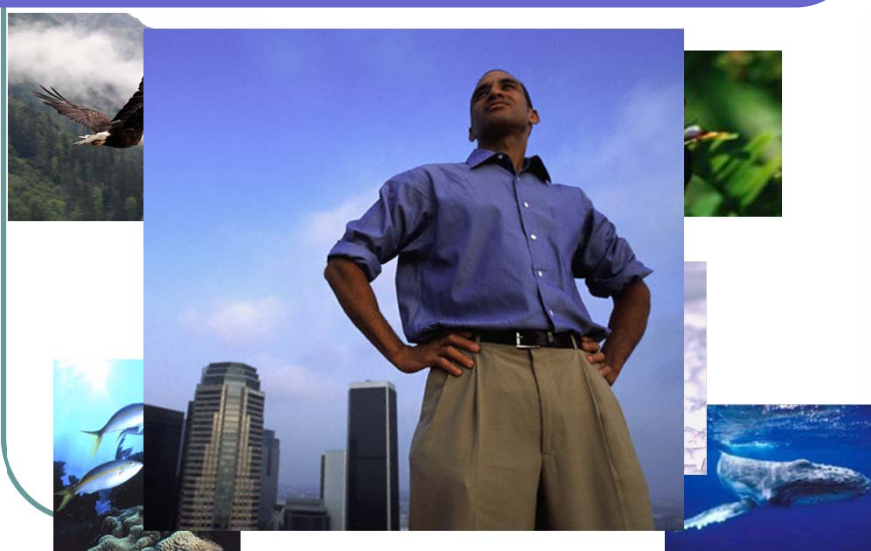


# Hypoxia

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## We are oxygen creatures



## Oxygen (O<sub>2</sub>) regimen

The flow of O<sub>2</sub> from the environment to the cells (resp. mitochondria) is carried out by an integrated system including:

- **Respiratory system** – airways, lungs, chest, respiratory pacemaker, respiratory muscles.
- **Blood hemoglobin**
- **Cardio-vascular system** – heart pump, systemic and pulmonary circulation, microcirculation
- **Mitochondria** – the “power stations” of the body

## Oxygen regimen includes the following functional stages:

1. Conveying of O<sub>2</sub> to the alveoli.
2. Transfer of O<sub>2</sub> to the blood
3. Binding of O<sub>2</sub> by the hemoglobin (Hb)
4. Transport of O<sub>2</sub> by the blood and its distribution in the organism.
5. Delivering of the O<sub>2</sub>, resp. O<sub>2</sub> extraction by the tissues
6. O<sub>2</sub> consumption by the tissues
7. Utilization of O<sub>2</sub> in the tissues

## The assessment of oxygen regimen relies on four parameters:

- Intensity
- Adequacy
- Economy
- Effectiveness



## I. Intensity = O<sub>2</sub> necessity

### ***Depends on:***

- Body weight (total amount of body cells and corresponding structures)
- Functional status (amount of functionally active units)
- Body temperature and temperature gradient organism – environment
- Metabolic status – substrates, active pathways, etc.
- Neurohormonal profile
- Structural balance of the organism
- Kata- / anabolic profile
- Presence (absence) of O<sub>2</sub> debt

## II. Adequacy = satisfied O<sub>2</sub> necessity

### **Recognized in:**

- Cells – cell hypoxic markers (HIF-1, HIF-2)
- Organs – tonometric detection of arterial-organ pH and pCO<sub>2</sub> changes
- Organism – metabolic markers for hypo- and anaerobiosis (concentration of blood lactate and the ratio lactate/pyruvate)

## III. Effectiveness = O<sub>2</sub> utilization

### **Assessed in:**

- **Cells, mitochondria and oxysomes** – by means of detecting the level of coupling of oxidative phosphorylation (for example the relation P : O ;  

$$\text{ATP} + 1/2\text{ADP} / \text{ATP} + \text{ADP} + \text{AMP} \approx 0.85 - 0.95$$
 ;
- **Organism** – determining the O<sub>2</sub> consumption per unit body mass or body surface and/or percent change in a given function (for example  $\Delta\text{VO}_2/\text{Watt}$  during exercise testing).

## IV. Economy = O<sub>2</sub> cost

Information about the biological cost of oxygen (O<sub>2</sub>) regimen is derived from the following equation:

$$\frac{\text{O}_2 \text{ spent for maintaining O}_2 \text{ convection (breathing + circulation)}}{\text{Total O}_2 \text{ consumption (total VO}_2\text{)}} \approx 15-16 \%$$

$$\text{VO}_2 \text{ (breathing + circulation) / total VO}_2 = 40/250 \approx 15-16 \%$$

## Hypoxia

### definition

From a clinical point of view, hypoxia has two main aspects:

- The state of **inadequacy** between delivery and necessity of O<sub>2</sub> for the cell (resp mitochondria), tissue, organ, organism.
- **Failure** of the oxygen regimen to satisfy the metabolic requirements of the organism for a normal lifestyle.

**As *inadequacy*,**

hypoxia represents acute, critical condition threatening the vital functions

It can be a consequence of:

- **Decreased O<sub>2</sub> delivery in case of normal necessity (frequently)**

**OR**

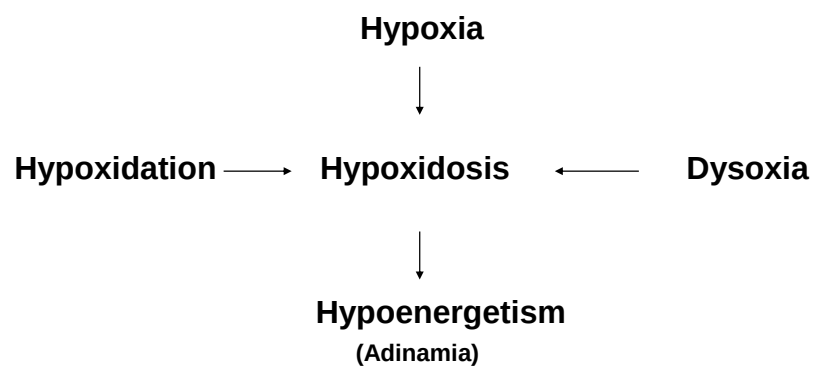
- **Normal (sometimes increased) delivery, but in case of even greater O<sub>2</sub> requirements (rarely)**

**As *failure*,**

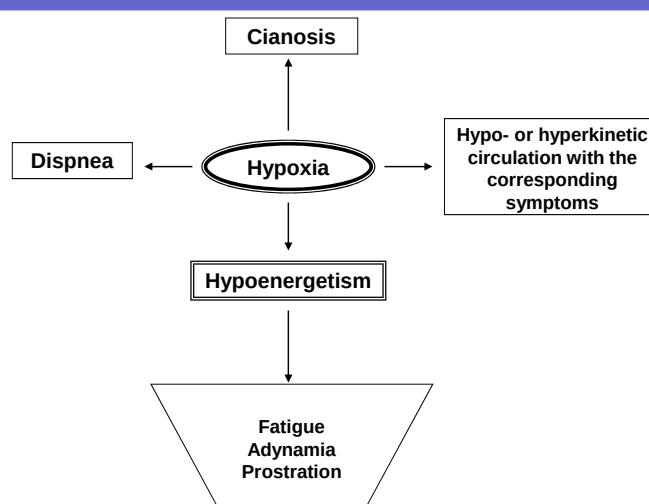
hypoxia represents stable, chronically "limited O<sub>2</sub> regimen":

- Incapable of satisfying the vital requirements of the organism and turning normal man into "patient".
- One or more stages in the O<sub>2</sub> regimen are impaired with effectiveness and economy decreased to different extent.
- Engaging of body compensations ensures some O<sub>2</sub> adequacy, but the level of daily activity is decreased and the lifestyle of the patient is altered.

## Disorders of aerobic metabolism



## Clinical signs of hypoxia



## Classification of hypoxias

### Anatomic

- Respiratory
- Blood
- Cardio-circulatory
- Tissue

### Distribution

- Isolated (local)
- General

### Occurrence

- Systemic hypoxia
- Tissue hypoxia

### Clinical

- Fulminant
- Acute
- Sub acute
- Chronic

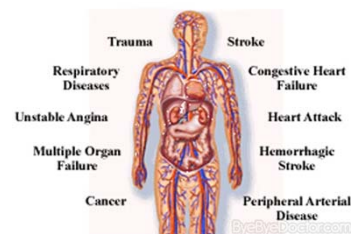
### Severity

- Light
- Medium
- Extreme
- Severe

## Pathophysiologic classification

- Hypoxic hypoxia
- Hemic hypoxia
- Circulatory hypoxia
- Histotoxic hypoxia
- Mixed hypoxia

### Hypoxic Conditions



## Hypoxic hypoxia

It is a consequence of physical or physiological impaired intake or diffusion of  $O_2$  in the lungs and can be divided into **exogenous** and **endogenous** hypoxic hypoxia.

Exogenous hypoxic hypoxia is due to  $O_2$  deficit in the inhaled air, as a result of:

- Lowering the barometric pressure – ***hypobaric hypoxic hypoxia*** (accidents in airplanes and spaceships, altitude disease).
- Breathing of gas mixture with low  $O_2$  content – ***normobaric hypoxic hypoxia*** (breathing in closed rooms, accidents, etc). The physical deficit of  $O_2$  causes decreasing of  $pO_2$  along the whole oxygen cascade. Oxygen regimen is intact. As a form of compensation it is forced to work at its maximum, with “struggle for  $O_2$ ” at all stages. As a result of this “struggle”, hypocapnia ensues.

## Characteristics and degrees of hypoxic hypoxia

### 1. Characteristics.

- In most cases appear to be hypoxia with independent deficit of  $O_2$ .
- Substrate delivery is not impaired.
- Elimination of end metabolites is not impaired
- Compensations are well expressed and effective.
- Cells get used to utilize normal amount of  $O_2$  in an environment with lower  $pO_2$ .

### 2. Degrees – mild, moderate, severe

## Hemic (blood) hypoxia

**The oxygen-transport capacity of Hb is decreased as a consequence of:**

- Absolute deficit of Hb – **anemic type**.
- Transport, binding and delivery of O<sub>2</sub> by the Hb is altered – **inactivity type**.
- Inadequate (ineffective) oxygen transport heme to heme interaction in Hb – **hypo- or hyperaffinity type**.
- Combination of the above mentioned types – **combined type**.

## Carboxyhemoglobinemia FCOHb >1% ( up to 10% in smokers)

Observed in case of breathing of air containing CO (incomplete burning).

Accumulation of CO in the blood is determined by:

- Higher affinity of CO to Hb (replaces O<sub>2</sub> in Hb)
- Slower dissociation of COHb than OxyHb – precondition for accumulation in case of low concentration.

## Methemoglobinemias

FMetHb >1%

- **Physiologic** – with protective functions:
  - Catalyzes the disruption of  $\text{H}_2\text{O}_2$ .
  - Binds HCN actively and turns it into relatively harmless cyanmethemoglobin.
- **Pathologic**. Can be inborn (congenital) or acquired.

## Methemoglobinemias

FMetHb >1%

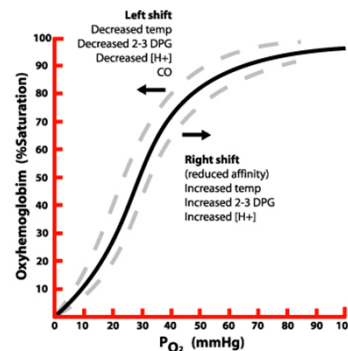
- **Inborn** (congenital) methemoglobinemia can be a consequence of:
  - Atypical structure of Hb.
  - Deficit of erythrocyte methemoglobin reductases.
- **Acquired** methemoglobinemia can be caused by the so called “methemoglobin developers” – nitrites, aniline derivatives, some medicines – atabrine, sulphonamides, etc.
- **Methemoglobin** shifts the *curve*  $p\text{O}_2/\text{ctO}_2$  to the left – impaired  $\text{O}_2$  delivery.

## Sulphhemoglobinemias

SHb = N/A

**Sulphhemoglobin** is irreversible inactive Hb (sulphonamides,  $\text{H}_2\text{S}$ ).

Its presence strongly shifts the  $p\text{O}_2/\text{ctO}_2$  curve to the right and leads to combination of normoxia with hyposaturation.



## Circulatory Hypoxia

- Circulatory hypoxia is due to **functionally insufficient local or general blood supply**.

The main pathogenetic unit is **insufficient tissue perfusion**. Metabolism from “*leader and conductor*” of the circulation is turned into dependent factor limited by blood flow.

- **Inadequate tissue perfusion** exists as two functional variants: **hyperkinetic** and **hypokinetic**.

## Hyperkinetic vs. Hypokinetic

**Hyperkinetic type** – hypoxia at extreme exercise (limitation of physical capacity).

**Hypokinetic type** – usually at deranged:

- O<sub>2</sub> transition in the lungs.
- O<sub>2</sub> transport to the tissues.
- O<sub>2</sub> distribution and/or
- O<sub>2</sub> supply for the cells or intracellular structures in a tissue, organ etc.

## Three types of circulatory hypoxia

- **Ischemic type** – spasm or occlusion of arterial blood vessel (Ischemic heart disease).
- **Congestive type** - impeded or completely stopped blood flow in one or more areas of the body (chronic heart failure, venous thrombosis, etc).
- **Mixed type** – with initial predominantly ischemic and subsequent predominantly congestive stage (different kinds of shock).

### Ischemic type is characterized with:

- Combination of  $O_2$  and substrate deficit, together with impaired end metabolites wash out – quick decompensation of cell metabolism.
- Predominantly hypoextraction tissue  $O_2$  deficit due to arterial-venous shunts and impaired tissue  $O_2$  diffusion.

### Congestive type is characterized with:

- Prolonged contact time blood/tissue with increased  $O_2$  extraction. Cells get more  $O_2$  than usual so venous hypoxia and hypoxemia ensue. The latter are the causes for increased arterial-venous  $O_2$  changes and cyanosis.
- Substrate delivery and end metabolites wash out are less affected.

## Impairment in O<sub>2</sub> utilization

**(dysoxia, O<sub>2</sub> utilization hypoxia, normoxic hypoxidosis)**

Exists in two main pathogenetic variants:

- Insufficient or impossible reduction and extraction of O<sub>2</sub> from the environment – histotoxic type, histohypoxia, histohypoxic hypoxia.
- Insufficient or lost utilization of the O<sub>2</sub> already entered the cells, resp. mitochondria – ineffective O<sub>2</sub> utilization.

## Ineffective utilization of O<sub>2</sub>

Can be seen in:

- **Substrate deficit in mitochondria:**
  - blocked shuttle mechanisms
  - suppressed Krebs cycle
  - incapable flavoprotein pathway for electron delivery for the transelectronases
  - selective block in substrate phosphorylation

## Ineffective utilization of O<sub>2</sub>

Can be seen in:

- **Uncoupling of oxidative phosphorylation**
  - pathogenic agents (decouplers) – 2,4 dinitrophenol, oligomycin, thyroid hormones, bacterial toxins, low molecular peptides, free fatty acids, etc
  - pathologic conditions – homeostatic disturbances, cell edema, excess of free radicals, jaundice, cholestasis, etc.

## Ineffective utilization of O<sub>2</sub>

Can be seen in:

- **Genetic or acquired** (intoxications and infections) **damage** to the mitochondrial membranes or the so called “special mitochondrial states”
  - Ca<sup>2+</sup> “leakage” from the mitochondria
  - suppressed anionic and nucleotide transport by alkalosis
  - blocked reverse electron transport by hyperoxia

### Decreased mitochondrial O<sub>2</sub> reduction (histotoxic hypoxia)

It emerges as a result of:

- Suppressed electron transport at the end of respiratory chain – transelectronases.
- Deficit of mitochondria in the cells.
  - high destruction rate and/or
  - suppressed synthesis of mitochondria and/or oxysomes.

Existing transelectronase block depresses O<sub>2</sub> reduction, resp. consumption. Cells cannot utilize already extracted O<sub>2</sub>. It passes in the venous blood. Venous hyperoxemia emerges with lower arterial-venous O<sub>2</sub> change.

### Hyperoxic dysoxia

Toxic effects of hyperoxia include:

- Formation of toxic O-radicals with risk of “oxygen explosion” of the cell.
- Block on the reverse electron transport with suppressed cytosol synthesis of substances.
- Accumulation of excess cyclic AMP in the cells – “excited cells”.
- Impaired CO<sub>2</sub> and H<sup>+</sup> “drainage” of the cells, resp. O<sub>2</sub> mediated cell intoxication with H<sup>+</sup>.

The most sensitive to O<sub>2</sub> damage are the cells of the retina, neurons in CNS and alveolar cells type II producing surfactant.

## Mixed hypoxia

It is the most common condition in the clinical practice and can be found in:

- Critically ill patients – combined traumas, acute intoxications, sepsis, adult respiratory distress syndrome (ARDS), etc.
- Influence of extreme factors on the organism – hypo- and hyperbaria, thermal stress, radiation etc.
- Weightlessness and prolonged space missions.
- Chronic mono- or polyorgan insufficiency - decompensated cor pulmonale chr.
- Hyperoxic intoxication seen in “enthusiastic” O<sub>2</sub> therapy.

## Tissue hypoxia

Tissue hypoxia is the end stage of different forms and pathogenetic variants of system hypoxia. It is a condition characterized with low tissue O<sub>2</sub> and passes through four stages (phases):

- **Saturation**                      Compensated O<sub>2</sub> deficit (*without* O<sub>2</sub> debt)
- **Adaptation**
- **Hypoaerobiosis**              Uncompensated O<sub>2</sub> deficit (*with* O<sub>2</sub> debt)
- **Destruction**

## Saturation phase

- Most frequently it is transitional phase, merging with the next one – metabolic modulation of the aerobic metabolism. Saturation phase is best revealed in striated muscles and the heart and is absent in the neurons of CNS.
- The cells function in low  $pO_2$  environment. Their work possibility and reserve functional capacity are decreased, resp. the product activity  $\times$  time is also lowered.

## Adaptation (metabolic) phase

Adaptive modulation of aerobic metabolism includes:

- Increased flow of reduction equivalents from the cytosol to the mitochondria.
- Mobilization of electron supply for cytochrome C (activate electron sideways).
- Complete utilization of  $O_2$  by oxysomes, resp. respiratory chains as a result of increased electron flow.
- Keeping  $O_2$  flow unchanged at low  $pO_2$ .
- Initial preservation and later increase of the coupling of oxidative, substrate and total phosphorylation in the mitochondria.
- Stimulating the synthesis of stress proteins by hypoxic signals.

### **Gains for the cells during this phase:**

- Increased cell resp. mitochondrial resistance in hypoxic environment.
- Chance to preserve function in progressively hypoxic environment.

### **Disadvantages for the cells as a result of adaptation:**

- Slow and imprecise response of the hypoxic cells to tele- and paracrine signals.
- Faster “wear and tear” of cell structures.
- Higher risk of activating cell’s apoptosis program.

## Hypoaerobiosis (dysoxic) phase

It is characterized with:

- Deficit of oxidative ATP production.
- Activating the production of non-oxidative ATP production– active glycolysis.
- O<sub>2</sub> delivery dependent O<sub>2</sub> consumption.
- Low respiratory mitochondrial control, resp. initial decoupling of the oxidative phosphorylation.
- Restructuring of the energy expenditures with restriction of facultative and supporting of the essential (vital) cell metabolism.

## Destructive (necrotic) phase

- It is consequence to extreme or medium but persistent and/or progressive tissue hypoxia.
- Cell's hypo- or anoxic alteration can be ***reversible*** or ***irreversible***.
- Cell's essential metabolism is not working properly or is entirely suppressed.

## Changes in cells

- **Mitochondrial changes** - transition to the so called “highly permeable state”
- **Cytosolic changes** - intracellular acidosis with secondary glycolytic block
- **Nuclear changes** - Suppressed polymerases
- **Lysosomal changes** - destroyed lysosomes and their enzymes spill in the cytosol

## Adaptation to hypoxia

### General principles:

- Adaptations are **effective in light**, relatively effective in medium and **ineffective in severe** hypoxic states.
- Adaptations are most stable in hypoxic hypoxia, less expressed in hemic and circulatory hypoxia and least stable in histotoxic hypoxia.
- The following factors influence the expression and effectiveness of compensation:
  - The degree and duration of hypoxia.
  - Pathogenetic factors forming different types of hypoxia.
  - Ontogenetic stage of the organism.
  - The hypoxic pattern – continuous, periodic, impulse, etc.
- Genetic integrity of O<sub>2</sub> dependent cell genes and mechanisms for their activation.

## Lung adaptations

- Increased lung and alveolar ventilation:
  - hemoreflex mechanism (hours, days)
  - compensatory change in the relation ventilation/perfusion -  $V_A/Q$  (months, years)
- Increased pulmonary blood volume with higher  $O_2$  extraction in the alveoli.
- Increased diffusion capacity of the alveolar-capillary membrane.

***More  $O_2$  brought to the organism***

## Cardio – vascular adaptations

- Increased cardiac output
  - increased heart rate (tachycardia)
  - increased stroke volume
- Rise in the arterial blood pressure
  - better tissue perfusion
- Increased vascularization and capillarization
  - recruiting of reserve capillaries
  - formation of new capillaries
- Augmented transition of interstitial fluid to the vessels
  - better rheology of the blood
  - easy  $O_2$  diffusion

***Larger amount of  $O_2$  transported and delivered to the cells.***

## Blood adaptations

They are among the most effective adaptations !

- Compensatory erythrocytosis:
  - Rapid – mobilization of erythrocytes from the depots.
  - Slow – intense erythropoiesis (as a result of erythropoietin production).
- Adaptive change of O<sub>2</sub> binding function of hemoglobin
  - High concentration of 2,3 DPG in erythrocytes, shift of Hb dissociation curve to the right with easier O<sub>2</sub> release.

***More O<sub>2</sub> bound and released per unit breathing area.***

## Cell adaptations

- Increased O<sub>2</sub> reserve in the cells with O<sub>2</sub> depots like myoglobin in muscles.
- More effective delivery of electrons to transelectronase enzymes.
- Increased O<sub>2</sub> affinity of the terminal cytochromoxydases.
- Growing number of respiratory chains in a mitochondrion and mitochondria in a cell.

***Complete extraction of all the O<sub>2</sub> by the cells.***

**Thank you !**