SVOA Neurology

ISSN: 2753-9180

ScienceVolks Open Access

Review Article

Neurologic and Metabolic Challenges at High Altitudes

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DOI: https://doi.org/10.58624/SVOANE.2024.05.0132

***Received:** February 27, 2024* ***Published:** March 25, 2024*

Abstract

Hypoxia resulting from a drop in the oxygen pressure in the atmosphere with elevation is a hallmark of the high altitude (HA) environment, with cold and requires acclimatization. Despite such environmental challenges, HA is a frequent exposition challenge for travelers, mountaineers, workers, and military personnel. Ambient or exercise-induced, muscle hypoxia triggers complex angio-adaptive responses in the skeletal muscle tissue and capillaries. These are due to the expression of several angio-adaptive molecules: Hypoxia-Inducible Factor (HIF) and Vascular Endothelial Growth Factors (VEGF) a polypeptide leading to the growth, and stabilization of muscle capillaries. A series of biochemical changes and released molecules occur at HA for hypoxia stimulation by HIF on circulation. This remarkable plasticity of the capillary network is referred to as adaptation at the cellular and subcellular levels. Other physiological adaptations occur in the heart, breathing, circulation, and hematopoiesis. Hypoxic stress might also be exploited for potential benefits. Endurance exercise might benefit if first done at HA, increasing hematocrit. This has been exploited in controlling skeletal muscle performance during physical exercise at HA and subsequently at low altitudes. The major skeletal adaptive responses to hypoxia will be discussed, including contraindications and advantages of HA exposition.

***Keywords:** High Altitude Cerebral Edema (HACE); Neuromuscular function; Low-oxygen conditions*

Introduction

At high altitudes, where oxygen levels are lower compared to sea level, the body undergoes various physiological adaptations to cope with the decreased oxygen availability. The plasticity of the capillary network is referred to as adaptation which includes changes at cellular and subcellular levels in the organism. Some adaptations impact both neuromuscular function and metabolism.

At HA, several challenges are present in different organs and tissues (Fig.1) the reduced oxygen levels can potentially lead to a condition called HA retinopathy, which involves changes in the blood vessels of the retina due to hypoxia. There are several ways to protect the retina from challenges at HA: proper hydration is essential to maintain blood flow, including to the retina. Dehydration can exacerbate the effects of reduced oxygen levels on the retinal blood vessels. A general principle is to ascend to HA during trekking gradually to allow your body to acclimatize to the lower oxygen levels, for instance no more than 300m. altitude per day. This helps reduce the risk of high-altitude sickness such as Acute Mountain Sickness (AMS) and High Altitude Cerebral Edema (HACE) the occurrence of brain microhemorrhages, which can also affect the eye and the retina.

The ultraviolet radiation exposure increases at HA, which can contribute to eye damage (Fig 1). Is recommended to use appropriate eye protection, such as dark glasses, during activities like skiing or mountaineering to prevent injuries from ultraviolet exposure, wind, or debris.

In extreme cases or for individuals with pre-existing eye conditions, supplemental oxygen may be necessary to ensure adequate oxygen supply to the retina and other tissues. It is essential to pay attention to any changes in vision or discomfort while at HA.

Neuromuscular function at HA might take into account a decreased motor performance since there is a reduction in maximal voluntary force output and power can occur due to the lower oxygen availability at high altitudes. At 5000 meters (Everest base camp, or Everest K2 Pyramid) VO2 max is reduced to about 50%. This can affect muscle strength, coordination, and overall performance.

Motor control challenges are observed since HA can also impair neuromuscular coordination and fine motor skills. This is due to changes in neural input to muscles, decreased neuromuscular transmission efficiency, and muscle fiber recruitment patterns.

Muscle fatigue is a common experience for trekkers, when walking at 4000 meters or above the risk of muscle fatigue is higher at HA as the muscles have to work harder to produce the same level of force due to reduced oxygen levels. This can impact both endurance and strength activities.

Metabolic adaptations are needed since at HA there is increased energy expenditure by muscle mitochondria. At HA, the body may require more energy to perform the same physical tasks due to the increased metabolic demands of working in cold or hypoxia in a rough environment. A shift in substrate utilization occurs: the body may rely initially more on anaerobic metabolism (glycolysis) at HA, as aerobic energy production is less efficient in low-oxygen conditions. Altitude acclimatization occurs slowly over time, the body can adapt to HA by increasing red blood cell production and hematocrit to improve oxygen transport and slowly enhancing mitochondrial density in muscle cells to improve aerobic capacity. This is mediated by Hypoxia Inducible Factor (HIF).

There are several implications for exercise performance: athletes and individuals engaging in physical activities at HA experience decreased performance initially due to neuromuscular and metabolic changes. However, with proper acclimatization and training, performance can improve over time, and this might benefit performance at lower altitudes. Accurate monitoring of hydration, nutrition, and recovery becomes crucial at HAs to support neuromuscular function and metabolic processes training protocols and vice versa can help athletes and individuals optimize their adaptations to HA environments and improve performance at lower levels.

Neurological Challenges at HA for People

Travel to altitude for people with neurological disorders is possible, considering a series of recommendations concerning people with migraine, headache, epilepsy, movement disorders, CNS, and PNS diseases (1).

People with neurological disturbances can go trekking but they need advice summarised with brief and clear guidelines; while it is generally possible for such individuals to trek it is important to consider their actual medical condition before embarking on such adventure since trekking involves physical exertion, and exposure to various environmental conditions, cold, wind, and potential challenges along the trail.

Considering such items it might be advisable a consult with a neurologist experienced in HA, it is also possible to perform Richalet's hypoxia sensitivity test in a specialized mountain ambulatory setting, which quantifies the cardiorespiratory response to acute hypoxia during a low-intensity exercise, with a heart rate of about130 bpm in normoxia, that tries to predict individual susceptibility to AMS (2).

Other individuals before ascent perform simulated hypoxic training in a nitrogen house to accelerate HA acclimatization. One can assess the individual's overall health, evaluate the risks involved, and provide customized guidelines. Understanding the neurological status of personal conditions and limitations: it is crucial to have a clear understanding of the specific neurological condition and its impact on physical capabilities.

Cerebrovascular circulation is modified in HA. Transcranial ultrasound and MRI studies demonstrated an increase in the middle cerebral artery diameter on acute exposure to both normobaric and hypobaric hypoxia (3). In acclimatized people no evidence of cerebral artery vasodilation was shown up to 6400m above this altitude vasodilation occurs and it is reversed rapidly with supplementary oxygen (3-4).

Migraine is a frequent condition, especially in women, who worry about possible attacks at HA. Also, people with migraine are more prone to develop AMS. Every mountaineer with migraine should know that at altitude his headache can increase in frequency and intensity (5). It is clear why high altitude is a migraine trigger since pain is based on activation of the trigemino-vascular system, and beyond this, there is an increased cerebral blood flow at altitude (6). Both migraine and AMS could be possibly activated by hypoxia action by signals generated at HA which may interfere with serotonin neurotransmission. (7)

Headache in migraine and AMS are linked to abnormal serotoninergic neurotransmission, in the manifestation of head pain recent evidence suggests that a low serotonin facilitates activation of the trigemino-vascular nociceptive pathway. The effects of triptans act on vasoconstriction and since they have an action on brainstem serotoninergic nuclei. The use of triptans seems to be safe and recent research suggests usefulness in AMS prevention (8). Migraine prevention can be done with aspirin, FANS, or triptans, and a second drug for potential prevention treatment such as. flunarizine or amitriptyline. Blood analysis to study thrombophilic states such as protein C or S is suggested. Any patient who suffers from migraines must be informed that their headaches can worsen at altitude, both in frequency and/or intensity.

Cerebrovascular disease challenges at High Altitudes

About one-third of stroke patients manage to maintain their independence without disability or with slight disability and resume normal activities, including traveling or recreational activities at altitude, like skiing or trekking, but the anecdotal occurrence of strokes is present (9).

Scientific literature has reported case studies of possible severe strokes at altitude (10-11) in healthy people. Indian soldiers had hospitalizationat HA for first-ever strokes frequently suggesting that stroke incidence might be high above 3500m (12). According to Kumar (13), a long-term stay at HA exposes a higher risk of stroke. Although all types of stroke were seen, ischemic stroke was the commonest, and massive infarcts were reported. Polycythemia might represent an important risk factor. Falla et al (14) evaluated the contrary that the risk of stroke in HA populations needs further assessment. Dehydration and polycythemia have as a consequence increased circulation and blood viscosity (15). Hypoxia might trigger both coagulation abnormalities and platelet aggregation (16). The use of a recent oral anticoagulant is a valuable addition.

Long-term stays at HA and congenital or acquired thrombophilia might predispose to cerebral venous thrombosis (CVT) since there is an association with a hypercoagulable state (17). The association of CVT with a single exposure to HA seems low, but the risk cannot as yet be specifically estimated (17-18). It is not known well known what the risk of cerebral emboli at HA is. Patent foramen ovale or other right to left shunts are possible risk factors for embolic stroke at altitude or similar neurological events during climbing (19-20).

Hypoxia can induce cardiac arrhythmias (21). Caution is advised in people with white matter leukoencephalopathy (22) and in a patient with a previous recent stroke or a transient ischemic attack (TIA), which is a reversible neurological condition manifesting as amaurosis fugax or limb paralysis lasting a short time (less than 24 hours) People at higher risk of developing CVA in the 3 months are the ones that suffered a TIA. Therefore, the diagnosis of this event should be certain and these patients must seek the advice of a neurologist before reaching altitude. Furthermore, a patient with previous TIA must be informed that the best treatment in case of recurrence or stroke is thrombolysis (when possible), and this treatment option is difficult to meet at altitude or in adverse environments. For all these reasons, people with recent ischemic cerebrovascular diseases and patients without a residual disability must be extremely carefully counseled about traveling to HA only after careful examination and risk evaluation either in an outpatient mountain medicine service, by a neurologist or by a physician with knowledge of traveling and high altitude risks All treatable risk factors should be first treated (such as severe carotid stenosis, blood pressure, other cardiac sources of emboli, etc.). TIAs have to be considered as contraindications for trekking when the diagnosis has to be done by a neurologist since, for instance, the occurrence of isolated vertigo or syncope is not TIA. It is therefore advisable that a mountaineer with a possible TIA undergoes a well-done consultation (23).

Tumors and other lesions

Patients with intracranial lesions are neurologically unstable and should not travel to altitude (24-25). Several explanations and case reports support this advice (26), since the skull is a rigid container any increase in any one of the volumes of the brain, cerebrospinal fluid is limited and once the compensative adaptation is exhausted, a severe and rapid elevation of intracranial pressure occurs. HACE occurs due to an increased tissue water content and swelling of perivascular glial end feet (26). Some tumors or masses might become symptomatic during long commercial flights (27-29). This unexpected event might be due to edema, an increase in cerebral blood flow, or increased cerebrospinal fluid pressure that exposes long-flight travelers, but also in HA auto trips.

Brain trauma, and damage

People with previous brain damage need caution, especially at HA where the brain repair resulting from a trauma appears slow. Indirect evidence suggests that an increased blood-brain permeability enhancing the action of free radicals is possible. Hypoxia is one of the possible secondary insults that affect short and long-term outcomes and is associated with poorer neurological outcomes in traumatic brain injury patients (30). For a patient with a traumatic or metabolic brain injury previous brain hypoxia, or metabolic dysfunction after an operation, it is not advisable to go to HA.

Multiple sclerosis (MS)

Multiple sclerosis is a chronic neurological condition that affects the central nervous system. This condition leads to impaired myelination in CNS or PNS manifesting with various symptoms such as fatigue, numbness, tingling, muscle stiffness, muscle weakness, and cognitive signs. It happens when the immune system attacks the myelin and causes damage to the nerve fibers. Patients with MS might be considered safe at relative HA and have been followed in centers up to 2500 meters. Although there is no cure for multiple sclerosis, there are various therapies and lifestyle changes that can help manage the condition and improve quality of life. Hiking is one such activity that has shown potential benefits for people with MS. Hiking at mid altitudes can improve fatigue, increase oxygen delivery to the skeletal muscles, and provide a sense of accomplishment and improved mental well-being. MS patients may develop new neurological signs and symptoms if they present an infection or if exposed to a cold; moreover, an exacerbation of a relapsing-remitting MS was recently reported with exposure to Mt. Fuji at 3.776 meters (31). Caution has to be advised to MS people who might suffer from limited cerebrovascular reactivity (32) MS people might complain of poor exercise tolerance and exertion fatigue that limit their daily living activities. As a result, people with MS often struggle with fatigue, reduced physical activity, and limited mobility. However, research on handicapped athletes (33) has suggested that HA trekking is a potential way to improve physical fitness and reduce fatigue in several instances.

Parkinson's disease and Cognitive Impairment

Prolonged exposure to high altitudes has been associated with an increased risk of neurodegenerative diseases such as Alzheimer's and Parkinson's disease (PD). People who are diagnosed with PD might feel that it's the end of the road and there is no turning around for the better. PD is a progressive nervous system disorder that affects movement and balance. And while there are treatments to help with the symptoms, there is only a symptomatic cure. Recently it has also been reported that chronic intermittent hypoxia due to obstructive sleep apnea syndrome (OSAS) contributes to the pathogenesis of PD increasing the a-synuclein levels (34). However, in several cases going hiking can contribute to balance and recuperating movement in PD.

On the other hand, hypoxia-induced oxidative stress can induce harmful Reactive Oxygen species (ROS) which can exacerbate muscle dysfunction and CNS function, for instance, the altered chemosensitivity present in PD can cause dyspnea (35).

It is important to note that the precise mechanisms and extent of CNS dysfunction are still under investigation. Various factors, including individual susceptibility, duration of exposure, and acclimatization, can influence the impact of HA hypoxia on cognitive function and CNS health.

For cases of neurological conditions like initial PD and mild forms of cognitive dysfunction exposure to trekking might exert a beneficial effect.

Exercise challenge at HA

Reduced oxygen levels at high altitudes can lead to an imbalance between the production and clearance of ROS. Excessive ROS can damage cellular components, including neurons and astrocytes in the CNS. Hypoxia can directly affect mitochondrial function in neurons, astrocytes, skeletal muscle, and other organs and mitochondrial oxidative phosphorylation may be compromised, leading to reduced ATP production and impaired energy metabolism. Reduced oxygen levels can impair mitochondrial function and lead to a shift in metabolism. In response to hypoxia, body tissues including skeletal muscles undergo several adaptations to optimize energy production and maintain cellular homeostasis.

One key adaptation is an increase in the number and size of mitochondria. This increase, or mitochondrial biogenesis, is regulated by various signaling pathways, such as the HIF pathway and PGC1 alfa. The mitochondrial adaptations aim to maintain cellular energy production and homeostasis under low oxygen conditions. Further, HA research is needed to fully understand the mechanisms underlying these adaptations and their implications for human adaptation at HA.

On the other hand, HA aerobic activities, such as running, biking, and walking might improve VO2 max. This has been observed in several conditions and might be part of professional training, basically trying different conditions for training. HA training can potentially improve endurance during intense exercises, such as cross-country skiing or running, and bicycling at HA can potentially improve endurance it might increase aerobic capacity, lactic acid tolerance, and oxygen flow to skeletal muscles to be used in lower-level performances.

Challenges of HA for people with peripheral nerve disorders and neuromuscular diseases

Sarcopenia is a condition characterized by the loss of muscle mass, strength, and function that occurs with aging, however, an important sarcopenia occurs at HA or in space travelers. HA environment might exert various effects on muscles, potentially exacerbating the development or progression of sarcopenia. Factors to be considered are hypoxia: hypoxia can contribute to muscle wasting and loss of muscle strength at the same time it affects muscle protein synthesis and increases protein breakdown, accelerating muscle loss. For people living at HA permanently, there are genetic adaptions to physical and physiological challenges (36). Adjusting occasionally to a HA environment can lead to different physical activity levels, resulting in muscle disuse and atrophy. The only population that has adapted for several thousand years, like the Sherpa has a better and more metabolically fitted type of mitochondria, which have been revealed by accurate proteomic studies by Gelfi et al.(37), while mountaineer biopsies have shown altered mitochondria for prolonged exposure to HA.HA, mountaineers like Messner do not reveal muscle biopsy any exceptional characteristic in laboratory studies and preserve their muscle performance at HA with experience, good adaptation well balanced nutrition.

Nutritional considerations at HA adequate nutrition is essential for maintaining muscle mass and function. If alpinists do not consume adequate protein and energy, it may result in muscle loss.

Inflammation and oxidative stress: HA environments can induce increased inflammation and oxidative stress due to factors such as increased free radical production and altered antioxidant defense systems.ROS plays a role in sarcopenia by promoting muscle protein breakdown and impairing muscle regenerative processes.

Balanced nutrition: consuming a well-balanced diet rich in high-quality protein, essential nutrients, and adequate calories is crucial and can support muscle maintenance and regeneration, improving HA sarcopenia. Monitoring and medical support: Regular monitoring of muscle mass, strength, and function is important in identifying early signs of sarcopenia. Working with physicians, nutritionists, and exercise specialists, can help develop personalized interventions and strategies for managing sarcopenia at HA.

Nerves are part of the PNS, they play a crucial role in transmitting signals between the spinal cord and different muscles. Nerve damage can lead to a variety of symptoms, depending on the affected type of neuropathy, with damage or dysfunction of one or more nerves that typically results in pain, tingling, or weakness in the affected areas, this can be affected at HA by cold exposure can have various effects on the body, including nerve vessels vasoconstriction (38), decreased muscle performance, and increased risk of hypothermia. HA environment has lower oxygen levels, which can lead to altitude sickness or other physiological changes such as energy restriction, often associated with fatiguability, which involves reducing calorie intake while maintaining adequate nutrition. Cold exposure at high altitudes can increase the risk of hypothermia, a condition where the body loses heat faster than it can produce it. Individuals with neuropathy may have impaired temperature sensation, making them less able to detect cold-related threats like hypothermia. This can result in a delayed response to warming up, leading to further complications.

The interplay of neuropathy, cold, hypoxia, and hypothermia at HA can create a challenging environment for individuals with neuropathy. Proper precautions, such as dressing warmly, staying hydrated, and acclimatizing gradually to high altitudes, are essential to minimize the risks and ensure safety in such conditions. For someone who is planning to be in HA, a cold environment with neuropathy, it's advisable to consult with a neurologist for personalized advice.

In sensory-motor peripheral neuropathies, both inherited or acquired there is a risk related to the foot's lack of sensitivity during walking or climbing. Microvascular abnormality is a characteristic change common in diabetic neuropathy (38). Such people must wear comfortable shoes that are not tight to help promote a continuous blood flow to peripheral nerves, another major consideration is to avoid immobility to prevent deep venous thrombosis and walk with warm comfortable stockings. HA is not dangerous for diabetics well-monitored, without evidence of previous peripheral damage they can go at altitude and some diabetic people have climbed Cho-Oyu, an 8000-meter peak, without damage. Many patients with neuromuscular diseases such as motor neuron diseases, Myotonic Dystrophy, or metabolic myopathies have also respiratory insufficiency and low drive. Therefore, patients with neuromuscular disorders should be screened for the presence of sleep apnoea, If a respiratory insufficiency is detected, they should check to travel with adequate support or oxygen.

Dietary supplementations ameliorate hypobaric hypoxia-induced muscle atrophy

Understanding these physiological adaptations and implementing appropriate strategies can help individuals perform better and mitigate the impact of altitude on physical performance. HA exposure leads to compromised physical performance with considerable weight loss. The major stressor at high altitude is hypobaric hypoxia which leads to disturbance in redox homeostasis. Oxidative stress is a well-known trigger for many HA illnesses and regulates several key signaling pathways under the control of molecules causing atrophy (FOXO, MURF1). Altered redox homeostasis is considered the prime culprit of high altitude-linked skeletal muscle atrophy. Hypobaric hypoxia disturbs redox homeostasis through increased ROS production and a compromised antioxidant system.

Increased ROS disturbs tissue homeostasis in multiple ways such as inflammation generation, altered protein anabolic pathways, and enhanced protein degradation pathways via activation of atrophy factors, there is an unbalance between protein synthesis and degradation, leading to a pre-cachectic state. Ultimately, all the cellular signaling pathways result in skeletal muscle atrophy. Dietary supplementation of physiological chemicals and micronutrients might antagonize, a safe and effective intervention to ameliorate skeletal muscle atrophy and enhance the physical performance of the personnel who are staying at high altitude regions. Unfortunately, studies of the specific effects of altitude on nutrient needs have been conducted at HA and described the downregulation of protein synthesis and increased protein requirements (39), changes in energy, and fluid turnover. Although these altitude-induced changes in metabolism have been less well studied than the typical low–moderate training altitudes, effects might be amplified when they interact with HA and the numerous camps used by climbers. Shifts towards greater carbohydrate utilization have sometimes been shown at HA (40), Considering that a diet with more than 2.0 g of protein per kilogram of body weight per day might not completely protect skeletal muscle loss during energy deficits at HA and that protein intakes in the range of 1.3 –1.8/ Kg per day distributed along the day in frequent meals will maximize the protein synthesis it is to consider additional careful addition of key branched-chain amino acids such as leucine, which can counteract as a substrate muscle protein loss.

Despite their greater caloric richness, a diet rich in fat is not appetizing for most climbers. In addition, the tolerance to fat food is low at HA (Fig1), even not well tolerated. Alpinists should be advised to eat fat in the form of unsaturated oils such as olive oil and animal sources of protein, if they present no appetite, should try to eat frequently small amounts of high energy-dense food, and could add salts and electrolytes to drinking water.

On high-intensity days, travelers should consider using a recovery drink after a workout and monitor hydration status. Also is important to try to drink frequently introduce water, and soups, and if possible consider leucine supplementation when there are problems achieving protein intake, could consider supplementation with vitamins for a prolonged stay at an HA.

As a result of erythropoiesis in acclimatization, depletion of iron storage might occur and be observed. Low levels of iron and ferritin can impair the increase in hemoglobin concentration. Due to the slow capacity of replenishment, iron storage must be fully replenished before the expedition.

Blood hyperviscosity due to excessive hematocrit on the other hand increases the risk of high-altitude thromboembolism. This fact must be considered when bearing in mind the adequacy of iron supplementation. HA exposure constitutes a risk of thromboembolic disorders including venous thrombosis, cerebral vein thrombosis (17), and deep vein thrombosis; a blood hypercoagulability study(18) indicates that people living in HA areas for one year experienced thromboembolic events several times more frequently than those living in low altitude areas.

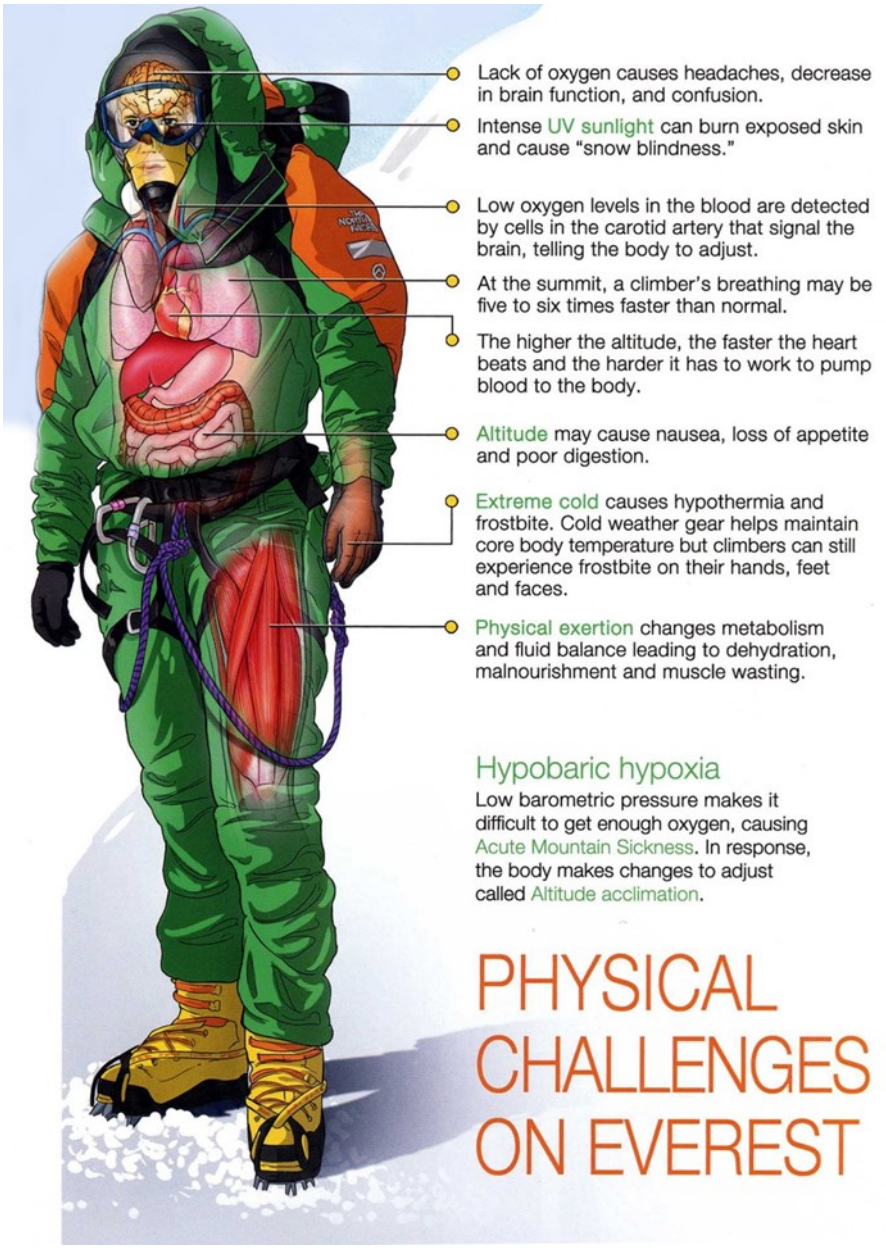

Fig.1 *Neurophysiological function challenges and metabolic consequences at High Altitude.*

Conflict of Interest

The author declare there is no conflict of interest.

Funding

None.

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Citation: Angelini C. Neurologic and Metabolic Challenges at High Altitudes. *SVOA Neurology* 2024, 5:2, 78-86.