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

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#### ABSTRACT

*Training at high altitude for prolonged periods can cause low oxygen tension which can developed complication of hypoxia. Hypoxia is a cascade activity from a level of down regulation and function of cell's nucleus. Early detection of biomarker and physiological changes are important in prevent the hypoxia at high altitude. Hyperbaric medicine is a new treatment that were used an oxygen therapy to treat hypoxic and inflammatory driven conditions which patients are treated with 100% oxygen at pressure greater than atmospheric pressure. The review discusses physiological changes associated with hypoxia, the response of biomarker hypoxia changes in high altitude and the role of hyperbaric oxygen therapy can play as part of the treatment for pilots and athletes training at high altitudes that suffering from disease with underlying hypoxia.*

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#### Background

Training at high altitude has been gaining popularity in recent decades. High altitude training ranges from pilot and athletes has potential significant health consequences. Not only the altitude and environmental factors a concern for the pilot and athlete's safety, but access is often a barrier to appropriate medical care. For safety reasons, proper acclimatization is important for those traveling to high altitudes. The air is "thinner" at high altitudes meaning there are fewer oxygen molecules per volume of air. Every breath taken at a high altitude delivers less of what tissue body require. While the effect is most dramatic at altitudes greater than 8,000 feet (2,438 meters) above sea level, it is noticeable even at 5,000 feet (1,524 meters) above sea level. To compensate for the decrease in oxygen, one of the body's hormones, erythropoietin (EPO), triggers the production of more red blood cells to aid in oxygen delivery to the tissue body (Brown et al., 2013).

## **Physiological and Complication of Hypoxia at High Altitude**

By training at high altitudes, can cause decreases in temperature and ambient humidity. These defining environmental feature also can cause decrease in barometric pressure, which causes by a decrease in the partial pressure of oxygen at every point along the oxygen transport cascade from ambient air to cellular mitochondria. This hypobaric hypoxia triggers a series of physiological responses, which, in most cases, help the individual tolerate and adapt to the low oxygen conditions (Semenza et al., 2011).

Training at high altitude has been a routine part of preparation for some of the high level to improves pilot and athlete's performance. Training at high altitude in military aircraft exposes pilots to significant degrees of decompression; a cabin altitude of 9000 m (30 000 ft) is equivalent to approximately 0.3 ATA. However, during their careers, three-quarters of pilots experience problems, and almost 40% of trainee pilots develop symptoms during hypobaric chamber testing to normal cabin altitudes. These Pilots may be at higher risk for developing hypoperfusion (low partial pressure of oxygen) that can lead to hypoxia which can be detected by inducing biomarker such as HIF-1 $\alpha$  and endothelin-1(intermittent hypoxia induced endothelin-dependent hypertension) (Zhang et al., 2010). These diseases can develop at any time from several hours to 5 days following ascent to a given elevation and can range in severity from mild with minimal effect on the planned travel itinerary to life-threatening illness.

## **Biomarker Correlated with Hypoxia in High Altitude**

Formenti et al., (2010) studied the effects of altitude training in patients with a rare genetic disorder, called Chuvash polycythemia or CP, and a group of equally fit people without CP. In people without the disorder, the body's reaction to high altitudes starts with a protein called hypoxia-inducible factor (HIF), which triggers a series of physiological changes (Mole et al.,2009). But in those with the disorder, a person's level of HIF remains elevated even when they are at sea level. This condition offered the researchers an opportunity to study the metabolic effects of permanently being in the "high-altitude" state. The researchers asked volunteers to pedal a bike at a constant rate while the resistance was slowly increased. The results showed those with CP had to quit the test early and achieved a work rate that was 70 percent that of those without CP. The metabolism of CP patients is different and leads to poorer physical performance and endurance. The differences seen in those with Chuvash polycythemia were large, and five patients were showed positive finding. Because the people with CP did more poorly than those without it, the researchers concluded that there are limits to the benefits of training at high altitudes, which also increases levels of HIF in the body.

On the other hand, hypoxia triggers various systemic, cellular, and metabolic responses necessary for tissues to adapt to low oxygen conditions. Hypoxia-inducible factor 1 (HIF-1) plays as an important role in the coordination of oxygen supply and cellular metabolism (Vadlapatla et al., 2013). When humans are exposed to hypoxia, systemic and intracellular changes operate together to minimize hypoxic injury and restore adequate oxygenation. The emerging role of HIF in systemic physiology, described here in terms of the response to high altitude, in fact translates to any clinical scenario in which hypoxia is a feature. (Marhold et al., 2015). The HIF-1 is the key regulator in the formation of erythropoietin (EPO), which elevates tissue O<sub>2</sub> concentration to counteract the injury of hypoxia. Under hypoxic conditions, O<sub>2</sub>-dependent hydroxylation of HIF-1 $\alpha$  is decreased which means the activation of HIF-1 $\alpha$ . Studies by Fangxin et al., (2015) found that the expression of HIF-1 $\alpha$  was seen in the high altitude groups, but rarely in plain group. They also found that the expression level of HIF-1 $\alpha$  was positively correlated with altitude increasing and tissue injuring.

## **The Useful of Hyperbaric Oxygen Therapy (HBOT)**

The deficit of oxygen for long period can causes complication of hypoxia in high altitude. Previous study found that new treatment of hyperbaric medicine can alters the concentration of oxygen in the plasma and assists hemoglobin to achieve full oxygen-carrying capacity. Hyperbaric medicine is a treatment comprises hyperbaric oxygen therapy (HBOT) which used oxygen at an ambient pressure higher than atmospheric pressure. In a hyperbaric oxygen therapy chamber, the air pressure is increased to three times higher than normal air pressure that means of delivering 100% of oxygen or increase in the oxygen transport capacity

of the blood. (Papadopoulou et al.,2013). This also help in fight bacteria and stimulate the release of substance called growth factors which promote for healing processes. Oxygen transport by plasma, however, is significantly increased using HBOT because of the higher solubility of oxygen as pressure increases (Thom et al., 2006).

### **The Procedure Used in HBOT**

The hyperbaric oxygen therapy (HBOT) uses 100% oxygen in a setting of local artificially elevated pressures generally in the range of 1–3 atm (Harch et al., 2010). These changes can become permanent within 25–35 treatments (Pasparakis et al., 2008). In the setting of HBOT at 3 atm of pressure, the amount of oxygen dissolved in the plasma is increased due to the increased partial pressure of oxygen. One atmosphere is equivalent to 760 mmHg; therefore, at 3 atm, the pressure is equivalent to 2,280 mmHg. At a pressure of 2,280 mmHg with 100% oxygen, the partial pressure of oxygen in the trachea is 2,233 mmHg. Of note, this is very close to the tissue oxygen demand at rest. Hemoglobin serves as a reservoir of oxygen, and the dissolved concentration in the plasma represents the river delivering the oxygen from the reservoir. HBOT offers a method to significantly enhance the size and flow of the oxygen river, thereby improving its delivery to stressed tissues. HBOT administration can thus be theoretically advantageous in regard to the calculated values of oxygen delivery.

### **Complication of HBOT**

The complication and risk of HBOT reported by complication of oxygen toxicity usually presenting as seizure attacks (central nervous system [CNS] toxicity) or pulmonary toxicity. These risks associated with HBOT, similar to some diving disorders (Ronit et al., 2018). Temporarily blurred vision (myopia) can be caused by swelling of the lens, which usually resolves in two to four weeks. Breathing high-pressure oxygen may cause oxygen toxicity. Besides that, changes of the pressure also can cause a 'squeeze' or barotrauma in the tissues surrounding which will have trapped air inside the body, such as the lungs collapse and also increased air pressure in ear that can cause middle ear injuries, including leaking fluid and eardrum rupture. While the high pressure (decompression) on central nervous system (CNS) can cause damage to spinal cord function leading to paralysis and sensory dysfunction or death. (Singhal et al., 2007).

### **Summary**

This both biomarker and hyperbaric medicine are important as diagnostic and treatment to prevent chronic disease of hypoxia in high altitude. HBOT give a possibility to a new treatments and require more research to determine exactly the dosing and indication for treating hypoxia disease.

### **Conclusion**

This biomarker is expected to be able detect the risk of developing hypoxia in the future and prevent the complication that could lead to poor prognosis which involved infarction (blockage of blood supply and tissue death) on central nervous system (CNS) and damaged to spinal cord function leading to paralysis and sensory dysfunction or death. Therefore, the use of hyperbaric medicine is an advance treatment to promote its potential in prevent and fight the death and disability on the pilots and athletes training at high altitudes along with detected of hypoxia biomarker.

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