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Cardiovascular system at high altitude: emerging advances from bibliometric and visualization analysis

Cardiovascular system at high altitude

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Abstract

BACKGROUND

When exposed to high-altitude environments, the cardiovascular system undergoes various changes, the performance and mechanisms of which remain controversial.

AIM

In this study, bibliometric and visual analyses were conducted to summarize the latest research advancements and focal points in the cardiovascular system at high altitudes.

METHODS

The literature was systematically retrieved and filtered using the Web of Science Core Collection of Science Citation Index Expanded (SCIE). Visual analysis of the identified publications was conducted employing CiteSpace and VOS viewer.

RESULTS

A total of 1674 publications were included in the study, with an observed annual increase in the number of publications spanning from 1990 to 2022. The United States of America emerged as the predominant contributor, while Universidad Peruana Cayetano Heredia stood out as the institution with the highest publication output. Notably, Philip N Ainslie demonstrated the highest productivity among researchers focusing on the cardiovascular system at high altitudes. Furthermore, Bärtsch P emerged as the author with the highest number of cited articles. Keyword analysis identified hypoxia, exercise, acclimatization, acute and chronic mountain sickness, pulmonary hypertension, metabolism, and echocardiography as the primary research focal points and emerging directions in the study of the cardiovascular system at high altitudes.

CONCLUSION

Over the past 32 years, research on the cardiovascular system in high-altitude regions has been steadily increasing. Future research in this field may focus on areas such as hypoxia adaptation, metabolism, and cardiopulmonary exercise. Strengthening interdisciplinary and multi-team collaborations will facilitate further exploration of the pathophysiological mechanisms underlying cardiovascular changes in high-altitude environments and provide a theoretical basis for standardized disease diagnosis and treatment.

Key Words: cardiovascular system; high altitude; bibliometric analysis; visualization

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Core Tip: In this study, bibliometric and visual analyses were conducted to summarize the latest research advancements in the cardiovascular system at high altitudes. Based on 1674 publications, we provided a comprehensive description about countries, institutions, authors, journals and keywords in this field. Our findings would be helpful in investigating the mechanisms that affect cardiovascular system at high altitude and the future clinical applications.

INTRODUCTION

Globally, a large number of people visit, work, or reside at high altitude. An estimated 81.6 million people live at altitudes > 2,500 meters above sea level and 14.4 million people live at altitudes ≥ 3,500 meters above sea level[1]. The oxygen levels decline with increasing altitude. Therefore, exposure to hypoxia significantly affects physical performance and the cardiovascular system[2]. Exposure to hypoxia or intermittent hypoxia activates compensatory cardioprotective mechanisms[3]. Several studies have shown that short-term intermittent hypoxia promotes cardioprotective

effects similar to ischemia preconditioning. For example, intermittent hypoxia protected cardiomyocytes against H2O2- and ischemia/reperfusion induced oxidative stress and cell death by maintaining Ca^{2+} homeostasis and the mitochondrial membrane potential, and upregulating the expression levels of the antioxidant enzymes[4].Intermittent hypobaric hypoxia exposure in rats induced cardiovascular protective mechanisms against oxidative stress[5]. However, prolonged exposure to hypoxia at high altitude increases the risk of cardiovascular disease by chronically activating cellular responses that are detrimental to cardiac function. The damage to cardiac cells at high altitude because of exposure to hypoxic and hypobaric environment results in elevated serum levels of myocardial enzymes to varying degrees; in severe cases, myocardial damage causes malignant arrhythmia, heart failure, and even sudden death[6]. Furthermore, at high altitudes, many subjects experience acute mountain sickness (AMS), high-altitude cerebral edema (HACE), high-altitude pulmonary edema (HAPE), chronic mountain sickness (CMS), and high-altitude pulmonary hypertension (HAPH) [7]. The prevalence of myocardial injury at high altitude was 18.6%-33.2%[8, 9]. Although several studies have reported adverse effects of high altitude on the cardiovascular system, the mechanisms are complex and unclear. Therefore, there is urgent need to identify the advances, trends, and hotpots in the research area of cardiovascular system at high altitude based on previous publications. This information would be beneficial for research investigators in this field to pursue studies in the right direction.

Bibliometric methods are used to investigate the productivity of researchers, institutions, and countries in specific subject areas to determine the research hotspots and future directions that can also be used to guide policy decisions[10]. Furthermore, bibliometric analysis is a good indicator of progress in a research field[11]. Moreover, co-citation is frequently used in the bibliometric analysis to identify links between authors, keywords, countries, and organizations.

Several bibliometric analyses have been performed in the field of the cardiovascular system in areas such as heart transplantation, future landscape of macrophage research

in cardiovascular disease, and heart failure[12-15]. In this study, we performed bibliometric analysis of studies based on the cardiovascular system at high altitude using the Science Citation Index Expanded (SCIE) index of the Web of Science (WOS) core collection. Our aim was to identify the current hotpots of research and the frontier directions that would be helpful in investigating the mechanisms that affect cardiovascular system at high altitude and the future clinical applications in this field.

MATERIALS AND METHODS

2.1 Bibliometric analysis

CiteSpace 6.1 R6 software and VOS viewer 1.6.18.0 software were used for the bibliometric analysis of countries, institutions, journals, and keywords of research related to the cardiovascular system at high altitude between 1st January 1990 and 31st December 2022. The CiteSpace software was used to simultaneously visualize the co-occurrence network between time, frequency, and betweenness centrality. Cluster view was used to label the clusters with phrases. Furthermore, the CiteSpace software was used for temporal analysis and the pruning algorithms were used to highlight the main structure of the network[16]. The co-occurrence analysis in CiteSpace was used to visualize the o-authorship network of countries, institutions, journals, and authors. CiteSpace software was also used to visualize the timeline view of keyword clustering and identify the development process and hotpots in cardiovascular system at high altitude. In CiteSpace, nodes size represented the frequency of publications and citations; purple rings represented centrality; nodes in the red inner rings represented the burst in research[17]. Furthermore, connections between points represented the co-citation relationship and the number of interconnections represented the strength of co-occurrence or co-citation of the collaboration.

VOS viewer is a popular tool for visualizing the knowledge map and provides a variety of tools for viewing keywords, co-institutions, co-authors, *etc.*, including Network Visualization, Overlay Visualization, and Density Visualizatio [18]. Co-citation analysis of cited references, journals, and authors, and the co-occurrence analysis of

keywords were visualized using the VOS viewer. The points in the co-citation maps represented different co-cited references, journals, or authors Size of the points represented the number of citations in individual publications. The lines between points showed co-citation relationships. The colored points represented different clusters and the colored lines represented different years.

2.2 Data Source and Literature search strategy

In this study, we searched for publications related to cardiac system at high altitude in the Science Citation Index Expanded (SCIE) index of the WOS Core Collection using the following keywords and combinations: TS = ((“high altitude” OR “plateau” OR “mountain”) AND (“cardiovascular” OR “heart” OR “cardiac” OR “myocardial”)). The time span was set between 1st January 1990 and 31st December 2022. The literature language was restricted to English. We identified 6605 publications that met these criteria. The literature types were limited to articles and reviews. The exclusion criteria are shown in Table 1. After initial search, we retrieved 5992 publications as potential candidates for inclusion. Subsequently, the titles, abstracts, and the full texts of the publications were manually examined by two investigators (MZ and SH) and the irrelevant articles were excluded. Finally, after removing duplicates, we included 1674 journal articles, including 1331 articles and 133 reviews for further analysis.

RESULTS

3.1 Descriptive statistics

This study included 1674 papers with 7433 authors from at 2041 organizations and 78 countries; these papers were published in 586 journals, and were cited in 44674 publications from 7775 journals (Table 2). Figure 1 shows the chronological distribution of publications in the field of research related to the cardiac system at high altitude. The number of papers published in this field increased e every year from 1990 to 2022, especially from 2012 onwards. The annual publication rate was >60, This suggested significant research in this area, especially after 2012.

3.2 Co-authorship network analysis based on countries, institutions, authors, and journals

We constructed a co-occurrence network of countries and institutions to evaluate the progress of studies on the cardiovascular system at high altitude in different countries and institutions, and also determine the potential co-operation between countries and institutions in this area. Figure 2A shows the interactions between countries and Figure 2B shows the interactions between institutions in this research area. The top 5 productive countries in this research area were USA (409 papers), People's Republic of China (367 papers), England (156 papers), France (129 papers) and Canada (124 papers) (Table 3). The top 5 countries for centrality were USA (0.41), People's Republic of China (0.21), England (0.20), Germany (0.16), Switzerland (0.13) (Table 4). The betweenness centrality was more than 0.1 for these 5 countries, thereby highlighting their leading role in research area. Table 5 shows the top 10 institutions in the research area of cardiovascular system at high altitude. The universities with the highest number of publications were as follows: Universidad Peruana Cayetano Heredia (57 papers), University of British Columbia (51 papers), Chinese Academy of sciences (48 papers), University of Innsbruck (48 papers), and University of Colorado (46 papers). The top ten countries in this area included six European countries (England, Germany, Switzerland, Italy, France, Netherlands), two North American countries (USA, Canada), one Asian country (People's Republic of China) and one South American country (Chile). These top ten countries accounted for 93.91% of the publications.

Next, we analyzed the literature to identify the main research scholars studying the cardiac system at high altitude. Figure 2C shows the network of author-co-author relationships in this field. Table 6 shows the authors who have published 16 papers or more in the area of cardiovascular system at high altitude. Ainslie PN from University of British Columbia contributed the most publications with 31manuscripts, 565 citations, and an average of 18 citations per article. In the second place, Burtscher M from University of Paris published 30 articles with 488 citations and an average of 16

citations article. Richalet, J-P from the University of Paris published 22 papers with 1226 citations and an average of 55 citations per article.

Impact factor of a journal refers to the importance of a journal in the research area of interest, and is calculated by the frequency with which the articles published in the journal were cited in other articles[19]. Table 7 shows the top 10 journals in the field of cardiovascular system at high altitude. The top three journals High *Altitude Medicine & Biology* (144 publications), *Journal of Applied Physiology* (81 publications), *Frontiers in Physiology* (55 publications). The top journals with the highest number of citations per article were The *Journal of Physiology (-London)* (41.62 citations per publication), *Journal of Applied Physiology* (37.71 citations per publication), and *American Journal of Physiology-Regulatory Integrative and Comparative Physiology* (37.68 citations per publication).

3.3 Co-citation analysis of cited references, journals, and authors

The number of citations reflects the quality of a study and is an indicator of the importance of the findings for the research field[20]. The most cited references provide a theoretical basis for studying the cardiovascular system at high altitude and guide researchers for further studies. We performed a bibliometric analysis of the cited references and obtained 44674 citations in this study. Then, using 30 citations as a threshold, we identified 75 articles for co-citation analysis of the cited articles. We then constructed a network of publications that were related to research regarding cardiac system at high altitude. We identified five clusters represented by different colors and the cited references were represented as nodes of different sizes (Figure 2D). Table 8 summarizes the top 10 most frequently cited references. The top 5 cited references were as follows: Hackett *et al* (2001) (123 citations), Naeije *et al* (2010) (107 citations), Penaloza *et al* (2007) (107 citations), Roach *et al* (1993) (97 citations), Ba□rtsch P *et al* (2007) (90 citations). Our study showed that the top three cited references were all reviews. The most cited publication was a review authored by Hackett PH *et al*, which described the epidemiology and risk factors, pathophysiological process, clinical manifestations, diagnosis, treatment, and disease preventive measures at high altitude[21]. The second and third most cited references also reviewed the pathophysiological processes of the

cardiopulmonary vascular system at high altitude. The second reference was published by Naeije R, mainly focused on the acclimatization of the cardiovascular system at high altitude[22]. The third reference was a review published by Penaloza D and Aria-Stella J in Circulation (2007) and was titled " The Heart and Pulmonary Circulation at High Altitudes Healthy Highlanders and Chronic Mountain Sickness"[23]. This review described physiology, pathology, pathogenesis, and clinical features of the heart and pulmonary circulation in healthy highlanders and patients with chronic mountain sickness[23]. The seventh most cited reference published by León-Velarde F *et al*, and the expert consensus statement on the chronic and subacute diseases at high altitude and described the criteria for selecting a specific methods or procedures to diagnose or manage these diseases[24]. The reference titled "Guidelines for Echocardiographic Evaluation of the Right Heart in Adult Patients: A Report by the American Society of Echocardiography" holds the tenth position in terms of citation count. This reference serves as a comprehensive document intended for healthcare professionals, providing them with guidelines for assessing the right ventricle and right atrium. It encompasses a range of parameters utilized for estimating both systolic and diastolic functions of the right ventricle, along with normal reference values derived from aggregated data.[25].

Subsequently, using a citation threshold of 300, we selected 39 journals for co-citation analysis. Table 9 shows the top ten most frequently cited journals. The co-citation network of journals consisted of three distinct clusters denoted by different colors (Figure 2E) *Journal of Applied Physiology* (5586 citations), *High Altitude Medicine & Biology* (2192 citations), and *circulation* (2051 citations) were the most cited journals. these three journals are esteemed publications within the JCR1 region.

Next, we sought to identify the leading researchers in this research area. We used a citations threshold of 100and identified 38 authors with a cumulative citation count of 29778. The co-citation network of these 38 authors demonstrated four distinct clusters (Figure 2F). Table 10 presents the top ten most cited authors in this network, with Bärtsch P (382 citations), Burtscher M (378 citations), and West JB (358 citations) being the three most prominently cited authors.

3.4 Co-occurrence analysis of keywords

Keywords are specific terms or phrases that summarize the main subjects and concepts presented in the article. Therefore, co-occurrence analysis of keywords can be used to identify the hotspots in a research area. In the present study, we used the VOSviewer software to construct a network of keywords in the 1674 articles included in this study. Subsequently, we identified103 keywords with a frequency of more than 20 (Figure 3A). In this network, size of the circle node denoted frequency the keywords. For example, if the circle node was large, it suggested that the keyword occurred at a higher frequency. Hence, we considered high frequency key words as research hotspots in the field of study. The line of nodes represented the strength of the association. A thicker line indicated that the two words co-appeared more times in the same article. Clusters of key words were represented by distinct colors. The top 10 keywords were high altitude (n = 598), hypoxia (n = 559), exercise (n = 269), acute mountain sickness (n = 214), adaptation (n = 209), heart (n = 167), acclimatization (n = 137), pulmonary hypertension (n = 133), heart rate (n = 117), blood pressure (n = 104) (Table 11).

Since the number and type of keywords were too complex, the research topics were ambiguous, and it was difficult to determine the current research hotspots and priorities. Previous studies have used keyword clustering to address this issue. Keyword clustering involves extracting representative phrases from keyword groups with similar meanings as specific cluster labels[12]. We used keyword clustering to determine the distribution of topics. The keyword clustering results were as follows: heart (clustering#0), autonomic nervous system (clustering #1), cardiac function (clustering #2), coronary artery disease (clustering #3), metabolism (clustering #4), acute mountain sickness (clustering #5), and endothelium (clustering #6) (Figure 3B). Based on the timeline view and clusters of keywords, we observed certain specific trends in the research hotspots regarding the study of cardiovascular system at high altitude. The main research hotspots between 1990 and 2022 were heart, cardiac function, coronary artery disease, metabolism, and acute mountain sickness. Autonomic nervous system and endothelium were also research hotspots in this field before 2015.

Furthermore, we compiled and summarized several significant points to revealed about high altitude cardiovascular system function based on the analysis of popular keywords (Table 12).

DISCUSSION

4.1 Countries distribution

The collaborations between countries have significantly advanced the understanding of the cardiovascular system at high altitude. USA accounted for the highest number of publications. Many of these publications focused on subjects regarding the cardiovascular system at altitudes ≥4000 ft [26-31]. It should be noted that altitudes above 2000 m are generally considered as high altitude. The risk of acute altitude illness is significantly higher an altitudes above 2500 m [32]. Therefore, it is not clear if all the studies included in this study can be considered as relevant for understanding the cardiovascular system at high altitude. Furthermore, except for China and Peru, the remaining eight countries in the top ten are considered as developed nations. Despite being categorized as a developing country, China ranks second in terms of publications in the field of cardiovascular system at high altitude. This can be attributed to an extensive population of China residing at altitudes ≥3,500 m [1] . Moreover, the world's highest plateau, the Qinghai Tibet Plateau, is in China [33]. Peru is another country with a significant population residing at high altitude. Those residing at a high altitude develop a variety of diseases, including diseases of the cardiovascular system. Therefore, extensive research has been conducted in these countries on the cardiovascular system at high altitude. Universidad Peruana Cayetano Heredia is one of the top ten institutions that have focused on studying cardiac health at high altitude[34, 35].

4.2 The most cited authors

The most cited author in this field was Peter Bärtsch from the Departments of Internal Medicine and Outpatient Medicine, Heidelberg University, Heidelberg, Germany. Bärtsch *et al* focused on the clinical manifestations, epidemiology,

pathophysiology, and treatment of common diseases at high altitude[36]. Bartsch and colleagues also describe described the acute physiological adjustments and early acclimatization of the cardiovascular system in healthy individuals who visited places at high altitude as well as altitude tolerance in patients with underlying cardiovascular diseases[37]. Furthermore, Bärtsch also described the health risks for athletes at high altitude and the methods by which the performance of athletes can be improved at high altitude[38, 39]. The second most highly cited author in this field was Martin Burtscher from the Department of Sport Science, University of Innsbruck, Austria. This is also an institution with the fourth highest number of publications. Burtscher published reports focused on the cardiovascular system at high altitude[40-42], treatment and prevention recommendations of hypoxia-related altitude illnesses[43, 44], and exercise at high altitude[45]. The third most highly cited research scholar was John B. WEST from the Department of Medicine, University of California San Diego, La Jolla, USA. West JB has published articles regarding high altitude-related medicine and physiology[46, 47], the technology of oxygen enrichment in room air[2, 48], and pulmonary function at high altitude [49, 50]. University of California, San Diego is also one of the top ten institutions for publications in the field of cardiac system at high altitude because of major contributions from West JB.

4.3 Keyword analysis

Keywords reflect the core themes and main content of an article. Therefore, they highlight the research hotspots in a specialized field and provide directions for future research. Based on the top 20 keywords in this study, exercise at high altitude was identified as an important research hotspot. Previous reports have shown that visits to an at high altitude may result in acute or chronic mountain sickness; the heart undergoes a range of pathophysiological changes resulting in pulmonary hypertension, oxidative stress, and altered metabolism[22]. In the highlanders, changes in heart rate, blood pressure, nitric oxide (NO) levels, and cardiac output are closely related with altitude adaptation and acclimatization. Furthermore, echocardiography is an useful tool for diagnosing cardiac diseases at high altitude.

Exercise at high altitude

Hypoxia training is a useful strategy for improving the performance of athletes. Intense physical activity, including training at high altitude or mountaineering does not increase the prevalence or severity of acute mountain sickness at moderate altitudes[39]. A meta-analysis demonstrated that training at natural or simulated altitude improved high intensity intermittent running performance of the team-sport athletes[51]. Several contemporary elite endurance athletes incorporate some form of altitude/hypoxic training within their year-round training plan to improve their performance[52]. However, intermittent hypoxia at rest does not improve athletic performance in competitions held at sea level [38]. Therefore, exercise training is recommended to improve adaptation at high altitude[53].High altitude pulmonary hypertension Pulmonary artery pressure is elevated at high altitude because of vasoconstriction. Acute hypoxia leads to closure of the oxygen-sensitive potassium channels in the vascular smooth muscle cells; subsequent depolarization induces calcium influx and contraction of the smooth muscle cells[54]. Chronic exposure to hypoxia increased pulmonary artery pressure in the highlanders, but the criteria for diagnosis of high altitude pulmonary hypertension (HAPH) is not clear. The prevalence of HAPH varied significantly for the highlanders depending on the diagnostic criteria. The prevalence of HAPH in the highlanders was 6% according to the expert consensus definition of chronic high-altitude disease and 35% according to the current definition of pulmonary hypertension proposed for the lowlanders[55]. Chronic exposure to high altitude is also associated with arterial remodeling[56].The proliferation of vascular smooth muscle cells in the alveolar wall is one of the first remodeling events that continues even after the elimination of hypoxic stimulation[57]. Furthermore, hypoxia promoted smooth muscle cell proliferation and pulmonary vascular thickening by impairing endothelial cell membrane integrity and stimulating the secretion of growth factor[58]. Moreover, chronic hypoxia promoted smooth muscle cell proliferation and pulmonary vascular thickening by maintaining fibroblasts in an activated state through epigenetic regulatory mechanisms[59].

Oxidative stress at high altitude

Oxidative stress is involved in the development of AMS, CMS, and HAPA [7]. Oxidative stress is elevated at higher altitude and may persist until return to the sea level. Exposure to hypoxia alters several signaling pathways, including generation of higher levels of reactive oxygen species (ROS) that may activate important adaptive responses[60]. Endothelial cell function is affected by hypoxia and oxidative stress. Furthermore, persistent impairment in the vascular function of lowlanders after exposure to high altitude is in part attributed to with oxidative stress[61]. Hu *et al* [62] demonstrated that the activity of the large-conductance Ca^{2+}-activated K^{+} (BKCa) channels in the uterine arteries of pregnant sheep was inhibited by increased oxidative stress in an hypoxic environment.

Altered cardiovascular function at high altitude

Major changes are observed in the cardiovascular function of subjects upon exposure to high altitudes, including increased left ventricular systolic function, preserved right ventricular systolic function, and changes in biventricular diastolic filling pattern without changing filling pressure[22]. These changes can be explained by varying degrees of sympathetic activation, reduction of preload, and the effects of long-term hypoxia on the myocardial muscle strength. High altitude exposure initiates cardiovascular response that is associated with increased sympathetic activities, increased cardiac output with tachycardia, absence of any change in output per vibration, and marginal increase in blood pressure temporarily[63]. After a few days of acclimation, cardiac output returns to normal, but stroke volume is reduced because the heart rate continues to increase. Furthermore, pulmonary artery pressure is elevated but the pulmonary artery wedge pressure remains unchanged [64]. It is worth noting that increased cardiac output is proportional reduced in arterial oxygen levels so that the total amount of oxygen delivered to the tissues remain constant. However, these changes in the cardiovascular system in response to hypoxia are temporary, The cardiac output return to normal after a few days and the changes plateau after a certain time of exposure at high altitude[65]. HIF signaling pathway is altered at high altitude and is

crucial for acclimatization. EGLN1 and EPAS1 are major is a major regulator of the hypoxic response[66-68].

Short-term exposure to high altitude causes hypoxia, which induces dilation of blood vessels resulting in decreased blood pressure; subsequently, rapid activation of the sympathetic nerve promotes contraction of the blood vasculature; therefore, blood pressure remains unchanged or slightly increased[22, 69, 70]. The prevalence of hypertension is higher upon long-term exposure to high altitude areas; the incidence of hypertension increased by 2% for every 100m increase in altitude in areas above 3000m[71]. Aryal *et al* performed ameta-analysis of 21 articles that included 40845 Tibetan residents living at 2400 m above sea level and reported that the average systolic and diastolic blood pressure increased by 17 mmHg and 9.5 mmHg, respectively for ana elevation of 1000 m[72]. However, long-term intermittent exposure to high altitude did not significantly alter blood pressure[73]. The increase in blood pressure at high altitude was proportional to an increase in the plasma levels of norepinephrine. This suggested that norepinephrine played a key role in the activation of sympathetic nerves. However, the use of α - and β-receptor blockers did not completely restore blood pressure back to normal. This suggested that other mechanisms such as erythrocytosis and the renin-angiotensin system also participated in the elevation of increase of blood pressure at high altitude[37].

Metabolomics at high altitude

Metabolomics is a promising tool for discovering and understanding the novel biochemical responses and metabolic changes to hypobaric hypoxia exposure; it can provide new insights for the field of medicine at high altitude and unravel the underlying mechanisms for the health problems that occur in subjects upon exposure to high altitude[74]. Xie *et al* delineated the landscape of metabolites in the myocardial tissues of rats exposed to high altitude using GS/MS-based metabolomics and reported significant changes in metabolites, including several branched chain amino acids, taurine, succinic acid, and others[75]. Extensive evidence of metabolic reprogramming and phenotypic transformation of fetal sheep pulmonary arteries induced by chronic

hypoxia has been revealed by metabolomics techniques, which may contribute to the development of persistent pulmonary hypertension[76]. Guo *et al* performed plasma metabolite profiling of 57 HAPE as well as 57 control subjects with ultra-high performance liquid chromatography coupled with Q-TOF mass spectrometry and showed that C8-ceramide, sphingosine, and glutamine were candidate diagnostic biomarkers for HAPE[77]. Liu *et al* performed integrated plasma metabolomics and transcriptomic analyses to demonstrate significant association between phenotypic variation under hypoxia and the arachidonic acid metabolism pathway [78].Liao *et al* used metabolomics approach to detect plasma metabolic changes in subjects exposed to high altitude and showed significantly changes in 44 metabolites and 4 related enzymes [79]. These results provided new insights into the pathophysiological mechanism underlying the early hypobaric hypoxia adaptations and other diseases associated with tissue hypoxia.

NO is a critical regulatory molecule *in vivo* that regulates oxygen transport cascade from the lung to the cardiovascular system, blood, and the mitochondria[80, 81]. A 2-day exposure of rats to hypobaric hypoxia increased NO synthesis and promoted cardioprotective mechanisms[82]. NO is important for the pulmonary circulation response to acute and chronic hypoxia. Elevated levels of the endothelial nitric oxide synthase played a counterregulatory role in the pulmonary vasoconstriction response to acute hypoxia in the Tibetan sheep adapated to high altitude[83]. Gonzales *et al* also showed upregulation of the heart mitochondrial nitric oxide synthase in male rats exposed to high altitude[84].

Echocardiography for diagnosis at high altitude

Ultrasound is widely used in the diagnosis of heart disease at high altitude. Echocardiography is used to screen for congenital heart disease in newborns at high altitude[85]. Ultrasound is the best method for the clinical assessment of AMS[86]. Boussuges *et al* [87] performed echocardiography on eight subjects at different altitudes simulating a climb of Mount Everest and found elevated pulmonary artery pressure, normal left ventricular ejection fraction, reduced biventricular systolic and end-diastolic

volumes, and decreased mitral E/A ratio. A study of the echocardiographic changes in 41 healthy volunteers who rapidly ascended to 4559m within 24 h demonstrated elevation of the tricuspid gradient from 16 to 44 mmHg and the mean pulmonary artery pressure to 32 mmHg, and reduction of the mitral E/A ratio from 1.4 to 1.1; this demonstrated atrial contractile fitness rather than a change in the diastolic function[69]. Echocardiography measurements of 58 plain residents exposed to 4000 m altitude showed the following characteristics: mean pulmonary artery pressure increased to 20-25 mmHg; E/A ratio of the right and left ventricles decreased; isovolumic relaxation time of the right ventricle prolonged; the Tei index of the right ventricle increased; and the ejection fraction remained normal; moreover, the pulmonary artery pressure increased further when the subjects were exposed to conditions simulating an altitude of 4850 m[88]. Compared with lowland residents, highlanders showed lower pulmonary arterial pressure, higher oxygen saturation, significant changes in the biventricular diastolic function, reduced left ventricular ejection fraction, and a more pronounced increase in the Tei index of the right ventricle[88].

CONCLUSION

In the present study, we performed a bibliometric analysis of publications in the field of cardiovascular system at high altitude to identify the future research hotspots and new perspectives. Our data showed that publications have increased rapidly over the past few decades in the field of cardiovascular system at high altitude. Future research in this field may focus on areas such as hypoxia adaptation, metabolism, and cardiopulmonary exercise. Our study provides essential information for researchers in this field and identifies potential collaborative partners to further exploration of the pathophysiological changes in the high-altitude cardiovascular system and provide a theoretical basis for standardized disease diagnosis and treatment.

Limitations and outlook

The present study has several limitations. Firstly, ensure the quality and integrity of the collected data, this study selected articles and reviews from the WOS Core Collection of SCIE and excluded other databases such as Scopus. However, the analysis data may not be comprehensive enough. Furthermore, quantitative analysis needs to analyze and interpret the data. This requires researchers with an adequate and comprehensive understanding of the field. Otherwise it will result in subjectivity.

In the future research, we need to integrate the literature from multiple databases to increase the data, and actively communicate with the scholars in this field to understand the frontier subjects of research in the cardiovascular system at high altitude.

ARTICLE HIGHLIGHTS

Research background

Individuals exposed to high-altitude environments experience various changes in the cardiovascular systems. Currently, there are no bibliometric reports on research related to the high altitude cardiovascular system.

Research motivation

To summarize the research on high-altitude cardiovascular system, it facilitates further investigation into the pathophysiological changes of the high altitude cardiovascular system, thereby offering insights for clinical diagnosis, treatment, and prevention.

Research objectives

The research objective is to gain insights into the future research trends in the field of high altitude cardiovascular system. Familiarizing oneself with the leading countries, institutions, journals, and scholars in this field is beneficial for further strengthening collaborations among countries, institutions, and researchers.

Research methods

Publications related to high-altitude cardiovascular system from the Science Citation Index Expanded (SCIE) index of the WOS Core Collection from January 1, 1990, to December 31, 2022, were retrieved and downloaded. Consequently, CiteSpace 6.1 R6 software and VOS viewer 1.6.18.0 software used for a bibliometric analysis on the countries, institutions, journals, and keywords of studies related to high altitude cardiovascular system.

Research results

The United States emerged as the foremost productive nation in cardiovascular research conducted at high altitudes. Ainslie PN stood out as the scholar with the highest contribution of publications in this particular research domain. Notably, the journal High Altitude Medicine & Biology garnered significant popularity within the scientific community. Bärtsch P emerged as the most cited researcher in the field of cardiovascular studies at high altitudes. Hypoxia, Exercise, acute mountain sickness, adaptation, and metabolism at high altitude have been focal points of research concerning cardiovascular function in individuals at high altitudes. Furthermore, the pathophysiological mechanisms, diagnosis, treatment, and prevention of high-altitude illnesses have been extensively investigated.

Research conclusions

In conclusion, future research may focus on areas such as hypoxia adaptation, metabolism, and cardiopulmonary exercise. Our study provides essential information for researchers in this field, facilitating further exploration of the pathophysiological changes in the high altitude cardiovascular system and providing a theoretical basis for the standardization of disease diagnosis and treatment.

Research perspectives

Future investigations in this field may focus on areas such as hypoxia adaptation, metabolism, and cardiopulmonary exercise. Enhancing collaboration among various

institutions and scholars is imperative for advancing the research pertaining to the high-altitude cardiovascular system.

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