Chapter

Physiological Adaptions to Acute Hypoxia

Erich Hohenauer

Abstract

When tissues are insufficiently supplied with oxygen, the environment is said to be hypoxic. Acute (exposures to) hypoxia can occur occupationally, within the scope of training and competitions or under pathological conditions. The increasing interest in acute exposure to altitude for training and research purposes makes it more important than ever to understand the physiological processes that occur under hypoxic conditions. Therefore, the scope of this chapter is to describe the main types of hypoxia on the oxygen cascade, to summarize the physiological consequences of acute hypoxia on the three main areas and to highlight the clinical consequences of acute hypoxia exposures for healthcare practitioners.

Keywords: hypoxia, altitude, oxygen, physiology, cardiorespiratory

1. Introduction

The human body cells need the energy to maintain their functions. This energy is mainly provided by sugar, carbohydrates and fat. To utilize these nutritive substances and to produce energy in return, inspired oxygen (O_2) from the air is needed. In the mitochondrial electron transport chain, O_2 is the final electron acceptor to generate ATP within the eukaryotic cells [1]. Whilst O_2 is needed for most life on earth, most of the earth's atmosphere does not contain a lot of O_2. From the surface of the planet, up to the border of space, the atmosphere contains a constant fraction of around 21% O_2 (often expressed as the F_iO_2 of around 0.21), 78% of nitrogen, 0.9% argon and 0.1% of other gases like carbon dioxide, methane, water vapor, etc. At sea level, the partial pressure of the above-mentioned gases can be estimated to be 593 mmHg for nitrogen, 160 mmHg for oxygen and 7.6 mmHg for argon. Indeed, the weight of air is responsible for atmospheric pressure.

It's well known that increasing altitude leads to quasi-exponential reductions in barometric pressure (P_B). At the summit of Mt. Everest (8848 m), the P_B is about one-third of the sea-level values. The reduced atmospheric pressure has therefore a direct influence on the partial pressure of inspired oxygen, which can be seen in **Figure 1**.

The inspired partial pressure of oxygen (P_iO_2) is lower than atmospheric oxygen partial pressure because water vapor is in the airways. The pressure of water vapor (PH_2O), which is not dependent on atmospheric pressure but temperature, should be taken into account when P_iO_2 is calculated [2]. The inhaled air gases will get humified and warmed by the airways and as a result, the PH_2O will adjust the partial pressure of all inhaled gases, including O_2.

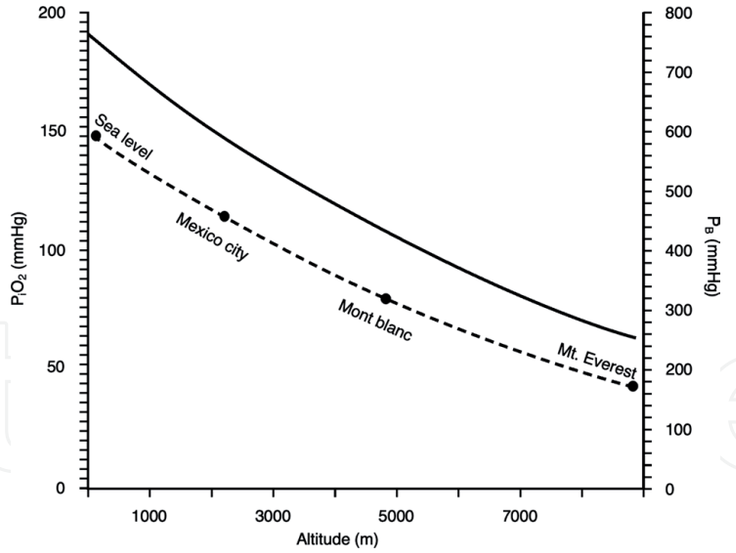

Figure 1.
Relationship between barometric pressure (P_B), partial pressure of inspired oxygen (P_iO_2) and altitude. P_B and P_iO_2 decrease exponentially with increasing altitude at a constant F_iO_2 of 21%. The solid line represents P_B and the broken line represents P_iO_2.

Accordingly, the product of P_iO_2 can be calculated using Eq. (1):

$$P_iO_2 = (P_B - PH_2O) \times F_iO_2. \quad (1)$$

Since P_B is known to be approximately 760 mmHg at sea level, PH_2O is normally about 47 mmHg and O_2 makes up to 20.93% (F_iO_2 of 0.2093), P_iO_2 is equal to 0.20932 multiplied by 713 mmHg.

Consequently, hypoxia is defined as a combination of P_B and the F_iO_2 that results in any P_iO_2 under a normoxic value of 150 mmHg [3]. However, the duration of hypoxic exposures as well as the magnitude of P_B reductions has a significant impact on the (patho-)physiological response. Examples of fast-changing normoxic to hypoxic environments are fast ascended on the mountain summits during mountaineering, military and rescue services and travels with fast transportation to altitude. Acute mountain sickness is well-known to occur due to extensive and fast decreases in P_b, normally beginning at an altitude of above 2500 m. The Lake Louis Consensus Group defined acute mountain sickness as the presence of headache in an unacclimatised person (recently arriving at an altitude above 2500 m), plus the presence of one or more of the following symptoms: gastrointestinal symptoms, fatigue and/or weakness, dizziness or a positive clinical functional score, resulting in a total score of ≥3 [4]. If not treated correctly, people with acute mountain sickness can develop high-altitude pulmonary oedema or high-altitude cerebral oedema [5]. However, if the human body is gradually exposed to hypoxic conditions, it can acclimatize and adapt.

The following chapters will focus on the main types of hypoxia, the physiological consequences of acute hypoxia and the clinical consequences of the current chapter.

2. Types of hypoxia

Insufficient O_2 supply to the human tissues can have various reasons and can lead to severely impaired body functions. There are four main types of hypoxia, which can be classified as hypoxaemic hypoxia, anemic hypoxia, stagnant hypoxia and histotoxic hypoxia.

2.1 Hypoxaemic type

One of the most common types of hypoxia is called generalized or hypoxic hypoxia, which is generated from the actual (natural/simulated) environment and inside the lungs. This type is caused by a reduction of the partial pressure of alveolar O_2 (P_AO_2) [6]. This value is well known and a great help to calculate the partial pressure of oxygen inside the alveoli (as it is not possible to collect gases directly from the alveoli), which can be used for potential cell diffusion [7]. The alveolar gas equation uses three variables to calculate the alveolar concentration of oxygen, which can be seen in Eq. (2):

$$P_AO_2 = F_iO_2 \times (P_B - PH_2O) - P_aCO_2 / RQ \quad (2)$$

where P_aCO_2 is the partial pressure of carbon dioxide which is under normal physiological conditions approximately 40 mmHg. RQ is the respiratory quotient which is, the ratio of the volume of produced CO_2 divided by the volume of consumed O_2 during the same time [8]. Dependent on metabolic activity and diet, RQ is considered to be around 0.825 [9], within a physiological range between 0.70 and 1.00. Consequently, P_AO_2 at sea level is: 0.2093 × (760–47) – 40/0.825 = 100.7 mmHg. P_AO_2 is the main driving factor for alveolar diffusion and thus O_2 supply on a cellular level.

Hypoxic hypoxia can be observed typically when F_iO_2 is low, during hypoventilation of the lungs or at the presence of pathological airway conditions. Low F_iO_2 levels can occur due to failure of gas delivery systems, inadequate supply from altitude simulating machines, or e.g., exorbitant inhalation of nitrous oxide during anesthesia [10]. Hypoventilation can occur due to insufficient respiratory rate, obstruction of airways, skeletal deformities, respiratory muscle paralysis, etc. Severe lung diseases (e.g., pulmonary fibrosis, pulmonary embolism) can also lead to alveolar-capillary diffusion blockade [11]. Hypoxic hypoxia affects the entire body. Typical symptoms are agitation and anxiety while low blood O_2 goes along with increased heart rate, dyspnea and bluish color of the skin.

2.2 Anemic type

Anemic hypoxia is caused by reduced oxygen transport capacity in the blood [12]. The red blood cells (erythrocytes) are responsible for the transport of O_2 through the body [13]. Around 90% of the erythrocyte is made up of haemoglobin, the iron-containing protein that binds O_2 on its heme. Although, the arterial oxygen tension is normal at this type, reduced erythrocytes/haemoglobin or functional insufficiency of haemoglobin leads to impaired oxygen delivery to the tissues [14].

A deficiency in the number of erythrocytes can result, for example, from excessive blood loss after trauma. Other forms of the reduced number of erythrocytes can be present in case of abnormal red blood cell breakdown (haemolytic anemia) [15]. Increased haemolysis can be observed during hereditary spherocytosis, sickle cell disease or autoimmune diseases (e.g., aplastic anemia) [16].

Deficiencies of different factors can also lead to severe anemia. Iron is the main component of haemoglobin, giving the blood the red color and is the prime carrier of oxygen. During the physiological haemolysis, iron will be bound to the glycoprotein transferrin for transportation to the bone marrow, where it will be reused for haemoglobin synthesis. This process helps to limit an extensive loss of iron from the body. However, iron deficiency is one of the main causes of anemia,

called microcytic hypochromic anemia [6]. This type of anemia can be caused by any factor which reduces the body's iron storage, leading to small erythrocytes with reduced haemoglobin mass [17]. In contrast, deficiencies in vitamin B_{12} or folic acid can cause anemia due to abnormally enlarged erythrocytes and their immature precursors, called macrocytic hyperchromic anemia [18].

Functional insufficiency of haemoglobin is associated with reduced oxygen binding capacity. An example is an intoxication through excessive carbon monoxide inhalation. Compared to oxygen, carbon monoxide has a 200–300 times higher affinity to haemoglobin. After inhalation, carbon monoxide reaches the respiratory gas exchange zone and binds on haemoglobin [10]. This chemical binding process leads to the formation of carboxyhaemoglobin. Consequently, oxygen-carrying capacity is decreased which will lead to reduced oxygen transportation to the tissues and as a consequence tissue hypoxia [19]. Another possibility of functional insufficiency for the transportation of oxygen is methaemoglobinemia. Haemoglobin changes to methaemoglobin, when bivalent iron (Fe^{2+}) is oxidized to Fe^{3+}, which is worthless for oxygen transport [20]. Under normal circumstances, methaemoglobin reductase limits the build-up of methaemoglobin through the reduction of haemoglobin oxidation [21]. Patients with a deficiency of methaemoglobin reductase, strong oxidative stress (e.g., smoking) and medication can therefor experience very low concentrations of tissue oxygenation, demonstrating comparable symptoms as seen in hypoxic hypoxia. However, it must be mentioned, that the unfavorable conditions of low tissue O_2 can be compensated better during hypoxic hypoxia than during anemic hypoxia.

2.3 Stagnant type

Stagnant, also called ischemic or circulatory hypoxia takes place as a cause of insufficient blood supply to the tissues while the blood is normally oxygenated. Ischemic hypoxia can be observed on a central and local level [6].

Central circulatory hypoxia can often be observed in patients with cardiac manifestations. If the left ventricular output is for example decreased, blood flow to the organs is impaired [12]. This can also happen during shock or, at a local level after strong vasoconstriction (e.g., cold exposures) or venous stagnation of blood [22]. Oxygen can only be stored to the very limited amount within the human cells. Even myoglobin, binding O_2 on its heme protein, has a very limited oxygen storage capacity [23]. Consequently, myoglobin is more involved in transportation than the storage of oxygen. Oxygen saturated myoglobin enables facilitated intercellular O_2 transportation, because the oxygen-enriched myoglobin molecules can "move" within the cells (facilitated diffusion) which is extremely important at a low partial pressure of O_2 (PO_2) [24]. Although, the gas exchange rate on the alveolar level, the concentration of haemoglobin, oxygen content and tension are on a normal level, O_2 extraction at the level of the capillaries will be increased [6]. This process will directly elevate the arteriovenous difference of blood O_2 content leading to venous hypoxia. However, as the increased oxygen extraction is normally insufficient to supply the tissue with an adequate amount of O_2, this process will lead to impaired cellular oxygen coverage and impaired functioning.

2.4 Histotoxic type

Histotoxic hypoxia or dysoxia is a state, where cells are unable to utilize oxygen effectively [12]. This is the case, when the mitochondrial terminal oxidation is disturbed while there is sufficient oxygen available in the blood. Dysoxia will therefore lead to a pathological reduction in ATP production by the mitochondria and is not preceded by hypoxaemia [6].

An example of histotoxic hypoxia is the intoxication with cyanides, which can occur from fire sources. Intravenous and inhalation of cyanide produce a more rapid onset of hypoxia than the oral or transdermal route due to the fast diffusion into the bloodstream [25]. The main effect of cyanide intoxication is related to the inhibition of oxidative phosphorylation, where oxygen is utilized for ATP production. Cyanide can reversibly bind to the enzyme cytochrome C oxidase, blocking the mitochondrial transport chain. This will cause cellular hypoxia and, as mentioned above, pathological low levels of ATP, causing metabolic acidosis and impairment of vital functions [26, 27].

3. Physiological consequences of acute hypoxia

Rapid ascends from sea level to altitude and sudden exposure to a hypoxic environment will immediately lead to acute physiological responses to adapt to the acute hypoxaemic situation [28]. The degree of acute hypoxic stress about time can lead to symptoms ranging from dizziness, feeling of unreality and dim visions to rapid unconsciousness [29]. Sudden exposure to the summit of Mt. Everest will for example lead to unconsciousness within 2 min. However, when the same amount of hypoxaemia is experienced over several days to weeks, one could function relatively well under these conditions. This adjustment is called acclimatization which is a complex process over time and shows great variability within individuals [29]. In the following chapters, the acute response to sudden exposure to a hypoxic environment is discussed.

3.1 Respiratory system

The respiratory system will directly respond to the low oxygen availability in the air and is often seen as the primary defense against the hypoxic environment. Chemosensory systems will rapidly lead to increased pulmonary ventilation because of compromised O_2 availability [30]. These regulatory responses can be attributed due to specialized chemoreceptors such as the carotid bodies in the arterial circulation and neuroepithelial bodies in the respiratory tract as well as the direct response of vascular smooth muscles to hypoxia [31].

Whilst hypoxia acts as a vasodilator in the systemic circulation, it has been observed, that the vessels of the pulmonary vasculature constrict under hypoxia, leading to pulmonary hypertension [32, 33]. Hypoxic vasoconstriction is intrinsic to the pulmonary vasculature smooth muscle cells and is initiated by the inhibition of K^+ channels which set the membrane potential [34]. This process will lead to depolarization, activation of Ca^{2+} channels as a result of the electrical impulse and, as a consequence, an increase in cytosolic calcium levels and therefore constriction of the myocytes [31]. Pulmonary hypertension might help to match ventilation and perfusion within the lungs. However, pulmonary hypertension can also lead to severe pathological situations (e.g., altitude-related right heart failure).

Carotid bodies, sensitive to monitoring a drop in arterial O_2 levels, and neuroepithelial bodies, detecting changes in inspired O_2, respond immediately to decreased O_2 supply [35]. Both respond by activating efferent chemosensory fibers to produce cardiorespiratory adjustments during hypoxic exposures [36, 37]. When low arterial PO_2 is detected, the carotid body signals the central respiratory center to increase the (minute) ventilation. The increased ventilation of the respiratory tract can be primarily associated with an elevated tidal volume and an even greater elevation in respiratory rate [38]. This hypoxic ventilatory response counteracts the hypoxic environment by decreasing P_ACO_2, increasing P_AO_2 and therefore improving oxygen delivery. Genetical determinants, as well as various external factors

(metabolic and respiratory stimulants), lead to wide inter-individual variety of ventilatory response intensity [39]. The increased ventilatory response demonstrates that adaptive processes are taking place and a "good" ventilatory response is known to enhance acclimatization and performance and that a very low response may contribute to the formation of illness [39, 40]. However, hyperventilation will subsequently lead to hypocapnia (increased pH) known as respiratory alkalosis by reducing the amount of carbon dioxide in the alveoli [41]. This condition will cause the oxygen dissociation curve to shift to the left and to further keep respiratory ventilation high. However, hypocapnia will also counteract the central respiratory center activation and thus limit further ventilatory increases [40, 42]. On the other hand, to reduce respiratory alkalosis, more bicarbonate will be produced from the kidneys to decrease the pH toward normal levels. This means that pulmonary ventilation is driven by low arterial PO_2 and limited due to hypocapnia-induced alkalosis at the same time. This becomes clear when looking into Eq. (3), defining the alveolar ventilation as follows:

$$V_A = 0.863 \text{ x } VCO_2 / P_ACO_2 \quad (3)$$

V_A is the alveolar ventilation, 0.863 is a constant, VCO_2 is the CO_2 output and P_ACO_2 is the alveolar CO_2. The ability to maintain oxygen homeostasis is essential and the physiological systems compete against each other to provide enough tissue O_2 but also to maintain pH-homeostasis.

3.2 Cardiovascular system

To compensate for tissue hypoxaemia, the cardiovascular system must respond to maintain body functions. This is accomplished by increasing cardiac output, which is the product of stroke volume and heart rate [43]. Consequently, an increase in one of these variables will also lead to an increased volumetric flow rate. Upon ascent to hypoxic environments, the sympathetic nervous system activation leads to an initial increase in heart rate, cardiac output and blood pressure via the release of stress hormones [40, 44]. Stroke volume remains low in the first hours which is a consequence of reduced blood plasma volume because of bicarbonate diuresis. This occurs as a result of the fluid shift from the intravascular space and the suppression of aldosterone [40]. Interestingly, the sympathetic nervous system activation remains increased even if one is well acclimatized to altitude [45]. In contrast to sympathetic activation, cardiac output decrease once a certain level of hypoxia is reached after several days [46]. After a few days, e.g., muscle tissue adapts and extracts more O_2 from the circulating blood by increasing the arterial–venous oxygen difference. This reduces the demand for higher cardiac output. Reductions in stroke volume can be attributed due to decreased plasma volume as well as the above-mentioned increased pulmonary vascular resistance. From the systemic circulation perspective, the endothelial autocoids nitric oxide and prostaglandins have received more attention as they are potentially mediating hypoxic vasodilation in the vessels [47]. Hypoxic-induced vasodilation will therefor quickly increase the blood flow to O_2-deprived tissues. Low P_aO_2 levels will increase Ca^{2+} concentration inside the endothelial wall which might lead to increased synthetization of vasodilating endothelial factors [48]. The smooth muscle cells of the blood vessels also have K^+ ATP-channels, that are activated once the ATP/ADP quotient drops due to hypoxia. As a result of the increased conductivity of K^+, the cell membrane is hyperpolarized, followed by relaxation of the vascular muscle cells and vasodilation. This is especially well evoked in coronary and vertebral vessels [49].

P_AO_2 is, as mentioned earlier, at sea level around 100 mmHg and will decrease at altitude. At sea level, around 96% of haemoglobin is bound to O_2 which can be seen in **Figure 2**. The oxyhaemoglobin dissociation curve plays a crucial role in O_2 transport and demonstrates the interaction between the oxygen carrying capacity of haemoglobin and changes in partial pressure of oxygen [50]. When P_AO_2 drops to 50 mmHg at altitude, only about 80% of haemoglobin sites are bound to O_2. The sigmoidal shape of the curve minimizes an abrupt decline in oxygen-carrying capacity of the blood. Another crucial adaptive process is, that the dissociation curve will shift to the left [51]. This is mediated by respiratory alkalosis and therefore rise in blood pH. This left shift causes that at a P_AO_2 of 50 mmHg, instead of 80%, around 90% of haemoglobin is bound to O_2. As a result, more oxygen is bound on haemoglobin and more oxygen can be unloaded to the tissues [52].

3.3 Cerebral system

The brain consumes around 20% of the available oxygen at rest and is very sensitive to insufficient O_2 supply [53]. The ability to process large amounts of oxygen (over a relatively small tissue mass) is necessary to support the high rate of ATP production to maintain an electrically active for the continual transmission of neuronal signals [54]. From this perspective, it is clear that hypoxia can have negative effects on cognitive function [55]. From the literature, it is well known that various factors have an important influence on cognitive impairment during hypoxia, in case they occur. These include the grade of hypoxia (e.g. altitude height), ambient temperatures, performing exercise tasks, individual physiological responses and the influence of P_B [56].

One of the most sensitive regions of the central nervous system is the cerebral cortex. However, acute exposure to extreme hypoxia can also cause changes within wide regions of the brain. Subtle changes in the white and gray matter were already observed during ascending Mt. Everest and K2, reducing movement control and planning [57]. Motor speed and precision are also negatively affected in altitude compared to sea level performance [58, 59]. The complexity of central execution

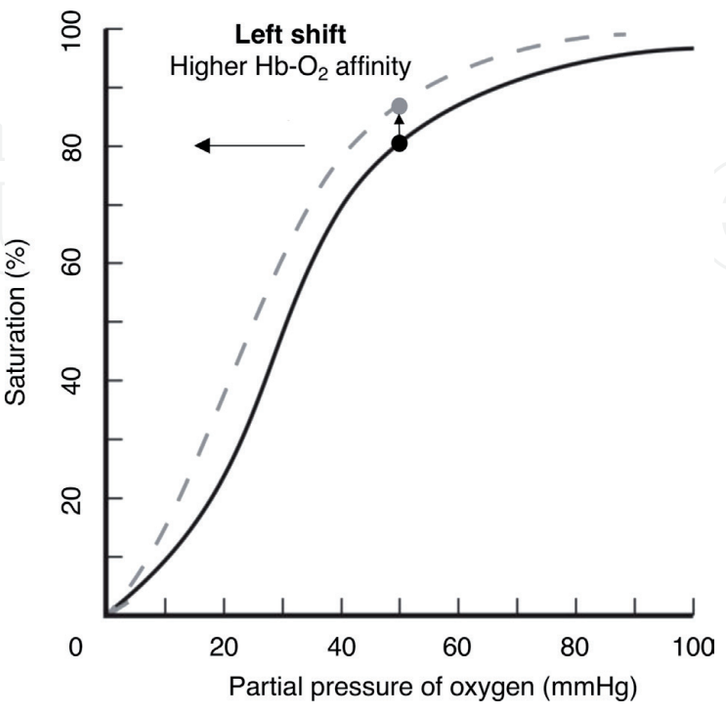

Figure 2.
S-shaped oxyhaemoglobin dissociation curve at sea level (solid black line). The curve is shifted left due to respiratory alkalosis under acute hypoxic exposure (broken gray line).

tasks seems to play an important role when cognitive impairment is evaluated. Cognitive impairment seems to be more prominent when complex tasks must be solved rather than simple tasks [60, 61]. Indeed, altitude accidents that occur under hypoxia might be more related to poor judgment of complex situations as a consequence of hypoxic depression of cerebral function. However, also small mistakes or even small increases in reaction time [62] can also have fatal consequences.

However, the underlying mechanisms, why cognitive performance can be impaired during hypoxia are not fully understood [61]. Cerebral circulation, which is the product of arterial oxygen content and cerebral blood flow, is dependent on the net balance between hypoxic vasodilation and hypocapnia-induced vasoconstriction. It is well documented, that cerebral blood flow is increased under acute hypoxia to maintain cerebral O_2-supply [54]. Cerebral blood flow increases, despite the hypocapnia, when arterial PO_2 is less than 60 mmHg (altitude greater than 2800 m). Although, interindividual varieties in cerebral blood are linked to individual variations in the ventilatory response to hypoxia [63], cerebral oxygen delivery and global cerebral metabolism are well maintained under moderate hypoxia. If cerebral oxygen consumption is constant, the question arises of what causes the cognitive impairment at altitude. Cognitive changes might be related to specific neurotransmitters that are affected by mild hypoxia (e.g., serotonin, dopamine). Furthermore, alterations in blood flow and sensory displeasure, hyperhomocysteinemia and potential neuronal damage, and a decrease in catecholamine availability combined with psychological factors appear to play a key role for reduction in cognitive function during hypoxia [61]. In case cerebral tissue oxygenation is not maintained, brain injury will occur with fatal consequences [35]. Compensatory hyperventilation, tachycardia and increased cerebral blood flow can partially maintain cerebral oxygen delivery, however, if these mechanisms work inadequately, the brain will be the first organ to be compromised.

4. Clinical consequences

This chapter aimed to give an overview of the main hypoxia types and the main physiological consequences. Hypoxia can occur due to occupational responsibilities, recreationally but also under pathological conditions. Ascend to altitude or exposure to environments that lower the P_iO_2 will have direct consequences to the entire body systems, however various modulators such as P_B, the severity of hypoxia, interindividual variability, health condition and others determine the physiological consequences and adaption processes. Exposing the body specifically to hypoxic environments can be used as a therapeutic tool, to increase sports performance or to achieve other goals [64]. However, it is important to precisely understand the different types of hypoxia and what consequences they have on the human body. Clinical manifestations of hypoxia underly inter-individual variations of cardiorespiratory and other physiological responses as well as the origin of hypoxia. In general, there are two major causes of hypoxia at the tissue level which are reduced blood flow to the tissues or reduced O_2 content in the blood itself [65, 66]. As a result, four main types of hypoxia arise. First, hypoxaemic hypoxia, where the O_2 transport to or through the alveoli is impaired [6]. Second, anemic hypoxia where the oxygen-carrying capacity is reduced due to e.g., severe blood loss, iron and folate deficiency, haemoglobin pathologies or functional insufficiency to carry O_2 [10, 12, 14]. Third, stagnant hypoxia where the transport of O_2 to the tissue is impaired while the blood may be sufficiently oxygenated [6]. Finally, histotoxic hypoxia exists, where the O_2 is delivered to the tissues but they are unable to utilize oxygen effectively [12].

It is important to understand, how these types influence oxygen delivery to the tissues. The product of O_2 content and blood flow is considered to reflect the oxygen delivery for the whole body (or to the individual organ system). As oxygen content is the sum of dissolved oxygen and that bound to haemoglobin, total oxygen delivery can be calculated according to Eq. (4):

$$DO_2 = \left(SaO_2 / 100 \times [Hb] \times 1.34 + P_aO_2 \times 0.023\right) \times \text{blood flow} \quad (4)$$

DO_2 is the O_2 delivery (ml min^{-1}); P_aO_2 is the partial pressure of oxygen (kPa); S_aO_2 is the arterial oxygen saturation in percentage; Hb is the haemoglobin content (g dl^{-1}); 0.023 is the solubility of oxygen (in ml dl^{-1} kPa^{-1}); 1.34 is Hüfner's constant, the oxygen-carrying capacity of saturated haemoglobin (ml g^{-1}); and blood flow (i.e., cardiac output) in dl min^{-1} [67]. From this equation, it can be seen that hypoxaemic hypoxia (via reduced P_aO_2 and S_aO_2), stagnant hypoxia (via reduced blood flow) and anemic hypoxia (via reduced haemoglobin content) may cause tissue hypoxia, as these three types reduce oxygen delivery. In contrast, there is no oxygen delivery deficiency in histotoxic hypoxia but rather an impairment of the tissue to use O_2 [35]. Reduced oxygen tension, hypoventilation, ventilation-perfusion mismatch, right to left shunt and impaired diffusion of oxygen can all lead to hypoxia in the body [12].

The primary measurement to evaluate the hypoxic disease state is the analysis of arterial blood gas. Using this measurement, important parameters such as partial pressure of oxygen, partial pressure of carbon dioxide, acidity (pH), oxyhaemoglobin saturation and bicarbonate concentration in arterial blood can be assessed [68]. Management and treatment of persons under hypoxia should be started as soon as the evaluation has been successfully finished, and follows three categories: maintaining patent airways, increasing the oxygen content of the inspired air and improving the diffusion capacity [69–71]. Without adequate adaption processes and management, an imbalance between oxygen demand and oxygen delivery will occur leading to impaired homeostasis within the body. Therefore, healthcare practitioners (e.g., physiotherapists, sports scientists, exercise physiologists and others) should be able to understand the causes, types and consequences of hypoxia.

5. Conclusion

In this chapter, an overview is presented on the main types of hypoxia and the physiological consequences of the main systems. Hypoxaemic, anemic, stagnant and histotoxic hypoxia originate from different etiologies. Hypoxia to the tissues can be caused by any obstacle in the oxygen cascade, beginning from the O_2 molecule in the atmosphere, until being the final electron acceptor within the mitochondria to generate ATP. However, the adult compensatory mechanisms to counteract the acute hypoxic state are mainly based on our ability to hyperventilate, adequately adapt the cardiovascular response and to increase oxygen uptake to provide enough tissue O_2. This chapter might contribute to improving the understanding of the different types of hypoxia and to understand the physiological responses.

Conflict of interest

The author declares no conflict of interest.

Author details

Erich Hohenauer[1,2,3,4]

1 University of Applied Sciences and Arts of Southern Switzerland, Landquart, Switzerland

2 International University of Applied Sciences THIM, Landquart, Switzerland

3 University of Fribourg, Fribourg, Switzerland

4 Vrije Universiteit Brussel, Brussels, Belgium

*Address all correspondence to: erich.hohenauer@supsi.ch

References

[1] Taylor CT. Mitochondria and cellular oxygen sensing in the HIF pathway. The Biochemical Journal. 2008;**409**(1):19-26

[2] Richalet J-P. CrossTalk opposing view: Barometric pressure, independent of , is not the forgotten parameter in altitude physiology and mountain medicine. The Journal of Physiology. 2020;**598**(5): 897-899

[3] Conkin J, Wessel JH 3rd. Critique of the equivalent air altitude model. Aviation, Space, and Environmental Medicine. 2008;**79**(10):975-982

[4] Roach RC, Hackett PH, Oelz O, Bartsch P, Luks AM, MacInnis MJ, et al. The 2018 Lake Louise Acute Mountain sickness score. High Altitude Medicine & Biology. 2018;**19**(1):4-6

[5] Wilson MH, Newman S, Imray CH. The cerebral effects of ascent to high altitudes. Lancet Neurology. 2009;**8**(2):175-191

[6] Pittman RN. Regulation of Tissue Oxygenation. Integrated Systems Physiology: From Molecule to Function to Disease. San Rafael (CA): Morgan & Claypool Life Sciences; 2011

[7] Hantzidiamantis PJ, Amaro E. Physiology, Alveolar to Arterial Oxygen Gradient. Treasure Island (FL): StatPearls; 2021

[8] Patel H, Kerndt CC, Bhardwaj A. Physiology, Respiratory Quotient. Treasure Island (FL): StatPearls; 2021

[9] Coleman MD. Chapter 2 - respiratory and pulmonary physiology. In: Duke J, editor. Anesthesia Secrets. Fourth ed. Philadelphia: Mosby; 2011. pp. 17-23

[10] Manninen PH, Unger ZM. Chapter 21 - hypoxia. In: Prabhakar H, editor. Complications in Neuroanesthesia. San Diego: Academic Press; 2016. pp. 169-180

[11] Brown LK. Hypoventilation syndromes. Clinics in Chest Medicine. 2010;**31**(2):249-270

[12] Bhutta BS, Alghoula F, Berim I. Hypoxia. Treasure Island (FL): StatPearls; 2021

[13] Rhodes CE, Varacallo M. Physiology, Oxygen Transport. Treasure Island (FL): StatPearls; 2021

[14] Lee EJ, Hung YC, Lee MY. Anemic hypoxia in moderate intracerebral hemorrhage: The alterations of cerebral hemodynamics and brain metabolism. Journal of the Neurological Sciences. 1999;**164**(2):117-123

[15] Phillips J, Henderson AC. Hemolytic Anemia: Evaluation and differential diagnosis. American Family Physician. 2018;**98**(6):354-361

[16] Sleijfer S, Lugtenburg PJ. Aplastic anaemia: A review. The Netherlands Journal of Medicine. 2003;**61**(5):157-163

[17] Chaudhry HS, Kasarla MR. Microcytic Hypochromic Anemia. Treasure Island (FL): StatPearls; 2021

[18] Nagao T, Hirokawa M. Diagnosis and treatment of macrocytic anemias in adults. Journal of General and Family Medicine. 2017;**18**(5):200-204

[19] Bleecker ML. Carbon monoxide intoxication. In: Handbook of Clinical Neurology. Vol. 131. 2015. pp. 191-203

[20] Ludlow JT, Wilkerson RG, Nappe TM. Methaemoglobinemia. Treasure Island (FL): StatPearls; 2021

[21] Benz EJ, Ebert BL. Chapter 43 - Hemoglobin variants associated with Hemolytic Anemia, altered oxygen affinity, and Methaemoglobinemias. In: Hoffman R, Benz EJ, Silberstein LE, Heslop HE, Weitz JI, Anastasi J, et al.,

editors. Hematology. Seventh ed. Philadelphia, PA, United States of America: Elsevier; 2018. pp. 608-615

[22] Cheung SS. Responses of the hands and feet to cold exposure. Temperature (Austin). 2015;**2**(1):105-120

[23] Feher J. 6.4 - oxygen and carbon dioxide transport. In: Feher J, editor. Quantitative Human Physiology. Second ed. Boston: Academic Press; 2017. pp. 656-664

[24] Wyman J. Facilitated diffusion and the possible role of myoglobin as a transport mechanism. The Journal of Biological Chemistry. 1966;**241**(1):115-121

[25] Graham J, Traylor J. Cyanide Toxicity. Treasure Island (FL): StatPearls; 2021

[26] Pauluhn J. Risk assessment in combustion toxicology: Should carbon dioxide be recognized as a modifier of toxicity or separate toxicological entity? Toxicology Letters. 2016;**262**:142-152

[27] Huzar TF, George T, Cross JM. Carbon monoxide and cyanide toxicity: Etiology, pathophysiology and treatment in inhalation injury. Expert Review of Respiratory Medicine. 2013;**7**(2):159-170

[28] Goldfarb-Rumyantzev AS, Alper SL. Short-term responses of the kidney to high altitude in mountain climbers. Nephrology Dialysis Transplantation. 2013;**29**(3):497-506

[29] Dietz TE, Hackett PH. 42 - high-altitude medicine. In: Keystone JS, Kozarsky PE, Connor BA, Nothdurft HD, Mendelson M, Leder K, editors. Travel Medicine. Fourth ed. London: Elsevier; 2019. pp. 387-400

[30] MacIntyre NR. Tissue hypoxia: Implications for the respiratory clinician. Respiratory Care. 2014;**59**(10):1590-1596

[31] Michiels C. Physiological and pathological responses to hypoxia. The American Journal of Pathology. 2004;**164**(6):1875-1882

[32] Duke HN, Killick EM. Pulmonary vasomotor responses of isolated perfused cat lungs to anoxia. The Journal of Physiology. 1952;**117**(3):303-316

[33] McMurtry IF, Davidson AB, Reeves JT, Grover RF. Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. Circulation Research. 1976;**38**(2):99-104

[34] Post JM, Hume JR, Archer SL, Weir EK. Direct role for potassium channel inhibition in hypoxic pulmonary vasoconstriction. The American Journal of Physiology. 1992;**262**(4 Pt 1):C882-C890

[35] Kane AD, Kothmann E, Giussani DA. Detection and response to acute systemic hypoxia. BJA Education. 2020;**20**(2):58-64

[36] Peers C, Kemp PJ. Acute oxygen sensing: Diverse but convergent mechanisms in airway and arterial chemoreceptors. Respiratory Research. 2001;**2**(3):145-149

[37] Lopez-Barneo J, Pardal R, Ortega-Saenz P. Cellular mechanism of oxygen sensing. Annual Review of Physiology. 2001;**63**:259-287

[38] Hallett S, Toro F, Ashurst JV. Physiology, Tidal Volume. Treasure Island (FL): StatPearls; 2021

[39] Paralikar SJ, Paralikar JH. High-altitude medicine. Indian Journal of Occupational and Environmental Medicin. 2010;**14**(1):6-12

[40] Hackett P, Roach R. High Altitude Medicine. Maryland Heights, MO, United States of America: Mosby; 2001. pp. 1-37

[41] Brinkman JE, Sharma S. Respiratory Alkalosis. Treasure Island (FL): StatPearls; 2021

[42] Lipsitz LA, Hashimoto F, Lubowsky LP, Mietus J, Moody GB, Appenzeller O, et al. Heart rate and respiratory rhythm dynamics on ascent to high altitude. British Heart Journal. 1995;**74**(4):390-396

[43] Talbot NP, Balanos GM, Dorrington KL, Robbins PA. Two temporal components within the human pulmonary vascular response to approximately 2 h of isocapnic hypoxia. Journal of Applied Physiology. 2005;**98**(3):1125-1139

[44] Mazzeo RS, Wolfel EE, Butterfield GE, Reeves JT. Sympathetic response during 21 days at high altitude (4,300 m) as determined by urinary and arterial catecholamines. Metabolism. 1994;**43**(10):1226-1232

[45] Domej W, Schwaberger G. Physiologie der mittleren, großen und extremen Höhen. In: Berghold F, Brugger H, Burtscher M, Domej W, Durrer B, Fischer R, et al., editors. Alpin- und Höhenmedizin. Berlin, Heidelberg: Springer Berlin Heidelberg; 2019. pp. 337-354

[46] Wagner PD. Reduced maximal cardiac output at altitude--mechanisms and significance. Respiration Physiology. 2000;**120**(1):1-11

[47] Busse R, Pohl U, Kellner C, Klemm U. Endothelial cells are involved in the vasodilatory response to hypoxia. Pflügers Archiv. 1983;**397**(1):78-80

[48] Franco-Obregon A, Lopez-Barneo J. Low PO2 inhibits calcium channel activity in arterial smooth muscle cells. The American Journal of Physiology. 1996;**271**(6 Pt 2):H2290-H2299

[49] Pohl U, de Wit C. Der Sauerstoff im Gewebe. In: Brandes R, Lang F, Schmidt RF, editors. Physiologie des Menschen: mit Pathophysiologie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2019. pp. 365-375

[50] Brown JP, Grocott MP. Humans at altitude: Physiology and pathophysiology. Continuing Education in Anaesthesia, Critical Care and Pain. 2012;**13**(1):17-22

[51] Thorborg PAJ. CHAPTER 40 - blood gas analysis. In: Papadakos PJ, Lachmann B, Visser-Isles L, editors. Mechanical Ventilation. Philadelphia: W.B. Saunders; 2008. pp. 457-470

[52] Kenney WL, Wilmore JH, Costill DL. Physiology of Sport and Exercise. 6th ed. Champaign, IL, United States of America: Human Kinetics; 2015

[53] Attwell D, Laughlin SB. An energy budget for signaling in the grey matter of the brain. Journal of Cerebral Blood Flow and Metabolism. 2001;**21**(10):1133-1145

[54] Hoiland RL, Bain AR, Rieger MG, Bailey DM, Ainslie PN. Hypoxemia, oxygen content, and the regulation of cerebral blood flow. American Journal of Physiology Regulatory, Integrative and Comparative Physiology. 2016;**310**(5): R398-R413

[55] Nakata H, Miyamoto T, Ogoh S, Kakigi R, Shibasaki M. Effects of acute hypoxia on human cognitive processing: A study using ERPs and SEPs. Journal of Applied Physiology. 2017;**123**(5): 1246-1255

[56] Virués-Ortega J, Buela-Casal G, Garrido E, Alcázar B. Neuropsychological functioning associated with high-altitude exposure. Neuropsychology Review. 2004;**14**(4):197-224

[57] Di Paola M, Bozzali M, Fadda L, Musicco M, Sabatini U, Caltagirone C. Reduced oxygen due to high-altitude exposure relates to atrophy in motor-function brain areas. European Journal of Neurology. 2008;**15**(10):1050-1057

[58] Berry DT, McConnell JW, Phillips BA, Carswell CM, Lamb DG,

Prine BC. Isocapnic hypoxemia and neuropsychological functioning. Journal of Clinical and Experimental Neuropsychology. 1989;**11**(2):241-251

[59] Hornbein TF, Townes BD, Schoene RB, Sutton JR, Houston CS. The cost to the central nervous system of climbing to extremely high altitude. The New England Journal of Medicine. 1989;**321**(25):1714-1719

[60] Petrassi FA, Hodkinson PD, Walters PL, Gaydos SJ. Hypoxic hypoxia at moderate altitudes: Review of the state of the science. Aviation, Space, and Environmental Medicine. 2012;**83**(10): 975-984

[61] Taylor L, Watkins SL, Marshall H, Dascombe BJ, Foster J. The impact of different environmental conditions on cognitive function: A focused review. Frontiers in Physiology. 2015;**6**:372

[62] Cavaletti G, Tredici G. Long-lasting neuropsychological changes after a single high altitude climb. Acta Neurologica Scandinavica. 1993;**87**(2):103-105

[63] Ainslie PN, Poulin MJ. Ventilatory, cerebrovascular, and cardiovascular interactions in acute hypoxia: Regulation by carbon dioxide. Journal of Applied Physiology. 2004;**97**(1):149-159

[64] Heinonen IH, Boushel R, Kalliokoski KK. The circulatory and metabolic responses to hypoxia in humans - with special reference to adipose tissue physiology and obesity. Front Endocrinol (Lausanne). 2016;**7**:116

[65] Gaspar JM, Velloso LA. Hypoxia inducible factor as a central regulator of metabolism - implications for the development of obesity. Frontiers in Neuroscience. 2018;**12**:813

[66] Mesarwi OA, Loomba R, Malhotra A. Obstructive sleep Apnea, hypoxia, and nonalcoholic fatty liver disease. American Journal of Respiratory and Critical Care Medicine. 2019;**199**(7):830-841

[67] McLellan SA, Walsh TS. Oxygen delivery and haemoglobin. Continuing Education in Anaesthesia, Critical Care and Pain. 2004;**4**(4):123-126

[68] Sharma S, Hashmi MF. Partial Pressure of Oxygen. Treasure Island (FL): StatPearls; 2021

[69] Chen DW, Park R, Young S, Chalikonda D, Laothamatas K, Diemer G. Utilization of continuous cardiac monitoring on hospitalist-led teaching teams. Cureus. 2018;**10**(9):e3300

[70] Vali P, Underwood M, Lakshminrusimha S. Hemoglobin oxygen saturation targets in the neonatal intensive care unit: Is there a light at the end of the tunnel? (1). Canadian Journal of Physiology and Pharmacology. 2019;**97**(3):174-182

[71] Saito-Benz M, Sandle ME, Jackson PB, Berry MJ. Blood transfusion for anaemia of prematurity: Current practice in Australia and New Zealand. Journal of Paediatrics and Child Health. 2019;**55**(4):433-440