Hypoxia

Blagoe Marinov, MD, PhD
Pathophysiology Dept.
Medical University of Plovdiv

We are oxygen creatures
Oxygen (O₂) regimen

The flow of O₂ 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 O₂ to the alveoli.
2. Transfer of O₂ to the blood
3. Binding of O₂ by the hemoglobin (Hb)
4. Transport of O₂ by the blood and its distribution in the organism.
5. Delivering of the O₂, resp. O₂ extraction by the tissues
6. O₂ consumption by the tissues
7. Utilization of O₂ in the tissues
The assessment of oxygen regimen relies on four parameters:

- Intensity
- Adequacy
- Economy
- Effectiveness

I. Intensity = $O_2$ 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 $O_2$ debt
II. Adequacy = satisfied $O_2$ necessity

**Recognized in:**
- Cells – cell hypoxic markers (HIF-1, HIF-2)
- Organs – tonometric detection of arterial-organ pH and $pCO_2$ changes
- Organism – metabolic markers for hypoxia and anaerobiosis (concentration of blood lactate and the ratio lactate/pyruvate)

III. Effectiveness = $O_2$ utilization

**Assessed in:**
- **Cells, mitochondria and oxysomes** – by means of detecting the level of coupling of oxidative phosphorylation (for example the relation $P : O$; $\frac{ATP + 1/2ADP}{ATP + ADP + AMP} \approx 0.85 – 0.95$);
- **Organism** – determining the $O_2$ consumption per unit body mass or body surface and/or percent change in a given function (for example $\Delta VO_2$/Watt during exercise testing).
IV. Economy = O₂ cost

Information about the biological cost of oxygen (O₂) regimen is derived from the following equation:

\[
\frac{O_2 \text{ spent for maintaining } O_2 \text{ convection}}{\text{Total } O_2 \text{ consumption (total VO}_2\text{)}} \approx 15-16 \%
\]

\[
\frac{VO_2 \text{ (breathing + circulation)}/\text{total VO}_2}{40/250} \approx 15-16 \%
\]

Hypoxia

definition

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

- The state of **inadequacy** between delivery and necessity of O₂ 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\(_2\) delivery in case of normal necessity (frequently)
  OR
- Normal (sometimes increased) delivery, but in case of even greater O\(_2\) requirements (rarely)

As **failure**, hypoxia represents stable, chronically “limited O\(_2\) regimen”:

- Incapable of satisfying the vital requirements of the organism and turning normal man into “patient”.
- One or more stages in the O\(_2\) regimen are impaired with effectiveness and economy decreased to different extent.
- Engaging of body compensations ensures some O\(_2\) adequacy, but the level of daily activity is decreased and the lifestyle of the patient is altered.
Disorders of aerobic metabolism

Hypoxia

↓

Hypoxidation → Hypoxidosis ← Dysoxia

↓

Hypoenergetism (Adinamia)

Clinical signs of hypoxia

Cianosis

Dispnea

Hypoxia

Hypoenergetism

Fatigue
Adynamia
Prostration

Hypo- or hyperkinetic circulation with the corresponding symptoms
Classification of hypoxias

**Anatomic**
- Respiratory
- Blood
- Cardio-circulatory
- Tissue

**Clinical**
- Fulminant
- Acute
- Sub acute
- Chronic

**Distribution**
- Isolated (local)
- General

**Severity**
- Light
- Medium
- Extreme
- Severe

**Occurrence**
- Systemic hypoxia
- Tissue hypoxia

Pathophysiologic classification

- Hypoxic hypoxia
- Hemic hypoxia
- Circulatory hypoxia
- Histotoxic hypoxia
- Mixed hypoxia
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 $O_2$ 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 $O_2$ 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, same medicines – atebrine, sulphonamides, etc.
- **Methemoglobin** shifts the curve $\text{pO}_2/\text{ctO}_2$ to the left – impaired $\text{O}_2$ delivery.
Sulphhemoglobinemias
SHb = N/A

**Sulphhemoglobin** is irreversible inactive Hb (sulphonamides, H$_2$S).

Its presence strongly shifts the curve $pO_2/cO_2$ 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 pathrogenetic 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. Hypokynetic**

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

**Hypokinetic type** – usually at deranged:
- $O_2$ transition in the lungs.
- $O_2$ transport to the tissues.
- $O_2$ distribution and/or
- $O_2$ 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 O₂ utilization**

(dysoxia, O₂ utilization hypoxia, normoxic hypoxidosis)

Exists in two main pathogenetic variants:

- Insufficient or impossible reduction and extraction of O₂ from the environment – histotoxic type, histohypoxia, histohypoxic hypoxia.
- Insufficient or lost utilization of the O₂ already entered the cells, resp. mitochondria – ineffective O₂ utilization.

**Ineffective utilization of O₂**

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 phosphorilation
Ineffective utilization of O₂

Can be seen in:

- **Uncoupling of oxidative phosphorilation**
  - 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 O₂

Can be seen in:

- **Genetic or acquired** (intoxications and infections) **damage** to the mitochondrial membranes or the so called “special mitochondrial states”
  - Ca²⁺ “leakage” from the mitochondria
  - suppressed anionic and nucleotide transport by alkalosis
  - blocked reverse electron transport by hyperoxia
Decreased mitochondrial $O_2$ 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 $O_2$ reduction, resp. consumption. Cells cannot utilize already extracted $O_2$. It passes in the venous blood. Venous hyperoxemia emerges with lower arterial-venous $O_2$ 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$_2$ and H$^+$ “drainage” of the cells, resp. $O_2$ mediated cell intoxication with H$^+$.

The most sensitive to $O_2$ 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 polmonalae chr.
- Hyperoxic intoxication seen in “enthusiastic” $O_2$ 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 $O_2$ and passes through four stages (phases):

- **Saturation**  
  Compensated $O_2$ deficit (without $O_2$ debt)
- **Adaptation**
- **Hypoaerobiosis**  
  Uncompensated $O_2$ deficit (with $O_2$ 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 paracrinic 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.
- \( O_2 \) delivery dependent \( O_2 \) 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 O₂ 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 erythropoetin production).

- Adaptive change of O₂ binding function of hemoglobin
  - High concentration of 2,3 DPG in erythrocytes, shift of Hb dissociation curve to the right with easier O₂ release.

More O₂ bound and released per unit breathing area.

Cell adaptations

- Increased O₂ reserve in the cells with O₂ depots like myoglobin in muscles.
- More effective delivery of electrons to transelectronase enzymes.
- Increased O₂ affinity of the terminal cytochromoxygenases.
- Growing number of respiratory chains in a mitochondrion and mitochondria in a cell.

Complete extraction of all the O₂ by the cells.
Thank you!

Hemic (blood) hypoxia-2

- Combination of normal intake and transition of $\text{O}_2$ and impaired binding and transport forms a condition with arterial normoxia and hypoxemia. **In anemic type** normoxia is accompanied by normosaturation (functional and fractional). **In hemotoxic type** functional normosaturation is combined with low oxyhemoglobin fraction.
- For maintaining oxygen equilibrium more intensive use of the “functionally active breathing area” is needed. Often compensatory hyper kinetic circulation appears which determines the clinical complaints of the patient.
Mitochondrial changes

- Change in the functional ATP/ADP control – the relation daily $O_2-\Delta VO_2$ correlates with $\Delta pO_2$.
- Decreasing of rH potential with suppression of Krebs’ cycle.
- Increased permeability of the internal mitochondrial membrane – transition to the so called “highly permeable state” with opening of the “large pores”.

Cytosolic changes

- Activating of glycolysis and glycogenolysis.
- Accumulation of lactate and pyruvate – intracellular acidosis with secondary glycolytic block.
- “Shutting down” of cellular pumps.
- Preventing the binding of 40S subunit of the ribosome with RNA and 40S with 60S subunits – suppressed translation and synthesis of proteins.
Nuclear changes

- Marginal location and tightening of the chromatin.
- Suppressed polymerases. Transcription and post transcriptional RNA-modulation are stopped.
- Anoxic chromato- and cariolyis ensues.

Lysosomal changes

- Lysosomes are destroyed and their enzymes spill in the cytosol.
- Dystrophic cell proceeds to anoxic necrobiosis or necrosis.