

COVID-19 and High altitude-induced hypoxic conditions and its management: A perspective for managing through Yoga

**Sheetal J Gupta^(1,2), Rahul Tyagi^{(3)*}, Balaram Pradhan^{(2)*}, Disha Bhanushali⁽⁴⁾, Limaye Nitin
Rishi Nityapragya⁽⁴⁾, Deepali Mathur⁽⁵⁾, Rohin Vinayak⁽⁶⁾, Priya Battu⁽¹⁾, Kanupriya Sharma⁽¹⁾,
Akshay Anand⁽¹⁾**

¹ Neuroscience Research Lab, Department of Neurology, Postgraduate Institute of Medical Education and
Research, Chandigarh, India

² SVYASA, Bangaluru, India

³ Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India

⁴ Sri Sri Institute of Advanced Research (SSIAR), Bangaluru, India

⁵ Department of Biotechnology, KIIT University, Bhubaneswar, Odisha

⁶ Government Multi-Speciality Hospital, Sector 16, Chandigarh

*Correspondence to:

Dr. Balaram Pradhan

Deputy Registrar of Academics

Swami Vivekananda Yoga Anushandhan Samsthan University(SVYASA)

19, Eknath Bhavan, Gavipuram Circle, Kempegowda Nagar,

Bangalore - 560 019

Email ID: balaram.pradhan@svyasa.edu.in

Mob: (91)9483711185

*Co-Correspondence to

Dr. Rahul Tyagi, Ph.D

Post graduate Institute of Medical education and Research, Chandigarh

India- 160012

Email ID: rahul15tyagi@gmail.com

Mobile No: +91 99142 08886

Abstract

COVID-19, is caused by a virus called SARS-CoV-2 which was initially found in China in the city of Wuhan in 2020, WHO declared COVID-19 as a pandemic. Latest reports suggest that residing at high altitude may attenuate the infection and death. At high altitudes, the oxygen concentration available to the human body is low, hence people living there are chronically exposed to hypoxic conditions. Hypoxia is the condition where there is an inadequate supply of oxygen to the human body resulting in various symptoms including breathlessness, fatigue, and respiratory distress similar to COVID-19. Hypoxic pre conditioning (HPC) has been proposed to be non-invasive preventive measure against SARS-CoV-2 infection. This review article focuses on analysing coronavirus epidemiology at various heights under high altitude in order to demonstrate that its residents are less susceptible to developing COVID-19 related respiratory complications. A natural way of inducing intermittent hypoxia is Pranayama (Yogic breathing technique) which involves controlled breathing techniques. Yoga and breathing practices are known to enhance angiogenesis, reduces inflammation,

enhance tissue repair and cell survival through its intermittent hypoxia mechanism. Yoga breathing can be an alternative therapy technique for COVID-19.

Keywords: Hypoxia, High altitude, Yoga, SARS-CoV-2, COVID-19

1. Introduction:

Humans have physiological alterations and difficulties with the rarefied air at high altitude that has drastic effects on the human body. (Hackett & Roach, 2001). High altitude-related medical conditions were reportedly first observed more than 2000 years ago by Too-Kin where he talked about “Great and Little headache” on a mountain journey along the silk road (Paralikir & Paralikir, 2010; Rennie, 1986). Researchers have tried to broadly classify the altitudes as high altitude between 2500-3500m, very high altitude is between 3500-5800 m, and extremely high altitude is 5800m and above (Davis, Pattinson, Mason, Richards, & Hillebrandt, 2005). It has been found that exposure to altitude above 6000ft.(2500m) can result in disorientation and loss of awareness within a few minutes. Oxygen saturation maintained by the lungs vary at different altitudes. At high altitude, the SaO₂ falls below 90% and arterial oxygen pressure (PO₂) decreases below 60 mmHg resulting in hypoxemia. At extremely high altitudes, altitude illness characterized by marked hypoxemia and alkalosis is very common (Paralikir & Paralikir, 2010). Various types of high altitude illnesses have also been identified: High Altitude Pulmonary Edema (HAPE) and High Altitude Cerebral Edema (HACE) are diseases caused at high altitude, which can be dangerous to the life of a human being. On the other hand, Acute Mountain Sickness (AMS), a common condition which is usually found during rapid ascent to altitude in non-acclimatized people is relatively less dangerous (Rodway, Hoffman, & Sanders). Hypoxemia is unusual low levels of oxygen in the blood whereas hypoxia is lack of oxygenation at the tissue/organ level. Hypoxia or hypoxemia are threatening conditions leading to damage of multiorgan systems including brain, lungs, and heart. Drastically reduced oxygen saturation and silent hypoxia have also been observed as a crucial features in COVID-19 and dyspnea resulting in symptoms related to acute respiratory distress syndrome (ARDS).

1.1 Acute mountain sickness:

It occurs due to rapid ascent without proper acclimatization. It can result in symptoms such as headache, vomiting, dizziness, anorexia, and insomnia. Vitals such as Blood pressure (BP) and heart rate (HR) are usually stable at the time of acclimatization and pulse oximetry has limited diagnostic value for this situation. The headache is usually worse at night and on awakening (Roach & Hackett, 2001; Rodway et al.). This condition can be prevented by a slow ascent to allow acclimatization (becoming accustomed to a new climate or new conditions).

1.2 High altitude pulmonary edema (HAPE):

It generally occurs two to three days after exposure to high altitude. It is characterized by non-productive cough and shortness of breath. Tachycardia (medical terminology for heart rate above 100 beats per) and tachypnea (medical terminology for fast breathing) are common in such conditions (Schoene, 2008). These symptoms characterize challenges pertaining to acclimatization. It can be assumed that there are a lot of similarities in patients with COVID-19 pneumonia and high altitude disease as far as clinical features are concerned (Solaimanzadeh, 2020). Pulmonary edema at high altitude occurs when the blood vessels of the lungs constrict to more than the normal extent and the

covid-19 and high altitude-induced hypoxic conditions and its management: a perspective for managing through yoga

pressure of arteries and capillaries increase abnormally (Maggiolini et al., 2001). This results in a non-inflammatory and hemorrhagic alveolar-capillary leakage which may produce a secondary inflammatory response at later stages of the disease (Swenson et al., 2002) (Luks et al., 2020). Moreover, the the therapeutic strategies for symptomatic relief in both diseases should be different in view of infectious pathophysiology and immunological involvements. However, the preventive measure for both diseases could be similar.

1.3 High altitude cerebral edema (HACE):

HACE is a severe and potentially fatal condition which manifest in the late or end stage of acute mountain sickness. . In this condition, the brain swells due to fluid with occurrence of ataxia, confusion, drowsiness and altered mental status.

Earlier studies have proven that when the two population one from high altitude and one lowlander with a similar background in terms of age, height, weight, sex; high altitude population show huge chest circumferences (CC), total lung capacity (TLC), vital capacity (VC), residual volume (RV). They also show sizeable peak termination flow rates, forced expiratory volume in 1s (FEV1), forced vital capacity (FVC), and FEV1-to-FVC ratio as compared to the lowlanders. Generation belonging to high altitudes may have modifications in respiratory mechanics to grant for increased respiratory volumes (Droma et al., 1991; Havryk, Gilbert, & Burgess, 2002; Kapoor & Kapoor, 2005; Sun et al., 1990; Wood, Norboo, Lilly, Yoneda, & Eldridge, 2003). D-dimer and low-density lipoprotein (LDL) also show an increasing trend after hypoxia conditions (Griffin et al., 2020; Rydberg et al., 2004; von Känel, Loreda, Powell, Adler, & Dimsdale, 2005).

2. COVID-19 and its Pathophysiology

Calamities, manmade or natural, tests the human resilience to the ultimate, COVID-19 epidemic of 2020 is no different (Solaimanzadeh, 2020). COVID 19 has spread all over the world rapidly. COVID-19 with its high transmission rate, high morbidity, and mortality had an adverse impact on the global economy already burdened with health care systems. Owing to its drastic outcomes and yet-to-be-discovered complications, it was associated with the fear of the unknown. Front-line health care workers were the most unprotected to the psycho-emotional burnt-out with the response efforts made for COVID-19 (Vinayak, 2020). Capture of the virus into endothelial cells and lung cells of the cardiovascular system results in inflammatory exchange which include edema and dangerous degeneration. Changes in these are mediated by cytokines like interleukin-6 and 10, and tumor necrosis factors which are responsible for injury to the lung cells. Apart from the respiratory system, other systems can be involved resulting in damage to myocardial cells, intestinal epithelium, and intrinsic vascular injury. Hypoxemia leads to the generation of free oxygen species, change in intracellular pH, and aggregation of lactic acid which additionally exacerbated the cellular injury (Chiappelli, Khakshooy, & Greenberg, 2020). Downregulation of ACE2 (angiotensin-converting enzyme 2) in high altitude residents, might be the cause of less susceptibility to coronavirus, and understanding its location sites and functions is mandatory to get the detailed information regarding coronavirus pathophysiology (Zubieta-Calleja, Zubieta-DeUrioste, Venkatesh, Das, & Soliz, 2020).

COVID19 at high altitude

Interestingly, reports began to emerge suggesting that the inhabitants of high altitude regions are comparatively less prone to developing respiratory and hypoxic symptoms of COVID-19 (Arias-Reyes et al., 2020). It was noted that elongated manifestation to high land, activates a chemical reaction in the lungs involving a protein known as ACE2 that may intercept lung function, an issue which is very usual in coronavirus infected people. (Swenson et al., 2002). People living at high altitudes are constantly exposed to conditions similar to the COVID-19 induced hypoxia. Such exposure can make them physiologically acclimatized to the low oxygen environment, hence making them more resilient to the hypoxic manifestation of COVID-19 (Luks et al., 2020). This review paper highlights recently reported epidemiological information on hypoxia and COVID-19 and proposes its implications in disease management.

The disease originated in Hubei Province, Wuhan, China, and the first case was observed in Wuhan in December 2019. Later, more than 200 countries got affected, world health organization (WHO) declared COVID-19 as a pandemic on 30 January 2020. (Q. Li et al., 2020; Yuki, Fujiogi, & Koutsogiannaki, 2020; J. Zhang et al., 2020; Zheng et al., 2020). One-to-one transmission plays the most important role in the spread of a pandemic. Similarly, Covid-19 spreads from one human to the other mainly through pulmonary droplets and aerosol. Air-borne transmission might also be a possible route of spread (Greenhalgh et al., 2021). Additionally, studies have confirmed the presence of virus in sputum, pharyngeal swabs, and feces (Chen, 2020; Q. Li et al., 2020). The incubation time for coronavirus is usually 5.2 days and symptoms are present for 11.5 to 15.5 days. Hence, a 14 day quarantine period is recommended for those exposed to the virus (Huamaní, Velásquez, Montes, & Miranda-Solis, 2020; Xi et al., 2020). Underlying conditions like diabetes, hypertension, cardiovascular diseases, and liver diseases predispose the patients to a more severe presentation of the disease, often leading to fatal complications (Arias-Reyes et al., 2020). The symptoms of COVID-19 vary from individual to individual depending upon factors like genetics, age, comorbidities, ethnic background, and geographic location. (Pollard, Morran, & Nestor-Kalinoski, 2020).

SARS-CoV-2 mainly affects the pulmonary system with very little damage to the other organ systems (X. Li & Ma, 2020). The symptoms are predominantly lowered pulmonary tract infection and its related symptoms like cough, pyrexia (fever), dyspnea (Shortness of breath), etc. These symptoms range from nominal to highly serious hypoxia associated with ARDS (Acute Respiratory Distress Syndrome) (Q. Li et al., 2020; Yuki et al., 2020). As per Wuhan reports, the time interval of the inception of expression and the growth of ARDS is short of just nine days. The earlier SARS-Cov-2 variants reported symptoms and mortality in the people with existing illness and geriatric population, as compared to the children. (Chen, 2020; J. Zhang et al., 2020; Zheng et al., 2020). However, the emerging viral strains caused harm to the adult population as well. The covid-19 related ARDS, is observed to cause damage to the pulmonary alveolar epithelium cells (X. Li & Ma, 2020). The severity of destruction caused by the COVID-19 depends on the severity of the infection. This might include demolition of respiratory epithelial cells, thrombosis, thrombophilia, and vascular discharge leading to septicemia. Events like these sometimes lead to ARDS and in some patients, pulmonary fibrosis may also occur (Pollard et al., 2020). Covid-19 can be life-threatening in some cases as it can cause lung inflammation and respiratory collapse due to cytokine storm. This makes advance detection of COVID-19 more critical (Seyed Hosseini et al., 2020). Severe cases are often managed by mechanical

covid-19 and high altitude-induced hypoxic conditions and its management: a perspective for managing through yoga

ventilation and supportive therapy (Umakanthan et al., 2020). Increase in the level of spread of pro-inflammatory markers interleukin-6 and interleukin-10 (IL-6 and IL-10) may adversely affect the outcome. SARS-CoV-2 activates the trigeminal nerve endings, which might be a possible mechanism responsible for headache occurring in this condition (Bolay, Gül, & Baykan, 2020).

The SARS-CoV-2 is equipped with spike proteins that are used to enter the host cell by binding to ACE2 receptor, which is demonstrated in a diverse of human tissues and organs [30]. ACE2 is an enzyme that catalyzes the metamorphosis of angiotensin-II to angiotensin-(1–7). There is a link between entry of SARS-CoV-2 in a cell and activation of Hypoxia-inducible factor 1 α (HIF1 α) since it is shown to suppress ACE-2 receptor. Additionally, it is responsible for the upregulation of pro-inflammatory cytokines and the process of inflammation (Serebrovska, Chong, Serebrovska, Tumanovska, & Xi, 2020).

Accumulating evidence suggests that reduction of ACE2 levels and the disruption of the equilibrium between the ACE2/angiotensin-(1–7)/MAS and RAS after COVID inflammation may damage diverse organs in COVID-19. The ability to develop a furan cleavage site of the S spike protein depends upon the intensity of infection after mutations that occur in the receptor-binding domains. The interactivity between the ACE2 and virus disturbs the anti-inflammatory activity and increases the angiotensin-II effects (Schnitzler et al., 2020). Hence, the ACE inhibitors and the angiotensin II type-I blockers during the care of the COVID-19 were suggested. However, there is no clinical proof to support this (Accinelli & Leon-Abarca, 2020; Saavedra-Camacho & Iglesias-Osores, 2020). For originate a particular drugs and vaccines SARS-CoV-2 spike protein, which binds to the ACE2, is a likely to be targeted. Rejuvenating the equilibrium in RAS and ACE2/angiotensin-(1–7)/MAS may safeguard the organs from damage. ACE2 has substantial biological activities and can prevent the RAS (renin-angiotensin system) from functioning negatively in numerous diseases (Gupta, Banerjee, & Das, 2020; Prata, Rodrigues, & Bermejo, 2020; J. Segovia-Juarez, J. M. Castagnetto, & G. F. Gonzales, 2020). ARDS is a major complication caused by excessive activation of RAS due to SARS-CoV-2 and ACE2 might have a protective effect on respiratory distress in COVID-19 (Zhang, Li, & Niu, 2020). The above studies show that there is a role of hypoxic conditioning for activation of HIF-1 α which might be implicated in a decrease in the severity of the disease and functioning of vital organs in COVID-19 (Serebrovska et al., 2020). Hence drugs that enhance the activity of ACE2 may become a promising strategy for the treatment of COVID-19 (X. Zhang et al., 2020).

3. Prevalence of COVID-19 in high vs low altitude :

Investigators had studied the distribution of the human population as per altitude and, as per estimation, within 100 meters of vertical height from the sea level around 33.5% of the total population of the world lives. The median number of persons living at 194 m above sea level. Globally, 120 towns and cities are situated 3000 m above sea level. Data analysis of actual geographical region of COVID-19 epidemic was carried out for further support to the hypothesis (Cohen & Small, 1998). Analysis was done from 70 cities with altitude ranging between 1 to 3180m, the result shows a negative correlation of altitude and COVID-19, concluding that higher altitude has lesser infection and fatality rate (Cano-Pérez et al.; Jose Segovia-Juarez, Jesús M. Castagnetto, & Gustavo F. Gonzales, 2020). Researchers combined this data with the help of a digital elevation model for the illustration and distribution of global COVID-19 cases according to altitude. In Figure 1, it has been shown that as the altitude level

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increases, the number of COVID-19 cases decrease. It shows a distinct decrease in COVID-19 cases when the affected population lives above sea level of 3000m (Cohen & Small, 1998; Hijmans, Cameron, Parra, Jones, & Jarvis, 2005; Wilkerson, Adler, Shah, & Brown, 2020; Xu et al., 2020).

However, conflicting studies have also reported the higher frequency of COVID-19 in high land regions.

4. Altitude wise prevalence of COVID-19:

Out of Peru's 32 million residents, 32 % of people living in the regions that is higher than 8000 ft. (2500) m above sea level. According to reports, there are no asthmatic patients in Peru, which reflects on the respiratory wellness of the region. The first COVID-19 patient from Peru was detected on 7th March 2020 and so far 17.3 crore patients have been confirmed by RT-PCR IgM/IgG antibodies (Imai et al., 2008). Xi et al studied the confirmed cases of COVID-19 from Qinghai-Tibet Plateau (Yu et al., 2021). Epidemiological and clinical data results of all confirmed cases in Qinghai at high altitudes have been described. It was observed that there was no local transmission and very low infection rates. 18 patients were confirmed to have SARS-CoV-2 infection. Out of these, 15 patients were a part of four transmission groups. There were only three patients remaining who were infected by personal contact with no past of travel to Wuhan. But these three patients had co-morbidities like which were liver related disease and hypertension who suffered from severe COVID-19 illness. They recovered after invasive mechanical ventilation and intensive care. All these 18 patients were finally discharged (Arias-Reyes et al., 2020). The Central South American country Bolivia. by La Paz, at an high altitude ranging bwtween 2400 to 4000m above the sea leave were analysed for the impact of COVID-19 . The first case here was reported on 10th March 2020. Slowly, the total number were 36 cases. Amongst them, eight were imported and the remaining 28 were local infections. Slowly, the count increased to 54 COVID-19 paitient in Bolivian region located at highland. The low rate of transmission of infection at Bolivia's high altitudes was remarkable and did not show the expected rapid infection rates (Accinelli & Leon-Abarca, 2020; Schnitzler et al., 2020).

Santa Cruz de la Sierra which is the biggest and main region of Bolivia and is situated in Bolivia lowlands (400 m Altitude). The data obtained from the epidemiological study of

this country was very striking when a comparison was done with data from other regions. The first local case was found on 10th March 2020, a total of 100 cases were found till 7th April.

Additional 40 cases were found which were from the different regions of Santa Cruz. Hence, a total of 140 confirmed cases were detected. Hence, it was concluded, that the infection rate of COVID-19 at high altitude region in Bolivia is approximately threefold lesser than in the

Lowlands (Accinelli & Leon-Abarca, 2020; Saavedra-Camacho & Iglesias-Osores, 2020; Schnitzler et al., 2020).

Research on the importance of geographical elements to the COVID-19 outburst in India has been described as comparable to higher altitude, with people staying at lower altitudes has more susceptible to coronavirus infection (Gupta, Banerjee, and Das, 2020) (Saavedra-Camacho & Iglesias-Osores, 2020).

covid-19 and high altitude-induced hypoxic conditions and its management: a perspective for managing through yoga

An interesting correlation between higher temperatures and reduction in COVID-19 cases has also been reported. However, this is yet to be studied in higher altitude situations. Shi et al. found that temperature more than 8–10 °C would be a declining factor in the everyday numbers of COVID-19 infected patient in China (Prata et al., 2020). Prata et al. carried out a research study in Brazil and reported that every 1°C rise in temperature can lead to a declination of COVID-19 cases (Gupta et al., 2020). Together these reports indicate the importance of geographical factors in disease transmission.

5. Hypoxia in COVID-19 and the association with high altitude:

During the Coronavirus pandemic, cases from highland region including Europe, Africa, South America, North America, and Asia have been announced (Allali et al., 2020; Arias-Reyes et al., 2020; Wilkerson et al., 2020). Based on the epidemiological analysis done by Arias-Reyes et al, it was observed that there is a low incidence of COVID-19 infection at high altitudes and it can be assumed that there may be a weak transmission of the SARS-CoV-2 among inhabitants of high altitudes. Xi et al reported that there may be other possible reasons for such protection to people who live in mountainous regions, like physiological adaptation to hypoxia (like raised erythropoietin levels), genetic make-up, unfavorable environmental factors for viral transmission, civic lockdown measures, and disciplined activities by people (Arias-Reyes et al., 2020). Researchers have found that the inborn resilience of natives of high altitude region had made natives psychologically strong to accept the critical circumstance emerging out of Covid-19, thus reducing stress levels which further enhanced their immunity (Vinayak, 2020). Scientific and epidemiological data show a lower transmission of COVID-19 specifically in the people living at high altitudes in whom hypoxia adaptation might have been an intrinsic protective measure (Arias-Reyes et al., 2020; Wilkerson et al., 2020). Inhabitants of high altitude are more tolerant to hypoxic conditions, thereby making them more resilient to COVID-19 induced lung injury (Arias-Reyes et al., 2020).

Epidemiological data of high altitude regions e.g. Tibetan regions of China, Ecuador, and Bolivia, revealed fewer cases of COVID-19 as compared to lower altitude terrains (Wilkerson et al., 2020). Another investigator found that though the COVID infection rate was lower in high altitude regions, the mortality rate remained unaffected (Huamaní et al., 2020). Various potential mechanisms have been proposed for the lower transmission and decreased incidences of COVID-19 induced complications. First, a decrease of ACE2 expression related to altitude confers a protective measure against COVID-19 (Wilkerson et al., 2020). Second, a higher level of erythropoietin (EPO) in inhabitants of high-altitude regions provides a defense mechanism against hypoxic injury to tissues (Xi et al., 2020). Third, an increase in the level of ultraviolet rays at high altitudes impairs the survival of the virus (Wilkerson et al., 2020). Fourth, lower barometric pressures at high altitudes cause the reduction of air density which further inhibits the spread of the virus (Wilkerson et al., 2020). Due to insufficient evidence, all these mechanisms require investigation.

6. Molecular aspects and how high altitude or hypoxic conditions are useful for COVID-19:

As an initial response, epithelial cells and macrophages of the lungs get stimulated by the virus leading to secretion of pro-inflammatory factors and free radicals resulting in regional inflammation and mitochondrial dysfunction due to oxidative stress (J. Segovia-Juarez et al., 2020). The main function of mitochondria of the lungs is an alveolar gas exchange to maintain efficient ventilation. Therefore, the death of mitochondria results in impaired gaseous exchange and hypoxia (Soliz et al., 2020) (Tay,

Sheetal J Gupta, Rahul Tyagi, Balaram Pradhan, Disha Bhanushali, Limaye Nitin Rishi Nityapragya, Deepali Mathur, Rohin Vinayak, Priya Battu, Kanupriya Sharma, Akshay Anand

Poh, Rénia, MacAry, & Ng, 2020). The oxidative stress can lead to decay of the essential molecules like phospholipids (containing surfactant), which leads to a collapse of the lungs and result in severe respiratory failure (Piantadosi & Suliman, 2017). Altered vascular glycolysis, oxidative stress, and associated inflammatory processes provide a good media for virus replication. Hence, keeping in mind these inflammatory changes, reducing multiplication and transmission of the SARS-CoV-2 can be challenging (Cloonan & Choi, 2016).

7. Yoga induced hypoxic pre-conditioning may help in the prevention of COVID 19:

Hypoxic pre-conditioning (HPC) has been proposed to be preventive against COVID 19 infection (Joszt L. Experts highlight COVID-19 vaccine developments and remaining challenges. AJMC. 2020) through a protective mechanism via a variety of biological procedure including tissue repair, inflammation and angiogenesis.. Pre-conditioning with hypoxia can be presented as a non-invasive COVID-19 prevention technique. It has been reported by various studies that the prevalence of COVID 19 infection is lower in hypoxia. A natural way of inducing intermittent hypoxia is pranayama (Yogic breathing technique) which involves controlled breathing techniques (Malshe, 2011). Yoga and breathing practices like Sudarshan Kriya Yoga are known to enhance angiogenesis (Sharma, Pannu, Sayal, Bhalla, & Anand, 2020), reduces inflammation (Twal, Wahlquist, & Balasubramanian, 2016), enhance tissue repair (Woodyard, 2011) and cell survival (Lefrançais et al., 2017; Spicuzza, Gabutti, Porta, Montano, & Bernardi, 2000) through its intermittent hypoxia mechanism. Yogic breathing techniques are known to enhance the strength of expiratory and inspiratory muscles and hence may prevent respiratory diseases by improving pulmonary function along with improvement in oxygen saturation, lowers blood pressure, reduces anxiety, boost metabolism, immune system, and central nervous system (Bhanushali, Tyagi, Limaye Rishi Nityapragya, & Anand, 2020; Zope, Zope, Biri, & Zope, 2021). A study assessed the oxygen saturation capacity of healthy male adults after performing two yogic breathing exercises reported a significant increase in the oxygen saturation. (Bhattacharya, Pandey, & Verma, 2002). Alternate nostril breathing (anulom-vilom), particular pranayama, shows important results in deep breathing tests, orthostatic tolerance tests, and Heart Rate (HR interval) parameters, showing that alternative nostril breathing (anulom-vilom) has effects on the parasympathetic nervous system of young healthy participants (Sinha, Deepak, & Gusain, 2013).

Hypoxic pre-conditioning induced by yogic breathing is known to increase the infiltration of stem cells into the peripheral blood (Malshe, 2011; Zope et al., 2021), which can help in the management or prevention of COVID 19 infection through its regenerative mechanism as is shown through the stem cell transplantation studies (Fierro et al., 2015; Zope et al., 2021).

Besides the protective mechanism Yoga and pranayama practice improves psychological health which is majorly affected due to COVID 19 leading to major complications.

8. Conclusion

This review explores the relationship between hypoxia, COVID-19, and the high altitude regions. Usually, at high altitudes, hypoxia can have dangerous effects on the human body leading to high altitude illnesses of varying severity. Based on epidemiological and geographical data incorporated, it can be concluded that in high altitude regions even though people live in an environment with low atmospheric oxygen yet they do not seem to show symptoms of hypoxia. This could be due to the

covid-19 and high altitude-induced hypoxic conditions and its management: a perspective for managing through yoga

natural physiological adaptation of the body in terms of lung capacities and oxygen-carrying capacity of red blood cells. Besides, the genetic makeup of the inhabitants of places at higher altitudes can be one of the factors responsible for their resilience to low oxygen environments. High altitude residents may thereby become more tolerant of COVID-19 induced hypoxia and lung injury. Mind-Body Techniques (MBTs), such as yoga, yogic breathing exercise help to provide relaxation by minimizing stress and ensuring the timely removal of free radical development from the body, preventing conditions such as necrosis, stenosis, tissue starvation, and hypoxia, which can be an alternative therapy method of COVID-19.

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covid-19 and high altitude-induced hypoxic conditions and its management: a perspective for
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