



THE IMPORTANCE OF HYPOXIA INDUCIBLE FACTOR (HIF-1) IN DETECTING HYPOXIA AT HIGH ALTITUDE: A REVIEW

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ABSTRACT

The conventional definition of hypobaric hypoxia (HH) is that arterial blood O₂ saturation (SaO₂) in the body measurably begins to fall at altitudes >2500 m. It is one of the hypoxemic types, which is due to a decrease in the amount of breathable oxygen caused by the low atmospheric pressure of high altitudes, and in turn low maximal oxygen uptake (VO₂ max), and the arterial partial pressure of O₂ (PaO₂) in the body. The higher the elevation attained and the longer the duration of space flight, the greater the drop in PO₂ in the human body. These declines in oxygen tensions trigger a variety of physiologic responses in the cardiovascular system after the initial altitude hypoxia exposure that enable the individual to adapt to or compensate for the hypoxic environment. However, air crashes due to hypoxia while handling aircrafts and several detrimental health effects are the risk associated with high altitude exposures. Hence, a convenient biomarker that could detect hypoxia at high altitude could be lifesaving. This review highlights the usefulness of salivary HIF-1 α (hypoxia-inducible factor 1 alpha) as a biomarker that could help detect high altitude hypoxia rapidly.

1.0 INTRODUCTION

Aircrews exposed to high altitude with longer durations are at a higher potential risk for detrimental long term health consequences such as cardiovascular, respiratory and cognitive impairment [3]. The altitude and other environmental features are of concern for aircraft safety [1]. For safety reasons, proper acclimatization is important for those traveling to high altitudes. While the effect is most dramatic at altitudes greater than 8000 feet (2438 meters) above sea level, it becomes noticeable even at 5000 feet (1524 meters) above sea level. Among other important changes (e.g., decreases in temperature and ambient humidity), the defining environmental feature at high altitude is a drop in barometric pressure, which causes a decrease in the partial pressure of oxygen at every point along the oxygen transport cascade from ambient air to cellular mitochondria. Subsequently, there is also a decrease in the PO₂ at every point along the oxygen transport cascade from inspired air to the alveolar space, arterial blood, tissues, and venous blood. The higher the elevation attained and the longer the duration of spaceflight, the greater the drop in PO₂ in the human body [2].

Retrospective studies conducted after the Second World War give an account of a significant number of unexplained military aircraft accidents that were suspected to be due to hypoxia. Detection of possible hypoxia exposures during postmortem investigation of aircraft accidents has implications for determining flight safety [5]. A study conducted by Tripathi et al. from 1986 to 1995 in Army Aviation helicopters flying

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high-altitude sorties revealed 29 accidents, and hypoxia was a contributing factor in 24% of those cases. Pilot incapacitation attributable to hypoxia has been confirmed as the cause of the crash of IAF MiG at Sirsi, Karnataka, on April 11, 2002.

Following exposure to long duration of space flight, the drop in PO₂ in the human body is inevitable. This triggers a variety of physiologic responses in the cardiovascular system over a period of minutes to weeks after the initial altitude hypoxia exposure that enable the individual to adapt to or compensate for the hypoxic environment. Indeed, short-term altitude exposure can directly or indirectly affect the vascular tone of systemic resistance vessels and enhances ventilation and sympathetic activity through the activation of peripheral chemoreceptors. Studies have proved the cardioprotective effects of high-altitude exposure [8]. However, for those with existing cardiovascular diseases such as arrhythmias and coronary artery diseases, the risk of an acute cardiac event is high with exposure to low oxygen tension [9]. The altitude features are of concern for aircraft safety. Accidents due to hypoxia are rare, but hypoxia incidents are common. When fatal accidents occur, hypoxia may not be recognized as a primary cause among the multitude of other potential causes. One factor that makes hypoxia dangerous is its insidious onset, is the signs and symptoms that may develop gradually and well established before it can be recognize. Recent study found that HIF-1 is sensitive to high altitude and currently important hypoxia marker [5].

2.0 METHODOLOGY

Ascent to high altitude is associated with physiological responses that counter the stress of hypobaric hypoxia by increasing oxygen delivery and altering tissue oxygen utilization via metabolic modulation. At the cellular level, the transcriptional response to hypoxia is mediated by the hypoxia-inducible factor (HIF) pathway and results in promotion of glycolytic capacity and suppression of oxidative metabolism [3]. Hypoxia inducible factor-1 (HIF-1) plays a key role in oxygen homeostasis by facilitating oxygen supply to the tissues under hypoxic conditions, as during acclimatization to hypobaric hypoxia or in the hypoxemia or inflammation molecular response. HIF-1 is found in almost all body tissues. Under normoxic conditions, it is degraded through hydroxylation, but it does not undergo degradation in the presence of hypoxia [4].

Hypoxia inducible factor-1 is found in almost all body tissues. Under normoxic conditions it is degraded through hydroxylation but does not undergo degradation in the presence of hypoxia. Therefore, HIF-1 is a key transcription factor in the adaptive responses to low oxygen. Formenti's (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 (as control). 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. But in those with the disorder, a person's level of HIF protein remains elevated even when they are at sea level. This condition offered the researchers an opportunity to study the metabolic effects of most prolonged in the "high-altitude" state. 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 with 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, could be due to increased levels of HIF in the body.

This deserving condition provides an opportunity to study the metabolic effects of expose to high altitude. Recent study by Tomomasa et al. (2022) on effect of HIF-1 α in salivary gland development using *ex vivo* SMG, show that HIF-1 α was not expressed under normoxic (20% O₂) conditions but was expressed under hypoxic (5% O₂) conditions. Therefore, they hypothesized that HIF-1 α contribute to salivary gland development under hypoxic conditions. This result also supports the hypothesis of their study that the presence of HIF-1 α is necessary for salivary gland development under hypoxic conditions. The study also prove that the HIF-mediated ERK1/2 pathway is involved in salivary gland development. Saliva is a clinically informative, biological fluid (biofluid) that is useful for novel approaches to prognosis, laboratory or clinical diagnosis, and monitoring. It is easily collected and stored and ideal for early detection of disease as it contains specific soluble biological markers (biomarkers) [6]. Saliva contains multiple biomarkers which make it useful for multiplexed assays that are being developed as point-of-care (POC) devices, rapid tests, or in more standardized formats for centralized clinical laboratory operations. Salivary

diagnostics is a dynamic field that is being incorporated as part of disease diagnosis and clinical monitoring. This is especially true since most of the biomarkers present in blood and urine can also be detected in a sample of saliva.

3.0 DISCUSSION

Hence, detection of hypoxia often relies on strategies for the detection of HIF protein expression. There are several techniques to detect hypoxia by targeting HIF protein, including western blot, immunoassay (ELISA, Luminex), immunochemistry (IHC), and flow cytometry. These techniques require specialized equipment and complex data analysis. It also takes time to get the results. Due to the importance of early detection of hypoxia to avoid acute symptoms and the limitation of detection by using the current techniques, we developed lateral-flow assays (LFAs) to early detect hypoxia via targeting HIF protein. LFAs are quick, simple, and cheap assays to analyse various samples at the point of care or in the field, making them one of the most widespread biosensors currently available. Lateral-flow assays (LFAs) have become one of the most widely used point-of-care (PoC) sensors in a variety of disciplines ranging from diagnostics to environmental and safety analysis due to their ease of use and low cost. Their success lies in their general design, which has remained almost unchanged since their first use as pregnancy tests in the 1970s. Although all LFAs simply rely on capillary forces to move the sample along a test strip to generate a measurable signal, their fabrication is far from straightforward.

Practicality and future perspectives of HIF-1 salivary PoC testing. From a user perspective, the operation of a well-designed LFA is strikingly simple: the assay is executed by adding the sample onto the lateral-flow strip (LF strip), and after a short incubation time, the positive or negative outcome of the test is revealed by the appearance of a line. As salivary HIF-1 sample detection is non-invasive, the practicality of this PoC for on-site use is highly convenient. Therefore, in the future, this method is hoped to serve as a readily available lifesaving PoC for aircraft pilots both in the military and civil settings.

4.0 CONCLUSION

The HIF-1 α expression would potentially be used as a diagnostic tool in detecting physiological change's effects at high altitude. The exploitation of this biomarker detection would potentially be used as early and alarming sign of hypoxia as precaution and early prevention to the pilot.

5.0 CONFLICT OF INTEREST

The authors declare no conflict of interest.

6.0 AUTHORS' CONTRIBUTION

Shaharuddin, S. (Methodology; Validation; Formal analysis; Investigation; Writing -original draft)

Miskan, M. (Formal analysis; Investigation)

Abu Hassan, H. (Supervision; Project administration)

Ab. Rahim, S. N. (Conceptualisation)

Mohd S. (Review & editing)

Hashim, R. (Review & editing)

Mohammad, Z.; (Methodology)

Nordin, M. K. N. (Methodology)

Zainal N. S. (Methodology)

Hashim F. R. (Conceptualisation)

Abdul Razak, H. R. (Formal analysis; Investigation)

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