HYPOXIA

Emanuel Nečas

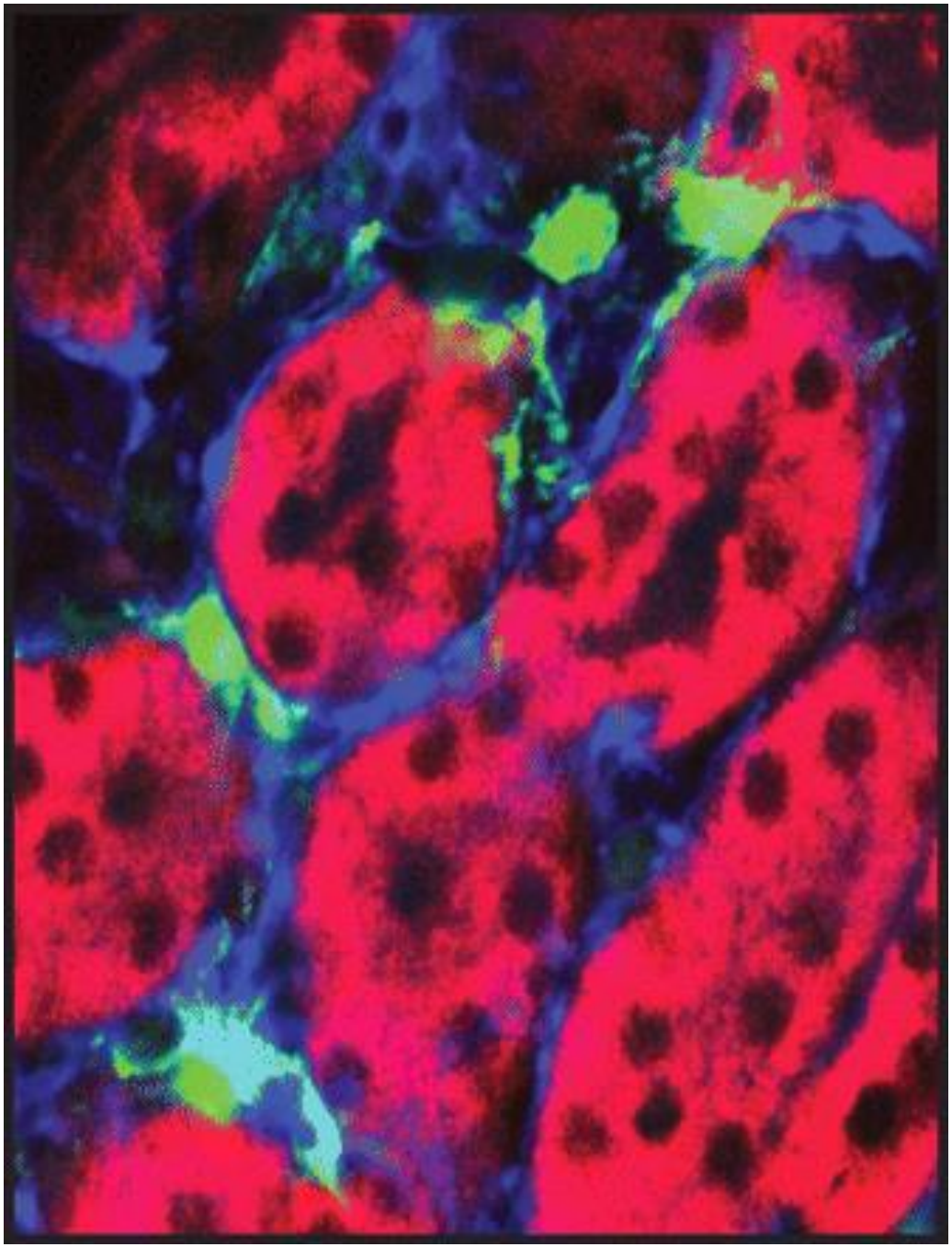
22-10-2019

The Nobel prize in Physiology or Medicine 2019

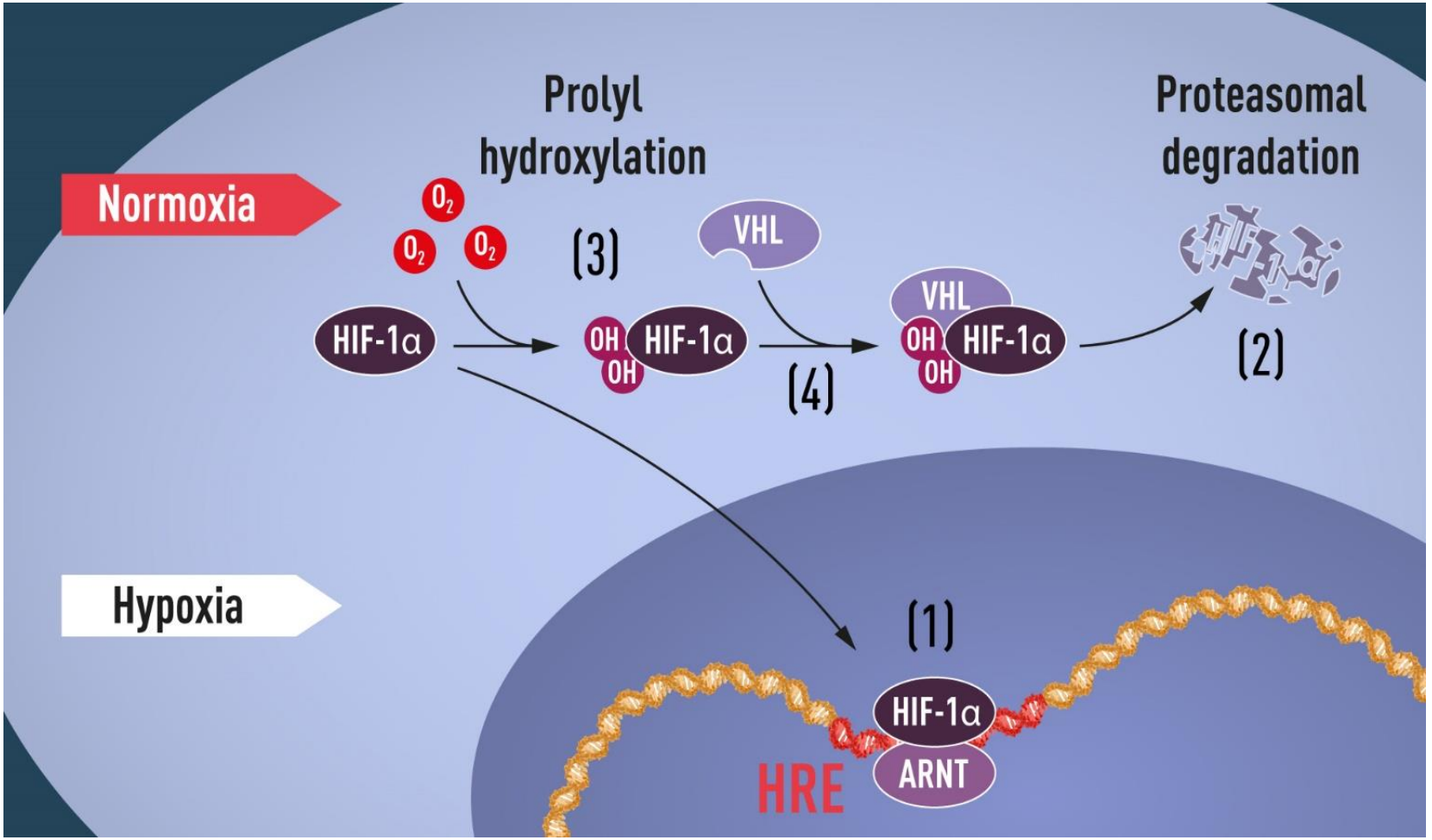
„how cells sense oxygen“

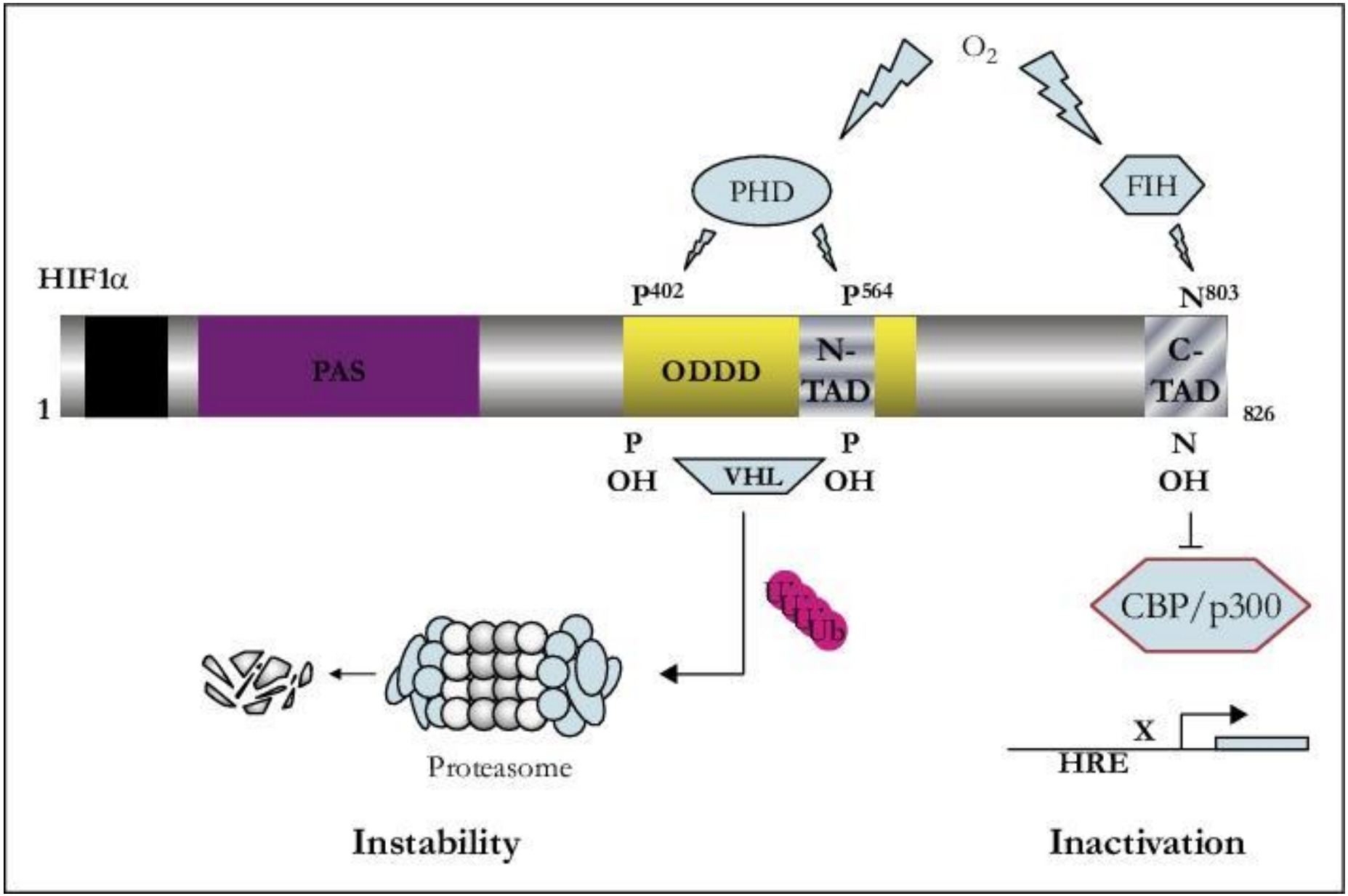
William G. Kaelin, MD, of Harvard University, Boston, Massachusetts, Gregg L. Semenza, MD, PhD, of Johns Hopkins University in Baltimore, Maryland, and Sir Peter J. Ratcliffe, FMedSci, of Oxford University in the United Kingdom have been awarded the 2019 Nobel Prize in Physiology or Medicine for their discoveries on how cells sense oxygen and adapt to it.

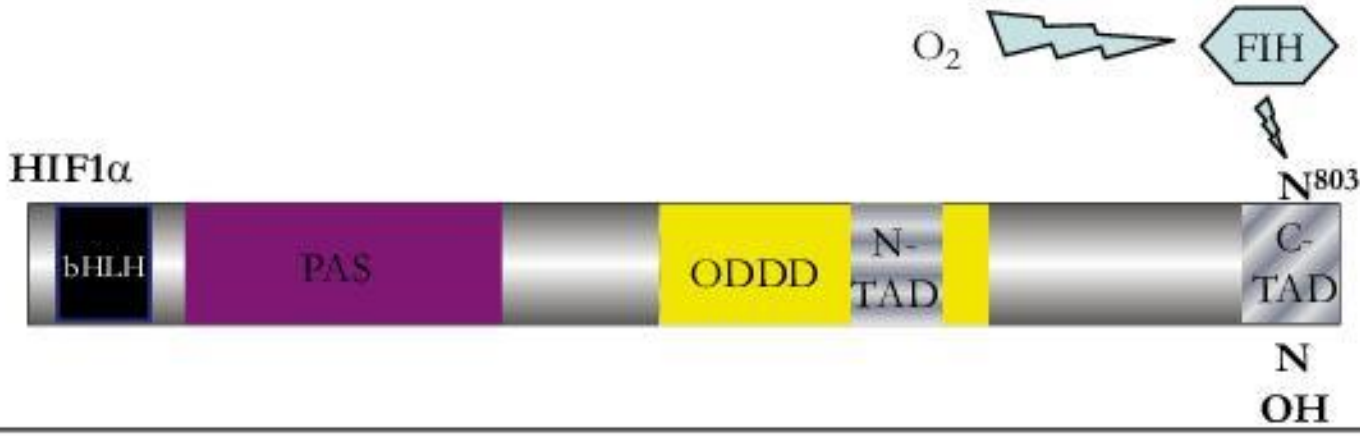
Some cells in the kidney secrete erythropoietin accoring to oxygen supply

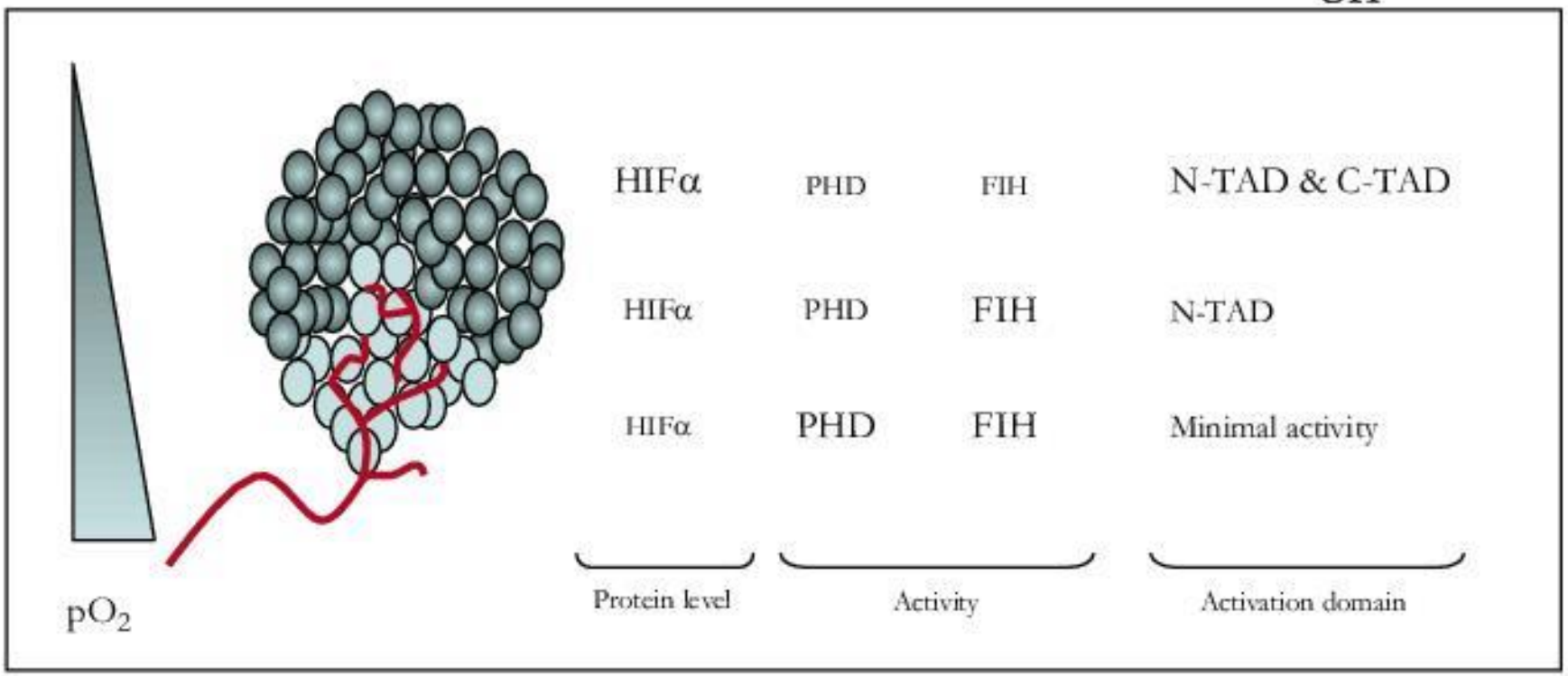


Intracellular pO_2 translated into gene response

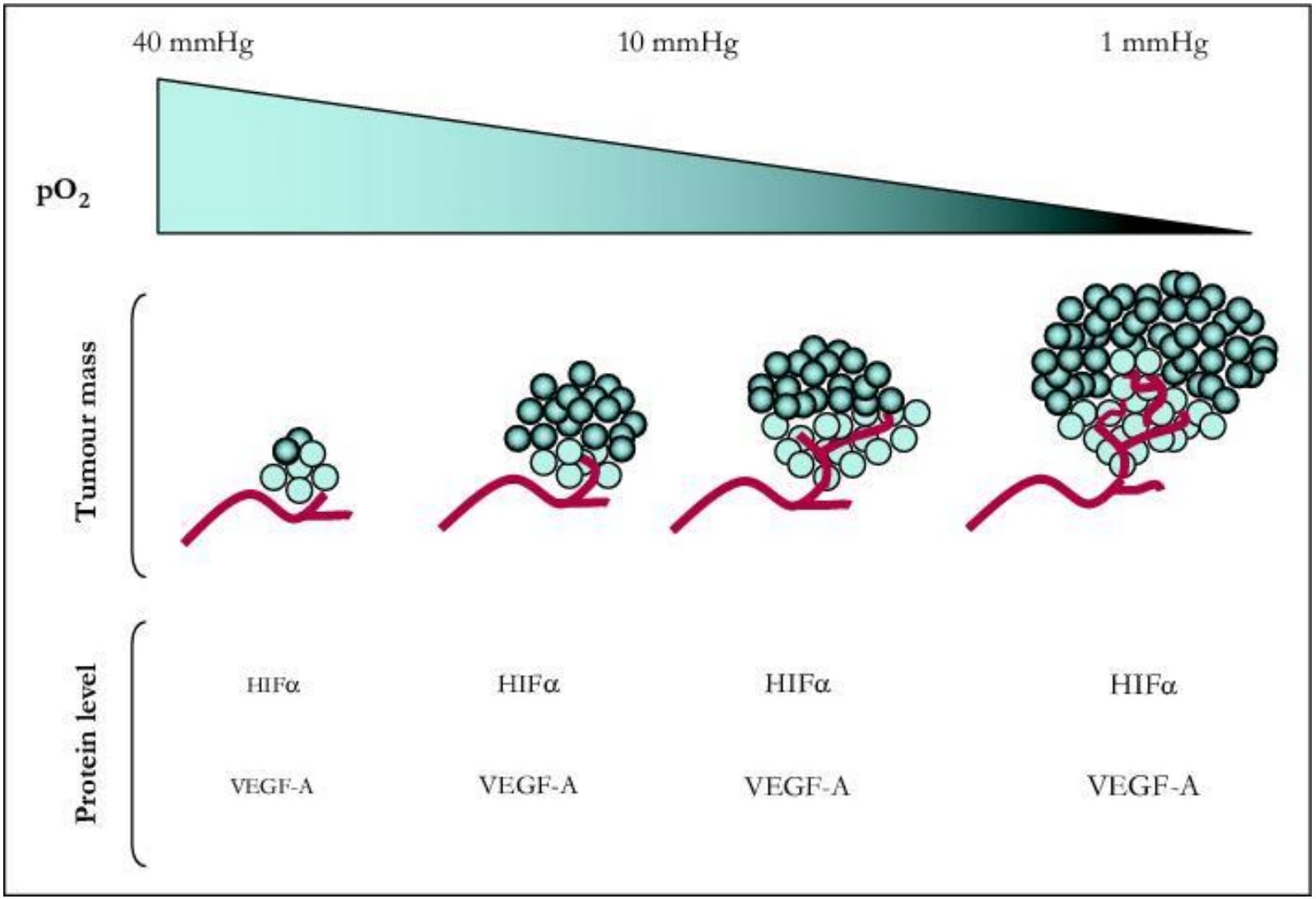



O2
PHD
FIH
HIF1α
P402
P564
N803
PAS
ODDD
N-TAD
C-TAD
1
826
P
OH
VHL
P
OH
N
OH
Ub
CBP/p300
X
HRE
Proteasome
Instability
Inactivation

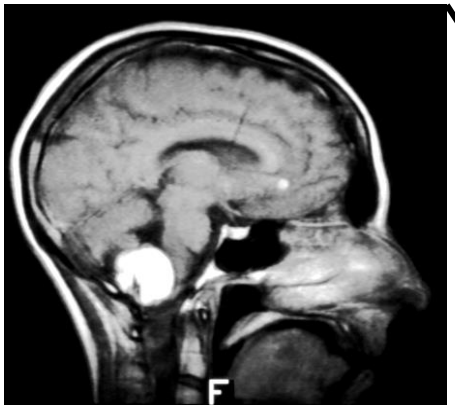

O2
FIH
HIF1α
N803
bHLH
PAS
ODDD
N-TAD
C-TAD
N
OH


pO2
HIFα
PHD
FIH
N-TAD & C-TAD
HIFα
PHD
FIH
N-TAD
HIFα
PHD
FIH
Minimal activity
Protein level
Activity
Activation domain

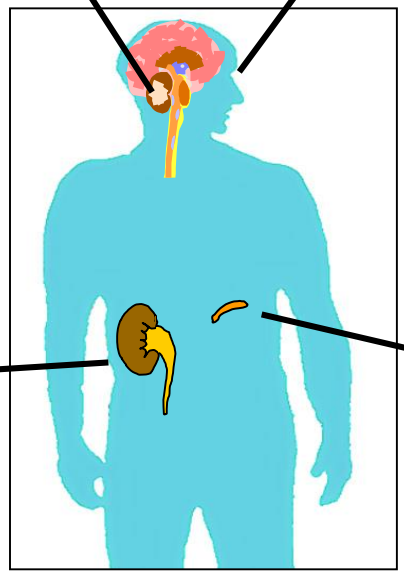
Tissue hypoxia in growing tumour induces angiogenesis (throught cytokine VEGF)



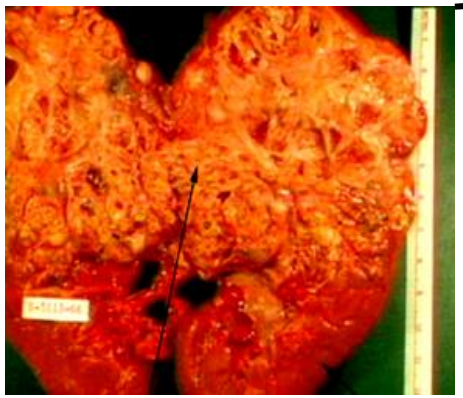
The von Hippel-Lindau Syndrome



Cerebellar & Spinal Haemangioblastoma



Retinal Haemangioblastoma



Renal Cell Carcinoma

Phaeochromocytoma

autosomal dominant

Patrick Maxwell,2002

HYPOXIA

1. Significance of Oxygen

2. Oxygen Availability and Delivery to Tissues

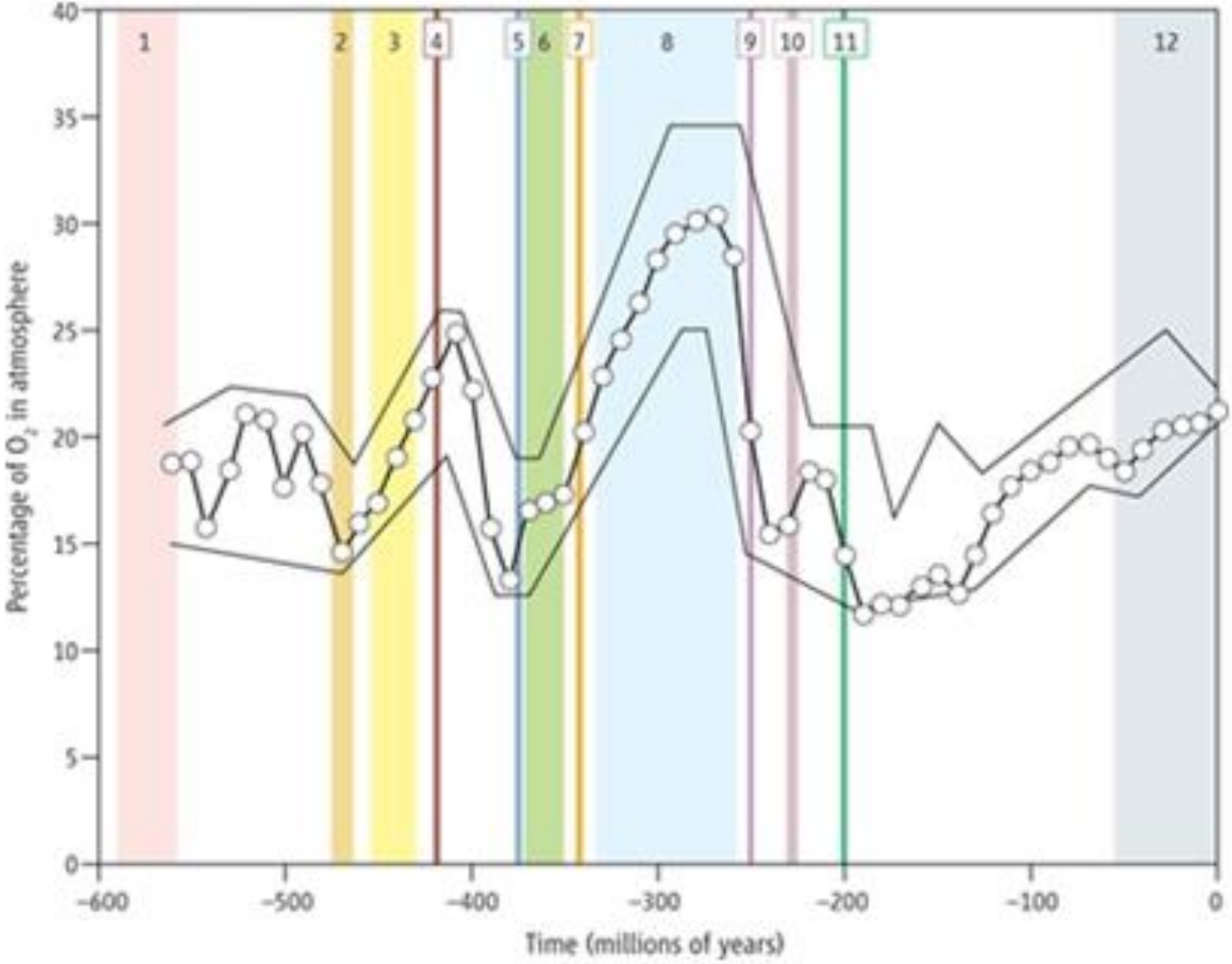
3. Causes of Hypoxia

4. "Lung and Blood Hypoxia" vs. "Tissue Hypoxia"

5. Classification of Hypoxia

6. Tissue and Cellular Responses to Hypoxia

7. Oxygenotherapy


1
2
3
4
5
6
7
8
9
10
11
12
40
35
30
25
20
15
10
5
0
Percentage of O_2 in atmosphere
−600
−500
−400
−300
−200
−100
0
Time (millions of years)

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Significance of oxygen for the organism –

production of ATP

and

some metabolic reactions

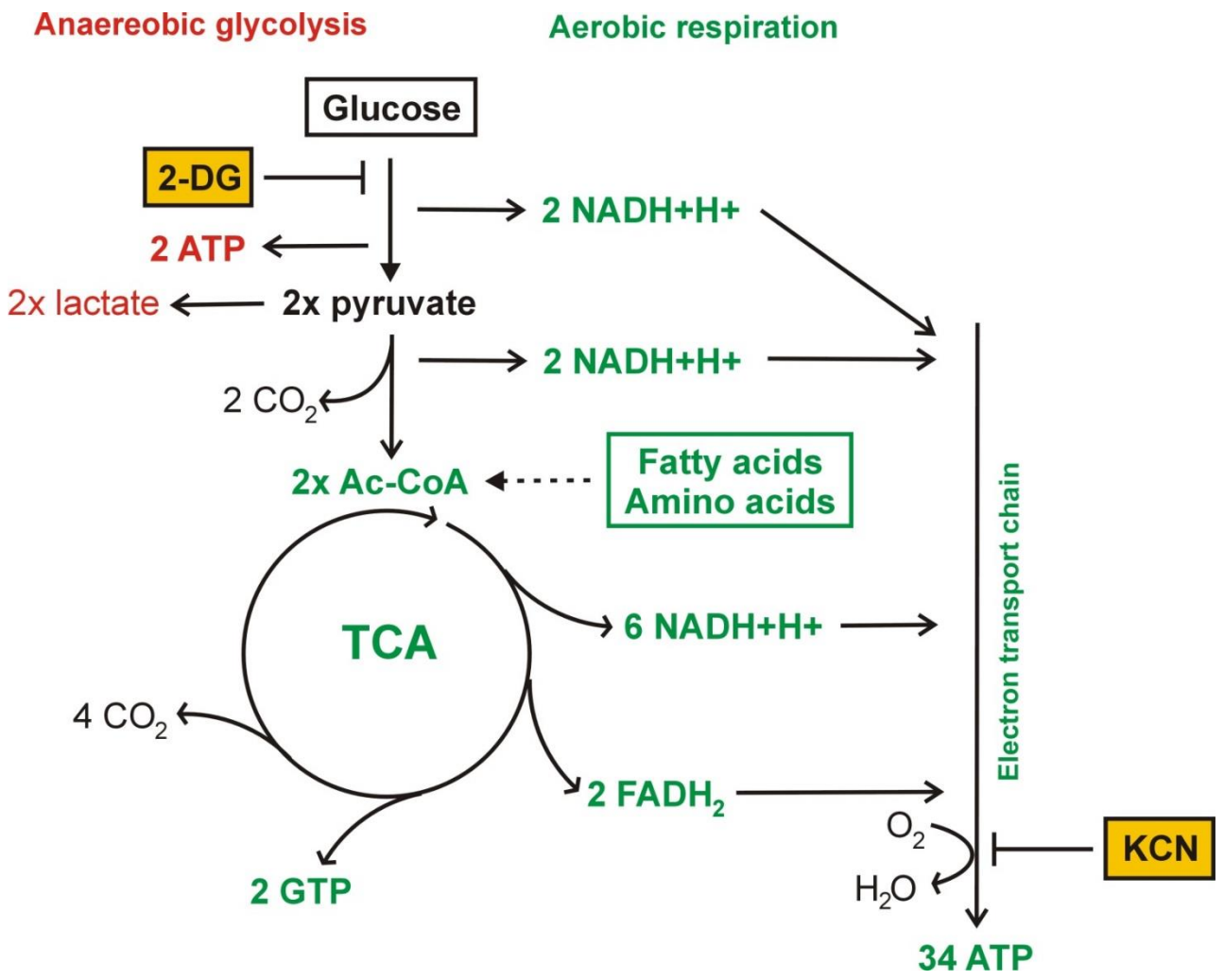
(e.g. hydroxylations).

ATP must be continuously generated in all cells !!!

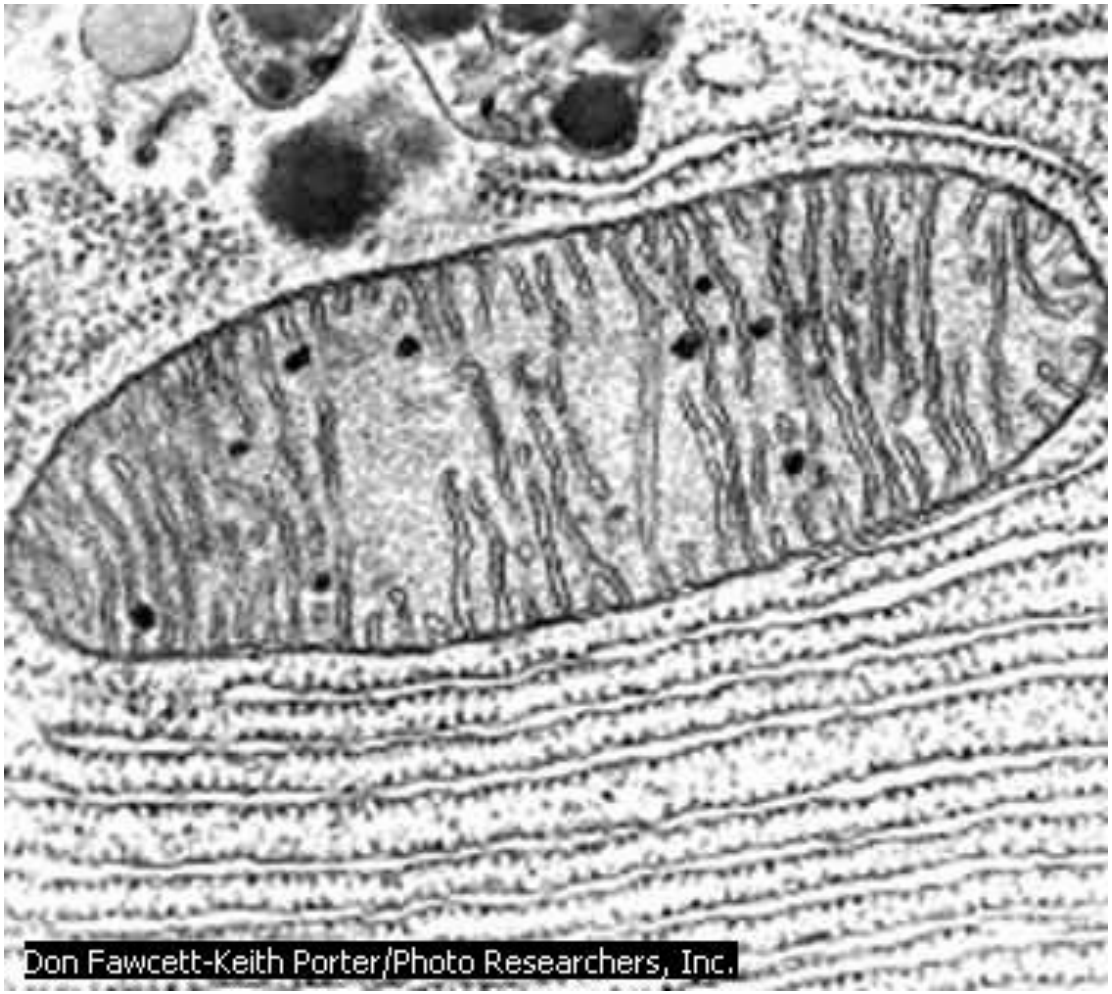
Signs and consequences of hypoxia (anoxia)

- fatigue, sleepeness, decreased mental performance, loss of consciousness
- decreased physical performance
- pain (myocardial infarctions, claudications, sickle cell anaemia – *lactic acid*)
- cell apoptosis
- cell necrosis (swelling, Na^{+}, Ca^{2+})

ATP production by oxidative phosphorylation is 18 fold more effective compared to anaerobic glycolysis, and can use alternative substrates to glucose



Mitochondria utilize >90 % of oxygen to make ATP



They need
pO_2
higher than

1 mm Hg

(0.13 kPa)
to function well

HYPOXIA

1. **Significance of Oxygen**

2. Oxygen Availability and Delivery to Tissues

3. **Causes of Hypoxia**
4. **"Lung and Blood Hypoxia" vs. "Tissue Hypoxia"**
5. **Classification of Hypoxia States**
6. **Tissue and Cellular Responses to Hypoxia**
7. **Oxygenotherapy**

pO_2 and the oxygen content in body fluids

Oxygen content (e.g. mM O_2/L or ml O_2/L)
is **lineary positively correlated with pO_2**
in body fluids,
those without
haemoglobin or myoglobin
(plasma, interstitial fluid, cytoplasma of most cells).

Hemoglobin significantly increases
(~50 fold) oxygen content in the blood at existing (physiological) pO_2 values.

Oxygen transporting mechanism in the body

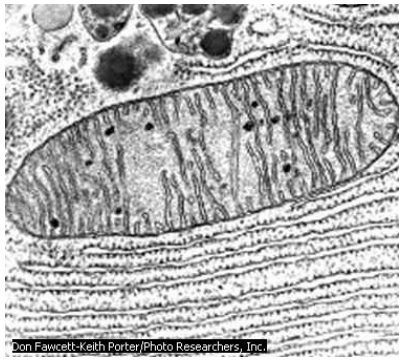
(lungs, circulation, red blood cells)

The aim:

to supply every cell, every mitochondria with a concentration of oxygen that is not limiting for the function, particularly ATP production -

pO_2 > 1 mmHg (0.13 kPa)

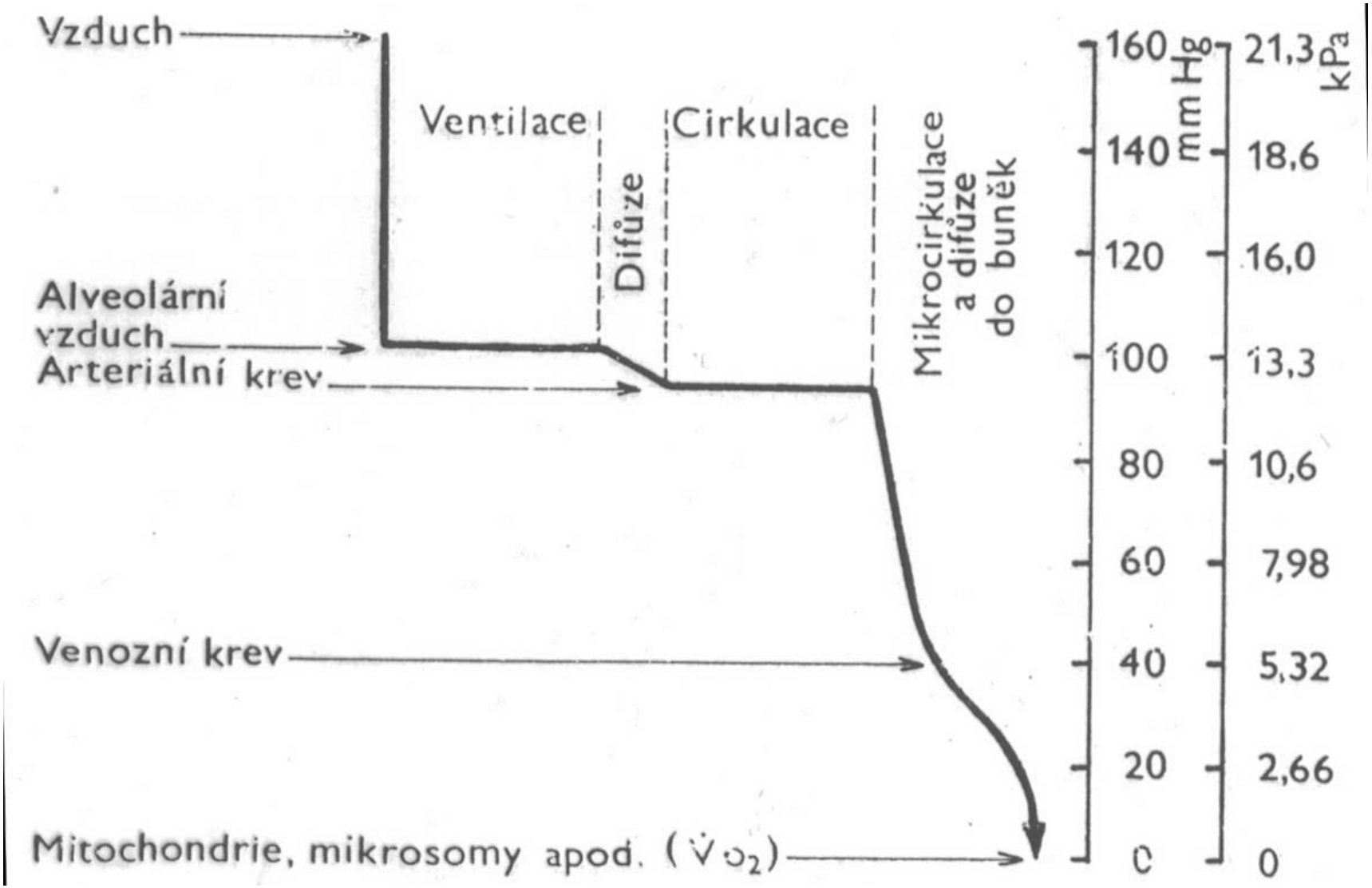
(„a critical oxygen tension“)



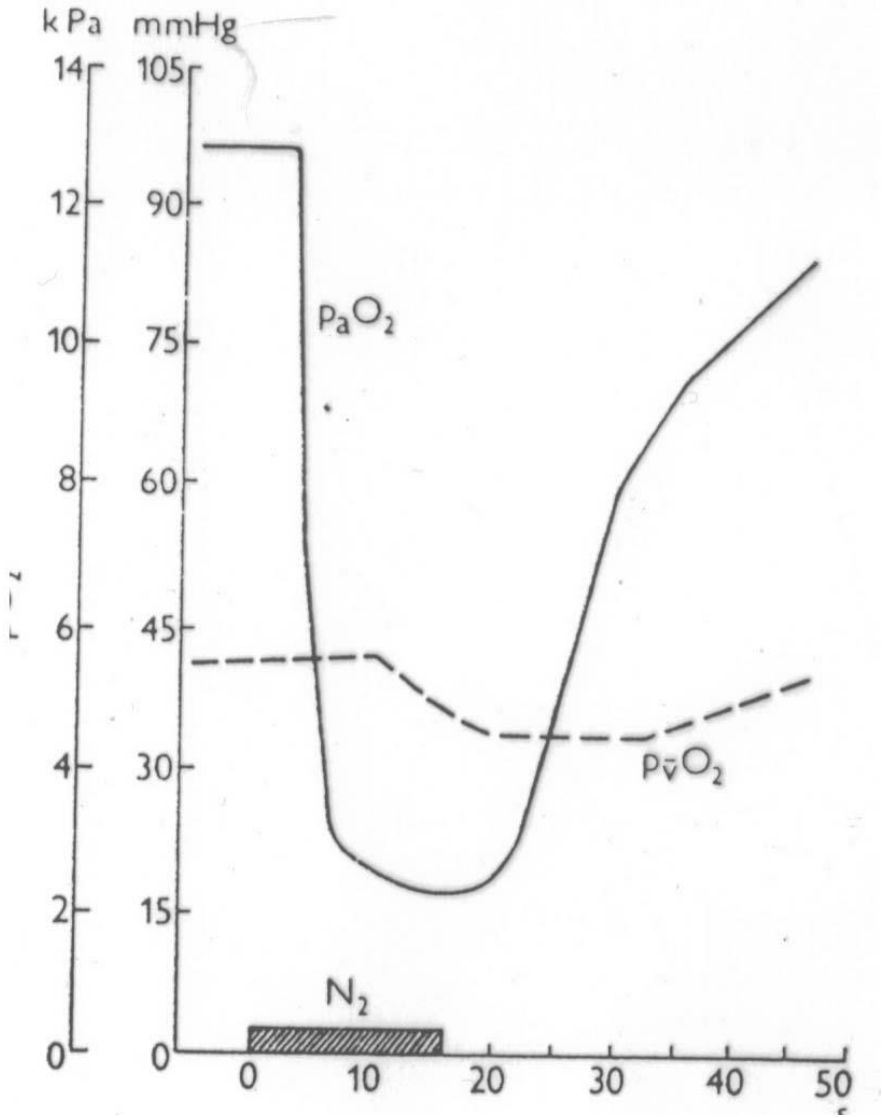
- **Oxygen molecules move alonside their concentrations gradients –** i.e. from the air towards mitochondria

- *In principle, the direction of oxygen flow can reverse*

Oxygen tension (pO_2) steadily decreases between the air and mitochondria



Oxygen flows along the pO_2 gradient, consequently it can be washed from tissues if its pO_2 is low in the a breathing gas

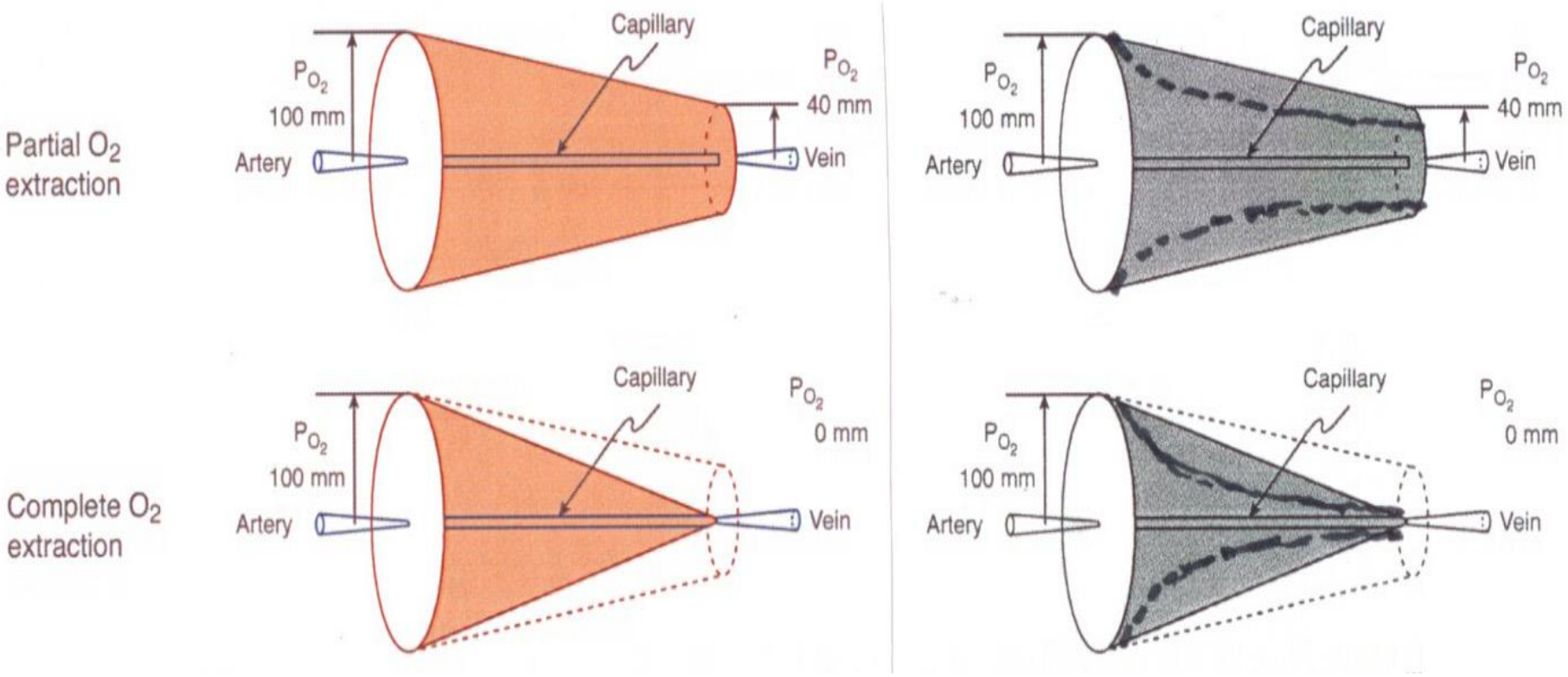


This experiment also shows that there are negligible reserves of oxygen in the body.

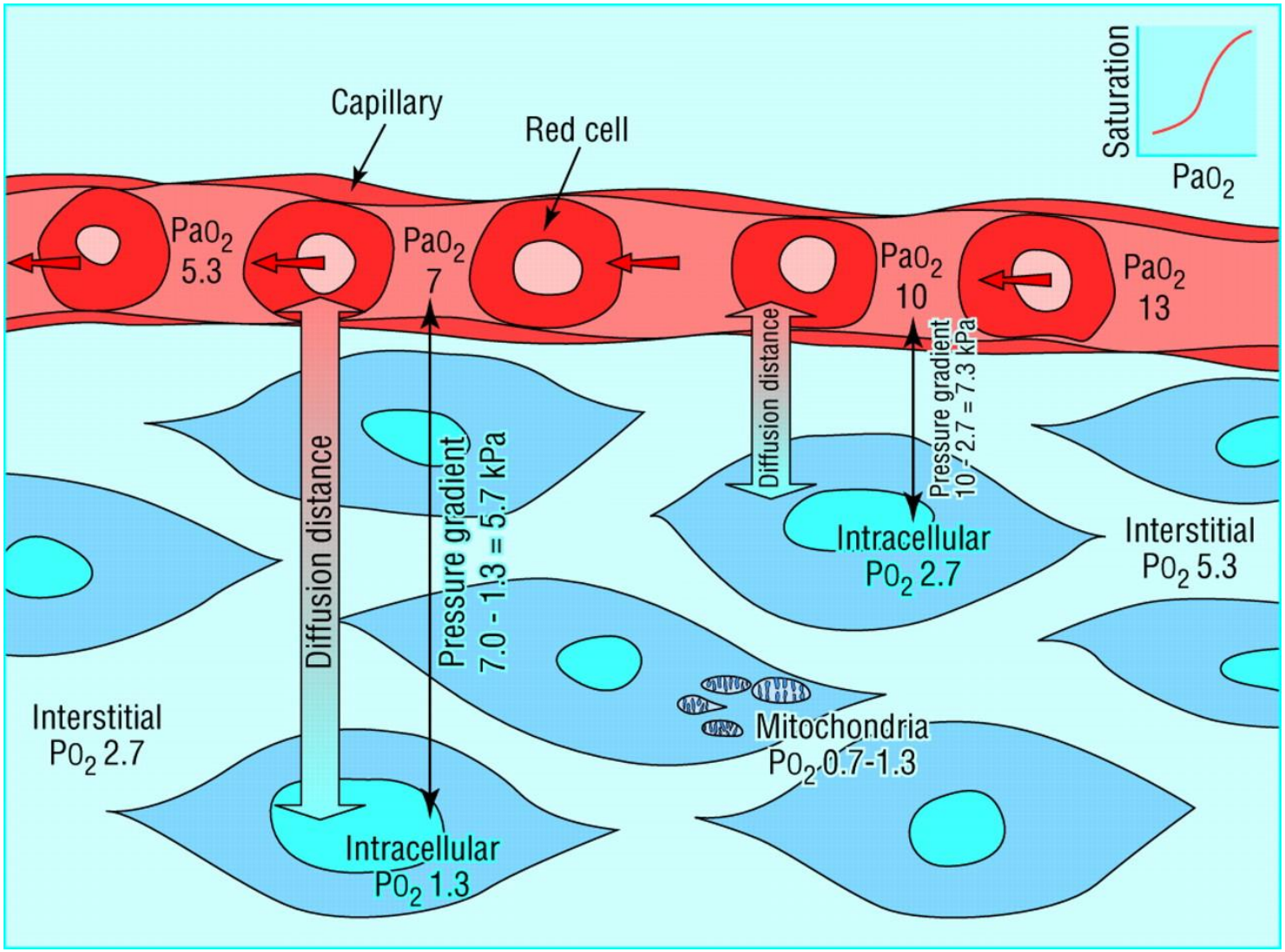
Even at rest and maintained circulation they suffice for ~2 minutes.

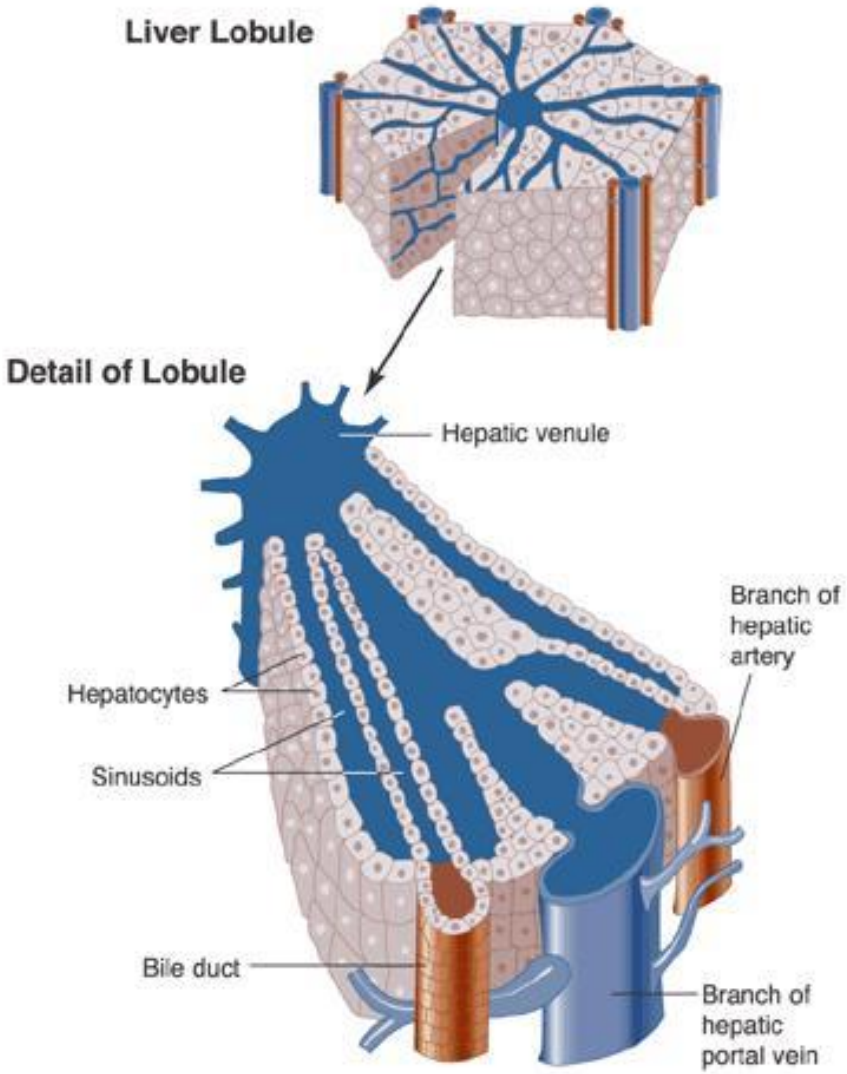
After circulatory arrest oxygen in tissues is consumed during ~10 seconds.

pO_2 in capillary blood vessel



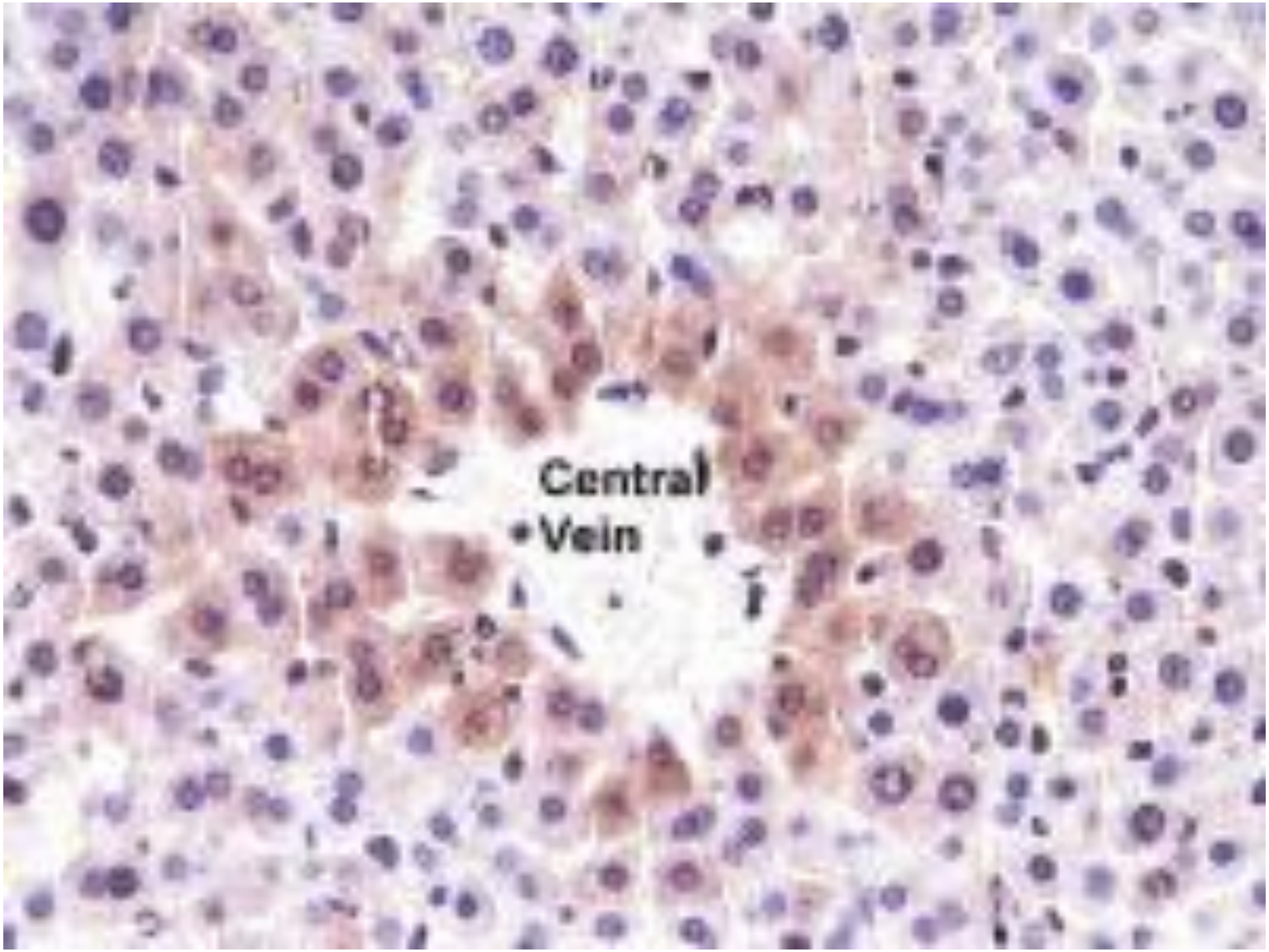
Amounts of oxygen diffusing to mitochondria depends on steepness of pO2 gradients

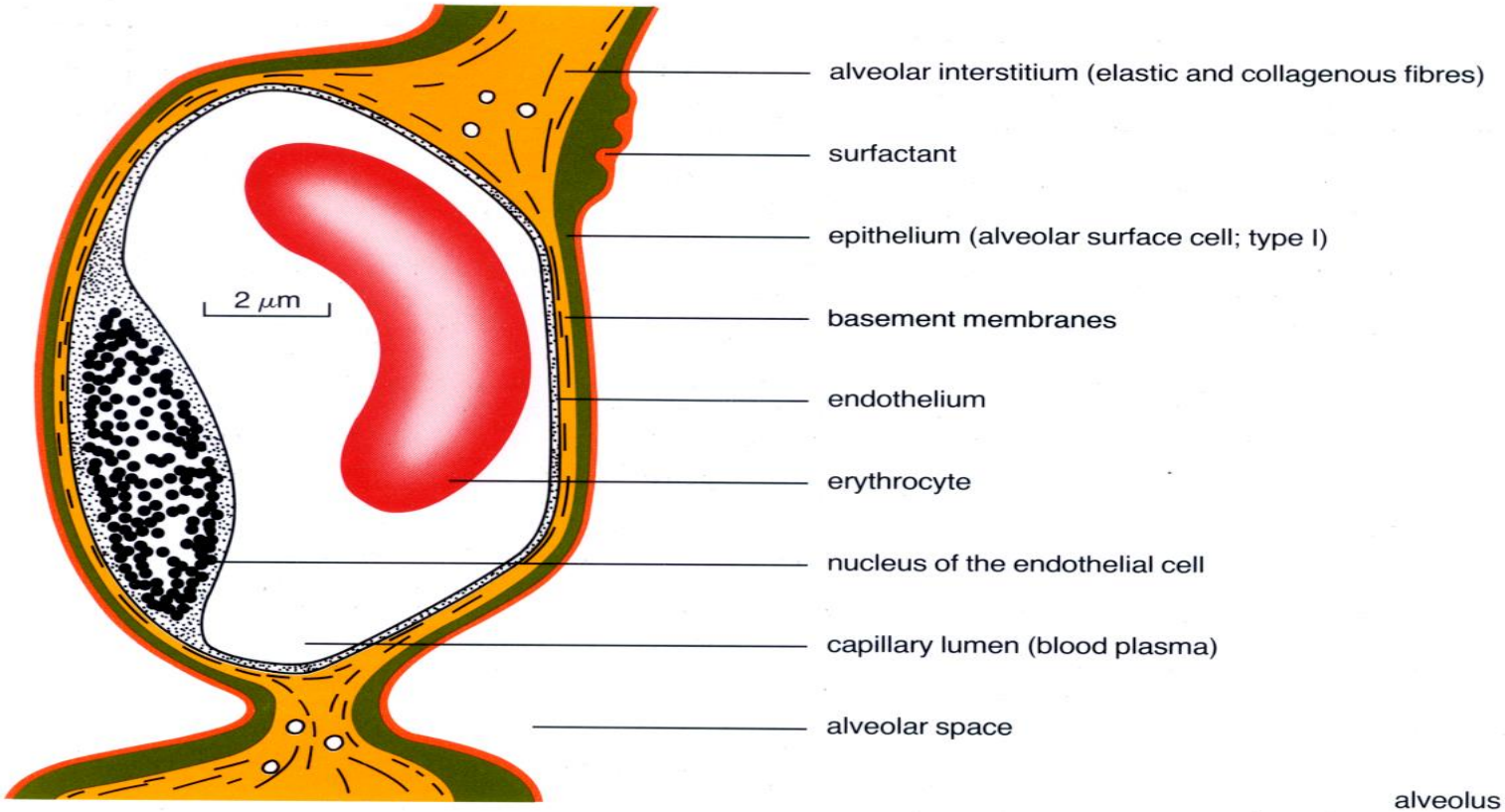


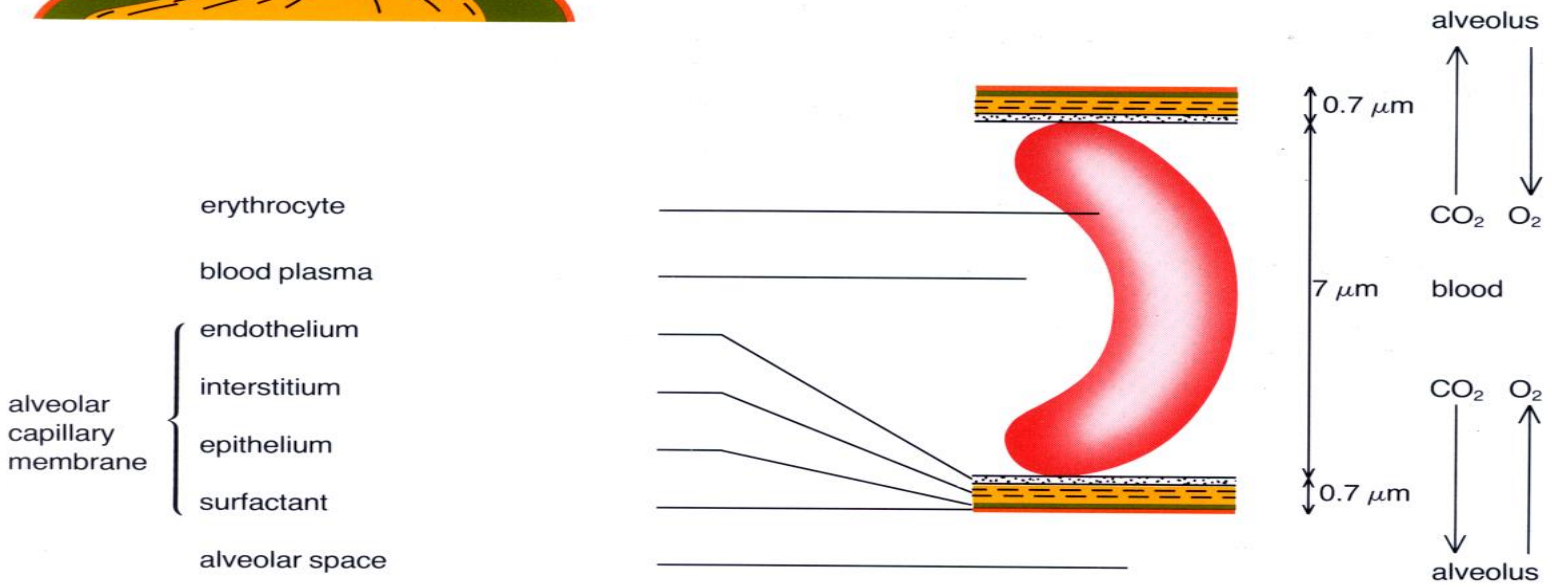


Unfavorable microcirculation in the liver:
the parallel arrangement of capillaries predisposes to low pO_2 values arround the central vein

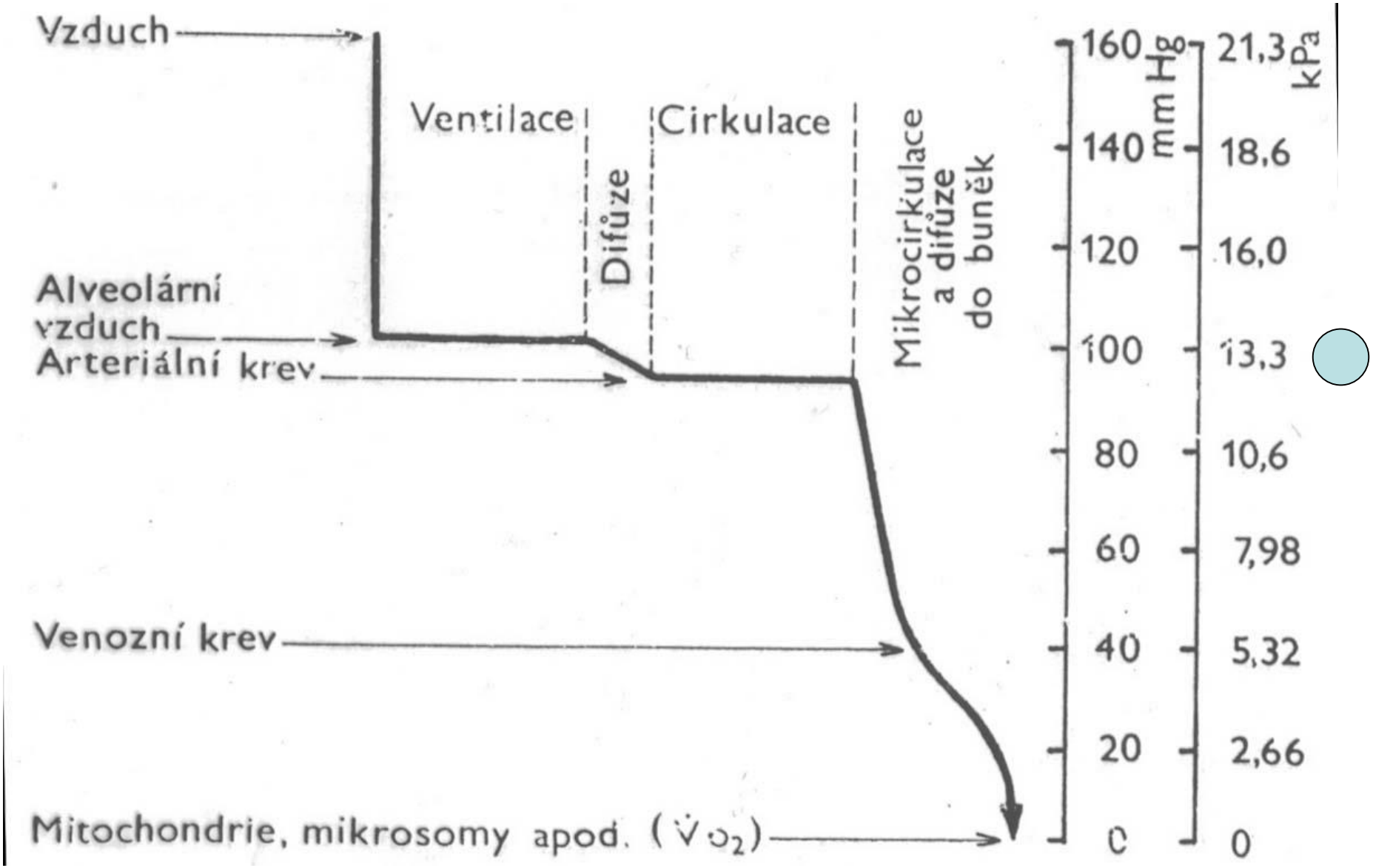
Hypoxie v jaterní tkáni



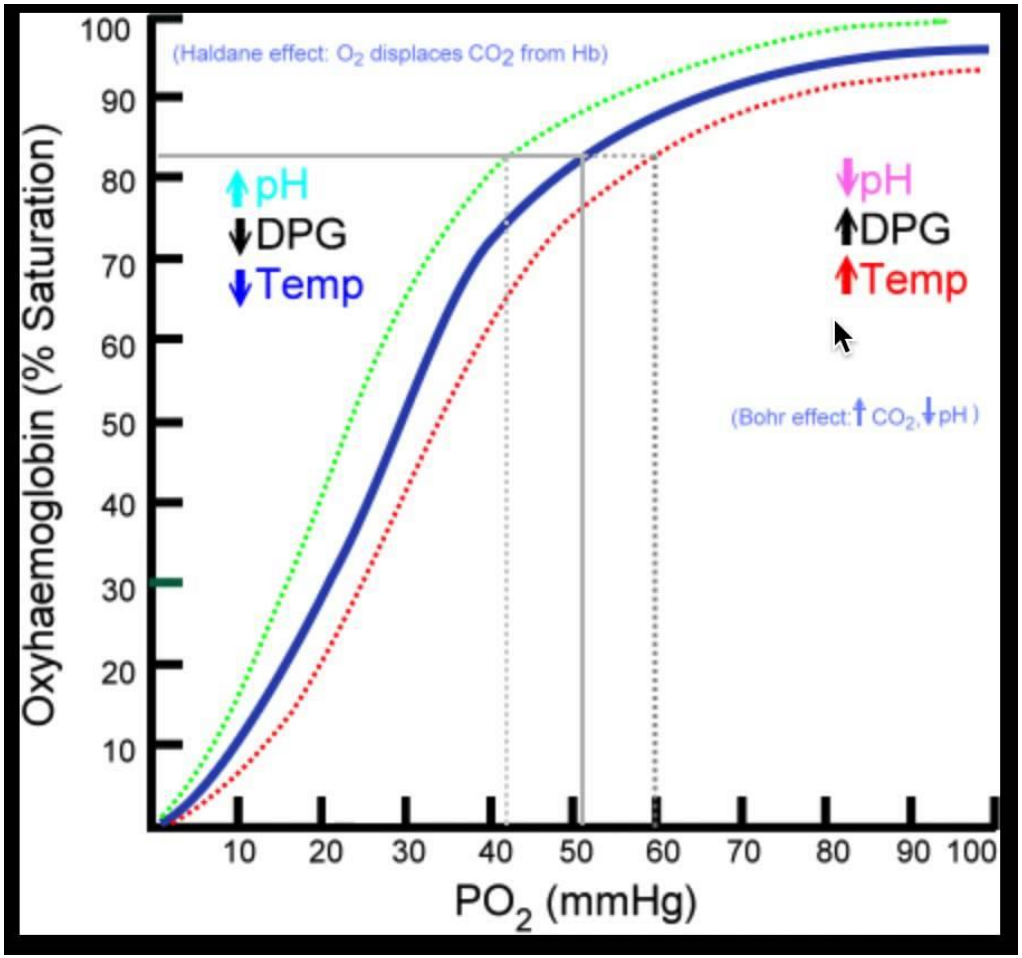

alveolar interstitium (elastic and collagenous fibres)
surfactant
epithelium (alveolar surface cell; type I)
2 μm
basement membranes
endothelium
erythrocyte
nucleus of the endothelial cell
capillary lumen (blood plasma)
alveolar space


erythrocyte
blood plasma
alveolar capillary membrane
endothelium
interstitium
epithelium
surfactant
alveolar space
0.7 μm
7 μm
0.7 μm
alveolus
CO2
O2
blood
CO2
O2
alveolus

Oxygen tension (pO_2) in different parts of the body



Oxygen disociation curve (blood)



The oxygen transporting mechanism

Lungs

- lung ventilation
- diffusion of oxygen into blood in pulmonary circulation

Circulation

- transport of oxygen by blood and circulation to capillaries

Red blood cells

- diffusion of oxygen from capillaries into surrounding tissues

Favorable for oxygen supply are:

- **a high pO_2 in the capillary**
- **short diffusion distances**
- **large surface of the microcirculation** (the surface to tissue volume ratio)

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6. Tissue and Cellular Responses to Hypoxia

7. Oxygenotherapy

Conditions causing hypoxia

- Environmental causes

- **Respiratory diseases and disorders**
- **Circulation disorders**
- **Anaemia, COHb, MetHb**
- **Tumour**
- **Wound (chronic unhealing)**

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Acute vs. chronic hypoxia

- Hypoxia can be ***fulminant*** (e.g. interruption of the circulation due to ventricular fibrillation, a massive pulmonary embolism, suffocation), ***acute*** or ***chronic***.
- Hypoxia can be ***systemic*** (e.g. due to lung diseases, anemia, CO intoxication, the heart failure) or ***local*** (e.g. trombosis, tissue injury, tumor).

An acute complete interruption of oxygen supply

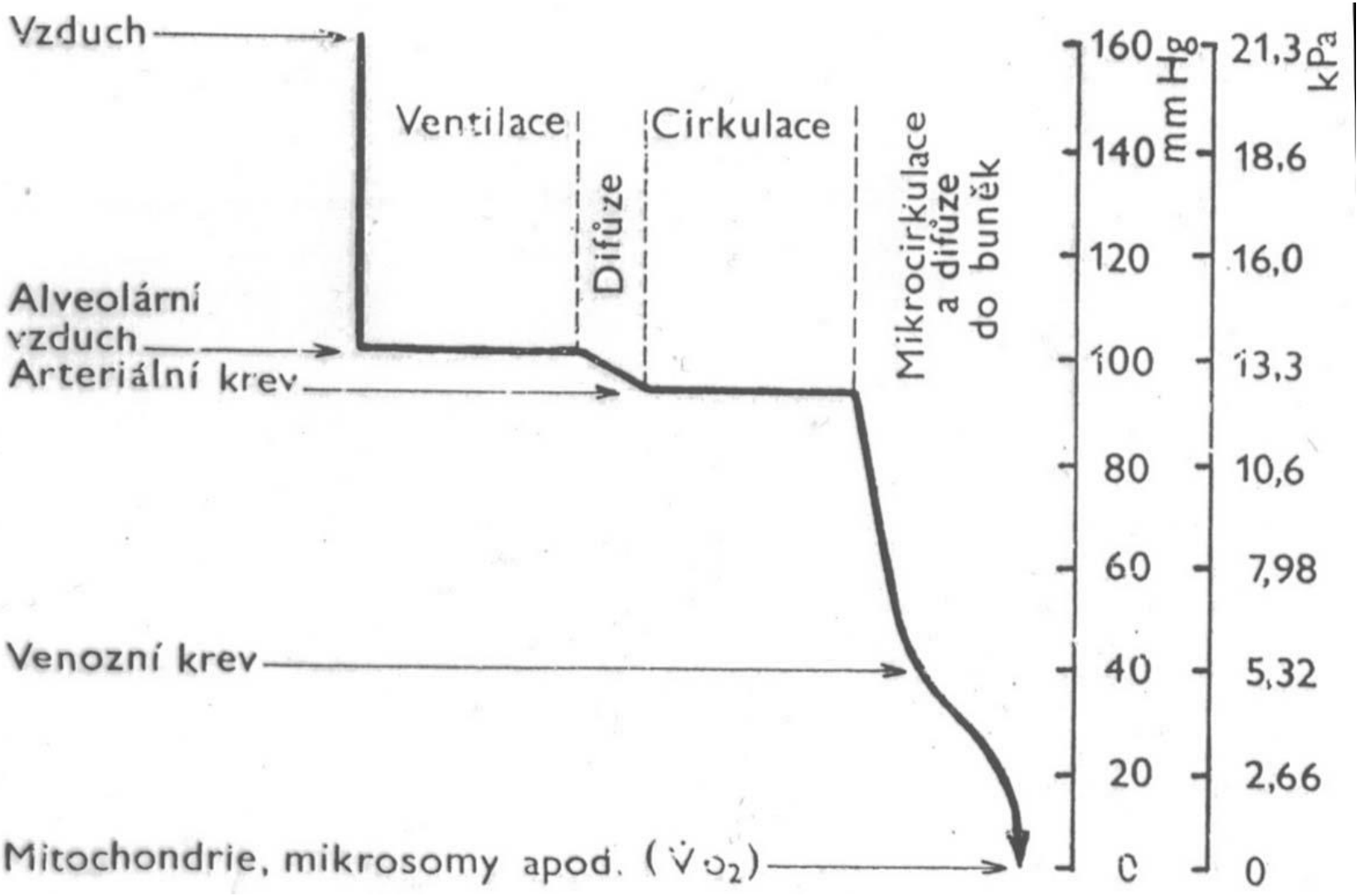
- breath holding
- suffocation
- inhalation of a gas lacking oxygen
- arrest of the circulation (ventricular fibrillation most often or a heart arrest)

Types of Hypoxia

- **Hypoxic hypoxia**
- **Anemic hypoxia**
- **Circulatory hypoxia**
- **Histotoxic hypoxia**

Hypoxic hypoxia

decreases alveolar and arterial pO_2



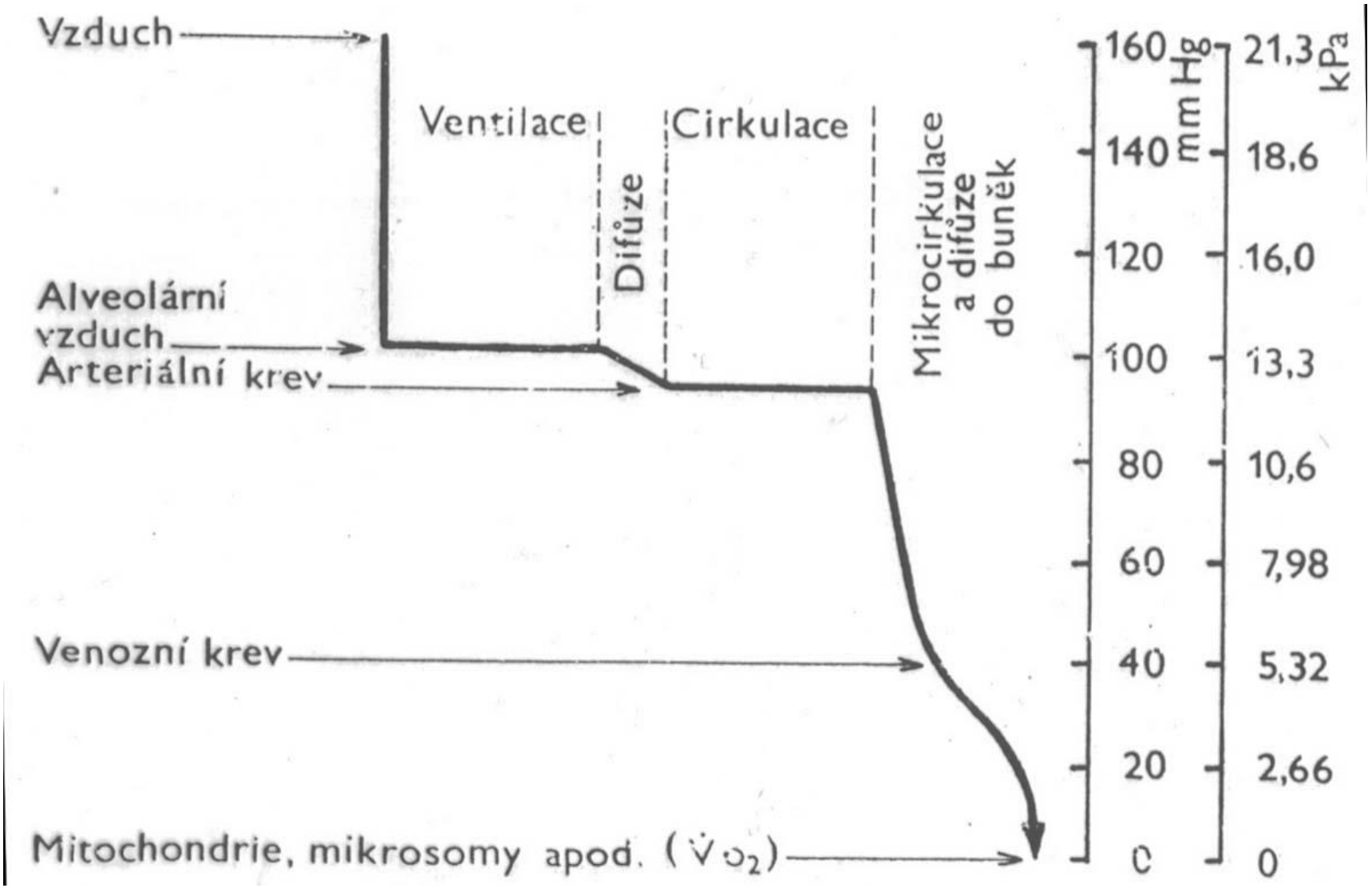
A low oxygen (pO2) in the air and respiratory diseases

- acute mountain sickness, a high altitude lung edema
- chronic mountain sickness - Mong´s disease,
- oxygen consumption in a closed “airtight” room

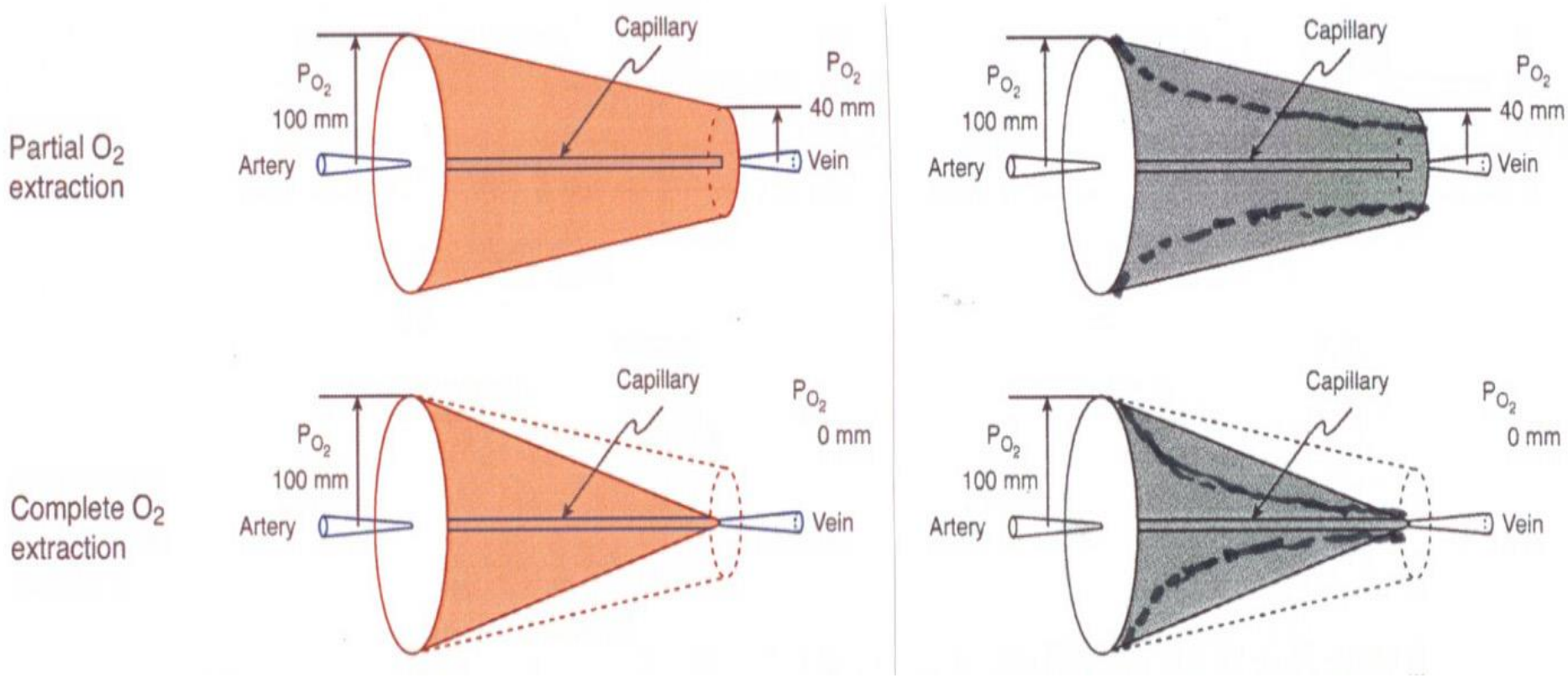
- ***Respiratory diseases causing „respiratory insufficiency“***

Anemic hypoxia

decreases mean capilary pO_2



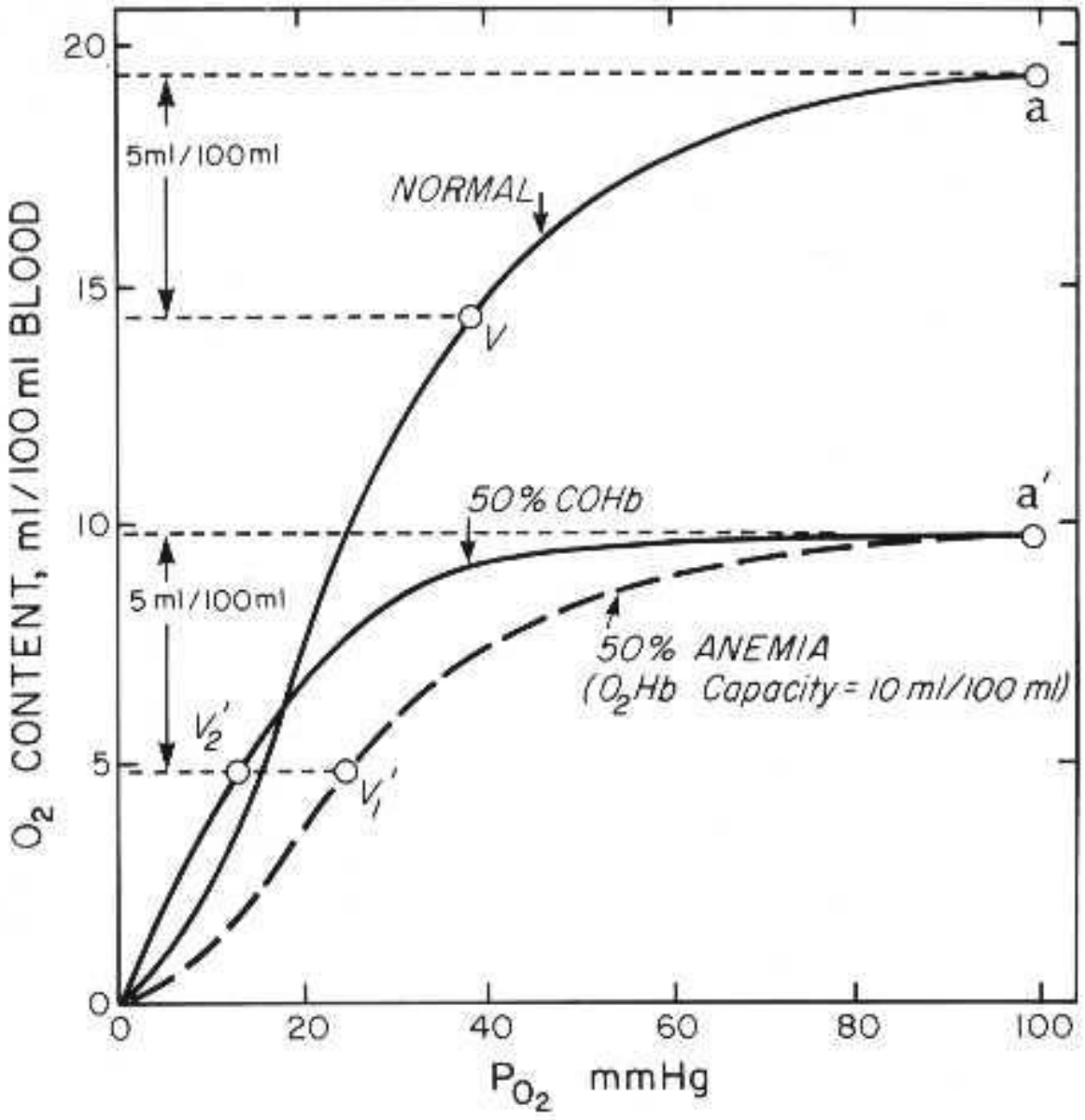
Anaemia and capillary pO_2



Anemia or a compromised functioning of hemoglobin

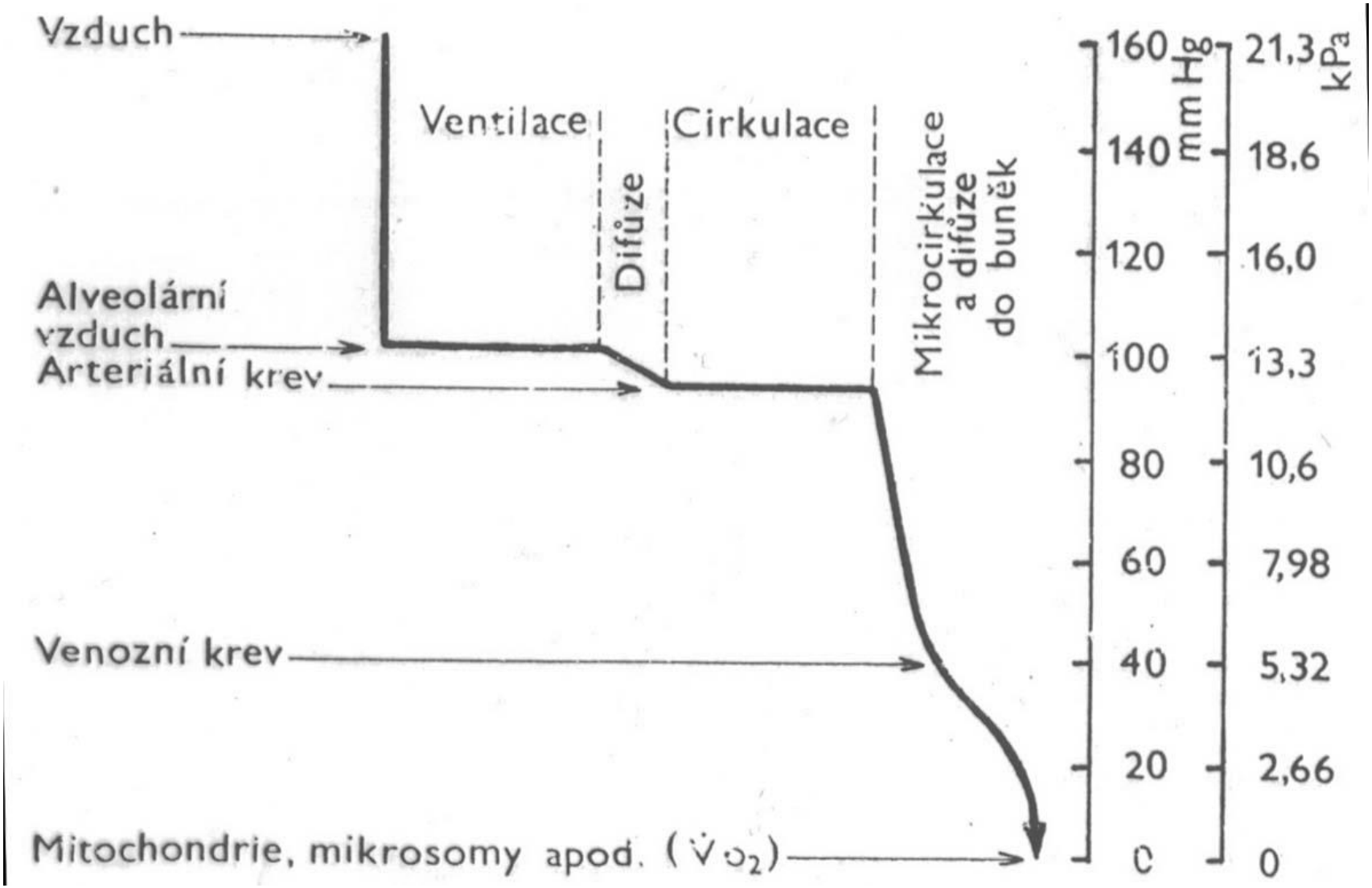
- anemia
- carboxyhemoglobin,
- methemoglobin, some

(hypothermia, hypocapnia)


20
15
10
5
0
0
20
40
60
80
100
O_2 CONTENT, ml/100 ml BLOOD
P_{O_2} mmHg
5ml/100ml
5 ml/100ml
NORMAL
50% COHb
50% ANEMIA
(O_2Hb Capacity = 10 ml/100 ml)
a
a'
V
V_2'
V_1'

Circulatory hypoxia

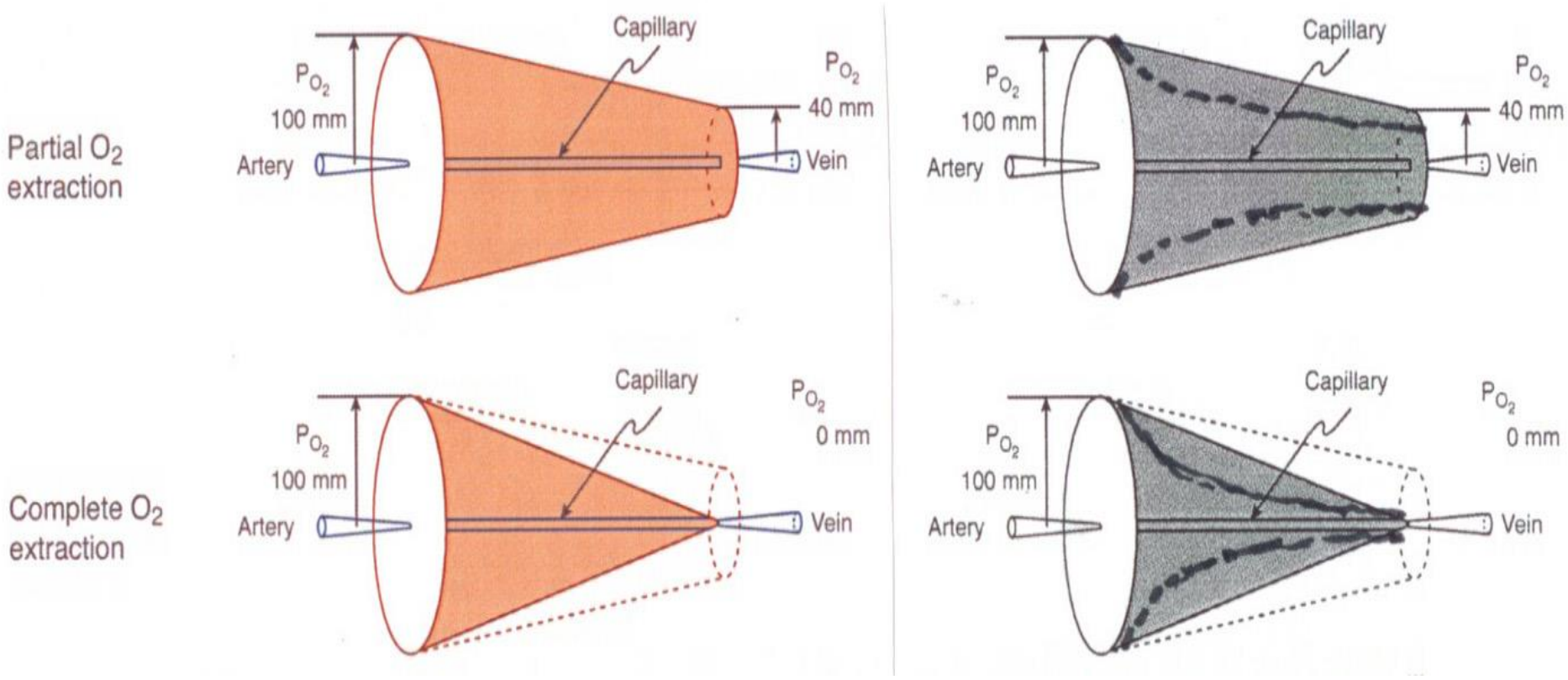
decreases mean capilary pO_2



Failure of the circulation
(systemic or local)
(ischemia or stagnation)

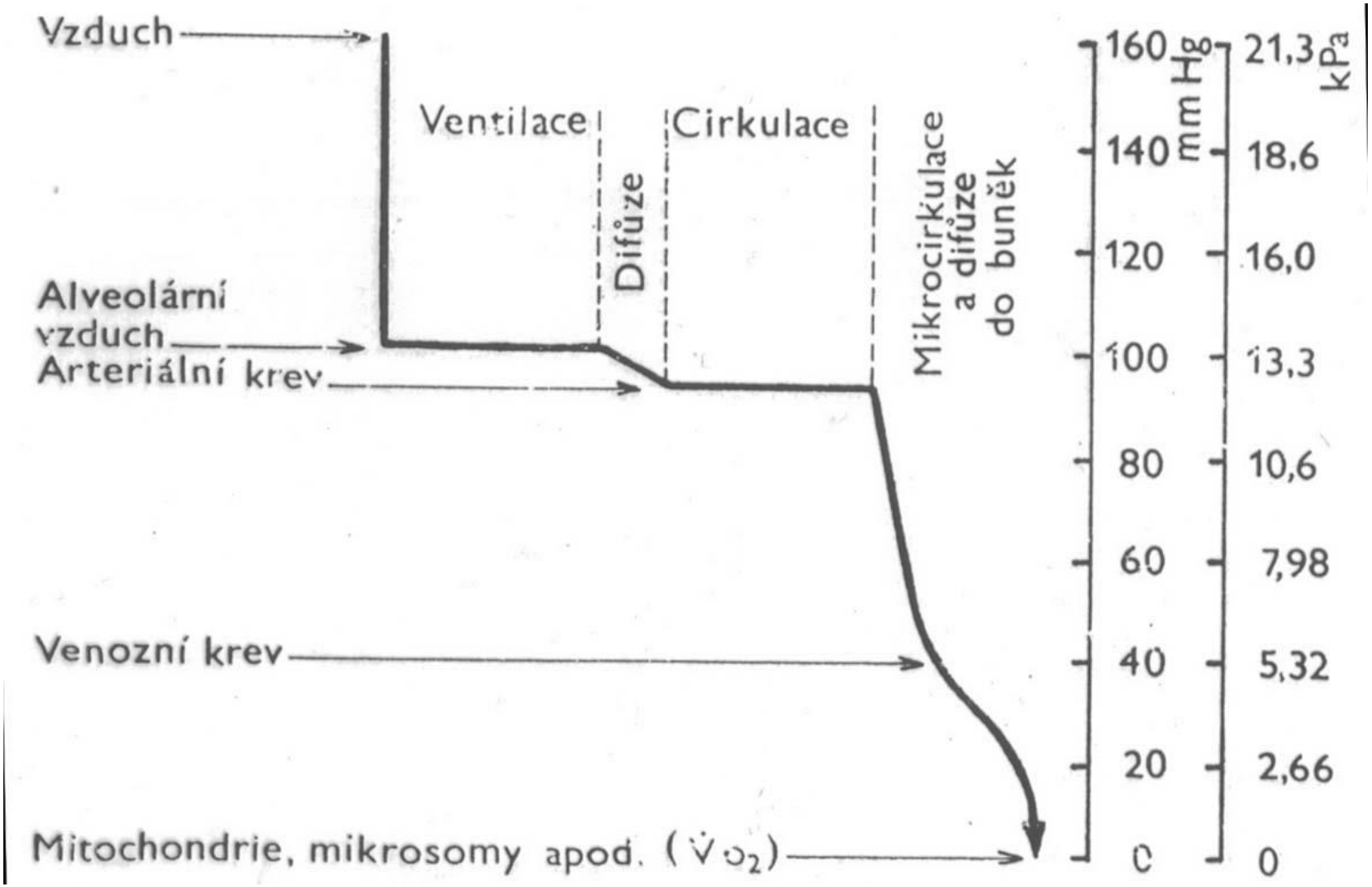
- congenital heart defects causing right-to-left shunts
- low cardiac output (valvular diseases, heart failure)
- circulatory shock (arterial hypotension)
- local compression of the circulation
- trombosis and embolisation
- tissue edema (particularly of the brain)
- arterio-venous shunts

A low blood flow and capillary pO_2

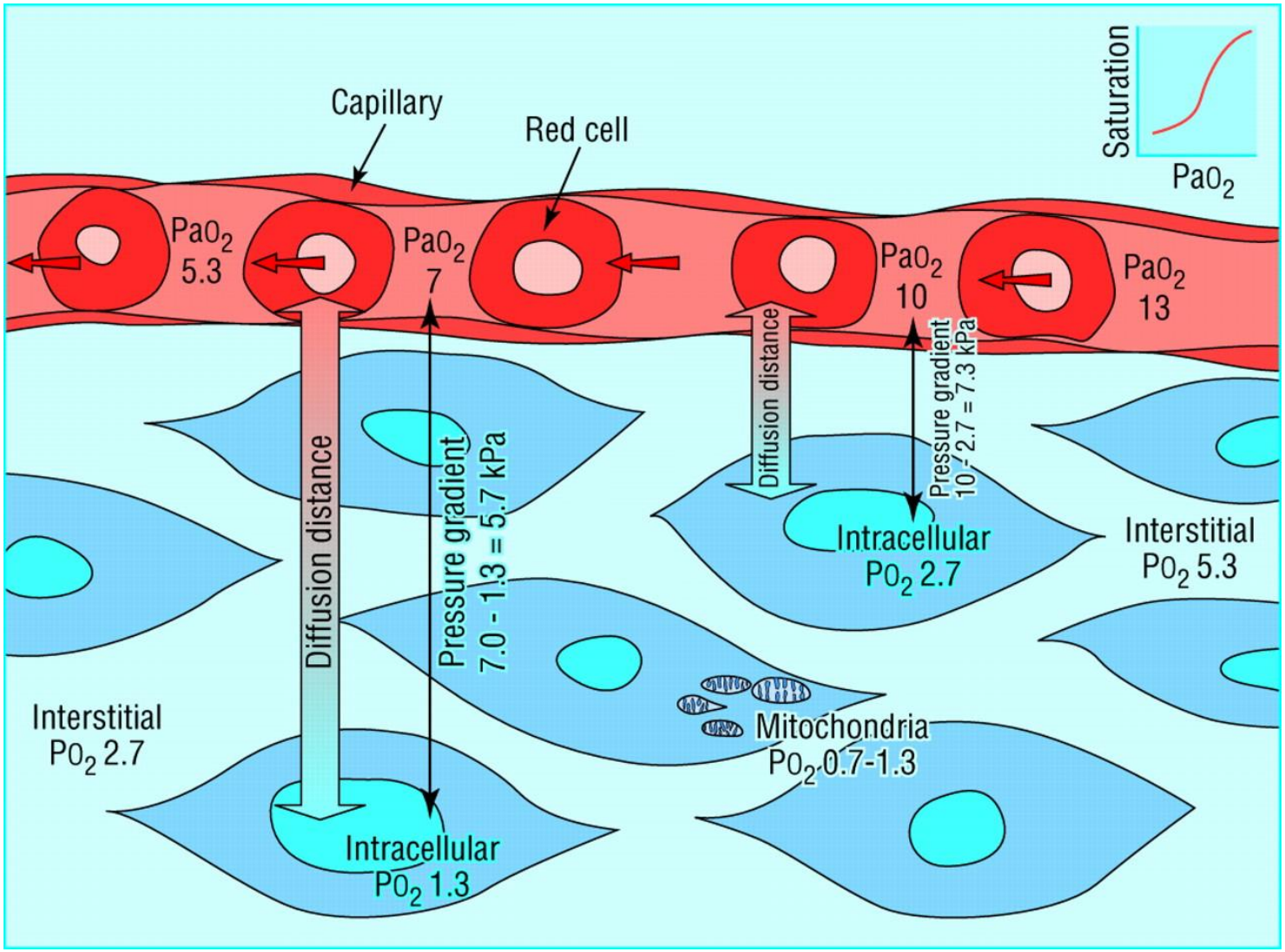


Histotoxic hypoxia

decreases capillary-mitochondria pO_2 gradients



Amounts of oxygen diffusing to mitochondria depends on steepness of pO2 gradients



Intoxications interfering with oxygen utilization by mitochondria

- (e.g. cyanide intoxication) - so called “histotoxic or cytotoxic hypoxia” - there is, in fact, **an increased amount of oxygen in tissues and in venous blood (causing a bright red color of the venous blood**, skin and muccosae).

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Oxygenotherapy

The aim is to increase pO2 in hypoxic cells

(not always an easy task)

Pure oxygen breathing

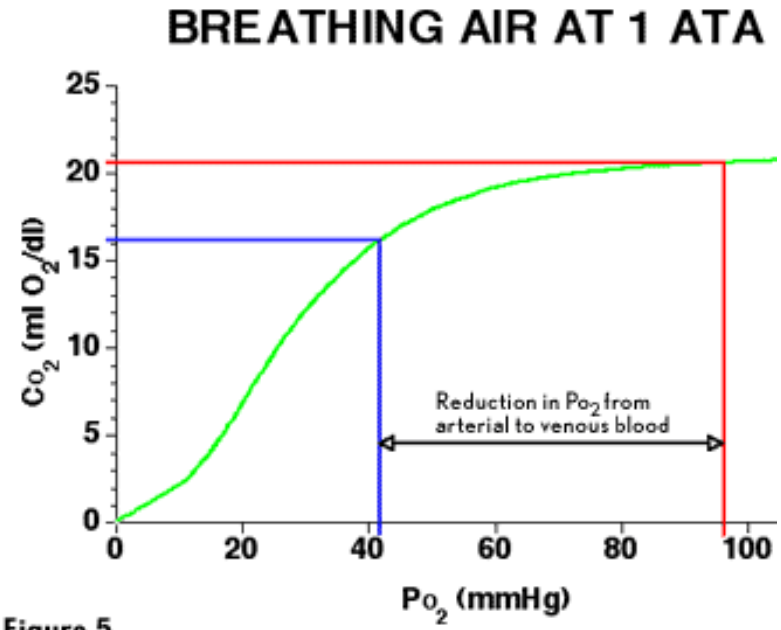

Figure 5

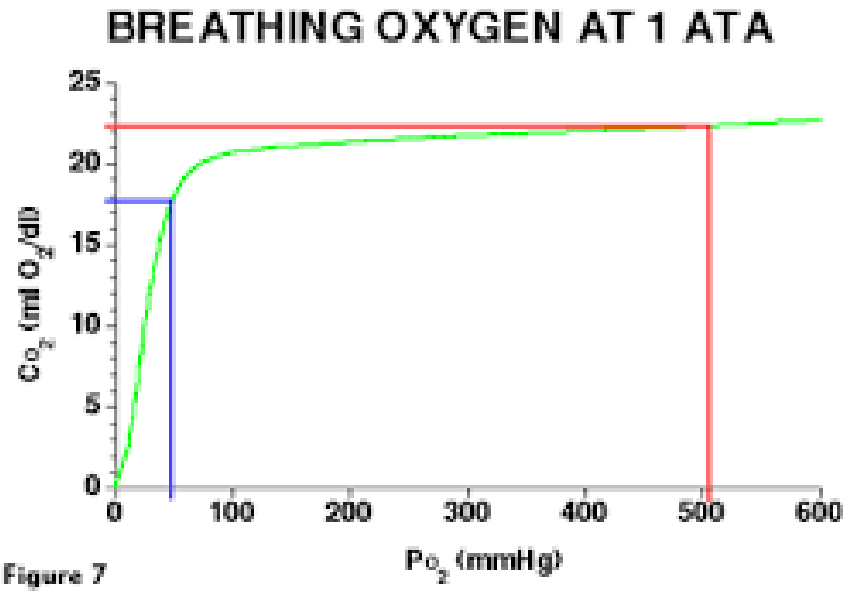

Figure 7

Oxygenotherapy

is highly effective in

„**hypoxic hypoxia**“

caused by environmental hypoxia or some lung diseases (chronic bronchitis, emphysema, asthmatic atack)

Oxygenotherapy

in the lung diseases when pathologies cause that a fraction of the blood flowing through the lungs bypasses the air-filled alveoli – presence of the so called **„pulmonary shunt“**

oxygenotherapy is less effective

(pnemonia, atelectasia, tumor)

Oxygenotherapy

in

„anemic hypoxia“

„circulatory hypoxia“

a limited efficiency

and in

„histotoxic hypoxia“

has NO benefficial effect at all

Hyperbaric oxygenotherapy

is based in breathing 100 % oxygen by a mask in a hyperbaric chamber with air compressed to 2 to 3 atmospheres

pO_2 in the arterial blood may then become very high

(treatment of chronic wounds, **acute intoxication with carbon monoxide**)

End

of the

Lecture