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THE RESPONSE OF HYPOXIA BIOMARKERS TO HYPERBARIC OXYGEN THERAPY IN PREVENTING HYPOXIA AT HIGH ALTITUDE

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ABSTRACT

A protracted period of training at high altitude can result in low oxygen tension, which can lead to the development of hypoxia-related complications. The downregulation and dysfunction of the cell's nucleus underlie the cascade activity of hypoxia. Detecting biomarkers and physiological alterations at an early stage is crucial for preventing hypoxia at high altitudes. Hyperbaric medicine is a novel treatment that uses oxygen therapy to treat hypoxic and inflammatory conditions. Doctors administer 100% oxygen to patients at a pressure that surpasses atmospheric pressure. This review investigates the physiological changes associated with hypoxia, the response of biomarkers to hypoxia changes at high altitude, and the potential role of hyperbaric oxygen therapy in treating pilots and athletes who train at high altitudes and have underlying hypoxia-related diseases.

1.0 BACKGROUND

In recent decades, there has been an increase in the prevalence of training at high altitude. From pilots to athletes, high-altitude training has the potential to have substantial health consequences. Not only do altitude and environmental factors threaten the safety of the pilot and athlete, but they frequently obstruct access to appropriate medical care. Proper acclimatisation is crucial for individuals who are travelling to high altitudes for safety factors. The air is "thinner" at high altitudes, which means that there are fewer oxygen molecules per volume of air. At high altitudes, each inhalation is insufficient to meet the body's tissue needs. Although the effect is most dramatic at elevations exceeding 8,000 feet (2,438 meters) above sea level, it is discernible at 5,000 feet (1,524 meters) above sea level. One of the body's hormones, erythropoietin (EPO), induces the production of additional red blood cells to facilitate the delivery of oxygen to the body tissue in response to the decrease in oxygen [1].

2.0 PHYSIOLOGICAL AND COMPLICATION OF HYPOXIA AT HIGH ALTITUDE

Training at elevated altitudes may induce dips in ambient humidity and temperature. Additionally, a decrease in the partial pressure of oxygen at each location along the oxygen transport cascade from ambient air to cellular mitochondria can cause a decrease in barometric pressure due to these environmental characteristics. In many cases, these physiological responses assist the individual in adapting and tolerating the low oxygen conditions in response to hypobaric hypoxia [2].

Some of the highest-level athletes and pilots have undertaken routine training at high altitudes to enhance their performance. Pilots undergo substantial decompression during training at high altitudes in military aircraft; a cabin altitude of 9000 m (30 000 ft) is equivalent to approximately 0.3 ATA. However, three-quarters of pilots encounter issues during their careers, and nearly 40% of trainee pilots develop symptoms during hypobaric chamber testing at normal cabin altitudes. These pilots may have an elevated risk of hypoperfusion (low partial pressure of oxygen), which can lead to hypoxia. This condition can be

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identified by inducing biomarkers such as HIF-1α and endothelin-1 (intermittent hypoxia-induced endothelin-dependent hypertension) [3]. Following an ascent to a specific elevation, these diseases may manifest at any point within a range of several hours to five days. Their severity can vary from mild, with negligible impact on the intended travel itinerary, to life-threatening illness.

3.0 BIOMARKER CORRELATED WITH HYPOXIA IN HIGH ALTITUDE

Formenti *et al*. (2010) investigated the impact of altitude training on a group of individuals who were equally fit and did not have Chuvash polycythemia (CP), an uncommon genetic disorder [4]. The body's response to high altitudes in individuals without the disorder commences with a protein known as hypoxia-inducible factor (HIF), which initiates a sequence of physiological changes [5]. However, the level of HIF in individuals with the disorder remains elevated even when they are at sea level. The metabolic effects of perpetually being in the "high-altitude" state were the subject of the researchers' investigation under this condition. Researchers requested that volunteers maintain a consistent pedaling pace while gradually increasing the resistance on a bicycle. The results indicated that individuals with CP were required to terminate the test prematurely and obtained a work rate that was 70% of those without CP. The metabolism of CP patients is distinct, resulting in diminished physical performance and endurance. Five patients exhibited positive findings, and the differences observed in those with Chuvash polycythemia were substantial. The researchers concluded that individuals with CP performed worse than those without CP, restricting the benefits of training at high altitudes, which also elevates HIF levels in the body.

Conversely, hypoxia induces a variety of metabolic, cellular, and systemic responses that are essential for tissues to adjust to low oxygen levels. The coordination of oxygen supply and cellular metabolism is significantly influenced by hypoxia-inducible factor 1 (HIF-1) [6]. Systemic and intracellular alterations collaborate to mitigate hypoxic injury and restore sufficient oxygenation in humans when they are subjected to hypoxia. The emerging function of HIF in systemic physiology, which is described in this context in terms of the response to high altitude, is applicable to any clinical scenario in which hypoxia is present [7]. HIF-1 is the primary regulator of erythropoietin (EPO), which increases the concentration of oxygen, O_2 in the tissues to mitigate the effects of hypoxia. The activation of HIF-1α is reflected in the reduction of O_2 dependent hydroxylation of HIF-1α in hypoxic conditions. The expression of HIF-1α was observed in the high-altitude groups, but it was rarely observed in the plain group, according to research conducted by Zhang *et al*. (2015) [8]. Additionally, they discovered that the expression level of HIF-1α was positively correlated with tissue injury and altitude increase.

4.0 THE USEFUL OF HYPERBARIC OXYGEN THERAPY (HBOT)

In high altitudes, hypoxia complications may result from a prolonged oxygen deficit. A previous study discovered that a novel treatment of hyperbaric medicine can modify the concentration of oxygen in the plasma, thereby enabling hemoglobin to reach its maximal oxygen-carrying capacity. Hyperbaric medicine is a treatment that involves the use of oxygen at an ambient pressure that is higher than atmospheric pressure, known as hyperbaric oxygen therapy (HBOT). The hyperbaric oxygen therapy chamber elevates the air pressure to three times the normal air pressure, which results in a 100% oxygen delivery or an increase in the blood's oxygen transport capacity [9]. This also aids in the prevention of bacterial infections and the stimulation of the release of growth factors, which facilitate the healing process. However, HBOT substantially enhances plasma oxygen transport due to the increased solubility of oxygen as pressure increases [10].

5.0 THE PROCEDURE USED IN HBOT

Hyperbaric oxygen therapy (HBOT) generally involves the use of 100% oxygen in a localised artificially elevated pressure environment, typically within the 1–3 atm range [11]. These modifications may become irreversible within 25–35 treatments [12]. The elevated partial pressure of oxygen in the HBOT environment at 3 atm leads to an increase in the quantity of dissolved oxygen in the plasma. At 3 atm, the pressure is equivalent to 2,280 mmHg, as one atmosphere is equivalent to 760 mmHg. With 100% oxygen, the partial pressure of oxygen in the trachea is 2,233 mmHg at a pressure of 2,280 mmHg. Note that this closely resembles the oxygen demand in the tissue at rest. Hemoglobin functions as an oxygen reservoir, and the dissolved concentration in the plasma is analogous to a river that transports oxygen from the reservoir. HBOT provides a method to substantially increase the size and flow of the oxygen

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river, thereby improving its delivery to stressed tissues. In theory, HBOT administration may be advantageous in terms of the calculated oxygen delivery values.

6.0 COMPLICATION OF HBOT

Seizures (central nervous system [CNS] toxicity) or pulmonary toxicity (oxygen toxicity) typically indicate the complication and risk of HBOT. HBOT is associated with hazards that are comparable to certain diving disorders [13]. The lens can become swollen, resulting in temporarily impaired vision (myopia). This condition typically resolves within two to four weeks. Breathing high-pressure oxygen may result in oxygen toxicity. Additionally, changes in pressure can result in a "squeeze" or barotrauma in the adjacent tissues, which can result in trapped air within the body. This can lead to collapse of the lungs and high air pressure in the ear, potentially causing middle ear injuries such as eardrum rupture and fluid leakage. The high pressure (decompression) on the central nervous system (CNS) can detrimentally affect the spinal cord's function, leading to paralysis, sensory dysfunction, or even death [14].

7.0 CONCLUSION

This biomarker and hyperbaric medicine are noteworthy as diagnostic and therapeutic tools for the prevention of chronic hypoxia-related diseases in high-altitude environments. HBOT offers the potential for novel treatments and necessitates additional research to precisely determine the dosing and indication for the treatment of hypoxia disease. It is anticipated that this biomarker will be capable of identifying the likelihood of hypoxia in the future and preventing the complication that could result in a poor prognosis. This complication includes infarction (blockage of blood supply and tissue death) in the central nervous system (CNS) and damage to spinal cord function, which can lead to paralysis, sensory dysfunction, or death. Consequently, the utilisation of hyperbaric medicine is a cutting-edge treatment that has the potential to prevent and combat the mortality and disability of pilots and athletes who train at high altitudes, as well as the detection of hypoxia biomarkers.

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List of Reference

[1] Brown, J. P., & Grocott, M. P. (2013). Humans at altitude: physiology and pathophysiology. *Continuing Education in Anaesthesia, Critical Care & Pain, 13*(1), 17-22.

[2] Semenza, G. L. (2011). Oxygen sensing, homeostasis, and disease. *New England Journal of Medicine, 365*(6), 537-547.

[3] Zhang, X., & Le, W. (2010). Pathological role of hypoxia in Alzheimer's disease. *Experimental neurology, 223*(2), 299-303.

[4] Formenti, F., Constantin-Teodosiu, D., Emmanuel, Y., Cheeseman, J., Dorrington, K. L., Edwards, L. M., ... & Robbins, P. A. (2010). Regulation of human metabolism by hypoxia-inducible factor. *Proceedings of the National Academy of Sciences, 107*(28), 12722-12727.

[5] Mole, D. R., Blancher, C., Copley, R. R., Pollard, P. J., Gleadle, J. M., Ragoussis, J., & Ratcliffe, P. J. (2009). Genome-wide association of hypoxia-inducible factor (HIF)-1α and HIF-2α DNA binding with expression profiling of hypoxia-inducible transcripts. *Journal of biological chemistry, 284*(25), 16767-16775.

[6] Vadlapatla, R., Dutt Vadlapudi, A., & Mitra, A. K. (2013). Hypoxia-inducible factor-1 (HIF-1): a potential target for intervention in ocular neovascular diseases. *Current drug targets, 14*(8), 919-935.

[7] Marhold, M., Tomasich, E., El-Gazzar, A., Heller, G., Spittler, A., Horvat, R., ... & Horak, P. (2015). HIF1α regulates mTOR signaling and viability of prostate cancer stem cells. *Molecular Cancer Research, 13*(3), 556-564.

[8] Zhang, F., Wu, W., Deng, Z., Zheng, X., Zhang, J., Deng, S., ... & Wang, X. (2015). High altitude increases the expression of hypoxia-inducible factor 1α and inducible nitric oxide synthase with intest-inal mucosal barrier failure in rats. *International journal of clinical and experimental pathology, 8*(5), 5189.

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[9] Papadopoulou, V., Eckersley, R. J., Balestra, C., Karapantsios, T. D., & Tang, M. X. (2013). A critical review of physiological bubble formation in hyperbaric decompression. *Advances in colloid and interface science, 191,* 22-30.

[10] Thom, S. R., Bhopale, V. M., Velazquez, O. C., Goldstein, L. J., Thom, L. H., & Buerk, D. G. (2006). Stem cell mobilization by hyperbaric oxygen. *American Journal of Physiology-Heart and Circulatory Physiology.*

[11] Harch, P. G., & McCullough, V. (2010). The Oxygen Revolution: Hyperbaric Oxygen Therapy: The New Treatment for Post Traumatic Stress Disorder (PTSD), Traumatic Brain Injury, Stroke, Autism and More. Hatherleigh Press.

[12] Pasparakis, M. (2008). IKK/NF-κB signaling in intestinal epithelial cells controls immune homeostasis in the gut. *Mucosal immunology, 1*(1), S54-S57.

[13] Shapira, R., Solomon, B., Efrati, S., Frenkel, D., & Ashery, U. (2018). Hyperbaric oxygen therapy ameliorates pathophysiology of 3xTg-AD mouse model by attenuating neuroinflammation. *Neurobiology of aging, 62*, 105-119.

[14] Singhal, A. B., & Lo, E. H. (2008). Advances in emerging nondrug therapies for acute stroke 2007. *Stroke, 39*(2), 289-291.

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