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Review Article

Pathophysiological Basis of The Development of Hypoxia of the Nervous Tissue

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Abstract

All types of hypoxia at certain stages of their development are accompanied by impaired tissue respiration, that is, they lead to the development of secondary tissue hypoxia. The causes and development mechanisms of which we tried to discuss in this article. The development of hypoxic conditions and their compensation depend not only on this or that hypoxic perturbation and that part of the respiratory system, which is primarily targeted by its action, but also on the duration and the degree of exposure to the factor causing hypoxia, on the activity of urgent and long-term compensation mechanisms.

Keywords: hypoxia; brain; mechanisms

Introduction

All types of hypoxia at certain stages of their development are accompanied by impaired tissue respiration, that is, they lead to the development of secondary tissue hypoxia. The causes and development mechanisms of which we tried to discuss in this article.

The study of molecular, membrane, cellular, organ and system mechanisms of the development and compensation of hypoxic conditions, the approach to the study of respiration from the position of the system theory, the use of methods of mathematical modeling of the mass transfer process of respiratory and inert gases, the concept of oxygen regimes of the body, allowing objective assessment of the degree of hypoxia, have brought the previously descriptive nature of the study of hypoxia to the category of exact sciences. With the development of ideas about hypoxia, the terminology has naturally changed [4]. The term "hypoxia", meaning the decrease of oxygen content in arterial blood in the last century, was given a new meaning in the 20th century. Hypoxia became to be understood as all those states of the organism in which, for one reason or another, the parameters of oxygen delivery to the tissues decreased, hypoxemia - reduction of its content

(PO_2) in the blood [8].

Back in 1905 he proposed to distinguish between types of oxygen starvation depending on the causes, causing a violation of both oxygen delivery and oxidative processes in the very point of respiration - in the tissues.

The classification of hypoxia proposed by Barcroft in 1919, based on the extensive data of researchers from many countries already at that time and on the results of his own experimental studies of the role of hemoglobin in oxygen delivery, has gained wide popularity. It was quite simple, in it the type of hypoxia was determined depending on the changes in hemoglobin circulating in the blood and its ability to bind oxygen, its role in oxygen delivery to the tissues [13]. Therefore, tissue hypoxia was not included in Barcroft's classification. Later, in 1922, included histotoxic anoxia in the concept of "anoxia", i.e. such type of hypoxia, in which oxygen delivery to tissues is not impaired, but due to the damage of the cellular apparatus of its utilization the intensity of oxidative processes in cells is reduced [14].

The introduction of tissue hypoxia or histotoxic hypoxia into the classification of hypoxic conditions caused a discussion, which continues to the present day [11]. The concept of "tissue hypoxia" was very broad and had different meanings, implying tissue hypoxia as hypoxia resulting from primary damage of the cell respiratory apparatus by cyanides, drugs, etc [7].

Tissue hypoxia developing as a result of oxygen delivery impairments to the tissues (the final link in the pathogenesis of hypoxic conditions of different types). Thus, the concept of "tissue hypoxia" includes conditions of various etiologies with different pathogenetic mechanisms acting either on organ and tissue or cellular, subcellular, mitochondrial and molecular levels [5].

Depending on the etiology and pathogenesis, we propose to distinguish between primary and secondary tissue hypoxia. To the primary tissue (cytotoxic) hypoxia we propose to refer all states in which as a result of cyanide poisoning, drugs and other substances paralyzing tissue respiration, there is a primary lesion of the cellular respiration apparatus either at the level of cell organelles (mainly mitochondria) or at the molecular (enzymatic) level.

We propose to refer secondary tissue hypoxia to such conditions when, as a result of mismatch between the rate of oxygen delivery and cellular demand for it, oxygen tension in tissues and cells decreases below the critical level, respiratory enzyme activity drops, oxidative reactions are depressed, oxygen consumption rate decreases, macroergs formation decreases, underoxidized

products accumulate, anaerobic energy sources start to be used. Thus, tissue hypoxia can be both an independent type of hypoxia - primary tissue hypoxia (cytotoxic), and the final link in the pathogenesis of various types of hypoxic conditions, in which oxygen delivery to cells is disrupted - secondary tissue hypoxia [2].

Primary and secondary tissue hypoxia have both common and distinctive features. Common to both are inhibition of oxidative processes in cells, decreased intensity of oxygen consumption and formation of energy-rich phosphadenyl and creatine phosphorus compounds, accumulation of under-oxidized products, increased concentration of hydrogen ions, pH shift and acid-base state in tissues and venous blood towards acidosis, disturbance of ionic equilibrium, major changes in the structure and function of cells, tissues, organs and systems [17].

Primary and secondary tissue hypoxia differ both in etiology, pathogenesis and objective indicators. In primary tissue hypoxia the rate of oxygen transport by arterial and venous blood, oxygen tension in them and tissues is lower, and in secondary tissue hypoxia - below normoxic values [18].

The question arises to what extent cellular respiration, which provides ATP formation, depends on the level of PO_2. (concentration of oxygen in the cell). Under physiological conditions, the rate of ATP synthesis is directly proportional to the rate of oxygen consumption, since mitochondrial oxidative phosphorylation is the main source of cellular ATP.

The synthesis of ATP from ADP and inorganic phosphate occurs due to the fact that the oxidized cytochrome c, reducing, gives its electron to cytochrome c oxidase, which contains two copper-containing centers (CuA and CuB) and hemes a and a_3, through which electrons , finally, they go to oxygen.

In total, ATP synthesis in mitochondria can be represented as the following reversible reaction:

$$NADH + ADP + P_{in} \leftrightarrow NAD + ATP$$

The dependence of this reaction on oxygen is expressed by the equation

$$1/2O_2 + 2H^+ + 2e^- + ADP + P_{in} \leftrightarrow H_2O + ATP + \Delta Q.$$

In the absence of oxygen, electron transfer stops, the proton gradient drops, and ATP synthesis stops [20,21].

The reactions that are mentioned above predetermine the dependence of the intensity of respiration and ATP synthesis on several factors. According to the law of mass action, ATP synthesis in the first reaction will depend on the ratio between [NAD]/[NADN] and on the content of ADP and inorganic phosphorus; in the second reaction - on degree of reduction of cytochrome *c*. The dependence of the rate of ATP synthesis on the phosphate potential $[ATP]/[ADP] \cdot [P_{in}]$ has been experimentally confirmed by many authors, and the dependence of oxidized cytochrome *c* formation and ATP formation from PO_2, has been convincingly proved by experimental and theoretical (using a mathematical model) studies of D. Wilson et al. [7], who showed that oxidative phosphorylation depends on PO_2 in the whole range of its changes under physiological conditions, because the degree of cytochrome *c* reduction increases with decreasing PO_2 , starting from such high value as 144 mm Hg. When PO_2 = 144 mmHg cytochrome *c* is reduced by 20%, at 120 $_{mmHg}$ it is reduced by 23%, at 30 mmHg (which is very close to the mean value of PO_2 , in brain and muscle tissue) it is reduced by 29% (almost 1/3), at PO_2 = 12 and 6 mmHg - by 34 and 40%, respectively. Parallel to the reduction of cytochrome *c* in the decrease of oxygen tension in tissues, there is a decrease in phosphate potential, which, according to D. Wilson et al., when PO_2 = 50 mm Hg, it decreases twofold; at 19 mm Hg, it decreases more than fourfold. Despite changes in the degree of reduction of cytochrome c and reduction of phosphate potential, mitochondrial respiration rate does not decrease until PO_2 becomes lower than 12 mm Hg due to the participation of another regulatory effect - the ratio of oxidized to reduced NAD [13].

Thus, three intracellular regulatory influences determine the relatively high resistance of the mitochondrial respiration intensity to P reduction O_2 and low values of Km (the value of PO_2 , at which the respiration intensity is 50% of normal); these are the phosphate potential (not the absolute amounts of ATP, because the phosphate potential can decrease due to accumulation of ADP and inorganic phosphate), the degree of cytochrome *c* reduction and [NAD]/[NADH] ratio. Therefore, for different conditions (rest-muscular activity) in the same individual, in individuals of different sex and age, PO_2, at which the rate of oxygen consumption, the so-called critical level of PO_2, begins to decrease, is not the same [9].

Distinguish three critical levels of PO_2 : a critical level for mitochondria, i.e., such a value of PO_2 below which the maximum respiration rate of mitochondria begins to decrease; this level depends on the property of the mitochondria; an effective critical level of PO_2 for mitochondria, i.e., such a value of P below which the maximum respiration rate of the tissue begins to decrease; if the concentration of respiratory enzymes is elevated, the effective critical level of P for mitochondria may be lower than it, such value of PO_2 , below which the maximum respiration rate of the tissue begins to fall; if the concentration of respiratory enzymes is increased, the effective critical level of PO_2 for mitochondria may be below its critical level, since the maximum respiration rate of the tissue depends not only on the critical level of PO_2 for mitochondria, but also on the concentration and activity of respiratory enzymes; critical level of PO_2 oxygen delivery - such level of PO_2 in capillary blood, below which [17].

Many authors emphasize the importance of determining the PO_2 of the venous blood and distinguishing a "critical" level of PO_2 of the venous blood, a "critical" level of PO_2 of the arterial blood, below which the reduction of oxygen consumption by the organ and the organism as a whole begins. As will be shown further, the critical level of $_PO_2$ of the arterial blood can be considered 50 mm Hg. Since PO_2 of the arterial blood is in close dependence on PO_2 of the alveolar and inhaled air, we also distinguish the "critical" levels of partial oxygen pressure in the alveolar and inhaled air. The decrease of oxygen consumption by the organism occurs at PiO_2 = 90 mm Hg and PaO_2 = 55 mm Hg [15].

Carotid and aortic chemoreceptors are the most sensitive to oxygen tension decrease, as it was established in the 20s of our century. It is likely that high sensitivity of carotid and aortic chemoreceptors to hypoxia is determined by the peculiarities of their respiratory enzymes. There is evidence that cytochrome *a3* of the carotid body, even if PO_2 equates to 100 mm Hg, attaches to itself only 60-90% of oxygen. For its complete saturation, higher values of PO_2 are required. This means that PO_2 that is equal to 100 mm Hg is the "critical" level for the cytochrome of the carotid body, i.e. it is the level at which tissue hypoxia can already develop and ionic equilibrium can be disturbed, which will cause excitation in the receptor cells [8].

Historically, hypoxic hypoxia - oxygen deficiency arising in the body from inhalation of air with reduced partial pressure of oxygen - was studied before other types of oxygen deficiency. Its pathogenesis can be represented as the following simplified scheme: the decrease of the partial pressure of oxygen in the inhaled air leads to the decrease of PO_2 in the alveolar air and the arterial blood. If compensatory mechanisms were not activated, the rate of oxygen inflow into the lungs and alveoli, the rate of oxygen mass transfer by the arterial blood would decrease, resulting in lower oxygen delivery rate to the tissue, oxygen mass transfer rate by mixed venous blood, its PO_2 , oxygen tension in the tissues would fall to levels below the critical ones. The latter in turn would lead to increased reduction of cytochrome *c*, decreased phosphate potential, inhibition of tissue respiration and ATP synthesis, accumulation of acidic products, shift in ionic equilibrium, changes in mitochondrial and cell membranes, conformational shifts in proteins, disruption of cell, tissue and organ structure and function [12].

High sensitivity of the brain and especially its higher sections to hypoxia has been experimentally proved [21,9,10, 2]. Our studies showed that blood saturation of carotid artery and internal jugular vein with oxygen, oxygen content in blood, arterio-venous difference in oxygen decreases in nonacclimatized persons on the second day of stay at an altitude of 3800 mm. When inhaling oxygen-poor mixtures, the blood oxygen content decreases and, despite the increased blood flow rate, the oxygen consumption by the brain decreases. Parallel studies of the higher nervous activity of the same

persons testified to significant changes in both inhibitory and excitatory processes, violations of not only fine but also rough differentiation, manifestations of hypnotic states, pronounced changes in the second signal system. Mental performance worsened, the rate of proofreading work slowed down. All these changes were observed against the background of reduced PO2 in the carotid blood up to 58- 48 mm Hg, and in the internal jugular vein blood up to 34-26 mm Hg, and the higher nervous activity was more impaired in those individuals in whom arterial and especially venous hypoxemia were more pronounced [3].

Some authors believe that the initial response to brain hypoxia occurs in humans when PO_2 in the venous blood flowing from the brain decreases to 28 mm Hg, loss of consciousness occurs when PvO_2 equals 19 mm Hg, and death may occur at PvO_2 - 12 mm Hg [13]. According to the same authors, during normoxia in the brain, PvO_2 is excessive; during loss of consciousness and all the more so in life-threatening conditions, it decreases to 5-4 mm Hg According to the data, in normoxia PO_2 in the brain is not excessive. At the points of the worst supply it can be equal to 17 mm Hg At critical PO_2 in venous blood 28 mm Hg PO_2 in the "dead corner" decreases to 4 mmHg. According to Hirsch et al., a decrease in oxygen consumption by the cat brain is observed at PO_2 in the venous blood flowing away from the brain to 20 mm Hg [5].

Detailed experimental and theoretical studies of the conditions and mechanisms for the development of brain tissue hypoxia were carried out. The results obtained and literature data on this issue were presented [22]. According to K.P. Ivanov, the critical venous PO_2 for the rat brain is equal to 20 mm Hg, at such PO_2 of venous blood flowing from the brain, in some parts of the brain oxygen tension does not exceed 1.0-0.5 mm Hg.

In cells of tissues less sensitive to oxygen deficiency, a drop of PO_2 below the "critical" level also leads to a decrease in the intensity of oxidative processes. Experiments with isolated tissues (liver, heart and skeletal muscles) have shown that the intensity of oxidative processes in them decreases if PO_2 in incubation medium is reduced from 159 mm Hg to 33 mm Hg [1].

The critical level of PO_2 for liver mitochondria is 8 mm Hg [18]. For isolated mitochondria, the critical value of PO_2 is in the range of 0.5-1 mm Hg. [8].

The critical PO_2 level for cytochrome oxidase is low [4].

The average value of tissue oxygen tension obtained from polarographic measurements with macroelectrodes does not accurately reflect the level of PO_2 in the intercapillary space. Studies using microelectrodes showed that the oxygen tension in tissues is almost impossible to express by any single number, as PO_2 in tissues varies from 95 mmHg to zero. Histograms give a more accurate picture of the distribution of PO_2 in tissues, but they also do not reflect the true topography of PO_2 in tissues. The most accurate reflection of the topography of P is obtained with the help of mathematical models of isobars [6].

The changes in the organism resulting from the decrease of PO_2 in the inhaled air are a consequence of both the damaging effect of hypoxia and the activity of compensatory mechanisms aimed at preventing this damaging effect, at increasing the delivery of oxygen to the tissues and increasing the efficiency of oxygen use delivered to them. In the experiment it is practically impossible to create such conditions, under which it would be possible to completely exclude the effect of compensatory mechanisms activity. In this respect, significantly greater opportunities are offered by the use of simulation models with biocontrol, based on a consistent description of physical, biophysical, physical-chemical and biochemical regularities of gas mass transfer process dynamics in the organism and on information about the magnitude of the control actions coming from the biological object under study [11].

We put more than 40 series of studies on such mathematical models in which the dynamics of changes in the partial pressure of oxygen and carbon dioxide in the alveolar air, its tension in the blood of pulmonary capillaries, arterial and mixed venous blood, arterial and venous sections of tissue capillaries were determined when oxygen content in the inhaled air decreased to 16, 14,12, 10, 8, 6, 4%, average PO_2 in the tissues of various organs (brain, heart muscle, skeletal muscles, liver, gastrointestinal tract, kidneys, bone tissue, skin), PO_2 mixed venous blood either in the absence or different degrees of severity of compensatory changes in pulmonary and alveolar ventilation, pulmonary, systemic and organ blood flow, respiratory function of blood, oxygen utilization mechanisms [4].

The results of these studies indicate that in the absence of compensatory effects when there are no changes in respiratory volume (550 ml), respiratory cycle duration (4 s), minute respiratory volume (8.250 ml/min), the ratio of alveolar ventilation (70%), minute blood volume (4100 ml/min), hemoglobin content in blood (14 g%), oxygen consumption rate (3.4 ml/min per 1 kg of tissue), oxygen tension drops not only in arterial, but also in mixed blood and tissues even in cases when the oxygen content in the inhaled air decreases only by one-quarter. At the same time in the tissues PO_2 is not yet below the critical level. But if the oxygen content in the breathing mixture decreased to 12%, the oxygen tension in the arterial and mixed venous blood and in the tissues would fall to levels close to critical, in these cases tissue oxygen consumption could decrease and secondary tissue hypoxia would develop [8].

Changes in PO_2 in alveolar air, arterial and mixed venous blood, and tissues in the absence of compensatory influences are proportional to its decrease in inhaled air, but the proportionality coefficients for PO_2 of alveolar air, arterial and venous blood of different tissues are not the same. Oxygen tension in arterial and especially in mixed venous blood and tissues decreases less than in inhaled and alveolar air. This indicates that in the system of oxygen mass transfer itself, even in the absence of compensatory influences, there is some compensation for the decrease of PO_2 in the inhaled air. The inclusion of compensatory influences, especially such as increasing the minute volume of breathing, the minute volume of blood, the redistribution of macro- and microcirculation of blood, can prevent the development of tissue hypoxia with a fairly significant reduction of PO_2 in the inhaled air. Tissue hypoxia, therefore, is not a necessary element of hypoxic state. It develops only under certain conditions (in the case of hypoxic hypoxia when PO_2 in the inhaled air is below 90 mm Hg). The development of tissue hypoxia is largely determined by how effective the compensatory mechanisms [17]. In acute hypoxia a significant role in the compensation of hypoxia belongs to such mechanisms of urgent compensation as increased pulmonary and alveolar ventilation, increased diffusion surface of alveoli, systemic and regional blood flow, the release of red blood cells from the depot and the associated increase in blood oxygen capacity, the shift of acid-base state and blood pH, which affects oxygen-binding properties of blood, changes in diffusion parameters in tissues [1].

Based on objective indicators of hypoxic conditions: changes of PO_2 in alveolar air, arterial and mixed venous blood, the rate of stepwise oxygen delivery to tissues and their oxygen consumption, indicators of acid-base state of blood, considering the activity of compensatory mechanisms and state of higher nervous activity, level of mental and physical performance capacity, we proposed to distinguish the following degrees of acute hypoxic hypoxia: latent, compensated, severe hypoxia with the onset of decompensation, uncompensated, terminal [6]. In some tissues hypoxia begins to manifest itself already in the second degree of hypoxic hypoxia. In subsequent degrees it is sharply expressed in all tissues [19].

Secondary tissue hypoxia can develop in hypoxic conditions of different types: in severe hypoxic, respiratory, circulatory, hemic hypoxia, in load hypoxia, in deterioration of oxygen mass transfer as a result of microcirculation disorders, in deterioration of conditions for oxygen diffusion from blood capillaries to mitochondria (increased diffusion radius, slowed blood flow, compaction of capillary and cell membranes, intercellular substance, fluid accumulation, etc.).

Given the shortcomings of the existing classifications of hypoxic conditions we proposed to apply a fundamentally new approach to the classification of hypoxia [6,19]. The classification of hypoxic conditions we propose is based on the system approach to the study of respiration. It takes into account the

changes occurring in all links of oxygen delivery and its utilization, since both external perturbations and perturbations occurring within the system in any of its links, changes in the pressure on the system (increase in the rate of oxygen consumption and carbon dioxide production) all lead to a pronounced change in the state of the system as a whole [19].

If the classification of hypoxic conditions is based on the system approach, then first of all we should highlight changes in the state of oxygen supply system, which occur in a healthy body under the influence of external disturbances: reduction of PO_2 in the inhaled air, increase of PO_2 in it, changes in the total barometric pressure, which affects the mass transfer of respiratory gases. External perturbations at the inlet to the system affect all of its links. Hypoxic conditions of this kind should be distinguished into separate types of hypoxia: hypoxic, hyperbaric and hyperoxic [14].

An increase in the system load - an increase in the rate of oxygen consumption and CO production, which is observed when the function of an organ or tissue is intensified, especially during muscular activity, also affects the system as a whole and all of its links. Hypoxic conditions arising from a significant increase in oxygen consumption, i.e., an increase in the load on the system, we allocate to a separate type - load hypoxia.

Internal disturbances resulting from pathological changes in the respiratory apparatus, cardiovascular system, blood system can also lead to the development of hypoxic conditions - respiratory, circulatory, hemic, but pathological changes in the tissue respiratory apparatus - to primary tissue (cytotoxic) hypoxia [22].

Thus, we propose to distinguish eight main types of hypoxia: hypoxic, hyperoxic, hyperbaric, respiratory, circulatory, hemic, load hypoxia and primary tissue (cytotoxic) hypoxia. Each type of hypoxia may include its different forms.

It should be noted that in some cases respiratory, circulatory, hemic and cytotoxic hypoxia may develop not only in diseases of internal organs, but also as a result of some external agents that have a selective effect on a particular part of oxygen delivery and utilization system. Thus, inhalation of carbon monoxide inactivates hemoglobin and the development of hypoxia is of hemic type, under the action of acceleration on the body, that causes redistribution of tissue blood supply - mainly of circulatory type, etc.

Each type of hypoxia has its own specifics and can be determined by objective criteria - primarily by the level of PO_2 in the environment, the alveolar air, the arterial and venous blood and tissues, by the rate of mass transfer of oxygen in the body and its consumption. As the main objective criteria of hypoxia parameters are used that characterize oxygen mass transfer modes, carbon dioxide mass transfer, changes in oxygen consumption and formation of macroergic compounds, pH of arterial and venous blood, its content of lactic and pyruvic acids, buffer bases and other indicators acid-base balance of blood [8].

Different types and degrees of hypoxia result in different changes in the body's oxygen regimes.

Hypoxic hypoxia is caused by a decrease in PO_2 in the inhaled air. It necessarily reduces PO_2 in the alveolar air, the arterial blood and the total air-venous gradient PO_2 decreases [20]. In hyperoxic hypoxia regardless of its form (respiratory, circulatory, cytotoxic) as a result of PO_2 increase in the inhaled air the total air-venous gradient PO_2 also increases, but the rate of oxygen transport by arterial blood and the rate of oxygen consumption by tissues decrease, peroxidized products accumulate, the acid-base state of blood changes [11, 12, 16].

Respiratory hypoxia is necessarily associated with decreased oxygen tension in arterial blood, arterial hypoxemia as a result of impaired gas exchange in lungs and mass transfer of oxygen through alveolar-capillary membrane without changes in PO_2 inhaled air with small changes in air-venous gradient PO_2 [12].

The cause of circulatory hypoxia can be disorders of cardiovascular system function, macro- and microcirculation. Distinctive signs of circulatory hypoxia are the decreased rate of oxygen mass transfer by arterial blood and the decreased rate of oxygen delivery to the cells. Oxygen content and oxygen tension in the arterial blood in this form of hypoxia can be within normoxic values.

Oxygen tension in tissues and the venous blood is decreased, resulting in increased venous-alveolar and total airvenous gradients PO_2 .

In hemic hypoxia due to decreased oxygen capacity of blood or oxygenbinding properties of hemoglobin, oxygen content in arterial and mixed venous blood decreases, and consequently, the rate of oxygen mass transfer by blood. Oxygen tension in tissues and mixed venous blood is reduced, PO_2 alveolar air and arterial blood are within normoxic fluctuations.

The proposed classification, as well as others, is conditional, since different types of hypoxia can develop simultaneously in a person's life (especially in a patient).

The development of hypoxic conditions and their compensation depend not only on this or that hypoxic perturbation and that part of the respiratory system, which is primarily targeted by its action, but also on the duration and the degree of exposure to the factor causing hypoxia, on the activity of urgent and long-term compensation mechanisms.

Reference

1. Anshu Rastogi , Pavel Pospísil, 2011-Spontaneous ultraweak photon emission imaging of oxidative metabolic processes in human skin: effect of molecular oxygen and antioxidant defense system.
2. Armin Biller , Stephanie Badde , Andreas Heckel , Philipp Guericke , Martin Bendszus , Armin M. Nagel , Sabine Heiland , Heimo Mairbäurl , Peter Bärtsch , Kai Schommer, 2021-Exposure to 16 h of normobaric hypoxia induces ionic edema in the healthy brain.
3. P. Bärtsch, B. Saltin, 2008-General introduction to altitude adaptation and mountain sickness.
4. Carla A. Di Maria , Marie A. Bogoyevitch, Douglas J McKitrick, Leonard F. Arnolda, Livia C. Hool, Peter G. Arthur, 2009- Changes in oxygen tension affect cardiac mitochondrial respiration rate via changes in the rate of mitochondrial hydrogen peroxide production.
5. Cong Zhang , Samuel Bélanger , Philippe Pouliot , Frédéric Lesage, 2015-Measurement of Local Partial Pressure of Oxygen in the Brain Tissue under Normoxia and Epilepsy with Phosphorescence Lifetime Microscopy.
6. Elvira di Pasquo , Arianna Commare , Bianca Masturzo , Sonia Paolucci , Antonella Cromi , Benedetta Montersino , Chiara M. Germano , Rossella Attini , Serafina Perrone , Francesco Pisani , Andrea Dall'Asta , Stefania Fieni , Tiziana Frusca , Tullio Ghi, 2022 -Short-term morbidity and types of intrapartum hypoxia in the newborn with metabolic acidaemia: a retrospective cohort study.
7. Erik Sedlák , Tibor Žár , Rastislav Varhač , Andrej Musatov , Nataša Tomášková , 2021- Anion-Specific Effects on the Alkaline State of Cytochromec.
8. Jared A. Sperling , Siva S. V. P. Sakamuri , Aaron L Albuck , Venkata N Sure 1, Wesley R Evans , Nicholas R Peterson , Ibolya Rutkai , Ricardo Mostany , Ryousuke Satou, Prasad V. G. Katakam, 2019-Measuring Respiration in Isolated Murine Brain Mitochondria: Implications for Mechanistic Stroke Studies.
9. Jeff F. Dunn , Albert M. Isaacs, 2021-The impact of hypoxia on blood-brain, blood-CSF, and CSF-brain barriers.
10. Justin S. Lawley , Benjamin D. Levine , Michael A. Williams, Jon Malm , Anders Eklund , David M. Polaner , Andrew W. Subudhi , Peter H Hackett , Robert C.

Roach, 2016-Cerebral spinal fluid dynamics: effect of hypoxia and implications for high-altitude illness.
11. Mervyn Singer , Paul J. Young , John G. Laffey , Pierre Asfar , Fabio Silvio Taccone , Markus B. Skrifvars , Christian S. Meyhoff , Peter Radermacher, 2021-Dangers of hyperoxia.
12. Nadezhda N. Barvitenko , Muhammad Aslam, Jessica Filosa, Elena Matteucci, Mikko Nikinmaa, Antonella Pantaleo, Carlota Saldanha, Oguz K. Baskurt, 2016-Tissue oxygen demand in regulation of the behavior of the cells in the vasculature.
13. Olav L. Schjørring , Thomas L. Klitgaard , Anders Perner , 2021- Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure.
14. Owen Davis Sanders , Lekshmy Rajagopal , Chandler Chase Barton , Jayalekshmi Archa Rajagopal , Olga Lopez , Kalei Lopez , Fayeza Malik , 2022- Does oxidative DNA damage trigger histotoxic hypoxia via PARP1/AMP-driven mitochondrial ADP depletion-induced ATP synthase inhibition in Alzheimer's disease.
15. P Bärtsch , B. Saltin,2008-General introduction to altitude adaptation and mountain sickness.
16. Piotr Liguzinski , Bernard Korzeniewski, 2007-Oxygen delivery by blood determines the maximal VO2 and work rate during whole body exercise in humans: in silico studies.
17. Roland N. Pittman, 2011-Regulation of Tissue Oxygenation.
18. R. Ubbink , M. A. Wefers Bettink , W. van Weteringen , E. G. Mik, 2020-Mitochondrial oxygen monitoring with COMET: verification of calibration in man and comparison with vascular occlusion tests in healthy volunteers.
19. Tejpreet Singh Lamba , Rihab Saeed Sharara, Anil C. Singh, Marvin Balaan, 2016-Pathophysiology and Classification of Respiratory Failure.
20. Usharani Nimmagadda , M. Ramez Salem, George J. Crystal, 2017-Preoxygenation: Physiologic Basis, Benefits, and Potential Risks.
21. Yilin Yang, Harleen K. Sandhu, Feng Zhi, Fei Hua, Min Wu, Ying Xia, 2015- Effects of hypoxia and ischemia on microRNAs in the brain.
22. Ylenia Della Rocca, Luigia Fonticoli , Thangavelu Soundara Rajan , Oriana Trubiani, Sergio Caputi , Francesca Diomede , Jacopo Pizzicannella , Guya Diletta Marconi, 2022-Hypoxia: molecular pathophysiological mechanisms in human diseases.