the trigger/cause)



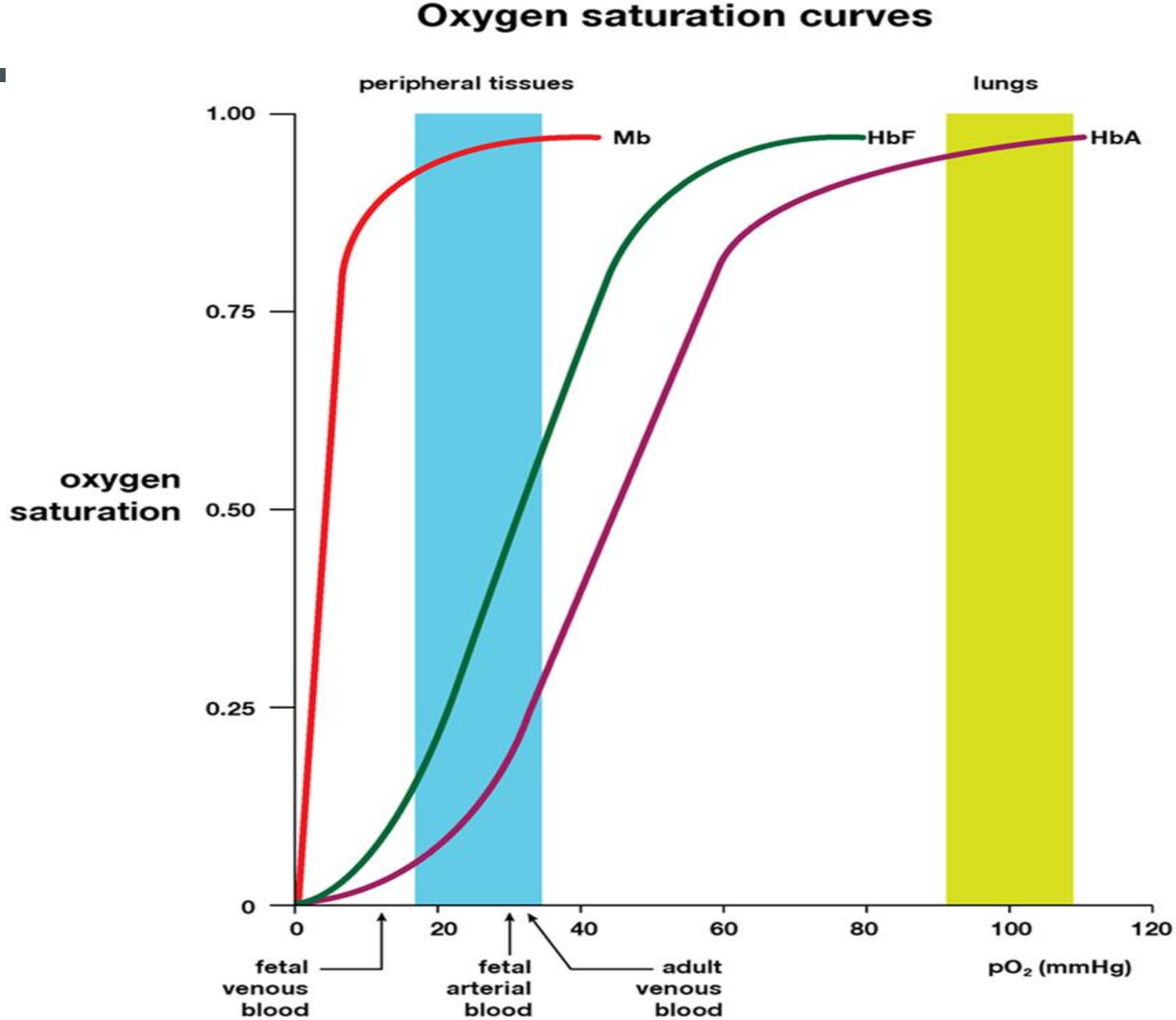
Acrocyanosis in postural orthostatic tachycardia syndrome (after 5 mins of standing)

https://upload.wikimedia.org/wikipedia/commons/thumb/a/a5/Acrocyanosis_in_POTS_patient.jpg/1024px-Acrocyanosis_in_POTS_patient.jpg

DIFFERENTIAL CYANOSIS

FOETAL HAEMOGLOBIN EFFECT ON CYANOSIS

- Foetal haemoglobin ($\alpha_2\gamma_2$)
  - His -> Ser substitution on binding site for 2,3-bisphosphoglycerate -> higher affinity to O2
  - P_aO_2 for saturation of 50 % Hb is lower than in adult HbA
  - Adaptation to relative hypoxia in umbilical vein (saturation approx. 70 %)
- Cyanosis manifests later!!
  - Adults -> S_aO_2 75–85 % reached at P_aO_2 = 50 mmHg (cca. 6,67 kPa)
  - Newborns and infants -> S_aO_2 75–85 % reached at P_aO_2 = 40 mmHg (cca. 5,33 kPa)



https://www.researchgate.net/publication/330707260/figure/fig2/AS:1143128124431846 6@1715889562541/Hemoglobin-oxygen-association-curves-Oxygen-saturation-curves-for-adult-hemoglobin-Hb.png

DIFFERENTIAL CYANOSIS - FORMS

1. Differential cyanosis
   - Presence of cyanosis on the lower half of body
   - Causes
     - Aortic arch interruption/critical coarctation of aorta + patent arteriosus duct (PDA) in R-to-L shunt (A)
     - Moderate coarctation of aorta (variant cyanosis degree) (B)
     - Pulmonary hypertension and R-to-L shunt via PDA

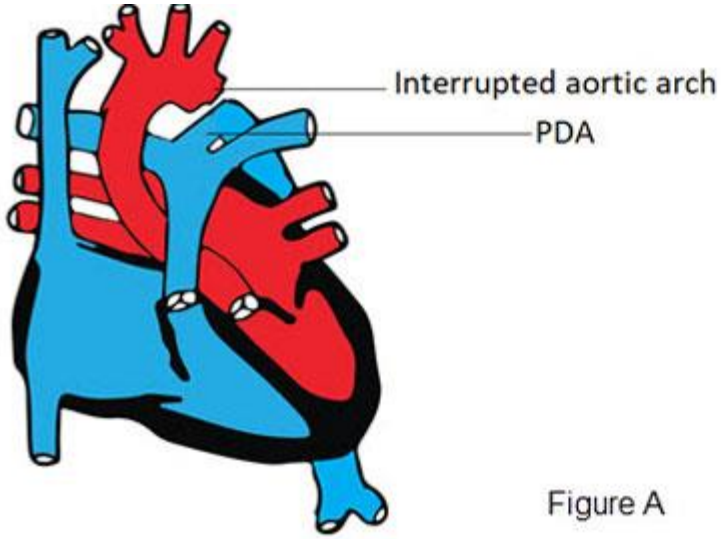
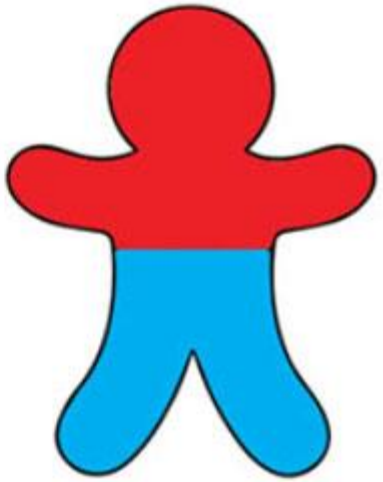
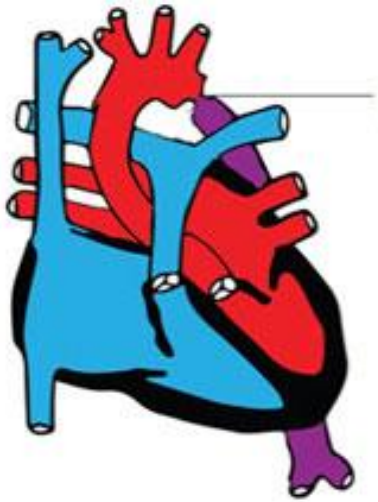


Figure A





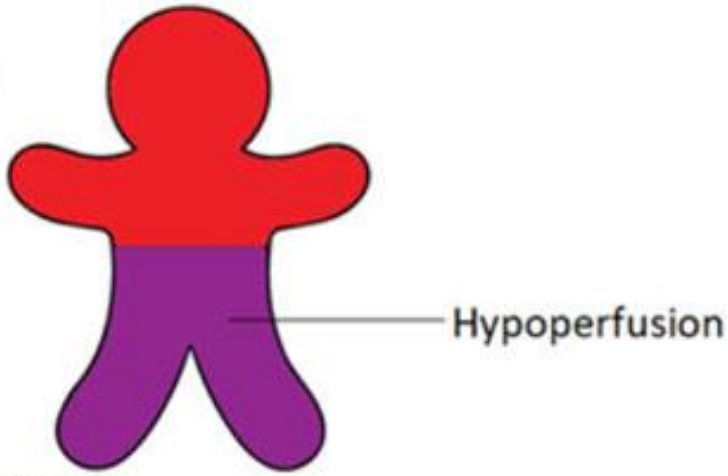


Figure B

https://www.utmb.edu/pedi_ed/CoreV2/Cardiology/Cyanosis_FigureA.jpg
https://www.utmb.edu/pedi_ed/CoreV2/Cardiology/Cyanosis_FigureB.jpg

DIFFERENTIAL CYANOSIS - FORMS

2. Reverse differential cyanosis
   - Upper body cyanosis
   - Causes
     - Transposition of great arteries + PDA + aortic arch interruption/critical coarctation of aorta (C)
       - Deoxygenated blood -> right ventricle -> aorta -> upper body part (cyanosis)
       - Oxygenated blood -> left ventricle -> pulmonary artery + PDA -> lower body part
     - Transposition of great arteries + PDA + suprasystemic pulmonary hypertension (D)
       - Deoxygenated blood -> right ventricle -> aorta -> upper body part (cyanosis)
       - Oxygenated blood -> left ventricle -> PDA -> lower body part

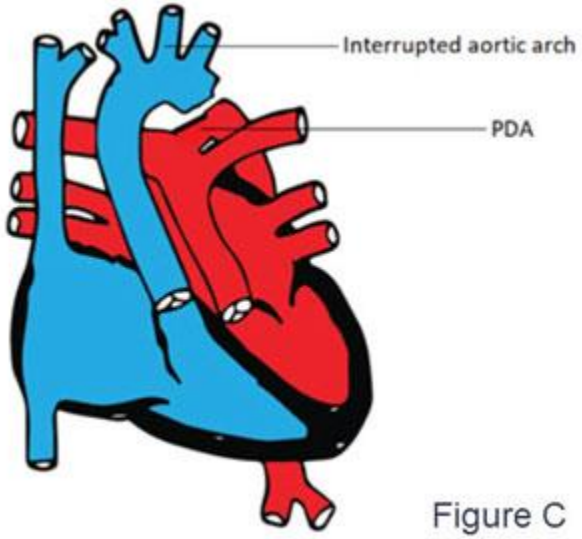


Figure C

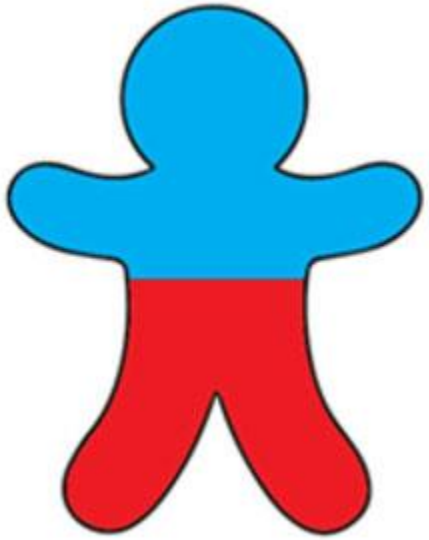
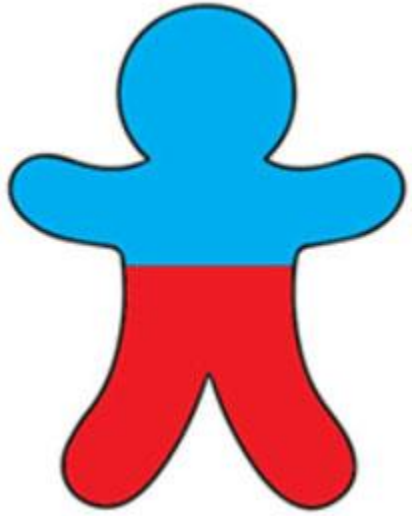




Figure D



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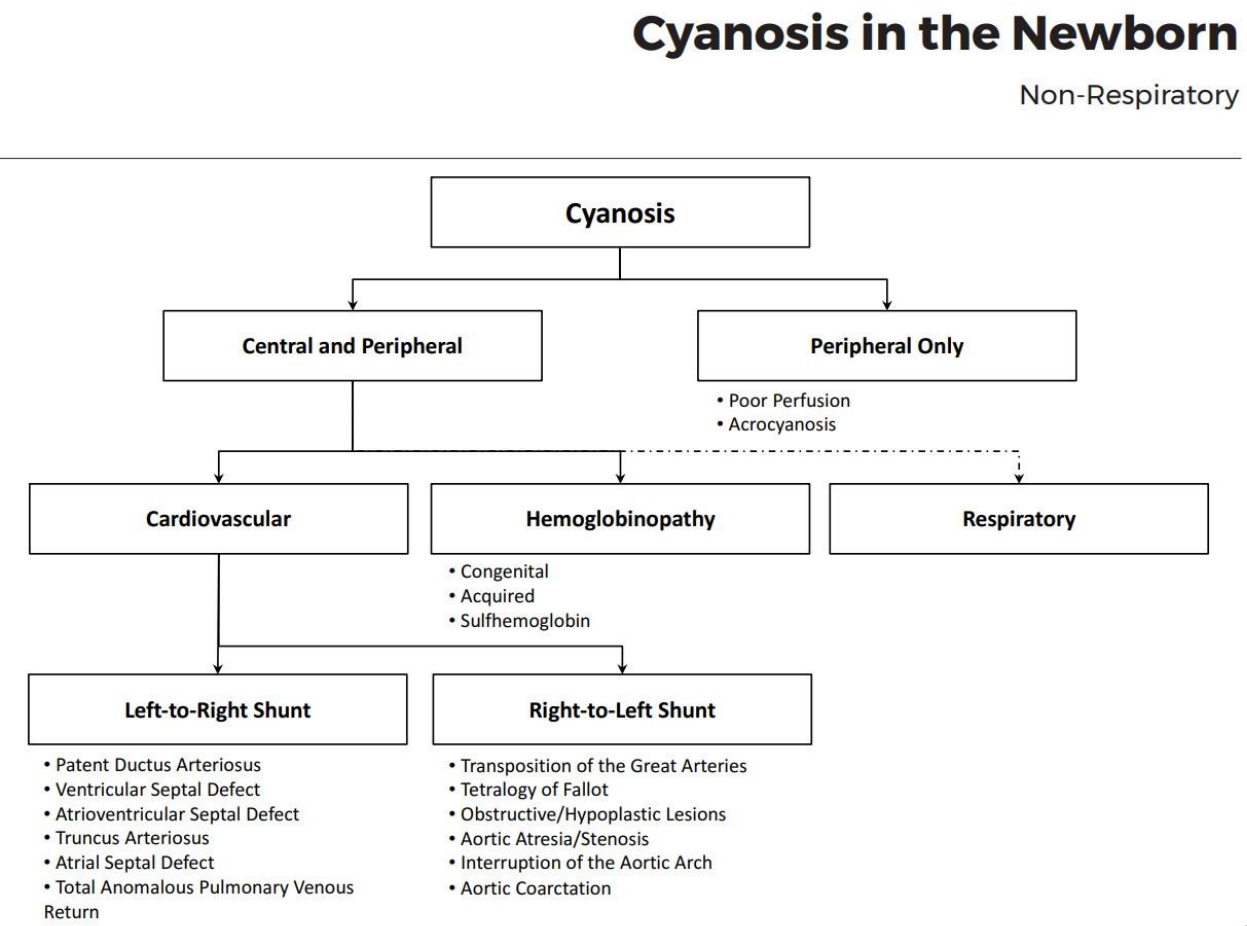
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https://www.researchgate.net/publication/338002645/figure/fig1/AS:837290091888641@1576636922942/Differential-cyanosis-The-patient-presented-in-this-report-Only-the-upper-right.png

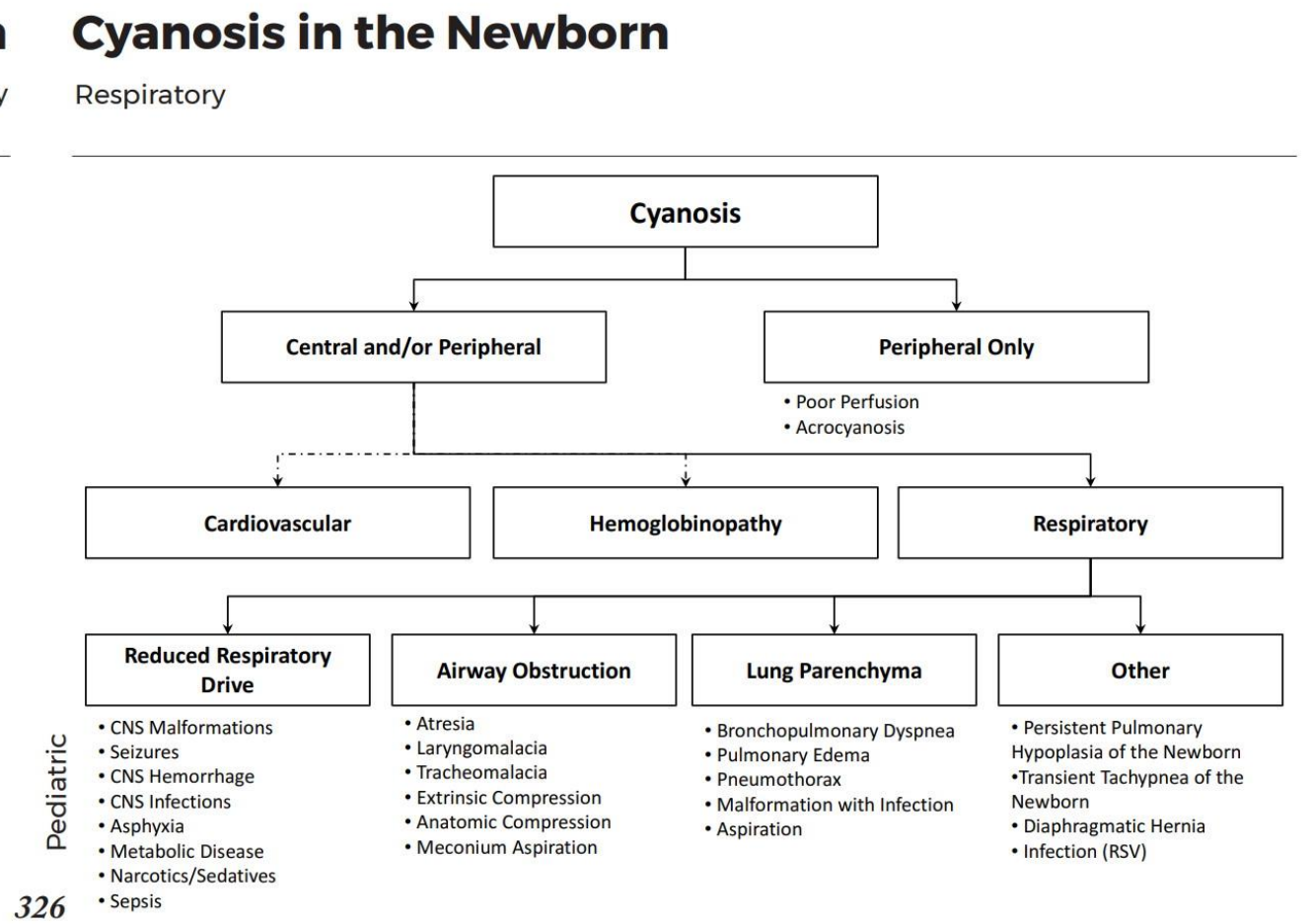
PECULIARITIES OF NEONATAL PERIOD CYANOSIS

NEONATAL CYANOSIS CAUSES

1. Respiration causes
   - Respiratory airways obstruction – choanae atresia, micrognathia, laryngomalacia
   - Pulmonary processes and V/Q mismatch – pneumonia, pulmonary hypoplasia, persistent pulmonary hypertension
2. CNS disorders leading to hypoventilation
   - Neonatal encephalopathy, seizures/cramps, intracranial haemorrhage
3. Haematological causes
   - *Methemoglobinemia* (pseudo-), polycythaemia
4. Cardiovascular causes
   - Cyanotic congenital heart defects – tetralogy of Fallot, transposition of great arteries, *truncus arteriosus*, anomalous pulmonary venous return, tricuspid atresia, hypoplastic left heart
   - Eisenmenger syndrome

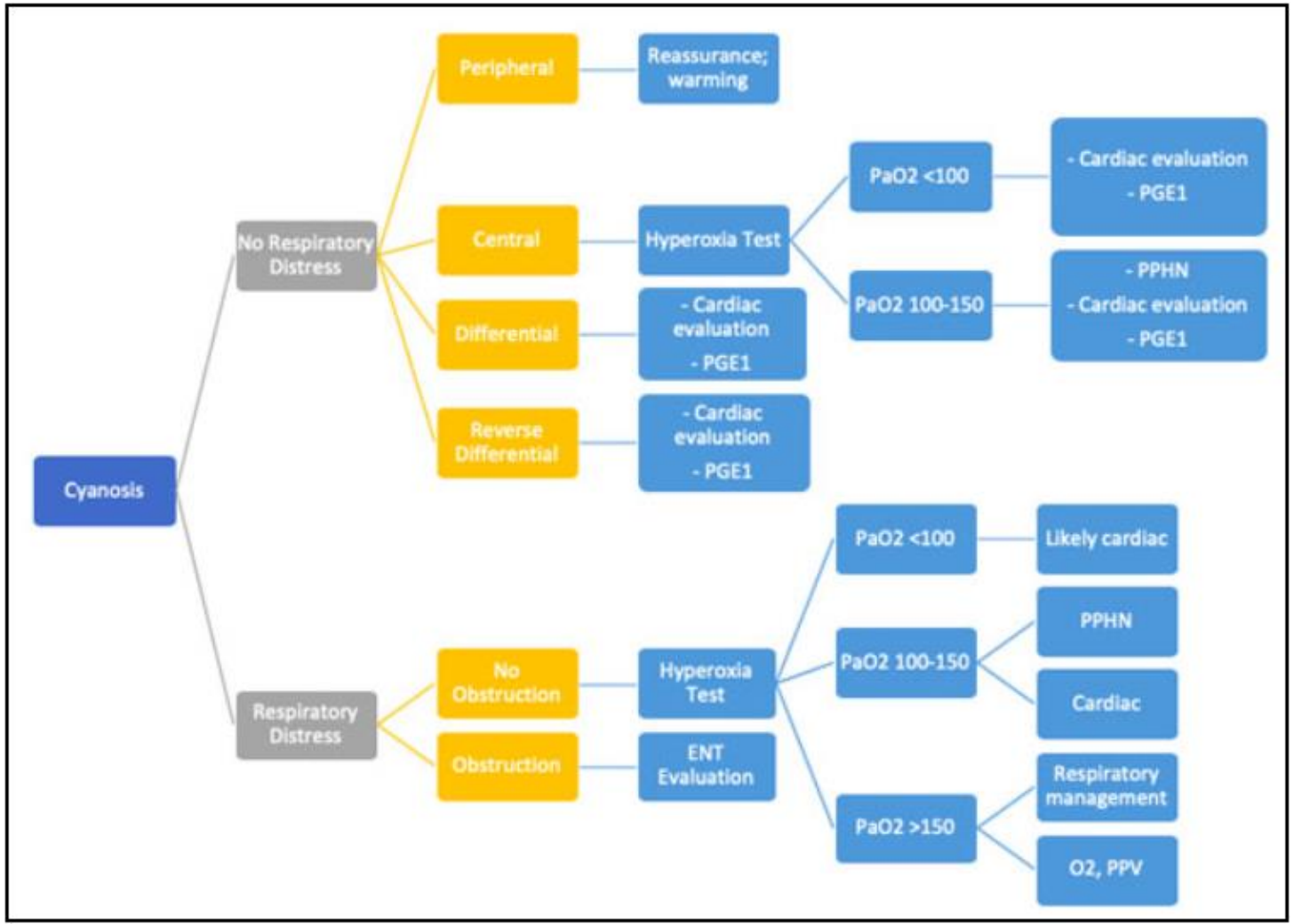
NEONATAL CYANOSIS DIFFERENTIAL DIAGNOSIS





https://img.grepmed.com/uploads/8652/peds-causes-differential-cyanosis-diagnosis-2200w.jpeg

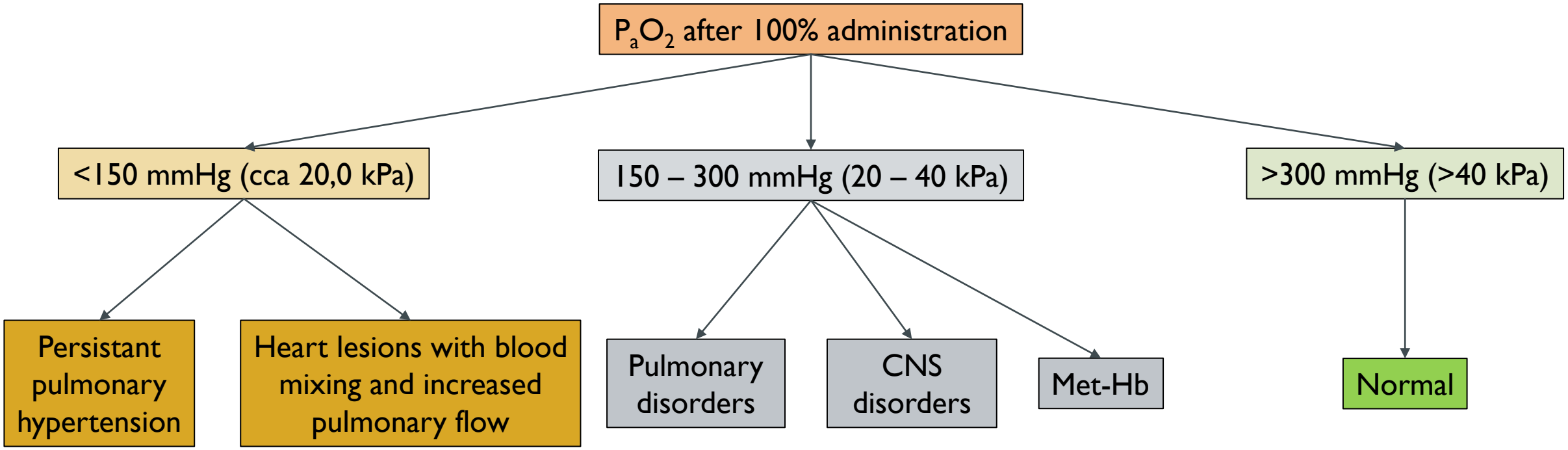
NEONATAL CYANOSIS DIFFERENTIAL DIAGNOSIS



https://www.utmb.edu/pedi_ed/CoreV2/Cardiology/Cyanosis_Evaluation_Neonate.jpg

HYPEROXIC TEST

- Inhalation of 100% oxygen for 10 minutes
- Aiding to determine prostaglandins administration (inferior to echoKG)



EISENMENGER SYNDROME AND POTENTIAL CONSEQUENCES

- Definition – turning of left-to-right shunt to right-to left due to developing pulmonary hypertension
- CAVE
  - Chronic hypoxaemia -> polycythaemia -> increased amount of immature and rigid red cells (microspherocytes, relative iron deficiency) -> microcirculation occlusion -> stroke
- Special procedures
  - Sufficient hydration
  - Iron supplementation
  - Oxygen therapy
  - Acetylsalicylic acid
  - Ev. vasodilation medications to pulmonary circulation, phosphodiesterase inhibitors, endothelin receptors antagonists, lungs and heart transplantation

PSEUDOCYANOSIS

METHEMOGLOBINEMIA – BLUE FUGATES SYNDROME, SULFHEMOGLOBINAEMIA

METHEMOGLOBINAEMIA

- Definition – increased methaemoglobin concentration (met-Hb) in circulating red cells
  - Haem iron is trivalent (Fe^{3+}) instead of physiologically bivalent (Fe^{2+})
  - Chocolate colour of blood
- Causes
  - Hereditary/congenital
    - NADH-cytochrome-b5-reductase deficiency (ar)
    - HbM disease of HbH disorders (thalassemia)
    - Pyruvate kinase deficiency, glucose-6-phosphate dehydrogenase deficiency
  - Acquired
    - Medications – ATB (trimethoprim, sulphonamides, dapsone), local anaesthetics (articaine, benzocaine, prilocaine, lidocaine); anillin colours; metoclopramide, rasburicase, umbelulone, chlorates, bromates, nitrates
    - Blue baby syndrome – children up to 6 months of age have decreased levels of NADH-cytochrome-b5-reductase -> intestinal bacteria convert nitrates to nitrites -> met-Hb

METHEMOGLOBINEMIA - PATHOPHYSIOLOGY

- Fe^{2+} to Fe^{3+} oxidation -> increased affinity of remaining tetramer subunits Hb with Fe^{2+} to O_2 -> tissue hypoxia
  - Possible oxidative stress effect and decreased antioxidant defence
- Fe^{3+} unable to bind oxygen!!!
- Result -> tissue hypoxia intensified

- Protective pathways (met-Hb reduction)
  - Major – NADH-cytochrome-b5-reductase
  - Minor – NADPH-cytochrome-b5-reductase

- Treatment – methylene blue, ascorbic acid





Dapsone induced methemoglobinemia

- Prior to treatment – A, C
- During the treatment – B, D (patient reporting – weakness, dyspnoea)

https://static.elsevier.es/multimedia/03650596/0000001000000002/v1_202503140625/S0365059624002538/v1_202503140625/en/main.assets/gr3.jpeg?xkr=ue/ImdikoIMrsJoerZ+w9/eUng1vrpKbIV+WbjTtysIq0cwxxjaMYv06TlJpDL+pRsYz0vh/hSBOXGOR6xAWzSdF8Ar0bpDteG0u/TFuA4WzSLwSbZz8MejS3D28XaXWSe9LoYELIMBTZZGtn+LNYw/MIh/3U2O2LcwzuLsBDZ7SbOU+RTj8QEcrKsxbI1v9db3eD2lctkvcEAZI5C4XZcQcb9PBSon1zdypaMyTB8Hmf54Snm++BIKcPdemTfrPOsUC/vc1G3Egjj/wVnkAwaM80WcElFPbcXkCbKlpI6aQNp29RibX6fexGebRJvDO





BLUE FUGATES SYNDROME (BLUE FUGATES; THE BLUE PEOPLE OF KENTUCKY)

- Family living in Kentucky since 19th century -> multiple members manifesting blue skin colour
- „Founders“ – Martin Fugate and Elizabeth Smith
  - Both heterozygotes for diaphorase deficiency (NADH-cytochrome-b5-reductase)
  - 4 out of 9 children manifested blue skin colour
  - Allele preserved in reproduction (limited genetic fond, isolated community)
- Benign disease, symptoms may vary
  - „The bluest“ Lucy Stacy – lived for 84 years; 13 children
- Haematologist Madison Cawein III treated them with methylene blue in 1960s
  - E. M. Scott – 1960 – Journal of Clinical Investigation -> observed similar phenomenon in native Alaskans
- The last Fugate – Benjamin Stacy (1975) -> quick improvement of condition, just fingertips being cyanotic





Luna Fugate Stacy (left) –
Benjamin Stacy‘s grandmother

https://images.immediate.co.uk/production/volatile/sites/7/2025/01/TheBluePeople-695603f-e1740148605100.jpg?quality=90&resize=620,414
https://cdn.thecollector.com/wp-content/uploads/2023/07/luna-fugate-stacy.jpeg?width=628&quality=55

SULFHEMOGLOBINAEMIA

- Definition – a rare condition resulting from sulfhemoglobin levels elevation (green colour) in circulating red cells (pseudocyanosis)
- Causes
  - Drugs – sulphonamides – e.g., sulfasalazine; sumatriptan, phenazopyridine
  - Accidental/professional exposure to sulphur compounds
  - ? Intestinal bacterial flora producing H_2S (? Shock, ? Sepsis)
- Pathomechanism
  - Sulphur atom/ion binding to β-pyrol ring -> H_2S/S^{2-} bond with Fe^{2+} -> irreversible loss of affinity to O_2
- Manifestations
  - Green/blue skin discoloration visible even at low sulf-Hb concentrations (0,5 % sulf-Hb from total Hb)
- Treatment
  - Spontaneous disappearance ev. blood transfusion (red cells lifespan 120 days)



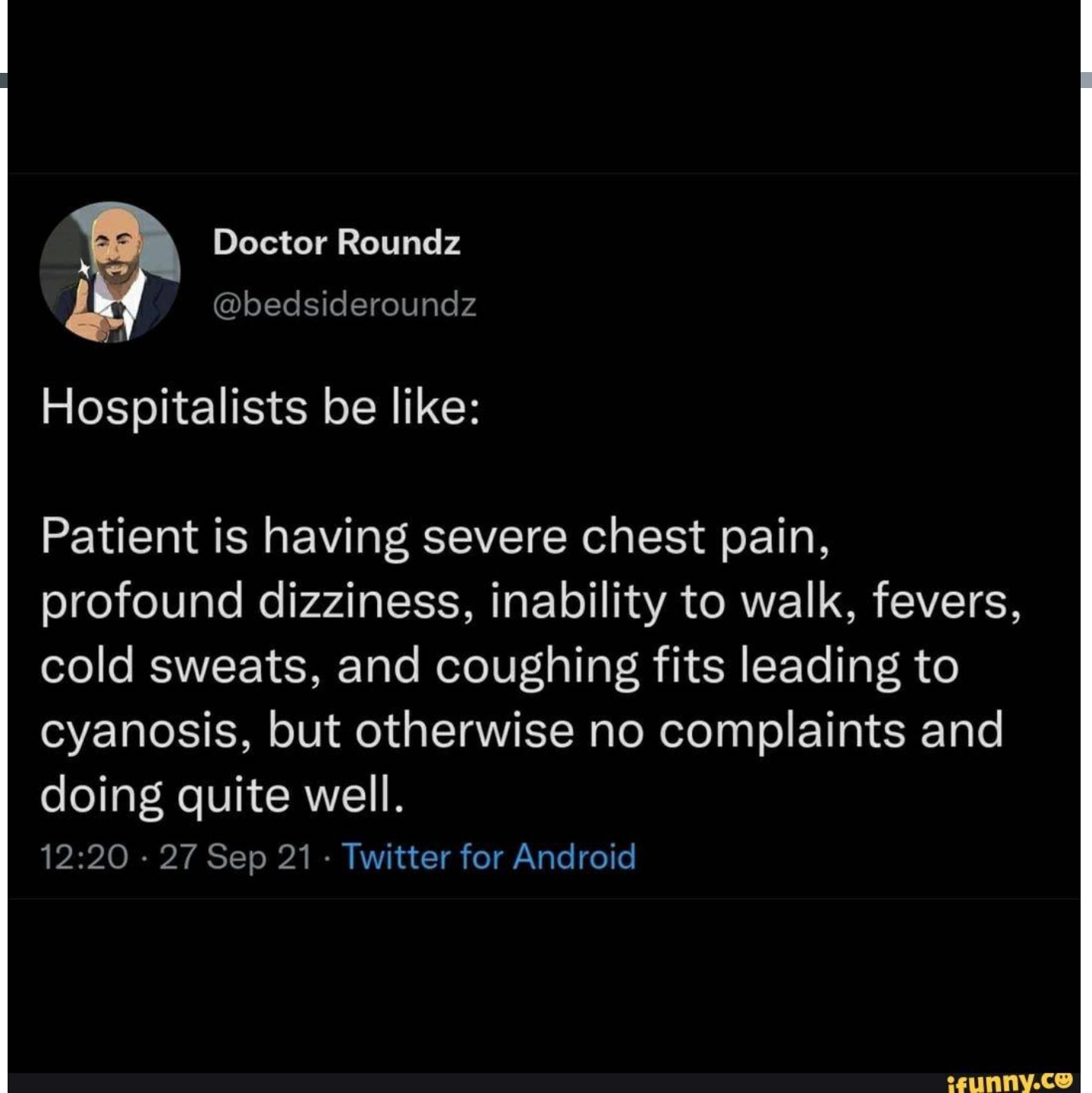
https://www.researchgate.net/publication/370273059/figure/fig1/AS:11431281153618397@1682514616784/Figura-1-Cianosis-en-dos-pacientes-con-sulfohemoglobinemia-En-la-primera-fotografia-a.png

COLOID SILVER DRINKING...



Paul Karason (1950 – 2013) alias „Papa Smurf“

https://upload.wikimedia.org/wikipedia/en/3/3d/Paul_Karason.jpg



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