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Review

# Multidimensional excavation of the current status and trends of mechanobiology in cardiovascular homeostasis and remodeling within 20 years

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ABSTRACT

Mechanobiology is essential for cardiovascular structure and function and regulates the normal physiological and pathological processes of the cardiovascular system. Cells in the cardiovascular system are extremely sensitive to their mechanical environment, and once mechanical stimulation is abnormal, the homeostasis mechanism is damaged or lost, leading to the occurrence of pathological remodeling diseases. In the past 20 years, many articles concerning the mechanobiology of cardiovascular homeostasis and remodeling have been published. To better understand the current development status, research hotspots and future development trends in the field, this paper uses CiteSpace software for bibliometric analysis, quantifies and visualizes the articles published in this field in the past 20 years, and reviews the research hotspots and emerging trends. The regulatory effects of mechanical stimulation on the biological behavior of endothelial cells, smooth muscle cells and the extracellular matrix, as well as the mechanical-related remodeling mechanism in heart failure, have always been research hotspots in this field. This paper reviews the research advances of these research hotspots in detail. This paper also introduces the research status of emerging hotspots, such as those related to cardiac fibrosis, homeostasis, mechanosensitive transcription factors and mechanosensitive ion channels. We hope to provide a systematic framework and new ideas for follow-up research on mechanobiology in the field of cardiovascular homeostasis and remodeling and promote the discovery of more therapeutic targets and novel markers of mechanobiology in the cardiovascular system.

## 1. Introduction

Mechanobiology focuses on how mechanical stimulation interacts with chemical signals to regulate cell and tissue functions and their molecular mechanisms. With the stress-growth law proposed by Y.C. Fung in 1990, which mentioned that the remodeling of blood vessels involving the growth or resorption of cells and extracellular materials is linked to mechanical stresses,[1] researchers have gradually turned their attention to the mechanism of the mechanical regulation of life processes. With the accelerated development of molecular biology and cell biology,

*Abbreviations:* AS, Atherosclerosis; CFD, Computational fluid dynamics; ECM, Extracellular matrix; ECs, Endothelial cells; EndMT, Endothelial–mesenchymal transformation; GAGs, Glycosaminoglycans; HF, Heart failure; LAE, Left atrial enlargement; LSS, Laminar shear stress; mTORC1, mammalian target protein complex 1; NETs, Neutrophil extracellular traps; OSS, Oscillatory shear stress; PDE5, Phosphodiesterase 5; TEAD, Tea-domain transcription factor; VSMCs, Vascular smooth muscle cells; WWTR1, WW domain-containing transcription regulator 1; YAP, Yes associated protein.

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a new interdisciplinary field, mechanobiology, has gradually emerged. Mechanobiology studies not only reveal the biomechanical mechanisms of normal growth, development and aging but also clarify the role of mechanical stimulation in the pathogenesis of diseases.[2] Although the vast majority of cells in the body are subjected to mechanical stimulation, most current research on mechanobiology focuses on the cardiovascular system.[3–5] The cardiovascular system, which is centered on the heart, pumps blood out of the heart to the entire body through the heart's mechanical pumping action, achieving energy transfer and material exchange. This process involves many mechanical effects, including the mechanical force generated by the beating of the heart and the mechanical stimulation of blood pressure and flow through blood vessels. Mechanical stimulation is a mechanical signal that is the main regulator of cell structure and function. It causes disturbances in the position and morphology of cells and the vascular microenvironment. Mechanosensitive sensors on cell membranes can sense these mechanical changes and transduce them into chemical signals, activating multiple signaling pathways and responding by remodeling, growth, and repair.[6]

Cardiovascular homeostasis and remodeling have always been research hotspots in the field of cardiovascular diseases. Cardiovascular homeostasis is a physiological state in which cardiovascular physiological functions as well as internal and external environmental compositions and properties are maintained in a relatively dynamic balance, whereas cardiovascular remodeling is a dynamic pathological process.[7] Mechanical stimulation is a key regulator of cardiovascular homeostasis and pathological remodeling.[8] Under physiological conditions, the cardiovascular system senses mechanical stimulation and then maintains the relative balance of cardiovascular composition, structure and function through various regulatory mechanisms to achieve cardiovascular homeostasis.[9] When mechanical stimulation is abnormal or the cardiovascular mechanosensation or mechanotransduction capacity is impaired, pathological cardiovascular remodeling can occur.[9–11] Different cardiovascular cells and components respond differently to abnormal mechanical stimulation, causing different cardiovascular remodeling events. Pathological remodeling changes in the cardiovascular system are manifested in both structure and function. Structural changes include intimal hyperplasia, thickening or thinning of the media, adventitial fibrosis, and ventricular concentric hypertrophy,[10,12] which in turn affect functional changes manifested as changes in vascular compliance and vascular regulation disorders.[9,13] The biological processes involved include the synthesis, degradation, and reorganization of the extracellular matrix (ECM), as well as the excessive proliferation, migration, and apoptosis of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs).[14–16] Pathological mechanical stimulation or mechanotransduction induces cardiovascular remodeling leading to a range of cardiovascular diseases, including hypertension, atherosclerosis (AS), heart failure (HF), and restenosis after vein grafting.[17–19] Therefore, in cardiovascular homeostasis and remodeling, a deep understanding of the biological effects of mechanical stimulation and how to produce biological effects is of great theoretical and clinical importance for identifying potential mechanics-related drug targets and new biomarkers and laying a mechanobiological foundation for the prevention and treatment of pathological cardiovascular remodeling diseases.

Currently, with the continuous development of mechanobiology in cardiovascular homeostasis and remodeling, the number of related articles has increased rapidly. Therefore, it is necessary to conduct a retrospective analysis of published articles in this field to better understand the status of past research and provide guidance for future research. Bibliometrics is a branch of informatics. It quantitatively analyzes relevant information in the scientific literature to understand the knowledge structure and research trends in a certain research field. It is an effective tool for objectively studying the current status of a discipline and reflecting its development.[20] Recently, many reviews related to bibliometrics have been published.[21–23] By using bibliometric analysis software to construct a knowledge graph, a comprehensive literature review of the proposed research dimension is conducted. It usually takes scientific publications as input, quickly organizes many published articles, generates interactive visualization maps of complex structures, visualizes the structure and dynamics of a certain research field, and then analyzes the results to determine the main research topics and frontiers.[24] CiteSpace is a bibliometric software for visual analysis of scientific literature. It presents the structure, laws and distribution of scientific knowledge by drawing a series of visual maps, helping researchers to better understand the development context of the research field.[25] This article uses CiteSpace bibliometric analysis software to conduct a bibliometric analysis of the field of mechanobiology in cardiovascular homeostasis and remodeling, comprehensively analyzes the development status and trends of this field, better elucidates the current research hotspots and emerging trends in this field, and promotes the development of this field.

## 2. Bibliometric methods

### 2.1. Data collection and retrieval strategy

The Web of Science is the world's largest information resource platform, covering the fields of natural sciences, engineering technology, biomedicine, social sciences, arts and humanities. It also includes the world's highest-level authoritative academic journals, monographs, conferences, abstracts and conference proceedings with powerful citation indexing and academic influence evaluation functions. In this work, the Web of Science Core Collection (WoSCC) is used as the data source, and the data are searched from 2004 to 2024 November as the time period. The search terms used were ALL=((cardiac OR vascular OR artery OR arterial OR vessel OR cardiovascular) AND (remodel* OR homeostasis)) AND (mechanobiology OR mechanics). A total of 2872 studies were retrieved, and 2796 studies were analyzed via bibliometrics after the duplicate articles were deleted. Standard bibliometric indicators were used to analyze the number of published articles, countries, institutions, authors, cited references, and keywords in CiteSpace 6.4.R1.

### 2.2. Bibliometric analysis tool - CiteSpace

This study selected 6.4.R1 from CiteSpace and used 2796 articles retrieved from WoSCC as the data source. This analysis included 2212 articles, 354 reviews, 95 proceedings papers, etc (Fig. 1). We Select January 2004 to November 2024 for time slicing, with each slice set to 1 year, the selection standard Top N set to 50, and the node types selected as author, institution, country, keyword, and reference to visualize the obtained valid literature data. The analysis results include annual publication analysis, national and institutional cooperation analysis, author analysis and citation explosion keywords. The relevant content is visualized in an information graph, and the key nodes and their connections in different graphs are analyzed. The higher the frequency of occurrence in the graph is, the larger the node. The color and thickness of the inner circle of a node represent the frequency of occurrence at different times, whereas the purple outer circle of the node indicates its high betweenness centrality, expressing the intermediary connection role of the node in the collinear network, which can be considered a turning point and plays a key role in the information graph. The connecting lines between nodes are represented as co-occurrence or co-citation relationships, and the thickness of the connecting lines indicates the strength of co-occurrence. The more connections there are and the thicker the connecting lines between nodes are, the closer the relationship is. Finally, the research hotspots are visually displayed through an information graph, and research trends are predicted.

## 3. Bibliometric analysis

### 3.1. Annual publication volume analysis

Since 2004, there have been a total of 2796 research articles in this field, increasing from 30 in 2004 to over 240, showing an overall upward trend. In 2021, more than 200 papers were published, reaching its peak.

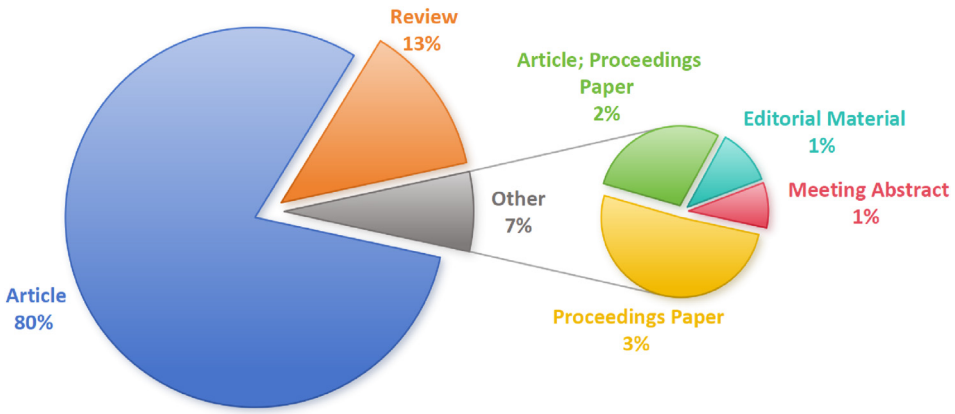


**Fig. 1.** Types of publications in the field of mechanobiology in cardiovascular homeostasis and remodeling from 2004 to 2024.

Within two years, the number of published articles remained at approximately 240. As of the search date, the number of papers published in 2024 was 197. The regression curves predict that the number of publications in this field will be 245 in 2024 (Fig. 2). With increasing social attention given to cardiovascular disease and the continuous development and improvement of strategies for disease modeling and treatment, this field has also received widespread attention. The stable upward trend of published articles indicates that this field has become a hot research topic in recent years and has attracted widespread attention.

### *3.2. Collaborative relationship analysis*

#### *3.2.1. Country/Regional cooperation network*

A total of 82 nodes and 893 connections of the country cooperation network map were obtained after visualized analysis with "country" as the node. Each node represents a country. The larger the node is, the more articles published by that country. The top five countries are the United States, China, Italy, the United Kingdom, and Germany(Fig. 3). The United States has the highest number of publications, with a total of 1449 articles (Fig. 4). Through CiteSpace visualization, it is possible to analyze the cooperative relationships between countries (Fig. 3), where the multiple and dense connections between countries indicate close cooperation between them. The cooperation between countries is as follows. The United States has close ties with China, the United Kingdom, Italy, Germany, Canada, France, and many of the countries shown

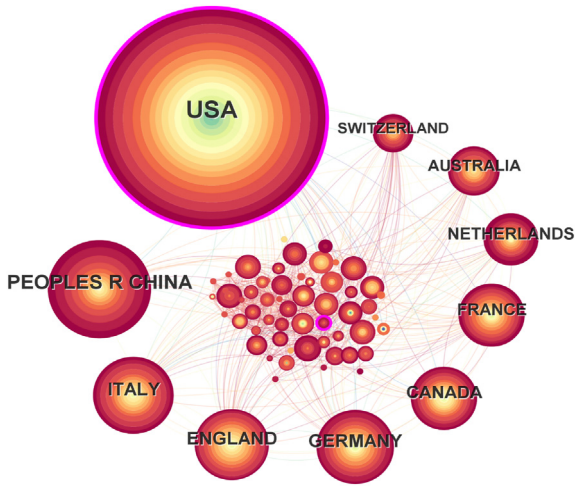


**Fig. 3.** Network diagram of the effects of national cooperation in the field of mechanobiology in cardiovascular homeostasis and remodeling from 2004 to 2024.

(Fig. 3); China has close ties with South Africa, Britain, Germany, Canada, France and other European and American countries, as well as Japan, South Korea and other Asian countries; Italy has close ties with

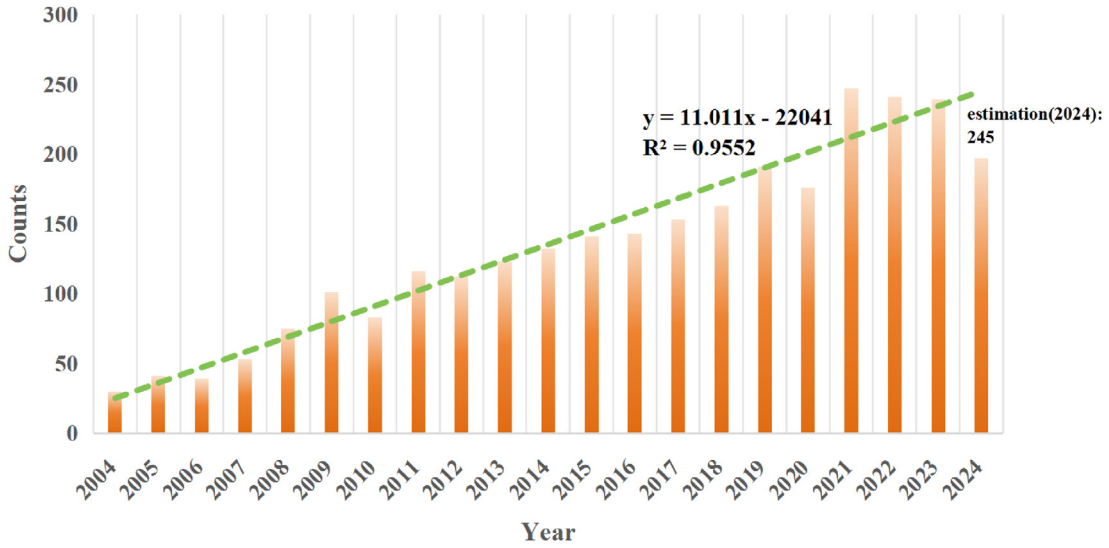


**Fig. 2.** Number of publications in the field of mechanobiology in cardiovascular homeostasis and remodeling from 2004 to 2024.

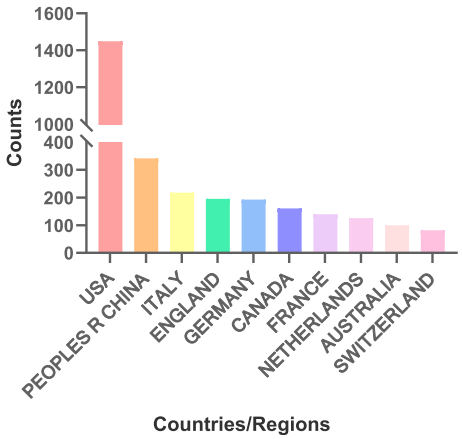


**Fig. 4.** Top 10 countries in the field of mechanobiology in cardiovascular homeostasis and remodeling in terms of publication volume.

France, Greece, Canada, the Netherlands and Australia; Britain has close ties with Switzerland, Singapore, Greece, Spain and India; and Germany has close ties with Belgium, Ireland, South Korea, Japan and South Africa. The top five countries in terms of centrality are the United States (0.35), South Africa (0.11), England (0.07), Egypt (0.07), and Slovenia (0.06). The centrality of America and South Africa is greater than 0.1, and the high centrality in the national cooperation network also indicates that these 2 countries have a certain influence on cardiovascular homeostasis and remodeling in the field of mechanobiology.

### 3.2.2. *Institutional cooperation network*

The information graph of articles published by institutions in various countries from 2004 to 2024 includes 441 nodes and 2906 connections. According to the institutional cooperation network (Fig. 5), the top ten institutions with the greatest number of publications can be obtained, among which the top five institutions are the University of California System, Harvard University, Yale University, Pennsylvania Commonwealth System of Higher Education (PCSHE), and University System of Georgia (Table 1). In the network diagram of institutional cooperation (Fig. 5), University of California System and University of California Davis, University of California Berkeley, University of California Irvine,

**Table 1**
Top 9 institutions in terms of publication volume from 2004 to 2024.

| Institution | Counts | Countries |
|---|---|---|
| University of California System | 159 | USA |
| Harvard University | 118 | USA |
| Yale University | 98 | USA |
| Pennsylvania Commonwealth System of Higher Education (PCSHE) | 93 | USA |
| University System of Georgia | 92 | USA |
| University of Texas System | 86 | USA |
| Georgia Institute of Technology | 85 | USA |
| Institut National de la Sante et de la Recherche Medicale (Inserm) | 84 | FRANCE |
| Stanford University | 76 | USA |

Austral University, University of Illinois System, University of California San Francisco, University of Illinois Chicago Hospital have close ties in the field of mechanobiology in cardiovascular homeostasis and remodeling. Harvard University works closely with Beth Israel Deaconess Medical Center, Harvard Medical School, and the Broad Institute. Yale University and Texas A&M University College Station, Texas A&M University System, Universitat Politecnica de Valencia and Universite de Montpellier have close links in this field. Pennsylvania Commonwealth System of Higher Education (PCSHE) and the University of Pittsburgh, the Mayo Clinic, the University of Pittsburgh Palermo, Boston Children's Hospital, the University of Limerick, Pennsylvania State University, Pennsylvania State University and Duke University cooperate and exchange. There are close ties between the University System of Georgia and the Georgia Institute of Technology, the US Department of Veterans Affairs, the Veterans Health Administration (VHA), Augusta University, the Atlanta VA Medical Center, and the Atlanta VA Health Care System.

The CiteSpace visualization of institutional collaboration network graphs reveals that the nodes of institutions such as University of Maryland Baltimore (0.27), CNRS - National Institute for Biology (INSB) (0.24), Johns Hopkins University (0.22), Brigham & Women's Hospital (0.2), National Institutes of Health (NIH) - USA (0.2), University of Toronto (0.19), University of California System (0.18), and Centre National de la Recherche Scientifique (CNRS) (0.17) all have purple outer circles, indicating that these institutions have high centrality and play important roles in research and development in this field (Fig. 5). Currently, the main research in this field is focused on schools, with few

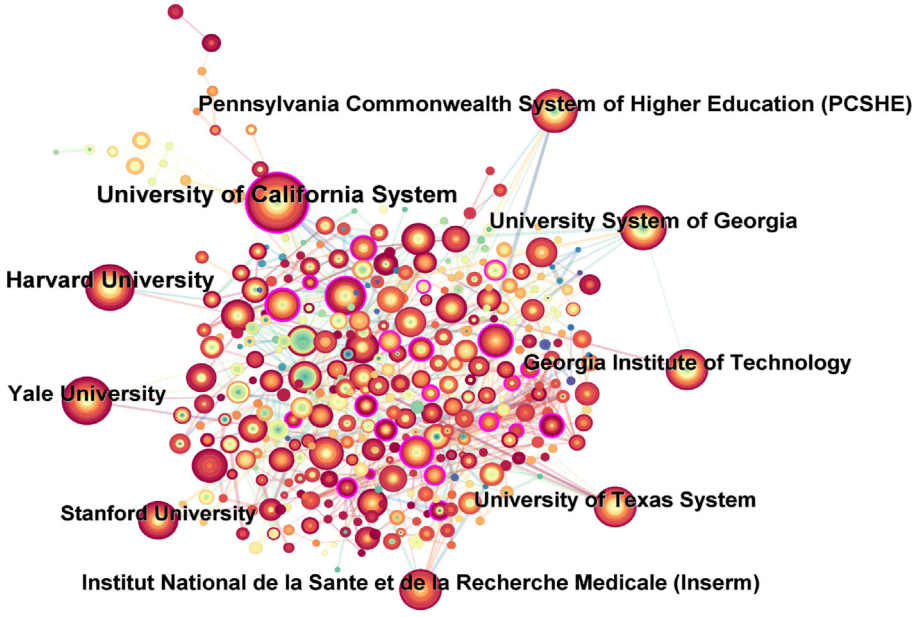


**Fig. 5.** Network diagram of institutional cooperation in the field of mechanobiology in cardiovascular homeostasis and remodeling from 2004 to 2024.

hospitals conducting related research. Approximately ninety percent of the top nine institutions in terms of publication volume are from the United States, which has a certain leading position in research in this field.

### 3.2.3. Author collaboration network

Through the analysis of the number of articles published by authors in the field of mechanobiology in cardiovascular homeostasis and remodeling, as well as the collaboration network, the collaboration network diagram includes 744 nodes and 1144 connections. The size of the nodes in the collaboration diagram represents the number of articles published by the authors, and the thickness of the connection lines reflects the strength of their collaboration relationship. According to the institutional cooperation network (Fig. 6), the top ten authors with the highest number of publications can be obtained, among which the top five authors are Jay D. Humphrey, and Marijana. Tadic, Dao Wen. Wang, Cesare. Cuspidi, Rudolph L. Gleason. Nearly half of the top 10 authors in the past 20 years are from the United States (Table 2).

The cooperative network diagram closely related to national and institutional cooperation is different. The cooperative relationships among scholars are relatively scattered, and scholars are closely connected on a small scale (Fig. 6). David A. Vorp and Jay D. Humphrey jointly published information about abdominal aortic aneurysms and biomechanical behavior research.[26] Marijana Tadic and Cesare. Cuspidi closely collaborated in the field of vascular research. Together, they have participated in a number of studies in the areas of hypertension, cardiac mechanics, and cardiology. Specifically in patients with hypertension, they collaborated to investigate the relationship between left atrial enlargement (LAE) and changes in heart structure and function, as well as the impact of these changes on prognosis.[27] Moreover, the prevalence of LAE and its association with left ventricular hypertrophy are also discussed in untreated and treated hypertension patients.[28] These collaborative results not only improve the understanding of vascular disease mechanisms, but also provide valuable insights for clinical practice.

The collaboration between Seungik Vorp. Baek and David A., in the field of vascular research, are reflected mainly in the joint research projects and published academic papers. They have collaborated on a number of occasions, including a special issue of Annals of Biomedical Engineering exploring cardiovascular biomechanics and biofluids, in particular, modeling cardiovascular structures.[29] In addition, they collaborated on the publication of research on multiscale modeling of blood vessels via a fluid–solid growth framework, which involves advances in medical imaging, vascular biology, and biomechanics and is expected to play an increasingly important role in clinical decision-making processes. Their collaboration highlights the importance of applying biomechanics and biofluidics to the progression of vascular disease and shows how to analyze aneurysm enlargement or wall stress through computational models. These collaborative results not only promote an understanding of the biomechanics of vascular diseases but also provide a new perspective and method for clinical treatment. The cooperative work of Chen, Chen and Wang, Dao Wen focused mainly on the mechanical pathogenic mechanism involved in the occurrence and development of HF and revealed a series of mechanically regulated signaling pathways.[30–32] The roles of miR-665, mammalian target protein complex 1 (mTORC1) and phosphodiesterase 5 (PDE5) in heart failure are closely related to the biomechanical properties of the heart. MiR-665 affects cardiac function by affecting phosphatase and tensin cognates, mTORC1 affects vascular tone and blood pressure via Yes-associated proteins, and PDE5 inhibition prevents cardiac fibrosis by affecting Smad signaling, all of which are important components of cardiac biomechanics research. Understanding how these molecules and signaling pathways regulate the mechanical properties of the heart could provide new strategies for the treatment of heart disease.

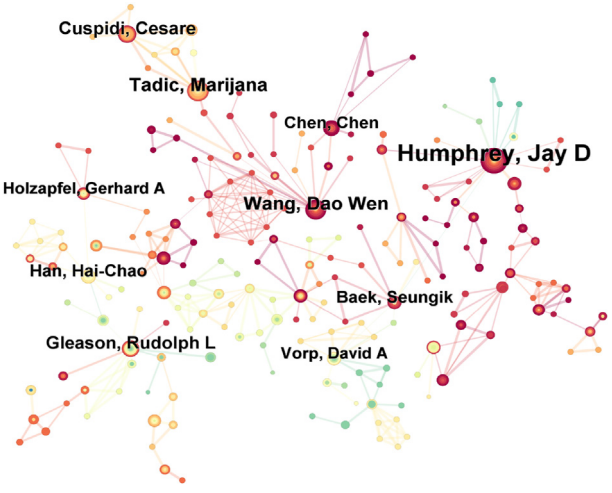


**Fig. 6.** Author collaboration network in the field of mechanobiology in cardiovascular homeostasis and remodeling from 2004 to 2024.

**Table 2**
Top 10 authors in terms of publication volume from 2004 to 2024.

| Authors | Counts | Affiliations | Countries |
|---|---|---|---|
| Jay D. Humphrey | 61 | Yale University | USA |
| Marijana. Tadic | 25 | Tadic, Marijana | GERMANY |
| Dao Wen. Wang | 24 | Union Hospital, Tongji Medical College, Huazhong University of Science and Technology | PEOPLES R CHINA |
| Cesare. Cuspidi | 21 | Università Milano-Bicocca | ITALY |
| Rudolph L. Gleason | 20 | Georgia Institute of Technology | USA |
| Hai-Chao. Han | 17 | University of Texas at San Antonio | USA |
| Seungik. Baek | 16 | Michigan State University | USA |
| Chen. Chen | 16 | Xidian University | PEOPLES R CHINA |
| David A. Vorp | 15 | University of Pittsburgh Swanson School of Engineering | USA |
| Gerhard A. Holzapfel | 15 | Graz University of Technology | AUSTRIA |

### 3.3. Research hotspot analysis

High-frequency keywords often reflect research hotspots in the field. To further study the current research hotspots and trends of mechanobiology in cardiovascular homeostasis and remodeling, a keyword co-occurrence network diagram (Fig. 7) was generated through CiteSpace, which contains 597 nodes and 6016 connections. The top 10 most frequently occurring keywords included "extracellular matrix", "shear stress", "smooth muscle cells", "heart failure", "endothelial cells", "blood pressure", "blood flow", "computational fluid dynamics", "myocardial infarction", and "hypertension", indicating that these are the most studied directions by researchers in the past 20 years. The research hotspots in the field of cardiovascular homeostasis and remodeling in mechanobiology influence each other. The fluid shear stress generated by blood flow mainly acts on ECs, and the mechanical load caused by blood pressure mainly acts on SMCs and cardiomyocytes. These cardiovascular cells regulate the remodeling process of the ECM in a paracrine manner. Cardiovascular cells can also influence each other in a paracrine manner. These findings indicate that cardiovascular remodeling and homeostasis constitute a complex overall process that is inseparable from the division of labor and cooperation among various cardiovascular components. On the basis of the top five most frequent keywords in the keyword co-occurrence network map, the following focuses on the role of the biological behavior of ECs, smooth muscle cells and the ECM under

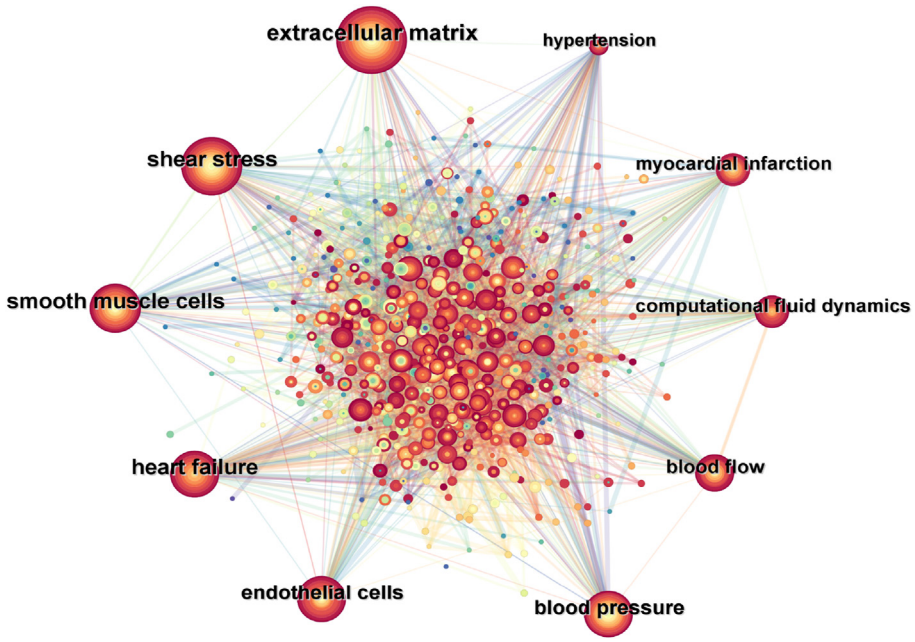


**Fig. 7.** Cooccurrence of key words in the field of mechanobiology in cardiovascular homeostasis and remodeling from 2004 to 2024.

mechanical stimulation in cardiovascular remodeling and homeostasis, as well as the mechanical regulatory mechanism in the occurrence and development of HF.

*3.3.1. Mechanobiology of the endothelial cell response to shear stress*

ECs, as the cells in direct contact with blood in vessels, are continuously exposed to hemodynamics and play an important role in the regulation of cardiovascular homeostasis and remodeling by mechanical stimulation, which has become the focus of researchers. Shear stress caused by blood flow is the main mechanical force sensed by ECs.[17,33] ECs have excellent mechanosensitive properties and mechanotransduction ability and can continuously sense the magnitude, pulsation and direction of shear stress.[8,34,35] ECs convert mechanical signals into intracellular biochemical signals through specific mechanosensitive sensors, such as ion channels, integrins, the glycocalyx and adhesion molecules.[33,36] This signal transduction process causes changes in the morphology, structure, function and gene expression of ECs and subsequently affects cardiovascular homeostasis or remodeling.[37–39] The hemodynamics of the cardiovascular system is complex, and shear stress manifests itself in many forms. In the vertical part of the cardiovascular system, blood flow is in a single direction, and shear stress manifests itself as laminar shear stress(LSS),[40] whereas in arterial bifurcations, bends, or valves, where blood flow is weaker and direction changes are complex, shear stress manifests itself as low oscillatory shear stress(OSS).[41,42] Different forms of shear stress stimulate ECs and cause different biological processes. Many studies have reported the protective effects of physiological LSS on endothelial function, including promoting the formation of tight cell junctions in ECs and exerting normal barrier functions.[43,44] It also regulates the balance of vasodilator and vasomotor substances secreted by ECs to maintain normal vascular tension.[45,46] Many studies have also investigated the role of LSS in maintaining the anti-proliferative, anti-inflammatory and anti-thrombotic phenotypes of ECs.[47–50] Recent studies have also shown that LSS promotes EC polarization and directional migration by regulating the remodeling of adhesion junctions between ECs and plays an important role in repairing and maintaining vascular integrity after vascular injury.[51]

Sustained stimulation by pathological shear stress induces endothelial dysfunction leading to cardiovascular pathological remodeling diseases, of which atherosclerosis is the most common and studied disease.[17,38,52–54] Shear stress is the main cause of the focal distribution of atherosclerotic lesions.[55,56] In AS-susceptible areas, ECs are exposed to OSS and low shear stress, increasing the expression of proinflammatory factors and cell adhesion factors[57–59] and activating the oxidative pathways that cause EC damage and the subsequent formation and development of AS lesions.[58,60–62] In addition, OSS or low shear stress disrupts the barrier function of ECs[63] and promotes the deposition of lipids and inflammatory cells under the endothelium, leading to inward remodeling of the vascular wall and causing the occurrence of atherosclerotic stenosis.[64,65] Similarly, pathological shear stress is also a major cause of heart valve disease,[66–68] and there is a spatial correlation between the location of the lesion and hemodynamics. Studies have shown that lipid deposition and calcification of the aortic valve are more likely to occur on the aortic side,[69–71] and shear stress manifests as low OSS, which may be related to the fact that low OSS promotes EC damage.[72,73] Moreover, abnormal shear stress in heart valve ECs promotes endothelial–mesenchymal transformation (EndMT), causing pathological remodeling of the aortic valve and leading to valvular dysfunction.[74] Low OSS plays an important role in the pathological remodeling process of aortic aneurysms.[75–77] Aortic aneurysms are in a disturbed blood flow environment. ECs are chronically stimulated by low OSS, and the pathological phenotype is activated, which manifests as increased oxidative stress, EndMT, and increased EC permeability.[78,79] In addition, ECs of the pathological phenotype secrete a variety of key growth factors and matrix-regulating proteins that regulate ECM remodeling and SMC phenotypic transformation,[80] and these processes are associated with aortic aneurysm growth and rupture.[80,81] Hemodynamic disturbances are also a major cause of poor prognosis in some surgical procedures such as angioplasty and stent implantation, with altered hemodynamics in the postprocedural region manifesting as low OSS, which promotes neoplastic endothelial proliferation by inducing EC injury.[82–85] Abnormal shear stress-induced EC dysfunction is also the primary cause of vascular stenosis after arterial bypass grafting.[86] When veins are suddenly exposed to the shear stress in the arterial system, and the magnitude of the shear stress is much greater than the shear stress previously carried by venous ECs, EC inflammation and apoptosis are included, promoting subsequent angiogenesis and intimal hyperplasia.[87–89] In summary, the effects of hemodynamics on EC physiology and pathology have been extensively studied and will continue to be a major focus in the future. Elucidating the role of blood flow patterns in EC dysfunction can provide insights into the pathogenesis of lesions in

specific regions of the cardiovascular system and help develop therapeutic strategies based on hemodynamics.

### 3.3.2. Mechanobiology in the extracellular matrix

The ECM is a three-dimensional structural entity within the cardiovascular system that mainly includes elastin, collagen, glycosaminoglycans (GAGs) and related proteoglycans. It is the main component of the cardiovascular microenvironment,[90] providing mechanical support for cells and maintaining the normal structure–function relationship of the cardiovascular system.[91,92] It is also the main conductor of mechanical force within the cardiovascular system, transmitting key signals to vascular cells, cardiomyocytes and interstitial cells.[93–95] Under physiological conditions, the ECM remains relatively stable to maintain normal cardiovascular function.[96] In pathological vascular remodeling events caused by abnormal mechanical forces, ECM remodeling is a key link, which manifests as changes in the composition of matrix proteins, matrix metalloproteinase-mediated matrix protein degradation, and changes in the topological characteristics of the ECM.[97–99] When blood vessels are exposed to LSS, the ECM composition is altered to exhibit pro-inflammatory and pro-tissue repair phenotypes, promoting the generation of an intravascular inflammatory microenvironment.[100,101] Increased circumferential stress can also trigger changes in the ECM components of the vascular wall, manifested as the breakage of elastic fibers and excessive deposition of collagen,[102–105] while also affecting the rearrangement of matrix proteins and proteoglycans.[105,106] The topological structure of the ECM can also change due to pressure overload.[105,107] The pathological remodeling of the ECM can lead to changes in vascular structure and function, manifested as thickening of the arterial wall, increased vascular stiffness, decreased compliance, and increased peripheral resistance.[90,106,108] A study revealed that the speed of the blood pressure pulse wave also affects the composition of the ECM, indicating that, in hypertensive patients, the relative content of collagen is positively correlated with the speed of the pulse wave, whereas the relative content of elastin is negatively correlated with it.[109] The occurrence and development of aortic aneurysms are related to changes in the ECM.[110–112] Pathological remodeling of the ECM in aortic aneurysms can affect the strength of the vascular wall. When the wall stress exceeds the wall strength, aortic dissection or rupture occurs.[113] Mechanical stimulation can also affect the ECM remodeling of heart valves. OSS increases the production of collagen and GAG.[66,114] Both cyclic stretching and pressure overload lead to remodeling of the ECM of the aortic valve, causing degenerative aortic valve disease.[115,116] Changes in the composition and structure of the ECM can also affect the response of cardiovascular cells to mechanical stimulation. Fibronectin can increase the mechanical sensitivity of cells to high shear stress, whereas the presence of collagen types I and IV and laminin can improve the mechanical sensitivity of cells to low shear stress.[117] In addition, the topological characteristics of the ECM help to resist the inflammatory and proliferative activation of ECs by turbulent flow.[101] In Marfan syndrome mice, the ECM structure of the heart valves is destroyed, and the proper structure-function relationship of the heart cannot be maintained under mechanical stimulation, resulting in pathological remodeling of the heart valves and myxomatous valvular disease.[92] In summary, ECM remodeling under mechanical stimulation has been a popular topic that researchers have explored over the past 20 years. The discovery of new mechanisms and perspectives in this field is a continuous improvement in the understanding of the pathogenesis of cardiovascular pathological remodeling diseases.

### 3.3.3. Mechanobiology in vascular smooth muscle cells

VSMCs are the main cellular components of the tunica media of the vascular wall and are mainly subjected to mechanical stimulation generated by pulsatile blood pressure in the form of cyclical stretch.[118] VSMCs are also important participants in vascular homeostasis and remodeling under mechanical stimulation.[119–121] VSMCs have a high degree of plasticity. Under vascular homeostasis, VSMCs exhibit a contractile phenotype to maintain normal vascular tension and function.[14,122] However, in a hemodynamic environment that promotes pathological vascular remodeling, VSMCs undergo phenotypic switching and differentiate into a more migratory, secretory, and proliferative synthetic phenotype, promoting the formation of vascular lesions.[123–125] An increasing number of studies have shown that mechanical stimulation regulates VSMC phenotypic switching through various mechanisms.[126] In the event of an acute increase in blood pressure, smooth muscle cells contract rapidly to maintain normal wall stress.[127] In arterial remodeling induced by chronically high blood pressure, the contribution of vascular smooth muscle is most pronounced, including chronic vascular constriction and luminal narrowing due to dysfunction and aberrant proliferation of SMCs, as well as vascular fibrosis resulting from the dedifferentiation of SMCs into myofibroblasts.[126,128,129] In addition, vascular smooth muscle is a key regulator of ECM remodeling after increased circumferential stress. It participates in vascular remodeling by secreting a variety of matrix metalloproteinases to regulate the remodeling of the ECM,[130,131] causing pathological remodeling of conduction arteries and resistance arteries.[130] The abnormal adaptation of SMCs to increased circumferential stress is also the main cause of pathological remodeling in aortic aneurysms.[132,133] In addition, VSMCs respond to mechanical stimulation of increased blood pressure by altering cell adhesion and the expression of ECM molecules.[134,135] In a healthy state, VSMCs are not directly exposed to shear stress. When atherosclerotic lesions rupture or invasive techniques such as angioplasty cause damage to ECs, VSMCs are directly exposed to blood flow, and receiving shear stress stimulation, leading to corresponding changes in intracellular molecular signaling and function. Physiological LSS inhibits the proliferation of VSMCs by increasing the expression of nitric oxide synthase and AMP-activated protein kinase phosphorylation.[136] However, low shear stress and OSS promote the proliferation and migration of VSMCs to the intima, resulting in an EC phenotype, with a significant increase in the expression of EC markers,[137] which contributes to the formation of focal neointima and promotes the formation of atherosclerotic stenosis lesions.[138–140] After endarterectomy, the exposure of VSMCs to high LSS leads to increased apoptosis, which helps reduce restenosis after vascular injury.[141] Similarly, in vascular grafts, high shear stress can inhibit smooth muscle cell proliferation and reduce neointima formation.[124] In summary, the phenotypic switching of VSMCs under mechanical stimulation has always been a hot area of research for researchers, and its mechanism of action may be a potential therapeutic target in the future.

### 3.3.4. Mechanobiology in heart failure

HF is a clinical syndrome and the endpoint of remodeling in most cardiovascular diseases.[142] Clinical manifestations include impaired cardiac pumping function and the inability of cardiac output to meet the metabolic needs of systemic tissues. Pathological features include ventricular enlargement and relative thinning of the ventricular wall.[143] In the early stage of mechanical overload, the heart is able to maintain cardiac output and cardiac systolic and diastolic function to maintain cardiovascular homeostasis through compensatory mechanisms of myocardial hypertrophy. However, as mechanical overload persists, cardiac remodeling becomes decompensated hypertrophy, accompanied by changes in structure, molecules, metabolism, and the ECM, leading to cardiac dysfunction and eventually HF.[144] Both pressure and volume overload are important pathogenic factors of HF,[145] leading to progressive remodeling of ventricular geometry and myocardial structure. These remodeling processes affect the mechanical properties of the heart, which in turn aggravates the cardiac remodeling process and eventually results in HF. Excessive ECM deposition is observed in HF induced by pressure overload, contributing to ventricular wall thickening,[146,147] whereas increased ECM degradation contributes to ventricular wall thinning and ventricular cavity dilation in HF induced by volume overload.[148] In the context of myocardial hypertrophy and dysfunction caused by pressure overload, many studies have shown that inflammation is an important pathogenic mechanism that causes cardiac

dysfunction by inducing cardiomyocyte death and damage.[149–152] In addition, mitochondrial dysfunction is a key pathogenic factor. Pressure overload promotes the development of HF by downregulating mitochondrial autophagy and causing mitochondrial dysfunction.[153] Similarly, the activation of the cardiac immune response mechanism is also involved in adverse cardiac remodeling and HF caused by mechanical overload.[154] Studies have shown that under the action of hemodynamic mechanical forces, metabolic remodeling of the heart precedes structural remodeling. Pressure overload reduces the expression of cardiac pyruvate kinase muscle isoenzymes, reduces the utilization of glucose by cardiomyocytes, and subsequently leads to cardiomyocyte death, aggravating myocardial dysfunction and fibrosis and ultimately causing HF.[155] Recent studies have shown that hypoxia can protect against the development of cardiac hypertrophy and HF caused by pressure overload by increasing the expression of hypoxia-inducible factor-1α and reducing the expression of genes related to pathological remodeling.[156] Many studies have also been conducted on the pathological remodeling mechanisms of HF volume overload. During volume overload, the left ventricle undergoes extensive remodeling, manifested as chamber dilation, increased myocardial wall stress, and progressive myocardial cell contractile dysfunction. The mechanisms involved include myocardial and EC apoptosis, altered cardiac fibroblast function, and extensive ECM remodeling.[148] Volume overload also leads to the upregulation of metabolic genes related to myocardial stress and glycolysis in the ventricle.[157] Hypertension and adverse ventricular remodeling after myocardial infarction can lead to HF. Hemodynamic changes after acute myocardial infarction cause pathological remodeling of cardiomyocytes, leading to left ventricular systolic and diastolic dysfunction.[158] In hypertension, enhanced cyclic stretch induces a hypertrophic response in cardiomyocytes by inducing NF-kB activation and increasing VEGF secretion, promoting pathological myocardial remodeling.[159] Research on the mechanobiology of heart failure has focused mainly on the influence of mechanical regulatory mechanisms under volume overload and pressure overload on the biological behavior of cardiac cells and ECM, which will continue to be a direction of interest in the future.

### 3.4. Emerging trends analysis

Keywords with the strongest citation bursts (Fig. 8) can indicate emerging research hotspots and provide a basis for exploring future research trends and cutting-edge topics. In the research on mechanobiology in cardiovascular homeostasis and remodeling, the keywords whose citation bursts have continued to the present are responses, homeostasis, fibrosis, and mechanisms, indicating that these four keywords may represent future research trends. In recent years, the mechanical regulatory mechanisms of cardiovascular remodeling and homeostasis have been continuously discovered, among which mechanosensitive transcription factors and mechanosensitive ion channel piezo1 have received the most attention. In the past, researchers focused their attention on the effects of mechanical stimulation on cardiovascular remodeling. In recent years, researchers have gradually focused on the role of mechanical regulation in cardiovascular homeostasis. In cardiac remodeling, cardiac fibrosis has recently attracted increasing attention from researchers, and mechanical-related regulatory mechanisms have been continuously discovered. The following is a detailed introduction to the research progress of these emerging research hotspots in the mechanobiology of cardiovascular remodeling and homeostasis.

#### 3.4.1. Mechanotransduction transcription factors

A core mechanism by which mechanical force affects cell behavior involves changes in gene expression, and various mechanosensitive transcription factors play key roles in this process. Mechanical stimulation regulates gene expression by activating different mechanosensitive transcription factors, thereby affecting the function of cardiovascular cells.[160,161] These include Krüppel-like factor 2, Krüppel-like factor 2, NF-kB and Yes associated protein (YAP)/WW domain-containing transcription regulator 1 (TAZ, also known as WWTR1)/TEA-domain transcription factor (TEAD).[162–165] In recent years, researchers have focused on the effect of mechanical stimulation on YAP/TAZ/TEAD and its role in cardiovascular homeostasis and remodeling and have obtained many valuable findings. YAP/TAZ, mechanosensitive transcriptional

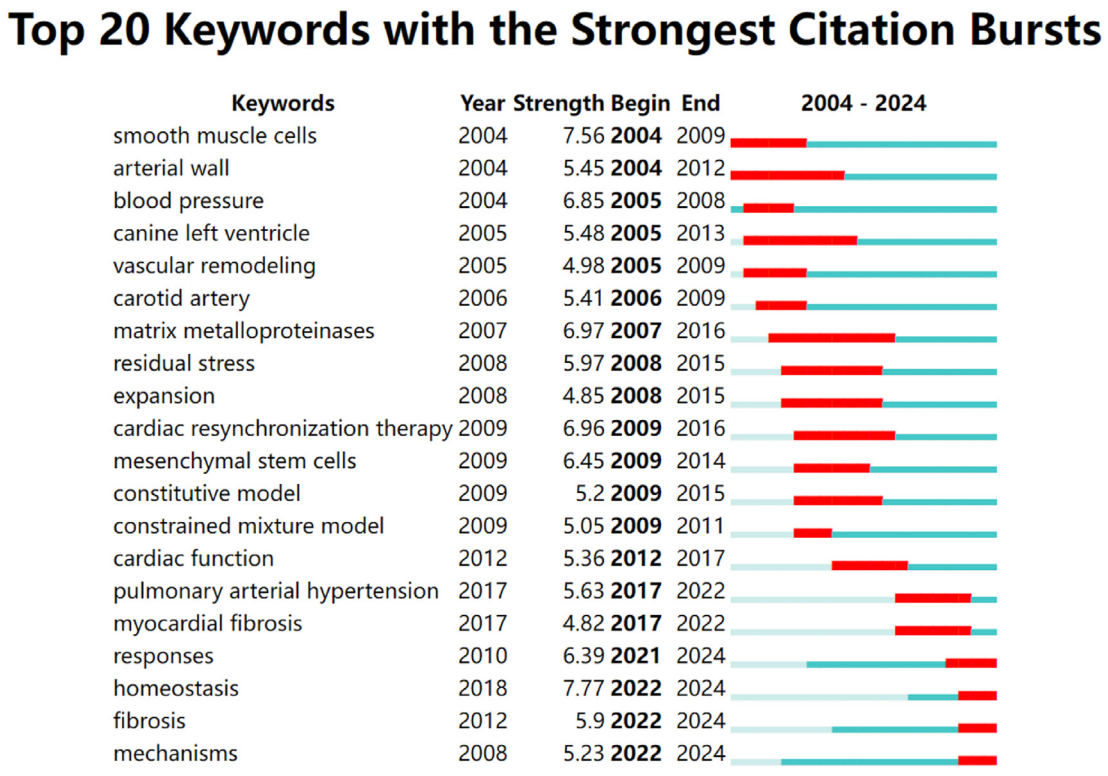


**Fig. 8.** Top 20 keywords with the strongest citation bursts in the field of mechanobiology in cardiovascular homeostasis and remodeling from 2004 to 2024.

coactivators that regulate the TEAD family of transcription factors, are the final effector molecules downstream of Hippo signaling.[166] It plays an integral role in the development of the cardiovascular system and the maintenance of cardiovascular homeostasis.[167–169] Many studies have shown that it is the most important mechanosensitive transcription factor activated by disturbance,[170–173] and can shuttle between the cytoplasm and the nucleus to respond to mechanotransduction.[172] Changes in cell morphology, rigidity and topology of the ECM, shear stress and stretching can affect the distribution of YAP within the cell and the corresponding biological effects.[174] The role of YAP in the mechanical conduction of ECs has been continuously studied and has attracted increasing attention. Studies have shown that LSS can inhibit YAP activity in ECs, thereby inhibiting inflammation and playing an anti-atherosclerotic role, whereas OSS induces YAP activation and translocation into the nucleus of ECs, leading to increased EC proliferation and monocyte adhesion factor expression, resulting in the occurrence of key pathogenic events in atherosclerosis, such as intimal thickening and foam cell formation.[173,175] These studies have laid a theoretical foundation for the use of YAP as a therapeutic target for mechanically stimulated atherosclerotic diseases. In myocardial ischemia–reperfusion injury, LSS exerts a protective effect on microvascular ECs by activating YAP and alleviating myocardial injury.[176] In hypertension, blood pressure overload increases YAP nuclear translocation in vascular ECs, promoting oxidative stress and inhibiting NO bioavailability, leading to endothelial dysfunction.[177] In heart valves, YAP activation is also affected by mechanical forces, affecting valve growth and remodeling.[67] In addition to ECs, YAP/TAZ also play important roles in the mechanotransduction of smooth muscle cells. Proper YAP/TAZ mechanotransduction in VSMCs is a key factor in maintaining the contractile phenotype and function of vascular smooth muscle and is essential for maintaining vascular homeostasis. In pressure overload, SMC-specific YAP/TAZ loss leads to decreased vasocontractility, impaired myogenic response, and increased compliance.[178,179] In addition, YAP/TAZ loss also affects the regulation of ECM remodeling by SMCs under pressure overload, which manifests as reduced assembly of elastic fibers and increased degradation of elastin, leading to the formation of aneurysms.[180,181] Pathological mechanical stretch downregulates enhancer of zeste homolog 2 via activation of the YAP-TEAD1 pathway, thereby exacerbating VSMC apoptosis and vascular remodeling.[182] These studies suggest that the balance of YAP/TAZ activation represents the balance of vascular cell function and that the deletion or increased nuclear translocation of YAP/TAZ causes the activation of downstream pathogenic signaling pathways, leading to the occurrence of vascular pathological remodeling. At present, the role of YAP/TAZ in cardiovascular homeostasis and remodeling is still in the stage of continuous in-depth study. In the future, many studies are needed to elucidate its specific mechanism of action and explore the regulatory factors affecting its activation/inactivation balance to provide a new perspective for the treatment of cardiovascular remodeling diseases.

#### 3.4.2. Piezo1 in mechanobiology

Piezo1 is a mechanosensitive cationic channel on the cell membrane that responds to different mechanical forces and converts them into intracellular signals, participating in the occurrence and development of cardiovascular remodeling diseases.[183–185] In recent years, its pathogenic mechanism in cardiovascular remodeling induced by mechanical stimulation has been continuously explored and enriched. In the heart, piezo1 is a key mechanical sensor that initiates mechanical-chemical signal transduction to cause cardiac remodeling.[186,187] Abnormal mechanical stretch upregulates piezo1 in cardiomyocytes, and the mechanical signal is converted into an intracellular oxidative stress signal.[188] Piezo1 is an important regulator of stretch-induced the expression of genes related to cardiac remodeling in cardiac fibroblasts.[189] After myocardial infarction, abnormal mechanical stress and mechanical load on the myocardium cause piezo1 upregulation, which induces pathological ventricular remodeling by activating multiple signaling pathways, including those that mediate inflammatory cascades[190] and disrupt intracellular calcium cycling dynamics in cardiomyocytes.[191] In pulmonary hypertension, enhanced cyclic stretch promotes endothelial–mesenchymal transition and stimulates SMC proliferation by upregulating piezo1,[192] whereas high shear stress caused by high flow causes the upregulation of piezo1 in ECs and activates endothelial inflammation.[193] The pressure overload-induced activation of piezo1 causes platelet activation and thrombosis, promoting the occurrence of hypertensive complications.[194] In addition, under pressure overload, piezo1 upregulation disrupts cardiomyocyte calcium homeostasis causing myocardial hypertrophic remodeling.[195] The role of piezo1 in AS has been extensively studied, and many new discoveries concerning the role of piezo1 in hemodynamically related atherosclerosis have recently been reported. The upregulation of piezo1 under OSS causes the activation and nuclear translocation of YAP, thereby mediating endothelial dysfunction and promoting the formation of atherosclerotic lesions.[196–198] In advanced atherosclerotic lesions, the activation of piezo1 is associated with increased plaque stability. The activation of piezo1 promotes foam cell apoptosis, reduces the expression of inflammatory factors, and increases the collagen content.[199] In addition, piezo1 has been found to be the target of many traditional Chinese medicines for the treatment of atherosclerosis which delay the progression of atherosclerotic lesions by inhibiting the expression of piezo1.[198,200] Activated neutrophils release neutrophil extracellular traps (NETs) to mediate inflammation, which plays an important role in the formation of early atherosclerotic lesions. A recent study revealed that low shear stress downregulates piezo1 to promote the generation of NETs.[201] In the response of SMCs to increased ECM rigidity, piezo1 is among the key mechanotransduction molecules whose activation causes an increase in SMC volume.[202] The discovery of these new mechanisms has provided some new insights into the mechanotransduction function of piezo1, which is a continuous improvement in the biological function of piezo1 and further enhances its status in cardiovascular diseases related to mechanical regulation.

#### 3.4.3. Cardiovascular homeostasis

In the past, researchers have focused mainly on the effects of mechanical stimulation on cardiovascular remodeling, but in recent years researchers have focused on the role of mechanical regulation in cardiovascular homeostasis. Mechanical homeostasis is the most important aspect of cardiovascular homeostasis and requires a combination of mechanical stimulation and mechanotransduction induced biological responses to maintain it.[9,203] The regulation of homeostasis is characterized by negative feedback regulation. In the cardiovascular system, when mechanical stimulation deviates from the optimal value or set value, the corresponding negative feedback regulatory mechanism is activated to restore the system to the normal range.[204,205] Blood pressure and flow homeostasis are essential for the physiological function of the cardiovascular system to ensure normal cardiovascular perfusion to cope with changing metabolic and physiological needs.[206] When surgical operations or changes in tissue perfusion cause blood flow to increase or decrease, ECs sense that shear stress deviates from the set point. ECs respond quickly by regulating vasoconstriction or dilation through corresponding mechanisms, thereby changing the diameter of the blood vessels, maintaining blood flow shear stress within the physiological range, and maintaining cardiovascular homeostasis.[206] When blood pressure increases acutely, the first to sense it in arterioles are SMCs, which maintain local hemodynamic homeostasis through myogenic contraction.[179,207] The homeostasis of the ECM is also important for cardiovascular homeostasis, which is reflected in the balance of quantity, composition, assembly and mechanical properties.[107,208] In different layers of the vascular wall, the components of the ECM also differ in terms of site specificity, which is a prerequisite for the normal physiological function of the cardiovascular system in the mechanical environment.[209] Most ECM components are not static but rather dynamically changing, constantly produced, degraded and assembled. In this process,

the production and degradation of the ECM maintain a relatively balanced state,[95] and these relatively balanced states are the prerequisites for maintaining mechanical properties.[107] The state of cells is also important in the regulation of cardiovascular homeostasis, and this state is reflected in the phenotype of cells. Changes in the cell phenotype affect the perception of mechanical stimulation, thereby affecting the biological processes caused by subsequent mechanical transduction. ECs are the barrier cells of the cardiovascular system, and maintaining the normal phenotype of ECs is crucial for maintaining cardiovascular homeostasis.[210] Studies have shown that a more flexible ECM promotes longer elongation and tighter cell junctions in ECs under LSS, and promotes the production of nitric oxide, indicating that the quality of the ECM is related to the phenotype of ECs. Furthermore, suggests that the homeostasis of the interaction between the ECM and ECs is crucial for the maintenance of vascular homeostasis under hemodynamic conditions.[211] Maintaining the contractile phenotype of VSMC is beneficial for resisting the pathological remodeling of the ECM caused by pressure overload and preventing the occurrence of aortic aneurysms.[212,213] Mitochondria are the energy centers of cells, and their homeostasis is crucial for the maintaining of the contractility phenotype of SMCs.[214] The homeostasis of the interaction between SMCs and the ECM can maintain normal vascular compliance and prevent arteriosclerosis.[118] Recent studies have shown that maintaining glutathione homeostasis in SMCs can prevent VSMC dysfunction and is an important means to improve pathological remodeling of the ECM in atherosclerosis and offset arterial stiffness.[215] In the future, the mechanical regulatory mechanisms of cardiovascular homeostasis will be revealed by an increasing number of studies, and the focus will gradually be refined from overall cardiovascular homeostasis to the homeostasis of the components of the cardiovascular system as well as the interactions among the components.

#### 3.4.4. *Mechanically regulated cardiac fibrosis*

Cardiac fibrosis is the pathophysiological basis of HF.[151,216] In recent years, many studies have investigated the role of mechanical regulation in cardiac fibrosis. Cardiac fibrosis is significantly related to hemodynamic changes. Pathological hemodynamics drives cardiac fibroblasts to differentiate into myofibroblasts through mechanotransduction,[217–219] causing excessive accumulation of ECM components and secretion of pro-fibrotic factors.[220–222] Myocardial mechanical overload has been confirmed to be the main driver of myocardial fibrosis in living myocardial slices that preserve structure and function.[223] Abnormalities in cardiac mechanics can also promote cardiac fibrosis. In patients with mitral valve prolapse, myocardial fibrosis was found to be associated with impaired myocardial longitudinal strain caused by mitral valve prolapse.[224] Another study revealed that decreased myocardial mechanical parameters, such as global longitudinal strain, circumferential strain and myocardial strain, can reflect the severity of myocardial fibrosis.[225] Activated fibroblasts and myofibroblasts are the main cellular effectors of cardiac fibrosis.[226,227] Studies have shown that ECs may also acquire a fibrotic phenotype through endothelial–mesenchymal transition under mechanical overload conditions, thereby promoting cardiac fibrosis.[228] In pressure overload mediated cardiac fibrosis, macrophage-mediated inflammation also plays a role in the differentiation of fibroblasts into myofibroblasts.[229] Many studies have confirmed that there is two-way communication between fibroblasts and the ECM. The mechanical properties of the ECM affect the behavior of fibroblasts, and the state of fibroblasts will also regulates the remodeling of the ECM. There is also a positive feedback loop between the two.[230,231] A decrease in the viscoelasticity of the ECM and an increase in linear elasticity will activate the mechanically sensitive pathway and cause fibroblast activation.[232,233] Activated fibroblasts are the main source of ECM proteins, causing increased ECM remodeling.[167,234] Cardiac fibroblasts can also sense mechanical stress through mechanosensitive receptors, ion channels, and integrins, activating the intracellular fibrosis cascade and leading to fibrosis caused by pressure overload.[235–239] The transformation of cardiac fibroblasts into myofibroblasts under pressure overload is significantly associated with intracellular metabolic changes, manifested by increased aerobic glycolysis and lactate production.[240] A recent study revealed that pressure overload activates reactive oxygen species production pathways to induce mitochondrial oxidative damage and promote myocardial fibrosis.[241] Exosomes also play important roles in cardiac fibrosis caused by pressure overload. Enhanced mechanical stretch induces cardiomyocytes to regulate the activation of cardiac fibroblasts through an exosome-mediated paracrine mechanism, thereby promoting cardiac fibrosis.[242] Crosstalk between fibroblasts and cardiomyocytes plays an important role in the process of cardiac fibrosis. A recent study revealed that during volume overload-induced cardiac fibrosis, integrinbeta-like1 is upregulated in fibroblasts, promoting cardiomyocyte hypertrophy.[243] Mechanical stimulation is an important driving factor of cardiac fibrosis. Although the mechanical-related pathogenic mechanism has received much attention from researchers in recent years, there is still much room for research in the future, including mechanism regulating the crosstalk between cardiomyocytes and fibroblasts under mechanical stimulation, as well as the positive feedback regulation between fibroblast activation and ECM remodeling.

## 4. Summary and prospects

In this study, we used CiteSpace bibliometric analysis software to analyze the scientific literature concerning the mechanobiology of cardiovascular homeostasis and remodeling over the past 20 years and quantitatively and visually reviewed the research achievements and progress in this field. First, we conducted a quantitative analysis of basic information such as annual publication volume, authors, institutions, and countries. Second, we conducted a co-occurrence analysis of keywords, obtained hot keywords in the field, and summarized the research progress of hot keywords. Finally, we analyzed the citation burst keywords, obtained the emerging research directions in the field, and explained its current research status.

Cardiovascular disease is currently the leading cause of death worldwide, and most cardiovascular diseases are associated with pathological remodeling caused by mechanical stimulation.[244,245] Over the past 20 years, owing to the continuous in-depth research on cardiovascular mechanobiology in various countries and the continuous development of technical means such as cell biology, molecular biology, in vitro mechanical stimulation models and mechanical simulation software, the number of published articles in this field has steadily increased. Among them, endothelial dysfunction induced by abnormal shear stress is the most concerning aspect for researchers, and many studies have been conducted on this topic. The focus of the research is this regulatory mechanism of abnormal stress on EC phenotypes. A large number of mechanosensitive signaling cascades have been discovered, and a deep understanding of these mechanosensitive signaling molecules will provide new potential targets for the treatment of cardiovascular pathological remodeling diseases. In the cardiovascular system, biological processes under mechanical stimulation are regulated by interactions between components within the system, including interactions between cardiovascular cells and the interaction between the ECM and cardiovascular cells. In addition, under mechanical stimulation, there are interactions between vascular cells that mediate vascular homeostasis. When blood flow increases and shear stress increases, ECs secrete vasodilator cytokines, inducing rapid relaxation of VSMCs and expansion of the arterial diameter, thereby restoring wall shear stress to the initial level.[246] The ECM can also initiate mechanical signaling through matrix–cell interactions to affect the behavior and function of vascular cells, playing a vital role in cardiovascular homeostasis and remodeling.[99,118,204] The quality and quantity of the ECM also affect the stiffness of blood vessels.[107] ECM–cell mechanotransduction interactions are mediated by focal adhesions and integrins. Focal adhesions connect the ECM and the cytoskeleton, and integrins transmit information about the chemical composition and mechanical state of the ECM to cells.[247,248] The most critical aspect of the effects of abnormal mechanical

stimulation on cardiovascular cells, the ECM and the interactions between them is the process of cellular mechanotransduction.[58,100] Mechanosensitive channels and mechanosensitive transcription factors play important roles in mechanotransduction and act as intermediate hubs for mechanical stimulation to elicit biological effects in cells.[161] Cardiovascular remodeling diseases such as hypertension and HF usually occur under abnormal mechanical stimulation through positive feedback. Abnormal mechanical stimulation activates related signaling pathways, such as inflammation, oxidative stress, and immunity, causing pathological remodeling, such as vascular stiffness and myocardial hypertrophy, and this structural and functional remodeling further promotes the activation of pathogenic signaling pathways.[249] Among these research hotspots and emerging research directions, mechanobiology has been continuously improved in cardiovascular homeostasis and remodeling, more mechanisms will be discovered in the future, and more potential therapeutic targets are expected to be identified in the clinic.

Although mechanobiology-related research on cardiovascular homeostasis and remodeling has made good progress in the past 20 years, there are still some challenges and difficulties in the future development process, which need to be solved and explored by researchers in the future. (1) More in depth, multiomics, and multidimensional research should be conducted on the mechanobiology of cardiovascular homeostasis and remodeling. Research progress on the role of mechanical stimulation in EC and VSMC dysfunction has revealed that its mechanism of action and effects, including mechanical sensing and mechanical transduction, have been continuously studied in depth. An increasing number of membrane-localized mechanical sensors and intracellular signaling molecule pathways have been discovered.[250,251] Conducting more in-depth and comprehensive research will provide a theoretical basis for the development of new drugs and enable these findings to truly enter the clinic, which is highly important for improving the precision treatment of cardiovascular remodeling diseases. (2) The transmission of mechanical force within blood vessels requires physically interconnected structures, such as the ECM, focal adhesions, cytoskeleton and cell nucleus.[99,252] The interaction mechanisms involved will require more research in the future, which will help to fully understand the mechanobiology of cardiovascular homeostasis and remodeling. (3) Currently, a complete quantitative system for evaluating the severity of lesions via mechanical stimulation is lacking. Many articles have reported the role of mechanical stimulation, such as pressure, circumferential wall stress, and shear stress, in diseases such as atherosclerosis, hypertension, and HF. However, it is still difficult to obtain accurate values at the lesion site, which limits its clinical application. Currently, most of them are simulated through computational fluid dynamics (CFD).[253,254] The accuracy of the numerical values depends largely on the accuracy of CFD modeling, which limits the precise quantification of the relationship between mechanical stimulation and the severity of lesions. In the future, technology can be continuously improved to improve the accuracy of computational fluid dynamics simulations. In combination with medical imaging, advanced computational fluid dynamics and flow field testing technologies, cardiovascular system modeling and quantitative analysis can be carried out to explore new noninvasive detection technologies for cardiovascular diseases and personalized treatment and surgical design to provide mechanobiology solutions for the diagnosis, treatment and early warning of cardiovascular diseases.

## CRediT authorship contribution statement

**Wei Liao:** Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yuxi Huang:** Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xiangxiu Wang:** Visualization, Software, Methodology, Investigation. **Ziqiu Hu:** Software, Investigation. **Chuanrong Zhao:** Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Guixue Wang:** Writing – review & editing, Writing – original draft, Resources, Project administration, Funding acquisition, Conceptualization.

## Ethical approval

This study does not contain any studies with human or animal subjects performed by any of the authors.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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