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Decreased Work Capability Related to High-Altitude Exposure

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Background: The unique environment of high altitude can affect the work capacity of those not accustomed to it, and in some cases, it can even endanger their lives. Studying the effect of high-altitude exposure on work capacity is important. Still, there are few reviews on this topic. We aimed to summarize the parameters used to evaluate work capability in a high-altitude environment, the potential pathophysiological mechanisms, and the available pharmacological and non-pharmacological strategies for improvement.
Methods: We conducted searches on PubMed, Google Scholar, and China National Knowledge Infrastructure to explore the existing literature including basic and clinical studies from 1968 to 2023, using keywords such as "work capability/performance and high-altitude hypoxia" or "work/exercise at high altitude". Conference proceedings, notes, and case reports were excluded. The CiteSpace 6.1.R3 was used for de-duplication.
Results: A total of 727 papers were identified through search terms from the database. 486 papers were eliminated following the de-duplication process, lacking full text and deemed irrelevant to this article. Among the remaining 241 papers, 21 investigate the underlying mechanisms of reduced work capability due to altitude exposure, and 94 papers discuss measures to improve work capability when exposed to high altitudes.
Conclusion: In conclusion, this review summarizes the evaluation of indicators, pathomechanisms, and improvement measures for high-altitude exposure-related changes in work capability. More basic research on its mechanisms and large-sample, randomized controlled clinical studies to validate its effects are needed.
Keywords: high altitude, hypoxia, pathophysiological mechanisms, work capability

Introduction

China has the world's largest plateau area, with more than 25% of its total area at elevations above 2500 m. The development of China's Western region, given its vast territory and long national borders, is important in terms of military, economic, and social terms.[1] With China's Western development strategy being implemented more deeply, more people are traveling to the plateau region for work, tourism, and other purposes. For instance, in 2023 alone, over 40 million tourists visited the Tibetan region.[2] However, the unique natural environment of the plateau region, as shown in Figure 1,[3] causes acute mountain sickness, high-altitude pulmonary edema/cerebral edema, and rapid decrease in work capability for those who enter the plateau without acclimatization, and in some cases, even endanger their lives. Over the period, there have been tremendous developments in preventing and treating acute mountain sickness, and high-altitude pulmonary edema/cerebral edema, such as acetazolamide, dexamethasone, and sildenafil.[4] However, decreased work capability related to high-altitude exposure was not mentioned in the latest Wilderness Medical Society Clinical Practice Guidelines. Research has revealed that individuals who are not accustomed to high-altitude environments experience a decrease in work capability of approximately 13% when exposed to an altitude of 3500 meters. This reduction in work capability further drops to about 19% when exposed to an altitude of 4500 meters, compared to the

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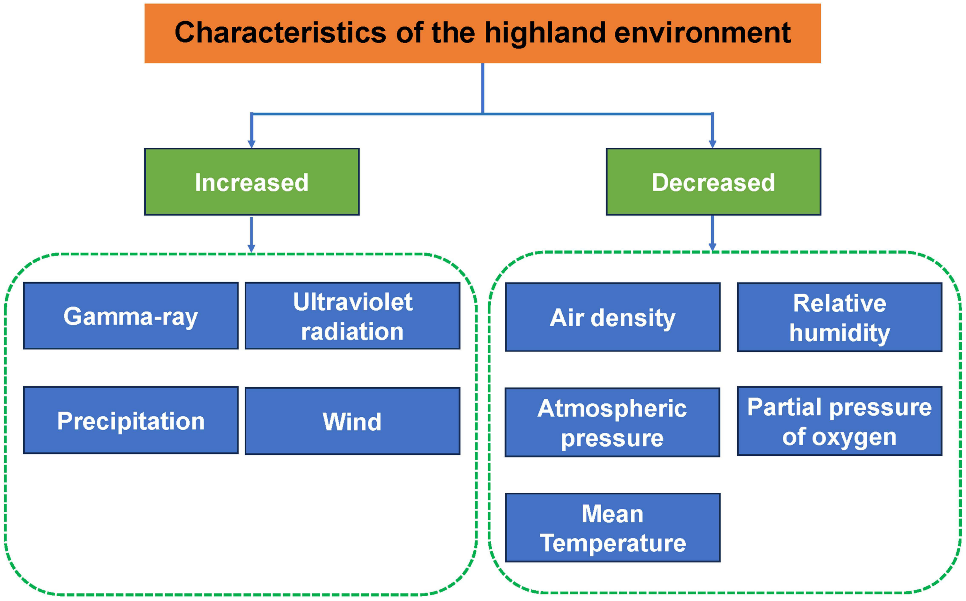

Figure 1 Characteristics of the highland environment with relation to sea level.

work capability at a lower altitude.[5] Therefore, it is important to conduct further research on the change in work capability in a high-altitude setting. While fundamental and clinical research on decreased work capability due to high-altitude exposure has made great progress, many scientific concerns remain unresolved. Further research is needed to understand the pathophysiology and therapy options for impaired work capability caused by high-altitude exposure.

In this paper, we aim to review recent research on the evaluation of indicators, pathomechanisms, and improvement measures on high-altitude exposure-related changes in work capability. This review makes suggestions for more in-depth studies in the future, aiming to give some ideas and insights for subsequent studies.

Methods

A comprehensive literature search was performed to include relevant sources related to work capability and high-altitude hypoxia from 1968 to 2023. The search was conducted in a single day to prevent bias resulting from daily database changes. The search was conducted in English using PubMed, Google Scholar, and China National Knowledge Infrastructure (CNKI), using keywords such as "work capability/performance and high-altitude hypoxia" or "work/exercise at high altitude". In addition, information from reputable websites focusing on high altitudes was also referenced to ensure a thorough review. Conference proceedings, notes, and case reports were excluded. The CiteSpace 6.1.R3 was used for de-duplication. Figure 2 shows the flow chart of the literature search.

Results

As shown in Figure 2, a total of 727 papers were identified through search terms from the database. 486 papers were eliminated following the de-duplication process, lacking full text and deemed irrelevant to this article. Among the remaining 241 papers, 21 investigate the underlying mechanisms of reduced work capability due to altitude exposure, and 94 papers discuss measures to improve work capability when exposed to high altitudes.

Parameters for Evaluating Work Capability in the High-Altitude Environment

Hypobaric hypoxia is a major environmental characteristic of high altitudes that can cause various changes in the human body, including a decrease in work capability. Work capability is a measure of an individual's performance in the workplace, which includes physical, intellectual, and mental factors. These factors work together to enhance individual operational effectiveness. To evaluate work capability, we can consider three aspects: individual physical fitness, brain function, and overall work efficiency.

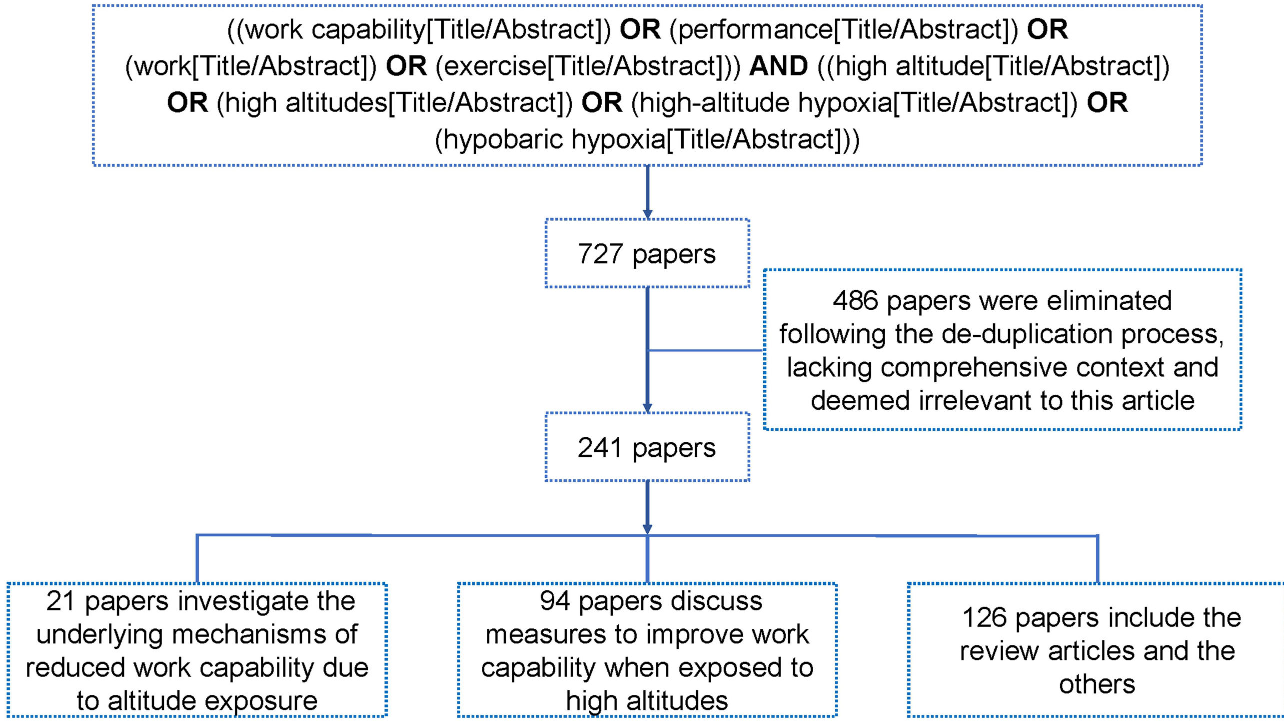

Figure 2 Flow chart describing details of literature search.

Individual Physical Fitness

The evaluation of individual physical fitness can focus on physiological function and motor ability. Physiological function centers on heart and lung function, and the main evaluation parameters are maximum oxygen uptake (VO_{2max}), PWC170 (physical work capability at a heart rate of 170 beats per minute), anaerobic threshold (AT), and brain work capability (BWC), step index, cardiac function index, and so on. The main evaluation indexes of exercise capability are explosive power index (50-m sprint running, 100-m sprint running, standing long jump, triple jump, etc), and endurance index (1 km running, 3 km running, sit-ups, push-ups, pull-ups, etc).[6]

VO_{2max}: This index is widely recognized as the best index for evaluating aerobic exercise capability worldwide.[7,8] It refers to the capability of oxygen uptake and utilization per unit of time during extreme exercise and reflects the aerobic metabolism capability of the organism, including oxygen inhalation, transportation, and utilization of oxygen by the organism. VO_{2max} can be obtained by both the direct measurement method and the indirect calculation method. The results obtained by direct measurement are accurate and reliable but require specialized equipment (eg, running table, power bicycle, swimming dynamometer, gas metabolism meter, etc). The indirect calculation method is simple and easy to implement, but the results are easily interfered with by other factors. Predisposing factors, gender, age, altitude, etc, can affect VO_{2max}. Depending on the altitude, VO_{2max} can be calculated using the corresponding formula.[9] Studies have shown that altitude is negatively correlated with VO_{2max}.[10] Figure 3 illustrates the correlation between altitudes and VO_{2max}.[11–14] Tibetans who have been living on the plateau for a long time have a higher exercise capability, but their VO_{2max} is lower compared to Han Chinese who first entered the plateau and have been accustomed to it.[15]

PWC170: also known as the “quantitative load” experiment, refers to the amount of work done per unit of time when the heart rate is 170 beats/min. PWC170 is closely related to the function of the circulatory system and the respiratory system and is not only an indicator of cardiac function but also an indicator of the body’s physical strength and endurance evaluation.[16] PWC170 can be obtained by both direct and indirect methods, and because the direct method is complicated and time-consuming, the indirect method is usually used. Subjects implement the test through the running platform, secondary steps, or bicycle power meter. The final evaluation result is then obtained by formula calculation using the relevant parameters. PWC170 is widely used at sea level, and due to the relative simplicity of its determination, it is also used at high altitudes, but the results are affected by more factors and are not as accurate as VO_{2max}.[17]

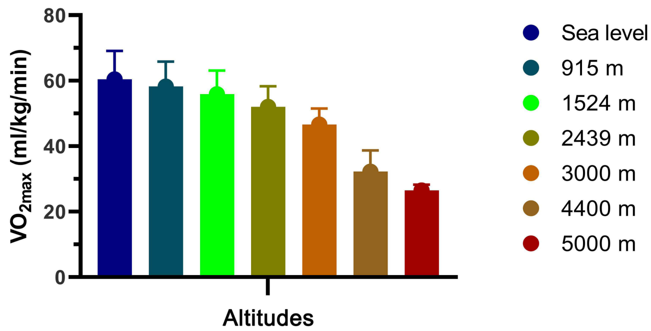

Figure 3 VO_{2max} at high altitudes.

AT: It is the critical value when the body converts from aerobic metabolism to anaerobic metabolism during the increase of loaded exercise, and is an important index for endurance evaluation. Because it is more affected by physical work intensity than VO_{2max}, it is used to evaluate aerobic endurance and physical work intensity and can effectively improve the body's maximum aerobic capability.[18] AT includes lactate anaerobic threshold, heart rate anaerobic threshold, ventilation anaerobic threshold, and so on. Lactate anaerobic threshold has been studied for a long period and is widely used in clinical practice, but the disadvantage is that blood specimens need to be collected several times during the testing process, which is an invasive way of testing. Tibetans who have lived on the plateau for many years have greater exercise capability, and their AT is higher compared to Han Chinese who are new to the plateau but have become accustomed to it.[15]

Step index: one of the evaluation parameters of cardiovascular system function, obtained by measuring the quantitative loading exercise time, the recovery period after loading exercise three times heart rate calculation. The step index evaluates the cardiovascular adaptive ability to strenuous exercise and the body's recovery after exercise. Because the operation and implementation of the test are simple, the step index is also used at high altitudes.[19]

The effects of environmental factors on individual operations can cause changes in the function of the nervous system, which will further lead to behavioral abnormalities, such as changes in mental mood, memory loss, motor coordination disorders, and so on, ultimately affecting operational performance. Brain cells are extremely sensitive to oxygen, and exposure to hypobaric hypoxia can worsen damage to brain tissues, leading to cognitive, linguistic, and behavioral impairments in severe cases. Therefore, it is of great significance to evaluate the cerebral working ability after plateau exposure. Currently, the Neurobehavioral Core Test Battery (NCTB) system recommended by WHO is widely used for neurobehavioral evaluation of occupational populations worldwide.[20] The NCTB consists of seven subscales with a fixed order, which are the Profile of Mood States test (POMS), Digit Span test (DSP), Santa Ana Dexterity test (SA), Digit Symbol test (DSY), Benton Visual Retention test (BVR), Pursuit Aiming (PA), and Simple Reaction Time test (SRT). Each item corresponds to the following neurobehavioral functions: affective state, attention/reaction speed, auditory memory, manual dexterity, perceptual-motor speed, visual perception/memory, and psychomotor stability. The systematic test is simple to administer operationally, less costly, and less affected by individual differences in educational qualifications, and is therefore widely used in various countries, especially where testing facilities are limited. Using the NCTB as a research tool, studies from the Department of Plateau Military Medicine, Third Military Medical University, have shown that plateau hypoxia exposure impairs neurobehavioral functioning, which can be further exacerbated by prolonged exposure to the plateau environment.[21]

Work efficiency is an important factor affecting work capability, involving the theory of human-machine-environment system engineering, and the specific evaluation includes anthropometric measurements and movement analysis.[22] By measuring the height, weight, morning pulse, lung capability, back strength, grip strength, VO_{2max}, NCTB, and other indexes of the plateau migrants, the researchers found that the hypobaric hypoxia of plateau has obvious effects on the physical strength of the plateau migrants, and the coordination of human movement has a long effect on time, indicating that the hypobaric hypoxia of plateau reduces the operational ergonomics of the plateau migrants, and the relative reduction of effective labor.[23] Studies have shown that plateau hypothermia is one of the most important factors affecting the operational ergonomics of railroad engineering workers in plateau operations.[24] A study simulating acute mild and moderate hypobaric hypoxia suggests that plateau exposure has a significant negative impact on human manual work ergonomics.[25] Prof. Luo Erping of the Air Force Medical University in China, focusing on the synergy of the man-machine-environment system, developed a series of high-altitude antioxidant equipment, which plays an important role in guarding and safeguarding the improvement of the operational efficiency of military personnel.[26]

Mechanisms of Reduced Work Capability Due to Altitude Exposure

Hypobaric hypoxia is the primary cause of reduced work capability in high-altitude environments. Even with mild physical exertion, the cardiorespiratory physiological indices in hypobaric hypoxia are already equivalent to or even exceed those of heavy physical work in the plains, especially for high-altitude-unacclimatized individuals. The function of the cardiovascular system decreases in a high-altitude hypoxic environment, which mediates the reduction of an individual's work capability.[27] During hypoxia, the cardiovascular system regulates and increases blood flow to meet the oxygen demand of peripheral tissues. However, hypoxia also limits the function of the cardiovascular system itself, which is the primary factor responsible for a decrease in the work capability of individuals in high-altitude environments.

Studies have shown that overly strenuous physical work in the plains leads to oxidative stress in the organism.[28] Oxidative stress results from various harmful stimuli, where the body produces excessive reactive oxygen radicals (ROS) and reactive nitrogen radicals (RNS), and the oxidative and antioxidative systems become imbalanced, resulting in tissue and organ damage. High-intensity operations lead to the overproduction of free radicals and other reactive oxygen species,[29,30] mainly in the aortic and myocardial tissues. Acute heavy physical load leads to the accumulation of malondialdehyde, a lipid peroxidation product, in the agonistic muscle,[31,32] as well as in the peripheral blood.[33,34]

It has been shown that oxidative stress is enhanced under acute and chronic plateau hypoxia exposure.[35,36] Does oxidative stress relate to the altered operational capability of the plateau organism? Studies have provided answers. In a randomized, double-blind, placebo-controlled trial as early as 1988, researchers found that plateau mountaineers showed a decrease in the anaerobic threshold and an enhancement of organismal lipid peroxidation. Vitamin E was able to attenuate the extent of the decrease in the anaerobic threshold and the reaction of organismal lipid peroxidation, which was beneficial in protecting the individual's operational capability.[37] After intense physical load, plasma lipid peroxidation product malondialdehyde correlates with creatine kinase, which is a marker of muscle damage.[38] Oxidative stress triggers fatigue and damage in skeletal muscle, which is considered an important mechanism affecting an individual's work capability.[39] Grape extract has been shown to protect body cells from oxidative stress damage and improve individual operational capability by reducing plasma creatine kinase concentration.[40] Ginkgo biloba plant extracts contain mainly ginkgo flavonoids and ginkgolides, which have strong free radical scavenging effects,[41] and its significant prolongation of swimming exhaustion time in mice under simulated plateau hypoxia is hypothesized to be related to its anti-oxidative stress effects.[42] In the hypobaric hypoxia environment of the plateau, skeletal muscle atrophy is considered an important factor contributing to reducing the individual's work capability. It has been shown that in acute plateau-exposed rats, oxidative stress induces an increase in protein oxidation, which is also an important factor in skeletal muscle damage.[43] Figure 4 shows oxidative damage as potential cause of decreased work capability following plateau exposure.[44–48]

Measures to Improve Work Capability Related to High-Altitude Exposure

Drugs to Improve Work Capability Related to High-Altitude Exposure

Research has shown that oxidative stress is highly correlated with high-altitude pulmonary arterial hypertension.[49–51] Moreover, pulmonary artery pressure limits exercise capacity at high altitudes.[44] Ghofrani et al were the first to report on the effects of sildenafil on high-altitude exercise performance in 2004. They discovered that sildenafil significantly improved exercise capability at high altitudes. They postulated that sildenafil increased hypoxic exercise tolerance by suppressing the pulmonary hypertensive response, lowering pulmonary artery pressure, and decreasing right ventricular afterload, allowing for an increase in cardiac output. Subsequently, more and more researchers have conducted studies on sildenafil's ability to improve performance in the high-altitude environment (Table 1).[52–65] A common feature of these

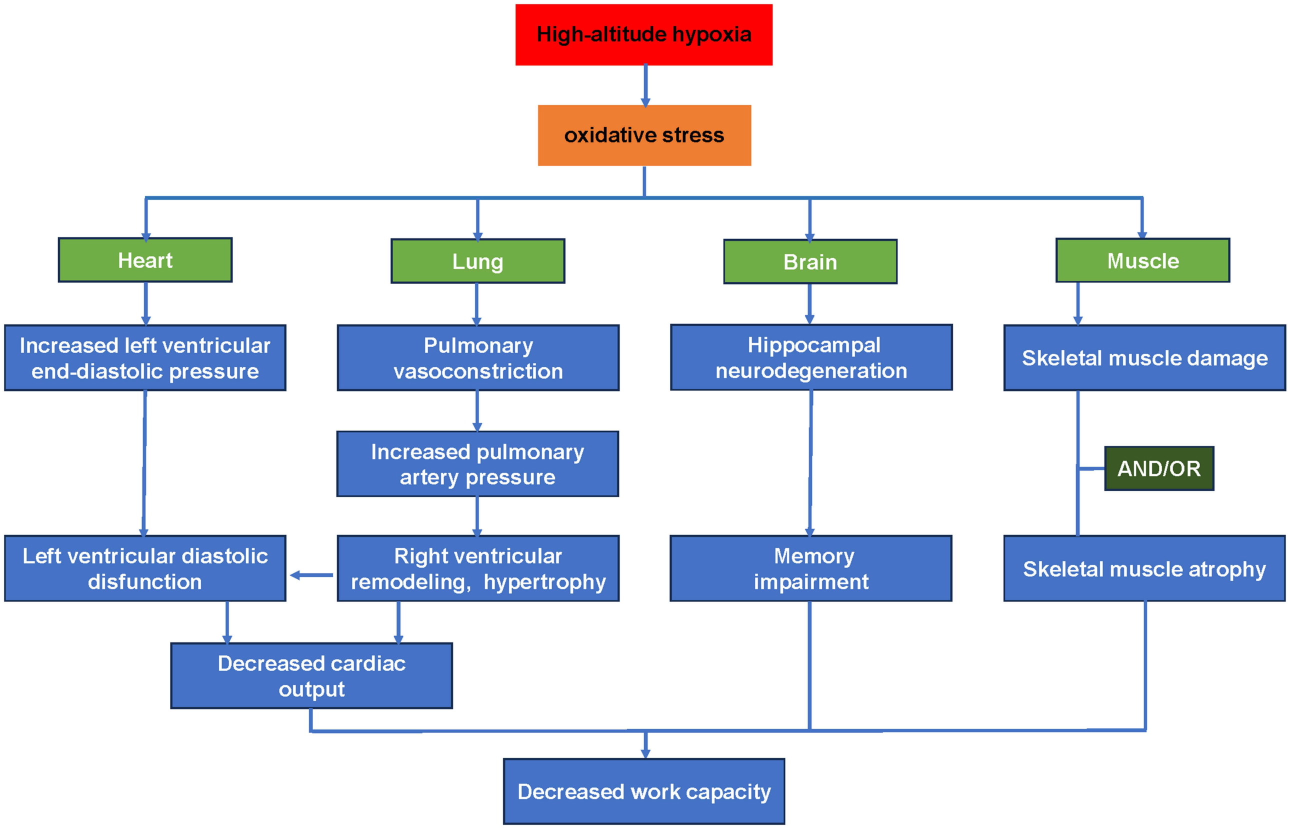

Figure 4 The underlying mechanisms of reduced work capability due to altitude exposure. Oxidative stress due to high-altitude hypoxia may damage the heart,[44,45] lungs,[46] brain,[47] and muscles,[48] decreasing work capacity.

studies is that the sample sizes are small, with the largest sample being only 35 cases.[61] Also, sildenafil may not affect exercise performance in hypoxic environments.[66]

Acetazolamide has been shown to prevent acute mountain sickness effectively; nevertheless, it appears to have varying effects on exercise performance at altitude.[67–70] Inconsistent conclusions between studies may be due to

Table 1 Research on the Use of Sildenafil in Hypoxia-Related to Exercise Performance

First Author	Journal	Year	Exercise Type	Exposure Type	F_IO_2	Altitude (m)	Dosage (mg)	VO_{2max} (mL/kg/min)
Zhao L[52]	Circulation	2001	Rest	NH	0.11	5000	100	NR
Ghofrani HA[53]	Ann Intern Med	2004	MAX	NH	0.1	5500	50	NR
Ricart A[54]	High Alt Med Biol	2005	SUBMAX	HH	0.21	5000	100	NR
Richalet JP[55]	Am J Respir Crit Care Med	2005	MAX	HH	0.21	4350	40	NR
Hsu AR[56]	J Appl Physiol (1985)	2006	SUBMAX	HH	0.128	3900	50	59.7±9.5
Faoro V[57]	High Alt Med Biol	2007	MAX	NH	0.1	5500	50	45±3
Reichenberger F[58]	Respir Physiol Neurobiol	2007	MAX	NH	0.1	5500	50	NR
Snyder EM[59]	Eur J Appl Physiol	2008	SUBMAX	NH	0.125	4300	100	36±6
Lalande S[60]	Eur J Appl Physiol	2009	SUBMAX	NH	0.125	4300	40	39.3±2.6
Jacobs KA[61]	High Alt Med Biol	2011	SUBMAX	NH	0.128	3900	50	51.7±7.5
Kressler J[62]	Eur J Appl Physiol	2011	SUBMAX	NH	0.128	3900	50	49.2±6.3
Rodway GW[63]	Wilderness Environ Med	2016	MAX	HH	0.21	2750	50	39.1±6.32
Toro-Salinas AH[64]	Int J Sports Med	2016	MAX	HH	0.21	4000	100	41.96±9.39
Carter EA[65]	PLoS One	2019	MAX	NH	0.147	3000	50	68.6±8.0

Abbreviations: F_IO_2, fraction of inspired oxygen; HH, hypobaric hypoxia; NH, normobaric hypoxia; NR, not reported; MAX, maximal exercise test to volitional exhaustion; SUBMAX, time-trial or submaximal intensity exercise bout; VO_{2max}, maximum oxygen uptake.

differences in exercise performance measurement methodologies, altitude, acclimatization status, and acetazolamide dosages. Further investigation into these factors is warranted.

Heart rate and oxygen saturation are important indicators of operational performance. Eicosanoids, a naturally occurring higher fatty alcohol, have anti-motor fatigue effects. Research suggests that eicosanoids can reduce resting and postoperative heart rate while increasing postoperative oxygen saturation in plateau-exposed individuals, improving the efficiency of human work and the cardiac reserve function in plateau environments. This, in turn, can enhance the human body's ability to perform operations in plateau environments.[71]

Research indicates that traditional Chinese medicine can boost hemoglobin, hematocrit, and antioxidant levels and improve adaptation to high-altitude environments.[72] Tibetan turnips can increase oxygen saturation and maximum oxygen uptake in hypoxic environments, delay the appearance of the anaerobic threshold, and improve cardiac function, which may be related to enhancing the body's antioxidant capability.[73] Panax ginseng, a traditional Chinese medicine, can increase the number of red blood cells and resist oxidative stress injury. A plateau field study showed that Panax ginseng could increase the step index and PWC170 of study subjects, and the mechanism was related to the increase of SOD to reduce MDA antioxidant damage.[19] Radix Codonopsis tablets, a Chinese medicine compound, can inhibit apoptosis of hypoxic brain cells, improve brain function, and increase the ATP and glycogen content in the mitochondria of rat brain tissue cells during hypoxia to reduce the free radical content in tissues. A plateau field study showed that the drug can effectively improve the soldiers' visual perception, transient memory, analog learning, hand reaction motor ability, movement speed, and stability.[74] Polyphenols found in plants, such as resveratrol, quercetin, and populin, have strong antioxidant and anti-inflammatory activities, and have a broad prospect in the application of anti-hypobaric hypoxia.[75] However, clinical antioxidant measures have also had some inconsistent findings.[76–78] Notably, these studies all have small sample sizes.

Hypoxia Training Improves Work Capability Related to High-Altitude Exposure

Hypoxia acclimatization training is a beneficial method for promoting adaptation to high altitudes and improving work performance. This training can be achieved through various means, such as a hypobaric oxygen chamber or a low-oxygen mask. Research has shown that intermittent hypoxic training at a simulated altitude of 4300 meters can enhance thumb muscle endurance and circulatory timing operational performance. This improvement may be due to an increase in ventilation, which in turn improves arterial oxygen saturation and oxygen transport.[79] Similarly, high-intensity intermittent hypoxic training at a simulated altitude of 3000 meters has been found to enhance the competitive performance of middle-distance runners by increasing VO_{2max}, without affecting immune function.[80] Studies have also shown that wearing a hypoxic respirator during training can effectively improve the physical work capability of recruits after being deployed to high-altitude regions, leading to a decrease in the incidence of acute high-altitude reactions.[81] The role of the hypoxic respirator was again verified in a later study at 4300 meters plateau.[82] The use of a special mask with an intermittent hypoxic-hyperoxic training approach has been found to improve cognitive function and functional motor performance in older adults.[83] However, hypoxic training has also had some inconsistent findings, presumably related to low training intensity.

Research has shown that respiratory muscle fatigue can attenuate exercise performance.[84,85] The common intervention for patients with COVID-19 at sea level was respiratory muscle training. This intervention showed positive results in improving physical and pulmonary functions, which are the main symptoms of the disease.[86] Meanwhile, at altitude, respiratory muscle training has been found to enhance swimming and cycling performance and overall exercise performance.[87,88]

Conclusion and Perspective

With the improvement of transportation conditions in the plateau region and the need for economic construction and national defense undertakings, more and more people are entering from the plains to work in the plateau region. The problem of the reduced work capacity of these people due to hypobaric hypoxia in the plateau cannot be avoided. Reduced work capability is a common reaction among people who first go to high altitudes. This raises important questions about how to effectively prevent and treat the reduced work capacity of people due to hypobaric hypoxia in the plateau. The research on its mechanism and clinical drug use is still insufficient, which leads to unsatisfactory prevention and treatment effects. This review focuses on the evaluation of indicators, pathomechanisms, and improvement measures on high-altitude exposure-related decreases in work capability. Although research on the above issues has made great progress, many studies still have some limitations. 1) Sildenafil is a very promising drug for improving reduced work capability at altitude, and more studies have shown positive effects, but the small sample size needs to be a concern. 2) Traditional Chinese medicine is often used alongside chemical drugs to achieve better results due to its fewer side effects, lower toxicity, and a broader range of targets for action.[89] Some traditional Chinese medicine has shown promise in improving work capacity after exposure to high altitudes, but more extensive clinical studies are necessary to confirm these findings. 3) Additionally, certain medical equipment, such as hypoxic masks and respirators, has shown potential in mitigating the decrease in operational capacity following altitude exposure, but further large-scale, randomized controlled clinical studies are needed to validate these results. 4) However, progress in translating research findings into clinical applications has been limited. Lastly, although oxidative stress is closely related to the alteration of work capability, clinical antioxidant measures alone do not improve the oxidative stress-induced reduction of work capability.[76–78] It is hypothesized that there are other mechanisms leading to the alteration of operational capability. Basic research has shown that both hypoxia and oxidative stress can induce and exacerbate endoplasmic reticulum stress.[90] Endoplasmic reticulum stress is closely related to a variety of clinical diseases such as obesity, diabetes insulin resistance, atherosclerosis, and tumors. A common feature of these diseases is the association with oxidative stress. Studies have shown that in rats exposed to simulated high altitudes, oxidative stress is first activated, followed by gradual activation of endoplasmic reticulum stress. This promotes apoptosis of alveolar epithelial cells as well as remodeling of the pulmonary vasculature, which plays an important role in the development of pulmonary hypertension.[50] However, it is still unknown if endoplasmic reticulum stress is associated with reduced work capability due to high-altitude exposure, and further research is needed in this area. In conclusion, this review summarizes the evaluation of indicators, pathomechanisms, and improvement measures for high-altitude exposure-related changes in work capability. More basic research on its mechanisms and large-sample, randomized controlled clinical studies to validate its effects are needed.

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Disclosure

The authors declare no conflicts of interest in this work.

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