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REVIEW

Exercise Dysfunction and Pulmonary Rehabilitation Strategies in COPD Patients at High-Altitudes: A Review

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Abstract: Chronic Obstructive Pulmonary Disease (COPD) presents significant challenges for patients at high-altitudes, where reduced oxygen availability exacerbates exercise dysfunction. This review explores the related factors behind exercise limitations in high-altitude COPD patients, including chronic hypoxia, impaired pulmonary function, cardiovascular responses, muscle dysfunction, and psychological factors. Effective pulmonary rehabilitation (PR) strategies are essential and should encompass individualized assessments, tailored exercise programs, supplemental oxygen therapy, and nutritional and psychological support. This review highlights the need for further research to develop specific PR protocols for high-altitude COPD patients, focusing on long-term outcomes and innovative approaches to improve access to rehabilitation services. By addressing both physiological and psychological aspects, these strategies aim to enhance the quality of life and functional capacity of COPD patients in high-altitude environments.

Keywords: chronic obstructive pulmonary disease, COPD, high-altitude, exercise dysfunction, pulmonary rehabilitation, hypoxia

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality globally, characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The World Health Organization estimates that COPD will become the third leading cause of death by 2030, affecting millions of individuals worldwide.[1] The disease significantly impairs physical functioning, leading to exercise dysfunction, which is a critical determinant of health-related quality of life in COPD patients.[2] COPD is primarily caused by exposure to noxious particles or gases, with tobacco smoke being the most common risk factor. However, in high-altitude regions, the pathophysiology of COPD can be further complicated by environmental factors such as hypoxia, which can exacerbate the disease and lead to additional complications, including pulmonary hypertension and right heart failure.[3,4]

High-altitude environments, typically defined as elevations above 2500 meters (8200 feet), present unique challenges for individuals with pre-existing respiratory conditions such as COPD. The reduced partial pressure of oxygen at high-altitudes can exacerbate hypoxemia, leading to increased respiratory distress and impaired exercise capacity.[5] The interaction between high-altitude and COPD is multifaceted. Chronic hypoxia at high-altitudes can lead to various physiological adaptations, including increased red blood cell production and changes in pulmonary vascular resistance. However, these adaptations may not be sufficient to counteract the effects of COPD, leading to further deterioration of pulmonary function and increased morbidity.[6] Moreover, the presence of pulmonary hypertension in COPD patients living at high-altitudes poses additional risks, as it can significantly impair exercise capacity and overall quality of life.[7] Patients with COPD often experience a pronounced decline in physical performance when exposed to high-altitude conditions, which can further complicate their management.[8] Exercise dysfunction in these patients is multifactorial, influenced by both pulmonary and extra-pulmonary factors, including muscle dysfunction, nutritional deficiencies, and psychological comorbidities.[9]

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Pulmonary rehabilitation (PR) has emerged as an essential component of COPD management, particularly for addressing exercise dysfunction. PR programs typically encompass exercise training, education, and behavioral interventions, aiming to enhance physical and psychological well-being.[10] However, the implementation of PR in high-altitude settings requires careful consideration of the unique physiological challenges posed by lower oxygen availability.

Despite the growing body of literature on COPD and PR, there remains a paucity of comprehensive reviews specifically addressing exercise dysfunction and rehabilitation strategies in COPD patients at high-altitudes. This review aims to synthesize current evidence on the impact of high-altitude environments on exercise capacity in COPD patients and to evaluate effective pulmonary rehabilitation strategies that can be employed in these settings.

Method

We conducted a comprehensive search on PubMed, Web of Science and China national knowledge infrastructure (CNKI) up to January 2025, for relevant studies. The search utilized a combination of keywords, including "COPD", " Exercise capacity", "Exercise training", "Pulmonary rehabilitation", "High-altitude", "Hypoxia", "Quality of Life", among others. Additionally, the reference lists of the retrieved articles were reviewed to assess their relevance to the focus of this review.

Epidemiology of COPD at High-Altitude

Prevalence of COPD at High-Altitude

Brakema et al reported that the incidence of COPD is higher in high-altitude areas and can be attributed to multiple factors, including environmental pollution and lifestyle choices. The study emphasized the need for further investigation into the role of household air pollution, which is prevalent in many high-altitude communities, as a contributing factor to the increased rates of COPD.[11] And some scholars have also observed a significant positive and partial correlation between altitude and the mortality rate of chronic lower respiratory diseases.[12] However, other study has yielded opposite results, showing a significant inverse correlation between prevalence/severity of COPD and altitude.[13] In summary, there are very few studies on the relationship between high-altitude and COPD prevalence, and due to the geographical limitations of these studies, more research is needed to confirm the relationship between the two.

Risk Factors for COPD in High-Altitude Populations

Hypoxia

Chronic exposure to low oxygen levels at high-altitudes can lead to physiological changes that may worsen COPD symptoms. Chronic hypoxia is a common trait among COPD patients living at high-altitudes, potentially leading to increased pulmonary vascular resistance and the development of pulmonary hypertension.[14,15]

Environmental Pollution

High-altitude regions often experience significant air pollution from various sources, including biomass burning and industrial emissions. This pollution can exacerbate respiratory conditions, including COPD.[11]

Socioeconomic Factors

Socioeconomic status can influence access to healthcare, education, and resources for managing COPD. Populations in lower socioeconomic brackets may be more susceptible to developing COPD due to limited access to preventive measures and treatment options.[12]

Genetic Predisposition

Genetic factors may also play a role in the susceptibility of individuals to COPD at high-altitudes. Studies have suggested that certain genetic markers may influence how individuals respond to hypoxic conditions, potentially affecting their risk of developing COPD.[16]

Unique Characteristics of High-Altitude COPD

COPD in high-altitude populations presents unique clinical characteristics that differentiate it from COPD at lower altitudes. For instance, patients living at high-altitudes may experience more pronounced symptoms due to the combined

effects of hypoxia and airflow limitation. In addition, Gonzalez-Garcia et al found that pulmonary hypertension is more prevalent among COPD patients residing at high-altitudes, which can significantly impair exercise capacity and overall quality of life.[7] Based on the particularity of the environment, the diagnostic criteria for COPD may need to be adjusted for high-altitude populations. Traditional spirometric measurements may not accurately reflect pulmonary function in these individuals due to the physiological adaptations that occur at high-altitudes.[4] Therefore, it is essential to consider altitude-related factors when diagnosing and managing COPD in these populations.

Exercise Dysfunction and Related Factors in Patients with COPD at High-Altitude

Exercise Dysfunction in COPD Patients at High-Altitude

The systemic effects of COPD lead to cardiovascular complications, muscle atrophy, and osteoporosis, which in turn result in lack of exercise and physical disorders. COPD patients from high-altitude showed significantly different in baseline characteristics, laboratory tests and pulmonary function test.[17] These differences have a direct impact on the health-related quality of life of patients with this respiratory disease. The hypoxic conditions encountered at elevated altitudes can lead to reduced oxygen saturation, which exacerbates respiratory symptoms such as dyspnea, cough, and sputum production.[18] In addition, high-altitude conditions impose additional strain on respiratory mechanics, resulting in a progressive decrease in exercise capacity, increased dyspnea, dynamic hyperinflation, restrictive mechanical constraints, and gas exchange abnormalities during exercise.[3] But there are also results indicating that living at higher altitude is associated with reduced functional exercise capacity as defined by 6MWD, but there is no differences in patient-reported outcomes as defined by symptoms or health status.[19]

Related Factors Leading to Exercise Intolerance in COPD at High-Altitude

Hypoxia and Its Effects on Exercise Capacity

Exercise dysfunction in COPD can be defined as an inability to perform physical activities at levels that are considered normal for healthy individuals of the same age and sex. Exercise dysfunction may be caused by respiratory limitation due to airflow obstruction, peripheral muscle dysfunction, and cardiovascular limitations.[20,21] It is often assessed using exercise tests, such as the six-minute walk test (6MWT) or cardiopulmonary exercise testing (CPET), which measure the distance walked, oxygen uptake (VO2), carbon dioxide output (VCO2), maximal minute ventilation (VE) or ventilatory equivalent for CO2 (VE/VCO2), respectively.[22,23]

One of the primary mechanisms contributing to exercise dysfunction in high-altitude COPD patients is hypoxia, which occurs due to reduced oxygen availability at elevated altitudes.[8] At altitudes above 2500 meters, the partial pressure of oxygen decreases, leading to lower arterial oxygen saturation (SaO2) levels. This hypoxic environment can significantly impair exercise performance, as oxygen is essential for aerobic metabolism and energy production during physical activity.[24,25] Hypoxia induces a series of physiological responses aimed at compensating for the reduced oxygen availability.[26] These responses include increased ventilation, elevated heart rate, and enhanced red blood cell production.[27–29] However, in COPD patients, these compensatory mechanisms may be insufficient due to pre-existing pulmonary function impairment.[26] High-altitude environments present additional challenges for COPD patients, as the lower partial pressure of oxygen can exacerbate existing exercise limitations. Therefore, COPD patients experience a significant decrease in exercise capacity when exposed to high-altitudes due to hypoxemia and increased work of breathing.[7] The combination of hypoxia and pre-existing respiratory dysfunction can lead to a vicious cycle of decreased physical activity, muscle deconditioning, and worsening respiratory symptoms.[30]

Impaired Pulmonary Function

COPD is characterized by airflow limitation and excessive expansion of alveoli, which can further exacerbate exercise dysfunction in high-altitude environments.[31] Besides, the lung tissue of patients with COPD exhibits an inflammatory response, releasing various inflammatory mediators.[4,32] This inflammation not only affects the airways but also leads to systemic effects, including muscle wasting and deconditioning.[33] These effects lead to the prevalence of skeletal muscle dysfunction in COPD patients and significantly affect their exercise ability.[34]

Free radicals and other active substances also play important roles in the pathophysiological processes of COPD.[35,36] When these substances overwhelm the availability of antioxidants, oxidative stress occurs, causing damage to lung tissue. These mediators can stimulate abnormal proliferation of endothelial cells and smooth muscle cells in the pulmonary artery, leading to thickening of the vascular wall and restricted blood flow, ultimately causing pulmonary hypertension and even right heart failure.[35,36] These changes can significantly impair gas exchange efficiency, particularly during physical exertion when the demand for oxygen increases. In high-altitude conditions, the impaired pulmonary function of COPD patients can lead to a greater mismatch between ventilation and perfusion, resulting in hypoxemia. Consequently, the combination of pre-existing lung function impairment and altitude-related hypoxia can severely limit exercise capacity in COPD patients.[31] Honge et al highlights that PPARA expression is downregulated in COPD patients at high-altitude, leading to dysregulation of the hypoxia-inducible factor pathway and exacerbated inflammatory responses.[36] PPARA signaling could be a promising therapeutic target for improving lung function and exercise tolerance in these individuals. Given the unique challenges faced by COPD patients at high altitudes, further research into PPARA's mechanisms can provide critical insights for developing optimized pulmonary rehabilitation strategies tailored to this population.

Cardiovascular Responses

The cardiovascular system plays a crucial role in supporting exercise performance by delivering oxygen-rich blood to the working muscles. In COPD patients, particularly those living at high-altitudes, the cardiovascular response to exercise can be compromised.

Chronic hypoxia can lead to pulmonary hypertension, a condition characterized by elevated blood pressure in the pulmonary arteries, which is common among COPD patients residing at high-altitudes.[37] Pulmonary hypertension can result in right ventricular dysfunction, further impairing the heart's ability to pump blood effectively during exercise. This can lead to reduced cardiac output and exercise intolerance.[38] Studies have shown that COPD patients with pulmonary hypertension experience greater limitations in exercise capacity compared to those without this condition.[7]

Additionally, the increased workload on the heart due to hypoxia can lead to arrhythmias and other cardiovascular complications, further exacerbating exercise dysfunction.[39]

Muscle Deconditioning and Dysfunction

Another significant factor contributing to exercise dysfunction in high-altitude COPD patients is muscle deconditioning. Skeletal muscle can alter its size and metabolic/contractile characteristics to cope with various stimuli, such as mechanical stress, neuronal activity, metabolic and hormonal effects, as well as environmental factors. Prolonged inactivity due to respiratory limitations can lead to muscle atrophy and weakness, particularly in the lower extremities, which are essential for ambulation and physical activity.[40] The combination of hypoxia and muscle deconditioning can create a vicious cycle, where reduced exercise capacity leads to further inactivity and muscle deterioration.

A slow-to-fast transition in fiber type is commonly found in lower limb muscles from patients with COPD, and exposure to high-altitude areas may exacerbate this transition. Therefore, high-altitude environment exacerbates exercise intolerance in patients with COPD and significantly affect their overall quality of life.[41] However, chronic inactivity and muscle deconditioning could result in the slow-to-fast fiber-type conversion in lower limb muscles during COPD, further exacerbating their intolerance to exercise. Moreover, COPD is associated with systemic inflammation and oxidative stress, which can negatively impact muscle function.[42] Elevated levels of inflammatory markers, such as cytokines, have been observed in COPD patients and can contribute to muscle wasting and dysfunction.[43] In addition, the presence of comorbidities, such as cardiovascular disease and metabolic syndrome, can further exacerbate muscle dysfunction and limit exercise capacity in this population.[44,45]

Psychological Factors

Psychological factors, including anxiety and depression, can also play a role in exercise dysfunction among COPD patients.[46] High-altitude environment pose risks of hypoxia, which can lead to psychiatric disorders such as anxiety, depression, and psychosis.[47] The experience of chronic respiratory symptoms, coupled with the challenges of living at high-altitudes, can lead to increased levels of anxiety and depression, which can further reduce motivation to engage in

physical activity.[48] These psychological issues can further complicate COPD management, as they may lead to decreased adherence to treatment regimens, reduced motivation to participate in pulmonary rehabilitation, and a general decline in health status. Effective management of COPD in high-altitude settings must address not only the physiological aspects of the disease but also the psychological health of patients to improve overall outcomes.

In summary, exercise dysfunction in COPD is a multifactorial issue that significantly impacts patients' quality of life and functional status (Figure 1). The challenges posed by high-altitude environments necessitate a deeper understanding of the mechanisms underlying exercise limitations and the development of targeted rehabilitation strategies.

Pulmonary Rehabilitation and Its Challenges at High-Altitudes

Goals and Efficacy of Pulmonary Rehabilitation in COPD

The primary goals of PR are to enhance the quality of life, increase exercise capacity, and reduce symptoms of dyspnea and fatigue. This comprehensive program typically includes exercise training, education, and behavioral interventions tailored to the individual needs of patients.[10] Numerous studies have demonstrated the positive impact of pulmonary rehabilitation on various health outcomes in COPD patients. Exercise training is a cornerstone of pulmonary rehabilitation, focusing on both aerobic and resistance training to improve physical endurance and muscle strength. Aerobic exercises, such as walking, cycling, and swimming, are essential for enhancing cardiovascular fitness, while resistance training helps to build muscle strength, which is often compromised in COPD patients due to inactivity and muscle wasting.[49] Education is another critical component of PR, providing patients with essential information about their condition, self-management strategies, and the importance of adherence to prescribed therapies. This educational aspect empowers patients to take an active role in managing their disease, leading to better health outcomes.[50] Psychosocial support is also integral to pulmonary rehabilitation, as COPD can significantly impact mental health. Counseling and support groups help address the emotional challenges faced by patients, fostering a sense of community and shared experience.[51] Despite its proven efficacy, the implementation of pulmonary rehabilitation programs can be challenging, particularly in specific populations, such as those living at high-altitudes.

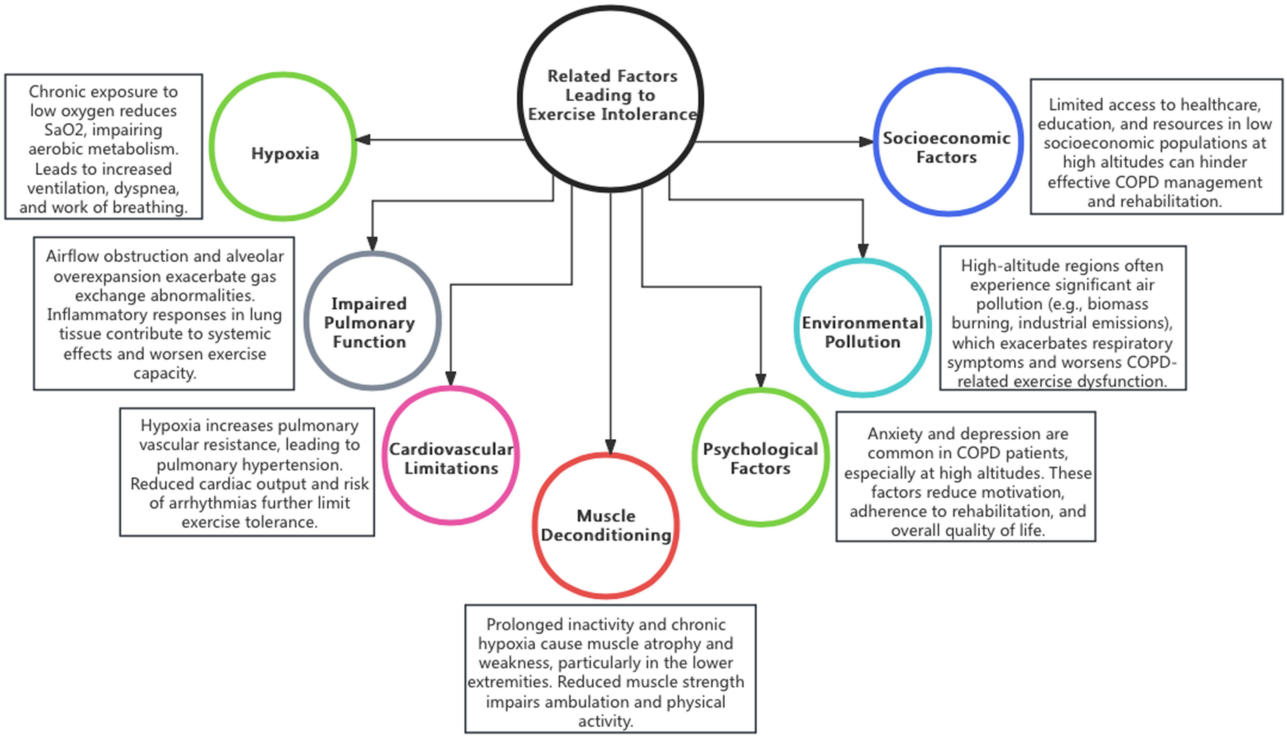

Figure 1 The related factors leading to exercise intolerance in COPD at high-altitude.

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Challenges of Implementing Pulmonary Rehabilitation at High-Altitudes

The reduced oxygen availability at high-altitudes can significantly impact the exercise capacity of COPD patients. Studies have shown that individuals with COPD experience greater exercise-induced desaturation and increased levels of perceived exertion when exercising in hypoxic conditions.[7] As a result, patients may struggle to adhere to rehabilitation protocols, leading to suboptimal outcomes. To address these challenges, successful pulmonary rehabilitation at high-altitudes requires specific adaptation strategies.

While pulmonary rehabilitation is a vital component of COPD management, its implementation at high-altitudes necessitates careful consideration of the unique challenges posed by the environment. The reduced oxygen availability can exacerbate symptoms and limit exercise capacity, making it essential to adopt specific adaptation strategies. Gradual acclimatization, supplemental oxygen, and individualized exercise plans are critical for optimizing rehabilitation outcomes in this patient population.

Pulmonary Rehabilitation Strategies for COPD Patients at High-Altitude

The unique characteristics of high-altitude environments present various challenges for pulmonary rehabilitation in COPD patients, making it essential to develop rehabilitation strategies tailored for COPD patients in these areas. First, personalized assessments should be conducted for COPD patients in high-altitude. Then, based on the patients' specific circumstances, pulmonary rehabilitation strategies should be formulated, including but not limited to aerobic exercise, resistance training, high-intensity interval training, breathing exercises, oxygen therapy, nutritional support, health education, and self-management (Table 1).

Individualized Assessment and Goal Setting

Before initiating a pulmonary rehabilitation program, a comprehensive assessment of the patient's baseline functional capacity, including exercise tolerance and symptom severity, is essential.[52] Tools such as the six-minute walk test (6MWT), the Borg Rating of Perceived Exertion (RPE) scale and assessing symptoms using the Modified Medical Research Council (mMRC) dyspnea scale can help determine the patient's current status and set realistic, achievable goals.[53] Individualized goal setting is crucial, as it fosters motivation and adherence to the program.[52] Individualized rehabilitation plans should be developed based on these assessments, taking into account the patient's specific needs, comorbidities, and altitude-related challenges.

Table 1 The Proposed Pulmonary Rehabilitation Measures for COPD Patients at High Altitudes

Project	Specific Measures
Individualized Assessment	Conduct baseline assessments using tools like the 6-minute walk test (6MWT), Borg RPE scale, and mMRC dyspnea scale. Set realistic, personalized goals to enhance motivation and adherence.
Aerobic Training	Focus on low to moderate-intensity exercises like walking, cycling, or swimming. Gradual acclimatization to high-altitude conditions. Perform 20–30 minutes of aerobic exercise, 3–5 times per week.
Resistance Training	Incorporate exercises targeting major muscle groups using body weight, resistance bands, or weights. Conduct sessions 2–3 times per week with gradual progression.
Interval Training	Use HIIT with alternating periods of high-intensity exercise and rest. Beneficial for reducing fatigue and improving exercise capacity.
Supplemental Oxygen Therapy	Provide supplemental oxygen during exercise to alleviate hypoxemia and improve tolerance. Base oxygen use on individual assessments of oxygen saturation during activity.
Breathing Techniques	IMT can improve inspiratory muscle strength, functional capacity, and pulmonary function.
Nutritional Support	Address nutritional deficiencies with high-protein, high-calorie diets to combat muscle wasting and improve overall health.
Education and Self-Management	Including patient education, disease understanding, self-monitoring, and management skills to enhance patient independence and quality of life.

Exercise Modalities

Aerobic Training

Aerobic exercises, such as walking, cycling, and swimming, are fundamental components of any exercise program for COPD patients.[54] At high-altitudes, training programs should be tailored to accommodate the reduced oxygen availability. Supplemental oxygen (FIO2 28% and 35%) can significantly increases the duration of exercise for COPD patients at high-altitude.[55] This article revealed that the administration of oxygen led to a significant improvement in exercise tolerance (ET) by reducing respiratory load, enhancing cardiovascular performance, and optimizing oxygen transport. However, the greater increases in PaO2 and SaO2 achieved with 35% FIO2 did not provide a notable advantage in ET. This observation carries important considerations for the use of oxygen in rehabilitation programs for COPD patients living in high-altitude regions.

At high-altitudes, low to moderate-intensity aerobic training is recommended to minimize the risk of hypoxemia and excessive fatigue.[56] Patients should aim for 20–30 minutes of aerobic exercise, 3–5 times per week, gradually increasing duration and intensity as tolerated.[2]

Resistance Training

Incorporating resistance training into the exercise regimen can help improve muscle strength and endurance, which are often compromised in COPD patients. Resistance exercises should focus on major muscle groups and can be performed using body weight, resistance bands, or weights. Training sessions should be conducted 2–3 times per week, with an emphasis on proper technique and gradual progression.[57]

Interval Training

High-intensity interval training (HIIT) involves alternating periods of high-intensity exercise with recovery periods and has gained popularity in recent years due to its effectiveness in improving exercise capacity in various populations.[58–60] HITT is an effective therapy for improving peak VO2 in patients with coronary artery disease and heart failure, without causing deterioration of cardiovascular disease risk markers, cardiac structure and function, and health-related quality of life.[59,61] A comprehensive multicentre randomized controlled trial revealed that HIIT potentially allowed COPD patients to experience multiple extrapulmonary benefits by reducing the ventilatory burden.[62] This approach can be particularly beneficial with hypoxemia, as it allows for short bursts of exertion followed by rest, reducing the risk of excessive fatigue.[63]

Supplemental Oxygen Therapy

For some COPD patients, supplemental oxygen may be necessary during rehabilitation at high-altitudes. Supplemental oxygen may facilitate muscular training adaptations, particularly in limb muscle dysfunction, thereby contributing to the enhanced training responses on maximal aerobic and functional capacity.[64] A meta-analysis revealed that for every 1000 meters of altitude gain, partial pressure of arterial oxygen in patients with COPD decreases by 0.84 kPa.[65] However, the decision to use supplemental oxygen should be based on individual assessments of oxygen saturation levels during exercise.[55]

Breathing Techniques

High-altitude exposure reduces inspiratory muscle strength, and exhibits increased dyspnea, dynamic hyperinflation, restrictive mechanical constraints, and gas exchange abnormalities during exercise in COPD patients.[8,66] Inspiratory muscle training (IMT) can reduce the decline in resting SpO2 at altitudes of 4880 m or higher.[67] The use of IMT alone in COPD patients can improve inspiratory muscle strength, functional capacity, and pulmonary function, without changing dyspnea and quality of life.[68] Instructing diverse breathing techniques in different positions is an important session of rehabilitation in asthma patients at high-altitude,[69] this measure may also have a positive effect on disease management for COPD patients living in high-altitude areas.

Nutritional Support

Loss of body mass and exercise intolerance are common findings in COPD and are often difficult to reverse despite optimal nutritional intake.[70] Hypoxia aggravates fasting-induced muscle wasting.[41] So, proper nutrition is essential for

maintaining health in COPD patients, especially at high-altitudes, where energy demands may increase. Unfortunately, there are currently no studies demonstrating nutritional support strategies for COPD patients at high altitudes. Nutritional interventions should focus on ensuring adequate caloric intake and addressing deficiencies that could impact muscle function and overall well-being.

Education and Self-Management

Education is a vital component of pulmonary rehabilitation, empowering patients to manage their condition effectively.[2] Self-management for asthma patients at high-altitudes can be used to maintain quality of life and asthma control.[71] Combined the sessions for training the conditional physical capabilities and the sessions for health education in COPD patients at high altitudes can improve Muscular strength, Physical activity level and Quality of life associated with health[72] so COPD patients should be educated about the importance of exercise, the physiological effects of high-altitude, and strategies for self-monitoring during exercise according to pulmonary rehabilitation guidelines.[2,73] Providing patients with tools to recognize their limits and adjust their activities accordingly can enhance adherence to the rehabilitation program and improve overall outcomes.[74]

Conclusion

COPD presents significant challenges for patients living in high-altitude environments due to the unique physiological stressors associated with reduced oxygen availability. This review highlights the exercise dysfunction, related factors and possible pulmonary rehabilitation strategies in patients with COPD at high-altitudes. Effective management strategies, particularly tailored pulmonary rehabilitation programs, are essential for addressing these challenges. Such programs should incorporate specific exercise regimens, nutritional support, and breathing techniques designed for high-altitude conditions. Moving forward, research should focus on developing and validating PR protocols specifically suited for high-altitude COPD patients. Investigating the long-term effects of high-altitude PR on disease progression, exercise capacity, and quality of life is essential for establishing best practices. Additionally, exploring the integration of telemedicine and remote monitoring could enhance access to PR services for patients in remote high-altitude areas, ensuring necessary support for effective disease management.

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Disclosure

The authors declare no conflicts of interest in this work.

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