

HYPOXIA

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DEFINITION AND CLASSIFICATION OF HYPOXIA

Hypoxia is defined as **lack of oxygen in tissues** (oxygen starvation) which can arise because of various reasons. Hypoxia is usually preceded by **hypoxemia** - decreased concentration of oxygen in blood. However, there can exist also hypoxia without hypoxemia. **Hypercapnia** (elevated concentration of CO₂ in blood) is frequently found in hypoxic state, but not in every case. Sometimes hypoxia even can be accompanied by **hypocapnia** (Tabs. 12.1 and 12.2)

The consequences of hypoxia depend on

- * time in which the hypoxia develops;
- * duration of hypoxia;
- * intensity and form of hypoxia itself;
- * sensitivity of the affected tissues.

In order to understand the pathogenetic mechanism leading to hypoxia, one should first clarify the basic external and internal factors responsible for adequate oxygen supply of the body. These are as follows:

- 1/ sufficient amount of oxygen in the inhaled air;**
- 2/ proper exchange of gases in the lungs (ventilation, diffusion and perfusion);**
- 3/ sufficient amount of hemoglobin capable of oxygen transfer;**
- 4/ proper function of cardiovascular system;**
- 5/ ability of tissues to use oxygen (terminal oxidation).**

The cardiovascular system [4] integrates the various parts of the system: it assures that **sufficient amount of oxygen [1]** through basic functions of the **respiratory system [2]** and the **red blood cells [3]** may reach the **tissues [5]**.

The peculiar structure and function of hemoglobin enables to pick up oxygen very quickly in the lungs, transport it at a considerable concentration to the tissues and - last but not least - release it through a very sophisticated molecular regulatory mechanism in the capillaries of the body.

Tab. 12.1. Concentration of gases in the air and in the blood

Gas	AIR		BLOOD	
	atmosphere Partial pressure in	alveolus kPa and (torr)	arteries kPa and (torr)	venes
O ₂	21 (158)	13.5 (101)	12.5 (95)	5.3 (40)
CO ₂	0.04 (0.3)	5.3 (40)	5.3 (40)	6.1 (46)
N ₂	79.6 (597)	76.2 (572)	76.2 (572)	76.2 (572)
H ₂ O*	0.7 (5)	6.3 (47)	6.3 (47)	6.3 (47)

*vapor pressure

Tab. 12.2 Concentration of O₂ and CO₂ in the blood

BLOOD		ARTERIAL	VENOUS
O ₂ bound to Hb	ml/l	210	154
	mmol/l	9.2	6.8
O ₂ physically dissolved	ml/l	2.9	12.0
	mmol/l	0.13	0.53
Ratio bound/dissolved		72	23
Hb saturation with O ₂ (SaO ₂)	%	97.1	75.0
CO ₂ *	ml/l	596	638
	mmol/l	22.1	24.4

*Detailed data on CO₂ and ⁻HCO₃ in plasma and red cells
-> acidobasic balance

The classification of various forms of hypoxia corresponds with the above mentioned external and internal factors leading to hypoxia:

* **Hypoxic hypoxia** (disturbed condition [1] or [2]). The basic reason is decreased concentration or pressure of oxygen in the inhaled air or a disturbance of respiration.

* **Anemic hypoxia** (disturbed condition [3]). Various anemic states, pathologic forms or blockage of hemoglobin transport function.

* **Circulatory (ischemic) hypoxia** (disturbed condition [4]). Total or local disturbance of circulation, venous stagnation of blood or ischaemisation due to arterial closure.

* **Histotoxic hypoxia** (disturbed function [5]). Inability to utilize oxygen in the tissues.

Another possibility is the classification of hypoxia according to its time course:

In everyday medical practice the most frequent hypoxia is that one which is an accompanying feature of chronic diseases of respiratory and cardiovascular system or blood and therefore this is **chronic hypoxia**.

Acute hypoxia is a less frequent condition. In addition to the acute form of **mountain sickness** it occurs at **suffocation, airway obstruction, inhibition of the respiratory centre, acute heart failure and shock**.

A special form from the view of onset speed is the **fulminant** hypoxia. It occurs for example at the damage of pressure cabin of airplanes in altitudes above 10 km. In this case the oxygen pressure in external environment is lower than the pressure in venous blood and therefore the organism **delivers** oxygen onto the external environment. Unconsciousness arises very soon and after 1-2 minutes death appears as a consequence of respiratory centre failure, without cramps, without any warning signs.

HYPOXIC HYPOXIA

The most common form of hypoxia, characterized by reduced oxygen tension in pulmonary capillaries. Hypoxic hypoxia can be observed at low oxygen pressure in inhaled air, at decreased ventilation of lungs or in the case of extensive pathological processes in respiratory system leading to alveolo-capillary blockage. At reduced oxygen tension in pulmonary capillaries hemoglobin in red cells cannot fully saturate with oxygen and therefore hypoxemia develops.

The actual reasons of hypoxic hypoxia can be divided to two groups:

1/ **"There is nothing to breathe"** - in high altitude above the sea level (normal concentration of oxygen, decreased pressure) or if the air contains decreased proportion of oxygen despite its normal pressure (e.g. in cellars filled with CO₂ instead of oxygen. Attention do not confound with CO intoxication!).

2/ "There is nothing to breathe with" - disturbed basic functions of the respiratory system outlined in Tab. 12.3 and described in detail chapter Respiration.

If compensatory hyperventilation is possible and effective (e.g. in mountain climbing) **hypocapnia and respiratory alkalosis** can ensue. Alkalosis further deteriorates the release of oxygen from hemoglobin. On the contrary, if the respiration is insufficient, **hypercapnia and respiratory acidosis** can develop.

Tab. 12.3. The most frequent respiratory diseases leading to hypoxic hypoxia

H Y P O V E N T I L A T I O N
*Obstruction of airways (corpus alienum, tumor) *Paralysis of respiratory muscles (poliomyelitis) *Deformities of skeleton (kyphoscoliosis) *Disturbances or inhibition of respiratory centre (morphin, respiratory distress syndrome, hypocapnia) *Superficial breathing (pain, injuries)
B L O C K A D E O F A L V E O L O C A P I L L A R Y D I F F U S I O N
*Decrease of the total area of normal alveoles capable of gas exchange (pneumonia, lung edema) *Alveolar or capillary fibrosis (beryllium and asbestos exposure, silicosis)
D I S T U R B E D R A T E O F V E N T I L A T I O N / P E R F U S I O N
*Areas with reduced ventilation and maintained perfusion (emphysema) *Perfusion of unventilated alveoli (atelectasis) *Disturbances of pulmonary circulation due to shunts (Fallot's tetralogy)

MOUNTAIN SICKNESS

Although the symptoms threatening travelers crossing the mountain passes of Himalaya (4 - 5 km above sea level) were known from ancient times, the research on this topic begun only at the end of the XIXth century (Tab. 12.4). The study of this problem became very important during the 2nd World War because of the necessity of high-altitude flying of warplanes.

Mountain sickness is a special case of hypoxic hypoxia in some circumstances associated with hypobaria. Its pathogenesis is slightly different in the case of mountain climbing (gradual decrease of oxygen tension and usually heavy physical burden) and in high-altitude flying (rapid rise without acclimatisation). The following description is valid for untrained healthy persons. Well-trained persons after proper acclimatisation and people living in high altitude (e.g. Hans Messmer, the Sherpas from Himalaya mountain and the Ketchuas in the Andes) are able to live and work in very high altitudes even without extra oxygen supply. On the

other side in persons with disturbed respiration and circulation the symptoms develop earlier than in healthy individuals.

Tab. 12.4. The history of mountain sickness

<p>ANCIENT TIMES - MIDDLE AGE</p> <p>Hui Jiao, a Chinese traveler, duke Mirza Muhammad Haidar and José Acosta, a Jesuitian monk independently from each other recognize the symptoms of the sickness affecting people dwelling in Himalaya and in the Andes mountains</p>
<p>NEW AGE</p> <p>1644; E. Torricelli - air pressure measurements</p> <p>1774; J. Priestly - discovery of oxygen</p> <p>1789; A. Lavoisier - no life without oxygen</p> <p>1783; The Montgolfiere brothers - hot air balloon flight</p>
<p>XIXth and XXth CENTURY</p> <p>1878, 1879; P.Bert and A.Mosso</p> <p>first scientific studies on high altitude hypoxia</p> <p>1930 -1950</p> <p>intensive military research on high altitude hypoxia</p> <p>1953; Sir Edmund Hillary and Sherpa Tenzig conquer the Mount Everest (8848 m)</p>

The first symptoms sometimes occur already in altitudes of about 2.5 km above sea level but only in some (about 15%) individuals who ascend to this level quickly and without acclimatisation; the symptoms include headache, fatigue, nausea, dyspnoe and sleep disorders. Signs of pulmonary edema can develop after 2 - 3 days in some persons around 3 km meters and at about 3500 meters brain edema with psychomotoric syndrom threatens. Most of these symptoms are not caused by hypoxia or hypoxemia but rather by compensatory mechanisms as cerebral vasodilatation (headache), pulmonary vasoconstriction (lung edema). The main problem in this type of hypoxia is that through compensatory hyperventilation **hypocapnia** and **respiratory alkalosis** develop and probably contribute to the disturbances of brain and pulmonary functions. In hypocapnia the activity of respiratory centre is diminished and **periodic breathing** can occur.

A very dangerous phenomenon occurring even in well-trained and acclimatized persons is the **high-altitude euphoria**. The affected persons behave as they were slightly drunk. They often underestimate the seriousness of situation (e.g. weather conditions, difficulties) and overestimate their own forces and abilities. This condition can be explained by the high sensitivity of the inhibitory functions of the cerebral cortex to hypoxia (a similar inhibition is seen in the first phase of alcohol intoxication). At higher altitudes gradual deterioration of the other cerebral functions - sensory, mental and motoric ensues. Above 5 - 6 km every single step requires enormous effort and psychological will.

ANEMIC HYPOXIA

Anemic hypoxia is caused by decrease of oxygen transport capacity of the blood (there is only a small proportion of oxygen physically dissolved in the blood fluids, the vast majority is bound to hemoglobin in red cells - Tab. 12.2). Insufficient transport function of hemoglobin can be caused by:

1/ Insufficient amount of hemoglobin in different types of anemia

2/ Functional insufficiency of hemoglobin (Tab. 12.5). In the blood there is enough hemoglobin, but its oxygen transport capacity is blocked.

Tab. 12.5. Functional insufficiency of hemoglobin

I n t o x i c a t i o n w i t h c a r b o n m o n o x i d e (C O) *
O x i d a t i o n o f i r o n i n t h e h e m e (m e t h e m o g l o b i n e m i a) * strong oxidative stress (smoking, phenylhydrazine) * nitrate/nitrite intoxication in newborns * inborn hemoglobinopathies (M type) * deficit of methemoglobin reductase
I n c r e a s e d a f f i n i t y o f h e m o g l o b i n t o w a r d s o x y g e n some inborn hemoglobinopathies, thalassemia alkalosis blockade of 2,3-BPG binding site (Hb glycation) decrease of 2,3-BPG concentration in the red cells

METHEMOGLOBINEMIA

Upon oxidation of divalent iron and binding of -OH moiety to hemoglobin **methemoglobin (metHb, HbOH)** arises which is worthless for oxygen transport. During normal circumstances the enzyme **methemoglobin reductase** (the enzyme exists in two forms working with coenzyme, NADH or NADPH, respectively) continuously reduces the oxidized hemoglobin and therefore in blood of healthy individuals only small concentration of metHb (0.1 - 0.4 % of total Hb) can be found. In heavy smokers not only the concentration of HbCO but also the concentration of MetHb (up to 8%) is elevated.

In patients with deficiency of **methemoglobin reductase** (type I or II) the concentration of metHb can rise to very high level. In other types of antioxidant system deficiency (e.g. in **glucose-6-phosphate deficiency**) hemolysis occurs and therefore the hypoxia is caused not due to methemoglobinemia but as a consequence of anemia.

The oxygen binding site of Hb is at the bottom of a pocket lined with hydrophobic amino acid side chains. In some inborn defects of Hb structure (commonly named as "M" hemoglobins or **inborn methemoglobinemias**) the configuration of the pocket is faulty and as a consequence not only the O₂ molecule but also the bigger water molecule can get to the binding site. Interestingly enough, this immediately leads to iron oxidation and metHb formation.

A special case of **acquired** methemoglobinemia is the **infant nitrate methemoglobinemia**, an alimentary methemoglobinemia of artificially nourished infants (up to 2 months of life). It occurs in the case of high concentration of **nitrates** (>100 mg/l) in the drinking water. Nitrate from water used to prepare the infant milk formula is reduced by intestinal bacteria to **nitrite** and after resorption into blood oxidize the Hb in the red cells of infants whose antioxidant systems is not yet fully developed. Only very high concentration of nitrate in water cause measurable methemoglobinemia in adults.

In severe methemoglobinemia the colour of blood is from dark red to brown. The skin of the patients looks cyanotic with an ashy taint but in this case the proportion of reduced Hb is not elevated and the symptom is called **pseudocyanosis**.

HIGH OXYGEN AFFINITY OF BLOOD AS CAUSE OF HYPOXIA

The sigmoid shape of oxygen dissociation curve of hemoglobin is a very important prerequisite of oxygen release in the tissues. The difference is evident when the properties of myoglobin and hemoglobin are compared. At high oxygen concentration both proteins bind oxygen almost up to 100 % saturation. In the tissues, however, the hemoglobin is able to release considerably more oxygen than the one-subunit myoglobin displaying a simple hyperbolic dissociation curve. The sigmoidity of the hemoglobin dissociation curve is maintained by two different mechanisms:

* **Through cooperation between the subunits of hemoglobin when they switch from high- to low-affinity configuration and vice versa.**

* **Through the effect of 2,3-bisphosphoglycerate on the dissociation curve.** This compound, ([2,3-BPG], a specific, and from energetic point of view unnecessary by-product of red cell glycolysis) binds to the terminal aminogroup of the β -chain of hemoglobin stabilizing it in the low affinity state. Similar effect on hemoglobin exert the increase of H⁺ (acidosis) and CO₂ concentration (Bohr effect).

Every shift of the curve to the **right** (elevated oxygen affinity) makes the release of the oxygen in the tissues more difficult and leads to hypoxia without hypoxemia.

These conditions include some **hemoglobinopathies** (with disturbed cooperativity between subunits or fixed high-affinity configuration of the subunits). These hemoglobinopathies may

but need not be associated with hemolytic anemia. In thalassemia and some other pathological conditions the concentration of fetal hemoglobin (F Hb) is elevated and this type of hemoglobin displays higher oxygen affinity as compared with Hb A (what is advantageous during intrauterine life). In glycated hemoglobin (Hb A_{1c}) the 2, 3-BPG binding site is blocked by glucose and has (in vitro) increased oxygen affinity. In severe hypophosphatemia and in some inborn disturbances of red cell glycolysis the concentration of 2,3-BPG can be abnormally low.

CIRCULATORY HYPOXIA

Circulatory hypoxia develops if the supply of blood to tissues is insufficient while the blood is normally oxygenated. It has two forms:

*** Total and local circulatory hypoxia**

Total circulatory hypoxia occurs at **heart failure or at shock**. Hypoxia of tissues is the consequence of insufficient left ventricular output, vasoconstriction (centralization of circulation) and stagnation of blood before an obstacle (right heart failure). There is no hypoxemia in (pure) circulatory hypoxia - the concentrations of Hb and pO₂ are normal. The extraction of oxygen by tissues is increased but because of insufficient supply of oxygenated blood the local pO₂ decreases to low values and pCO₂ is increased. In actual clinical situations the circulatory hypoxia is usually associated with other types of hypoxia - e.g. in left heart failure the exchange of gases in lungs is disturbed and in right heart failure the perfusion of lungs is decreased (**circulatory + hypoxic hypoxia**), in hemorrhagic shock the amount of Hb decreases and in burn shock the hemoglobin may be blocked by carbon monoxide (**circulatory + anemic hypoxia**).

Local circulatory hypoxia may be a consequence of arterial thrombosis (e.g. **myocardial infarct**), embolism, strong vasoconstriction or venous stagnation of blood.

HISTOTOXIC HYPOXIA

It originates when the cells are not able to utilize oxygen, that is there is a disturbance of the mitochondrial **terminal oxidation** while there is sufficient oxygen in arterial blood. This hypoxia is not preceded by hypoxemia. We can observe it especially in the case of intoxication with cyanides, which block cytochromoxidase. It also occurs at damaging the enzymes of Krebs cycle with monobromacetone or tetrachlormetane and at overdose of anesthetics which on the other hand interfere with the system of dehydrogenases.

THE MAIN SYMPTOMS OF HYPOXIA

CYANOSIS

The basic symptom of chronically developing hypoxia is cyanosis. It is a term for blue or bluish colouring of skin, mucosae or even of the inner organs. It occurs when the concentration of reduced hemoglobin in capillary blood reaches 50 g/l. One can observe it most conveniently on the nail bed, on the lips and ears, nose, face, hands and feet.

There are two basic forms of cyanosis:

* **central and peripheric cyanosis**

Central cyanosis (arterial, anoxic) develops when the arterial reaching the tissues is not sufficiently saturated with oxygen and contains a certain amount of reduced hemoglobin. It occurs at inborn heart failures with right to left shunts (Fallot's tetralogy) and in different pulmonary diseases.

In **peripheric cyanosis** (acral, venous, stagnational) the arterial blood is usually normally saturated with oxygen but its flow through tissues is slowed down and therefore the extraction of oxygen is increased. It is one of the symptoms of heart failure accompanied with prolongation of circulation time.

Local stagnational cyanosis ensues in the case of venous stagnation as a consequence of local processes - thrombosis, pressure of tumours, vasospastic diseases.

In mild cold environment cyanosis may manifest even in healthy persons on exposed locations because of constriction of skin arterioles and venules. The blood flow through capillaries is highly slowed down and more O₂ is removed from the blood. In strong cold environment, however cyanosis does not develop because the drop of skin temperature prevents the dissociation of hemoglobin and the consumption of O₂ in subcooled tissues is reduced.

In decompensated cor pulmonale chronicum and at chronic left heart failure the cyanosis is **combined (insufficient saturation of Hb + circulation failure)**.

Cyanosis does not develop in anemia because at low total concentration of Hb (e.g. 90 - 60 g/l) it is difficult to reach the deoxyhemoglobin concentration required for the manifestation of

cyanosis (50 g/l). On the other side cyanosis easily develops in polycythemic conditions. There is no cyanosis in carbon monoxide intoxication (the colour of HbCO is light red) and at histotoxic hypoxia since pO_2 and Hb saturation are normal here.

As above already mentioned, cyanosis-like colour of skin and mucosae can be also caused by high levels of methemoglobin in the blood.

DYSPNOE

The second most frequent clinical symptom of hypoxia is **dyspnoe**. It is hardened breathing with subjective feeling of air shortage. It can be characterized by anxious expression of face, accelerated breathing, deepening of breathing excursions, increased work of auxiliary respiratory muscles and movement of nostrils.

Dyspnoe arises when ventilation is increased 4-5 times as compared with ventilation at rest. At mild hypoxia there is first tachypnoe (accelerated breathing) and hyperpnoe (deepened breathing), dyspnoe occurs only later. Another type of dyspnoe occurs with left side heart failure

(due to pulmonary congestion -> Special Pathological Physiology).

These symptoms are often joined by general lassitude, fatigue at minimal exercise and symptoms from the side of nervous system including sleep disorders. Another group of symptoms arise as a consequence of compensatory measures.

MECHANISMS OF COMPENSATION IN HYPOXIC CONDITIONS

The oxygen supply of the body is assured by respiratory system, blood, cardiovascular system and tissues themselves. At damage of any of these mechanisms **all undisturbed systems or their intact parts join in the compensation.**

Hyperventilation (tachypnoe and hyperpnoe) is efficient in most cases of hypoxic hypoxia but appears in anemic hypoxia, too. Dyspnoe is also a compensatory mechanism but the maximal effort of respiratory muscles can consume a lot of oxygen and therefore the overall balance is often negative.

Tachycardia is an important compensatory mechanism both in hypoxic and anemic hypoxia, but it consumes oxygen, too. In hypoxic condition (e.g. shock, severe anemia) **centralization** of circulation develops. The objective of this mechanism is to maintain the blood and oxygen supply to the most important organs (heart, brain) at the expense of circulation of the skin, muscles and inner organs. In acute conditions it can save the life but after some hours irreversible organ damage (kidney, liver) develops and can lead to death even in the case of restoration of the circulation.

The activation of the renin-angiotensin-aldosterone system is advantageous in hypovolemic conditions (blood loss) but is harmful in circulatory hypoxia.

Erythropoietin is another kidney hormone released in every hypoxic condition. As the main regulatory factor of erythropoiesis, erythropoietin increases the production of red cells with the exception of some forms of anemia. **Polycythemia** is useful after blood loss but harmful (increased blood viscosity) in pulmonary and heart disease.

Better release of oxygen from blood in tissues is also possible due to elevated concentration of 2,3-bisphosphoglycerate and elevated concentration of CO₂ in blood and tissues (shift in the dissociation curve of the hemoglobin to the left).

In hypoxemia the tissues themselves are also capable to increase the oxygen extraction from blood.

MANIFESTATION OF HYPOXIA IN SOME ORGANS AND TISSUES

Brain tissue uses about 20 % of total oxygen consumption and is exceptionally sensitive to hypoxia. The most sensitive structure of CNS is the cerebral cortex. Therefore at heavy acute hypoxia (e.g. at heart stop) in the course of some seconds general seizures and unconsciousness appears. In slight hypoxia the permeability of cerebral capillaries increases and that may lead to cerebral edema.

At slow development of brain hypoxia gradual intellectual deterioration, headache, weakness of the memory, sleep disturbances and various neurological disturbances are the main symptoms.

The most sensitive structure of **heart** which uses 15 % of total oxygen consumption is the conductive system. Therefore at hypoxia there is a frequent increased irritability of conductive system what can result in various dysrhythmias. At chronic hypoxia there may arise also heavy structural changes - fibrosis of the heart muscle, hypertrophy and dilatation of the heart. As heart is one of the most important part of the oxygen supplying system, a vicious circle develops which even more deteriorates the oxygen supply to myocard.

In **lungs** hypoxia causes vasoconstriction of small pulmonary veins. The pulmonary vascular resistance is increased what increases the work of right heart.

Hypoxia of **kidneys** at acute renal ischemia causes structural and functional changes which can lead even to renal insufficiency (e.g. at a shock). In hypoxic kidneys the synthesis and release of erythropoietin and activated renin is increased.

In **liver** even at normal circumstances the cells located in the centre of liver lobe receive a limited dose of oxygen. It results from the structure of functional and nutritional circulation of the liver. Therefore in pathological conditions these centrilobular cells suffer as first. Centrilobular necrosis and consequent fibrosis can easily develop.

Hypoxia in **skeletal musculature** may occur even at excessive muscle activity when muscles gain energy through anaerobic glycolysis. If during the unadequate supply of oxygen the muscles are not able to acquire sufficient amount of ATP through glycolysis, painful contractures may appear.