ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2024 April 26; 16(4): 168-216

Published by Baishideng Publishing Group Inc

W J C World Journal of Cardiology

Contents

Monthly Volume 16 Number 4 April 26, 2024

ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

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The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJC* as 1.9; IF without journal self cites: 1.8; 5-year IF: 2.3; Journal Citation Indicator: 0.33. The *WJC*'s CiteScore for 2022 is 1.9 and Scopus CiteScore rank 2022: Cardiology and cardiovascular medicine is 226/354.

RESPONSIBLE EDITORS FOR THIS ISSUE

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NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone, Pal Pacher

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE
April 26, 2024

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World J Cardiol 2024 April 26; 16(4): 199-214

DOI: 10.4330/wjc.v16.i4.199

ISSN 1949-8462 (online)

SCIENTOMETRICS

The cardiovascular system at high altitude: A bibliometric and visualization analysis

Mao-Lin Zhao, Zhong-Jie Lu, Li Yang, Sheng Ding, Feng Gao, Yuan-Zhang Liu, Xue-Lin Yang, Xia Li, Si-Yi He

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Ong H, Malaysia

Received: November 22, 2023

Peer-review started: November 22, 2023

First decision: January 23, 2024

Revised: February 14, 2024

Accepted: April 1, 2024

Article in press: April 1, 2024

Published online: April 26, 2024

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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

To summarize the latest research advancements and hot research points in the cardiovascular system at high altitude by conducting a bibliometric and visualization analysis.

METHODS

The literature was systematically retrieved and filtered using the Web of Science Core Collection of Science Citation Index Expanded. A visualization analysis of the identified publications was conducted employing CiteSpace and VOSviewer.

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, Jean-Paul Richalet demonstrated the highest productivity among researchers focusing on the cardiovascular system at high altitude. Furthermore, Peter Bärtsch 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 hot research points and emerging directions in the study of the cardiovascular system at high altitude.

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; Hypoxia; Bibliometric analysis; Visualization

Core Tip: In this study, a bibliometric and visualization analysis was conducted to summarize the latest research advancements in the cardiovascular system at high altitude. Based on 1674 publications included, we provide a comprehensive description of countries, institutions, authors, journals, and keywords involved in this field. Our findings would be helpful in investigating the mechanisms that affect the cardiovascular system at high altitude and the future clinical applications.

Citation: Zhao ML, Lu ZJ, Yang L, Ding S, Gao F, Liu YZ, Yang XL, Li X, He SY. The cardiovascular system at high altitude: A bibliometric and visualization analysis. *World J Cardiol* 2024; 16(4): 199-214

URL: https://www.wjgnet.com/1949-8462/full/v16/i4/199.htm

DOI: https://dx.doi.org/10.4330/wjc.v16.i4.199

INTRODUCTION

Globally, a large number of people visit, work, or reside at high altitude. An estimated 81.6 million people live at altitudes > 2500 m above sea level and 14.4 million people live at altitudes ≥ 3500 m above sea level[1]. The oxygen levels decline with increasing altitude. 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 H_2O_2- 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 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 people experience acute mountain sickness (AMS), high-altitude cerebral edema, 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 the adverse effects of high altitude on the cardiovascular system, the mechanisms are complex and unclear. Therefore, there is an urgent need to identify the advances, trends, and hotpots in the research area of the cardiovascular system at high altitude based on previous publications. Such 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 a bibliometric analysis of studies 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 the cardiovascular system at high altitude and the future clinical applications in this field.

MATERIALS AND METHODS

Bibliometric analysis

CiteSpace 6.1 R6 software and VOSviewer 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 January 1, 1990 and December 31, 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 co-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 the cardiovascular system at high altitude. In CiteSpace, node size represents the frequency of publications and citations; purple rings represent centrality; and nodes in the red inner rings represent the burst in research[17]. Furthermore, connections between points represent the co-citation relationship and the number of interconnections represents the strength of co-occurrence or co-citation of the collaboration.

VOSviewer 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 VOSviewer. The points in the co-citation maps represent different co-cited references, journals, or authors. Size of the points represents the number of citations in individual publications. The lines between points show co-citation relationships. The colored points represent different clusters and the colored lines represent different years.

Data source and literature search strategy

In this study, we searched for publications related to cardiac system at high altitude in the 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 January 1, 1990 and December 31, 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 (Zhao ML and He SY) and the irrelevant articles were excluded. Finally, after removing duplicates, we included 1674 journal articles, including 1331 articles and 133 reviews for further analysis.

Table 1 Summary of data source and selection

Date source	Web of Science
Citation index	SCIE
Searching period	January 1, 1990 to December 31, 2022
Searching	TS = ((“high altitude” OR “plateau” OR “mountain”) AND (“cardiovascular” OR “heart” OR “cardiac” OR “myocardial”))
Subject category	“Physiology”, “Cardiac Cardiovascular Systems”, “Sport Sciences”
Document type	“Articles” or “reviews”
Language	“English”
Sample size	1674

SCIE: Science citation index expanded.

RESULTS

Descriptive statistics

This study included 1674 papers with 7433 authors from 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 cardiovascular system at high altitude. The number of papers published in this field increased 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.

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

Table 2 Descriptive statistics of the database

Criteria	Quantity
Publications	1674
Authors	7433
Journals	586
Institutions	2041
Countries	78
Cited references	44674

Table 3 Top 10 countries in the field of cardiovascular system at high altitude

Rank	Country	Publications	Citations	Average citations
1	United States	409	12146	29.70
2	People’s Republic of China	367	5268	14.35
3	England	156	4119	26.40
4	France	129	3296	25.55
5	Canada	124	3190	25.73
6	Italy	124	3065	24.72
7	Switzerland	113	3360	29.73
8	Germany	113	2330	20.62
9	Austria	79	1259	15.93
10	Peru	72	2431	33.76

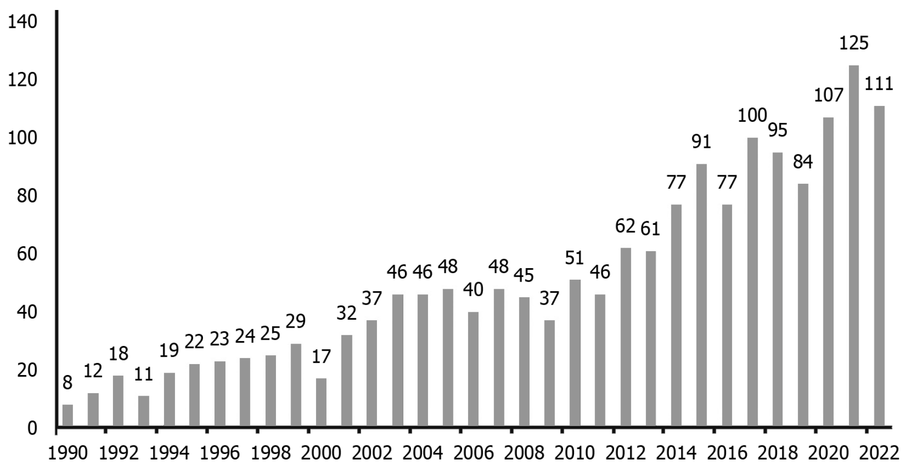

Figure 1 Distribution of publications from 1990 to 2022.

Figure 2B shows the interactions between institutions in this research area. The top 5 productive countries in this research area were United States (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 the United States (0.41), People’s Republic of China (0.21), England (0.20), Germany (0.16), and Switzerland (0.13; Table 4). The betweenness centrality was more than 0.1 for these 5 countries, highlighting their leading role in research area. Table 5 shows the top 10 institutions in the research area of the 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 10 countries in this area included six European countries (England, Germany, Switzerland, Italy, France, and Netherlands), two North American countries (the United States and 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.

Table 4 Top 10 countries with centrality value

Rank	Country	Centrality
1	United States	0.41
2	People's Republic of China	0.21
3	England	0.20
4	Germany	0.16
5	Switzerland	0.13
6	Italy	0.11
7	Chile	0.09
8	France	0.08
9	Canada	0.08
10	Netherlands	0.07

Table 5 Top 10 institutions in the field of cardiovascular system at high altitude

Rank	Institution	Publications	Citations	Average citations
1	Universidad Peruana Cayetano Heredia	57	1704	29.90
2	University of British Columbia	51	1505	29.51
3	Chinese Academy of Sciences	48	1140	23.75
4	University of Innsbruck	48	819	17.07
5	University of Colorado	46	2311	50.24
6	Loma Linda University	39	1006	25.79
7	The Third Military Medical University	36	307	7.87
8	University of Cambridge	32	1335	42.34
9	Université Sorbonne Paris Nord	31	1300	41.94
10	University of California-San Diego	31	1119	36.10

Next, we analyzed the literature to identify the main research scholars studying the cardiovascular 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 the cardiovascular system at high altitude. Jean-Paul Richalet from the University of Paris published 41 papers with 1616 citations and an average of 39 citations per article. In the second place, Philip N Ainslie from University of British Columbia contributed 31 articles with 565 citations and an average of 18 citations per article. Martin Burtscher from University of Paris published 30 articles with 488 citations and an average of 16 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 the cardiovascular system at high altitude. The top 3 journals were *High Altitude Medicine & Biology* (144 publications), *Journal of Applied Physiology* (81 publications), and *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).

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 68 articles for co-citation analysis of the cited articles. We then constructed a network of publications that were related to research regarding the cardiovascular system at high altitude. We identified five clusters represented by different colors and the cited references are 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 and Roach[21] in 2001 (123 citations), Naeije[22] in 2010 (107 citations), Penaloza and Arias-Stella[23] in 2007 (107 citations), Bártsch *et al*[24] in 2007 (90 citations), and Simonson *et al*[25] in 2010.

Table 6 Most important authors in the field of cardiovascular system at high altitude

Rank	Author	Documents	Citations	Average citations
1	Jean-Paul Richalet	41	1616	39.41
2	Philip N Ainslie	31	565	18.23
3	Martin Burtscher	30	488	16.27
4	Lan Huang	25	216	8.64
5	Mike Stembridge	23	387	16.83
6	Gianfranco Parati	21	381	18.14
7	Michael M Tymko	18	214	11.89
8	Jie Yu	17	206	12.12
9	Leon-Velarde Fabiola	16	799	49.94
10	Francisco C Villafuerte	16	316	19.75
11	Frantisek Kolar	16	267	16.69
12	Jie Yang	16	71	4.44

Table 7 Top 10 journals in the field of cardiovascular system at high altitude

Rank	Source	Publications	Citations	Average citations
1	*High Altitude Medicine & Biology*	144	2982	20.71
2	*Journal of Applied Physiology*	81	3070	37.91
3	*Frontiers in Physiology*	55	399	7.25
4	*Wilderness & Environmental Medicine*	38	622	16.37
5	*Journal of Physiology-London*	29	1207	41.62
6	*American Journal of Physiology-Heart and Circulatory Physiology*	29	827	28.52
7	*Plos One*	27	692	25.63
8	*European Journal of Applied Physiology*	26	489	18.81
9	*Experimental Physiology*	22	406	18.45
10	*American Journal of Physiology-Regulatory Integrative and Comparative*	22	829	37.68

Table 8 Top 10 references with highest citations

Rank	Ref.	Citations
1	High-altitude illness	123
2	Physiological adaptation of the cardiovascular system to high altitude	107
3	The heart and pulmonary circulation at high altitudes: Healthy highlanders and chronic mountain sickness	107
4	Effect of altitude on the heart and the lungs	90
5	Genetic evidence for high-altitude adaptation in Tibet	78
6	Consensus statement on chronic subacute high altitude diseases	77
7	Operation Everest II: Preservation of cardiac function at extreme altitude	67
8	Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia	65
9	Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American society of echocardiography	55
10	Two routes to functional adaptation: Tibetan and Andean high-altitude natives	52

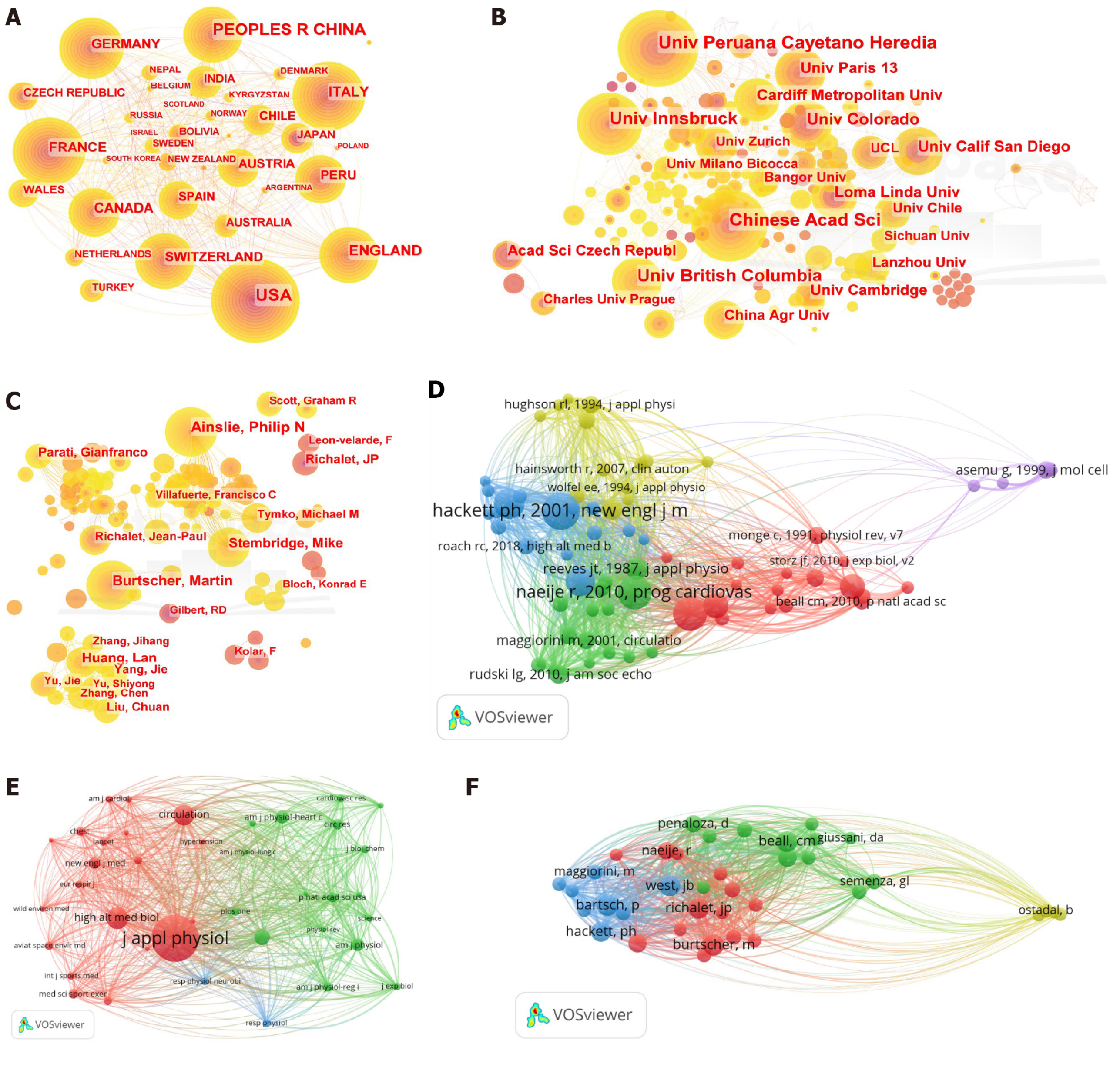

Figure 2 Co-authorship of countries, institutions, authors, and journals. A: Co-authorship between countries with more than 9 publications; B: Co-authorship between institutions with more than 14 publications; C: Co-authorship between authors with more than 9 publications; D: Co-citation of cited references; E: Co-citation of cited journals; F: Co-citation of cited authors.

Our study showed that the top 3 cited references were all reviews. The most cited publication was a review authored by Hackett and Roach[21], 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[22], mainly focused on the acclimatization of the cardiovascular system at high altitude[22]. The third reference was a review published by Penaloza and Aria-Stella[23] in *Circulation* and was titled "The Heart and Pulmonary Circulation at High Altitudes Healthy Highlanders and Chronic Mountain Sickness"[23]. This review described the physiology, pathology, pathogenesis, and clinical features of the heart and pulmonary circulation in healthy highlanders and patients with CMS[23]. The sixth most cited reference published by León-Velarde *et al*[26], reporting an expert consensus statement on the chronic and subacute diseases at high altitude, described the criteria for selecting a specific method or procedure to diagnose or manage these diseases[26]. 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[27].

Subsequently, using a citation threshold of 300, we selected 39 journals for co-citation analysis. Table 9 shows the top 10 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),

Table 9 Top 10 highest cited journals

Rank	Journals	Citations
1	*Journal of Applied Physiology*	5586
2	*High Altitude Medicine & Biology*	2192
3	*Circulation*	2051
4	*Journal of Physiology-London*	1433
5	*American Journal of Physiology-Heart and Circulatory*	1138
6	*American Journal of Physiology*	1107
7	*The New England Journal of Medicine*	980
8	*Circulation Research*	891
9	*Proceedings of the National Academy of Sciences of the United States of America -Physical sciences*	886
10	*American Journal of Physiology-Regulatory Integrative and Comparative Physiology*	792

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 100 and 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 10 most cited authors in this network, with Peter Bärtsch (382 citations), Martin Burtscher (378 citations), and John B West (358 citations) being the three most prominently cited authors.

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 identified 103 keywords with a frequency of more than 20 (Figure 3A). In this network, size of the circle node denotes frequency of the keyword. For example, if the circle node is large, it suggests that the keyword occurs at a higher frequency. Hence, we considered high frequency key words as research hotspots in the field of study. The line of nodes represents the strength of the association. A thicker line indicates that the two words co-appear more times in the same article. Clusters of key words are represented by distinct colors. The top 10 keywords were high altitude (n = 598), hypoxia (n = 559), exercise (n = 269), AMS (n = 214), adaptation (n = 209), heart (n = 167), acclimatization (n = 137), pulmonary hypertension (n = 133), heart rate (n = 117), and 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), AMS (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 the cardiovascular system at high altitude. The main research hotspots between 1990 and 2022 were heart, cardiac function, coronary artery disease, metabolism, and AMS. Autonomic nervous system and endothelium were also research hotspots in this field before 2015. Furthermore, we compile and summarize several significant points to reveal high altitude cardiovascular system function based on the analysis of popular keywords (Table 12).

DISCUSSION

Country distribution

The collaborations between countries have significantly advanced the understanding of the cardiovascular system at high altitude. The United States accounted for the highest number of publications. Many of these publications focused on subjects regarding the cardiovascular system at altitudes ≥ 4000 feet[28-33]. It should be noted that altitudes above 2000 m are generally considered as high altitudes. The risk of acute altitude illness is significantly higher at altitudes above 2500 m[34]. 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 the cardiovascular system at high altitude. This can be attributed to an extensive population residing at altitudes ≥ 3500 m in China[1]. Moreover, the world's highest plateau, the Qinghai-Tibet Plateau, is in China

Table 10 Top 10 highest frequency cited authors

Rank	Authors	Citations
1	Peter Bärtsch	382
P	Martin Burtscher	378
3	John B West	358
4	Beall Cynthia M	352
5	Jean-Paul Richalet	352
6	Hackett Peter	330
7	Lorna G Moore	265
8	Robert C Roach	261
9	Robert Naeije	235
10	Dante Penaloza	222

Table 11 Top 20 highest frequency keywords

Rank	Keyword	Occurrences	Total link strength
1	High altitude	598	2537
2	Hypoxia	559	2391
3	Exercise	269	1254
4	Acute mountain sickness	214	971
5	Adaptation	209	994
6	Heart	167	746
7	Acclimatization	137	728
8	Pulmonary hypertension	133	655
9	Heart rate	117	507
10	Blood pressure	104	526
11	Hypobaric hypoxia	101	528
12	Nitric oxide	99	442
13	Chronic hypoxia	93	432
14	Oxidative stress	90	408
15	Chronic mountain-sickness	80	375
16	Cardiac output	71	365
17	Intermittent hypoxia	66	190
18	Oxygen	56	170
19	Metabolism	54	149
20	Echocardiography	53	217

[35]. Peru is another country with a significant population residing at high altitude. Those residing at high altitude regions 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[36,37].

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. Luks *et al*[38] focused on the clinical manifestations, epidemiology, pathophysiology, and treatment of common diseases at high altitude[38]. Bärtsch and Gibbs[24] also described the acute physiological adjustments and early acclimatization of the cardiovascular system in healthy

Table 12 Critical aspects of the cardiovascular system at high altitude

Rank	Keyword	Significant points
1	Hypoxia	Hypoxia emerges as the predominant characteristic among individuals residing at high altitudes
2	Exercise at high altitude	Exercise training is advocated for enhancing adaptation to high altitude
3	Pulmonary hypertension	Pulmonary artery pressure increases at high altitude due to vasoconstriction
4	Oxidative stress	Oxidative stress is activity at high altitude
5	Metabolomics	Metabolomics has offered novel perspectives on the pathophysiological mechanisms that underlie adaptations to early hypobaric hypoxia, as well as other diseases associated with tissue hypoxia
6	Adaptation/acclimatization	Adaptation or acclimatization occurs in individuals residing at high altitudes for extended periods, including indigenous populations
7	Echocardiography	Echocardiography serves as a valuable diagnostic tool for identifying cardiac diseases in high-altitude environments

individuals who visited places at high altitude as well as altitude tolerance in patients with underlying cardiovascular diseases[24]. Furthermore, Bärtsch *et al*[39] 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[39,40]. 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 and Ponchia[41] published reports focused on the cardiovascular system at high altitude[41-43], treatment and prevention recommendations of hypoxia-related altitude illnesses[44,45], and exercise at high altitude[46]. The third most highly cited research scholar was John B West from the Department of Medicine, University of California San Diego, La Jolla, United States. West[47] has published articles regarding high altitude-related medicine and physiology[47,48], the technology of oxygen enrichment in room air[2,49], and pulmonary function at high altitude[50,51]. University of California, San Diego is also one of the top ten institutions for publications in the field of cardiovascular system at high altitude because of major contributions from John B West.

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 area at high altitude may result in AMS or CMS; 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 a 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 AMS at moderate altitudes[40]. A meta-analysis demonstrated that training at natural or simulated altitude improved high intensity intermittent running performance of the team-sport athletes[52]. Several contemporary elite endurance athletes incorporate some form of altitude/hypoxic training within their year-round training plan to improve their performance[53]. However, intermittent hypoxia at rest does not improve athletic performance in competitions held at sea level[39]. Therefore, exercise training is recommended to improve adaptation at high altitude[54]. 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[55]. Chronic exposure to hypoxia increases pulmonary artery pressure in the highlanders, but the criteria for the diagnosis of HAPH are not clear. The prevalence of HAPH varied significantly among 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[56]. Chronic exposure to high altitude is also associated with arterial remodeling[57]. 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[58]. Furthermore, hypoxia promoted smooth muscle cell proliferation and pulmonary vascular thickening by impairing endothelial cell membrane integrity and stimulating the secretion of growth factors[59]. Moreover, chronic hypoxia promoted smooth muscle cell proliferation and pulmonary vascular thickening by maintaining fibroblasts in an activated state through epigenetic regulatory mechanisms[60].

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 that may activate important adaptive responses[61]. 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 increased oxidative stress[62]. Hu *et al*[63] demonstrated that the activity of the large-conductance Ca^{2+}-activated K^+ channels in the uterine arteries of pregnant sheep was inhibited by increased oxidative stress in an hypoxic environment.

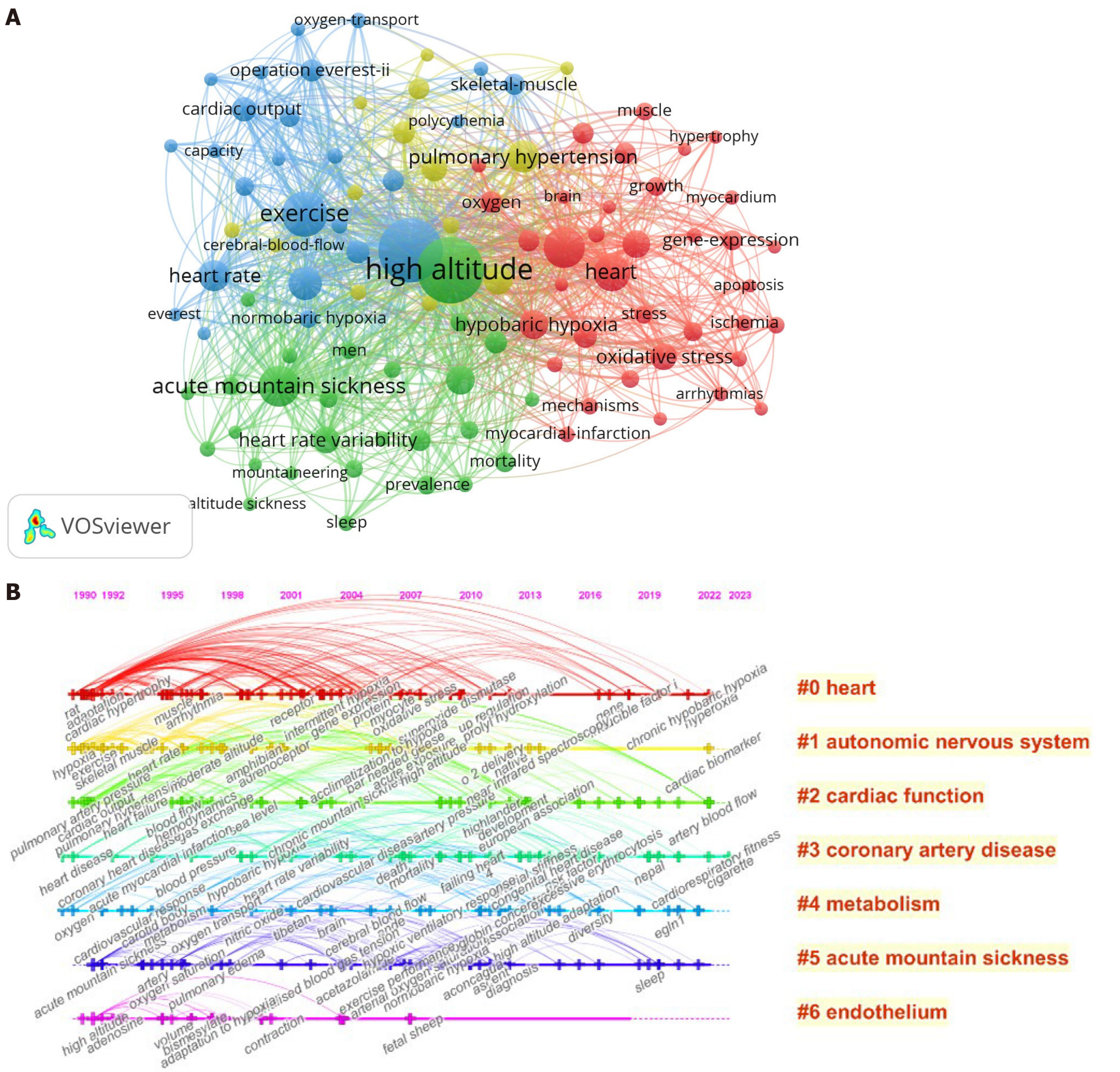

Figure 3 Co-occurrence analysis keywords. A: Keyword co-occurrence map of publications in high altitude cardiac research field; B: Map of timeline view in cardiovascular system at high altitude.

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 the 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[64]. 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[65]. It is worth noting that increased cardiac output is proportionally reduced to 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 returns to normal after a few days and the changes plateau after a certain time of exposure at high altitude[66]. The HIF signaling pathway is altered at high altitude and is crucial for acclimatization. EGLN1 and EPAS1 are major regulators of the hypoxic response[67-69].

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[22,70,71]. The prevalence of hypertension is higher upon long-term exposure to high altitude; the incidence of hypertension increased by 2% for every 100 m increase in altitude in areas above 3000 m[72]. Aryal *et al*[73] performed a meta-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 an elevation of 1000 m[73]. However, long-term intermittent exposure to high altitude did not significantly alter blood pressure[74]. The increase in blood pressure at high altitude was proportional to an increase in the plasma levels of norepinephrine. This suggested that norepinephrine plays 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 participate in the elevation of increase of blood pressure at high altitude[24].

Metabolomics at high altitude: Metabolomics is a promising tool for discovering and understanding the novel biochemical and metabolic responses 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[75]. Xie *et al*[76] 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[76]. 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[77]. Guo *et al*[78] performed plasma metabolite profiling of 57 HAPE as well as 57 control subjects by 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[79]. Liu *et al*[79] performed integrated plasma metabolomics and transcriptomic analyses to demonstrate a significant association between phenotypic variation under hypoxia and the arachidonic acid metabolism pathway[79]. Liao *et al*[80] used a metabolomics approach to detect plasma metabolic changes in subjects exposed to high altitude and showed significant changes in 44 metabolites and 4 related enzymes[80]. 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[81,82]. A 2-d exposure of rats to hypobaric hypoxia increased NO synthesis and promoted cardioprotective mechanisms[83]. 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 Tibetan sheep adapated to high altitude[84]. Gonzales *et al*[85] also showed upregulation of the heart mitochondrial nitric oxide synthase in male rats exposed to high altitude[85].

Echocardiography for diagnosis of heart diseases 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[86]. Ultrasound is the best method for the clinical assessment of AMS[87]. Boussuges *et al*[88] 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 early maximal ventricular filling velocity/atrial maximal ventricular filling velocity (E/A) ratio. A study of the echocardiographic changes in 41 healthy volunteers who rapidly ascended to 4559 m 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 [70]. Echocardiography measurements of 58 plain residents exposed to a 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[89]. 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[89].

CONCLUSION

In the present study, we performed a bibliometric analysis of publications in the field of the cardiovascular system at high altitude to identify the future research hotspots and new perspectives. Our data show that publications have increased rapidly over the past few decades in the field of the 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. The present study has several limitations. First, to 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. Thus, the 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 diversify 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.

FOOTNOTES

Author contributions: Zhao ML contributed to formal analysis, software, and manuscript drafting; Lu ZJ and Yang L contributed to software and visualization; Liu YZ contributed to visualization and manuscript drafting; Yang XL contributed to manuscript drafting; Li X contributed to software; Ding S contributed to reviewing and editing of the manuscript; Gao F contributed to supervision and manuscript reviewing and editing; He SY contributed to conceptualization, supervision, fund acquisition, and manuscript reviewing and editing. All authors read and approved the final manuscript.

Supported by Natural Science Foundation of Sichuan Province, No. 2022NSFSC1295; the 2021 Annal Project of the General Hospital of Western Theater Command, No. 2021-XZYG-B31.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

ORCID number: Si-Yi He 0000-0003-0275-1038.

S-Editor: Li L
L-Editor: Wang TQ
P-Editor: Zhao S

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