

Mechanical Force Signaling and Atherosclerosis and Coronary Heart Disease Research

Junyang Sun

Northeastern University, ShenYang, 110819 ,China

2485663@dundee.ac.uk

Abstract. The Global Burden of coronary heart disease (CHD) between 1990 and 2019 report shows that in 2019, there were about 9.14 million deaths from CHD globally, and other 197 million people suffered from CHD. At present, there are limitations in the cure of coronary heart disease, and also the research and treatment of some mechanisms. This paper discusses the pathogenesis and treatment of coronary heart disease from the perspective of the influence of mechanical force. This paper discusses the key role of mechanical force signaling in the occurrence and development of atherosclerosis and coronary heart disease (CHD). Studies have shown that mechanical forces such as shear stress and tensile stress significantly affect endothelial cell function and the stability of atherosclerotic plaques, factors that are critical for the progression of CHD. At the same time, it is pointed out that future studies should focus on revealing the specific mechanisms of different mechanical forces in atherosclerotic plaque formation, vascular remodeling and plaque vulnerability.

Keywords: Coronary heart disease, atherosclerosis, mechanical force signal, tensile stress, shear stress, plaque stability.

1. Introduction

Atherosclerosis, the main cause of vascular diseases, involves lipid deposits in the artery walls [1]. These deposits form unstable plaques that can rupture, leading to blood clots and acute cardiovascular events [2]. Atherosclerosis accumulates in the coronary arteries, reducing oxygen and blood flow to the heart muscle and causing CHD. This illness emphasizes how crucial it is to research mechanical force signaling in atherosclerosis in order to comprehend and treat CHD more effectively. Current treatments for CHD often address symptoms but not the underlying causes, such as endothelial dysfunction and plaque formation. By studying mechanical force signaling, new therapeutic targets may be identified, potentially leading to treatments that directly address plaque formation and instability, improving patient outcomes [3].

Mechanical force signals influence gene expression and cell function, impacting atherosclerosis and CHD. This research aims to explore the effects of mechanical stress on coronary heart disease, particularly its role in plaque formation and instability [4].

2. Mechanical Force Signals

The mechanical forces of the cell microenvironment continuously regulate cell growth, survival, apoptosis, differentiation and morphogenesis by reshaping the cytoskeleton and regulating actin

contraction. The microenvironment provides mechanical signals, triggering biochemical signals through mechanical conduction

2.1. Definition and classification

Blood flow shear force: shear stress (SS) refers to the frictional force exerted by flowing blood on endothelial cells within the walls of blood vessels. There are two main forms of mechanical bioforce: laminar flow shear force and frictional force parallel to the long axis of the blood vessel; the oscillatory shear force is a mechanical pull force which is vertical to the long axis of the blood vessels due to the beating of the heart. The shear force of blood flow is closely related to blood viscosity, blood flow velocity, and geometric anatomy of blood vessels [5].

Tensile stress refers to the stress acting on the wall of blood vessels or organs in both radial and circumferential directions, which is mainly caused by blood pressure and can affect the cells in the wall of blood vessels. In the heart, mechanical stress on the walls of the heart muscle is also similar to tensile stress. Tensile stress is essential in organ development and structure formation.

2.2. Biological basis

The role of mechanical force signaling in atherosclerosis and coronary heart disease is realized through a variety of mechanical force sensors and gene expression regulation. These mechanisms play a key role in sensing and transducing mechanical force signals:

Mechanical force sensor: ion channels: such as PIEZO1 and PIEZO2, these ion channels activate intracellular signal transduction pathways in endothelial cells by sensing mechanical forces such as shear stress and tension [6]. Integrins: Integrins, as key proteins in the connection between extracellular matrix and cytoskeleton, play an important role in the perception and transduction of mechanical force signals [7]. Glycoproteins: such as PECAM-1 and VE-cadherin, these molecules connect between endothelial cells and sense changes in mechanical forces caused by blood flow [8,9].

Mechanical force signals regulate gene expression by activating transcription factors such as KLF2, NF- κ B, etc., thereby affecting endothelial cell function and inflammatory response. The regulation of these genes is a key factor in the onset and progression of atherosclerosis and coronary heart disease [10].

3. Mechanical forces and coronary heart disease

The pathogenesis of coronary heart disease (CHD) involves a series of complex physiological and pathological processes, which mainly revolve around coronary artery atherosclerosis and myocardial ischemia.

3.1. Formation and development of atherosclerosis

The core pathological process of coronary heart disease is atherosclerosis, that is, atherosclerotic plaque formed by the accumulation of lipids in the inner wall of the artery. These plaques, which are usually made up of cholesterol, calcium and other substances, build up over time and can lead to narrowing and hardening of the arteries, restricting blood flow.

Mechanical stress significantly affects the pathophysiological process of atherosclerosis. The interaction between mechanical forces and cellular responses is critical to understanding the formation and development of atherosclerotic plaques [11].

For example, HIF-1 α is activated by mechanical stress in vulnerable arterial sites with abnormal blood flow shear. It is a key regulator under hypoxic conditions, and its activation leads to changes in a range of gene expression, promoting the inflammatory response and dysfunction of endothelial cells. The activation of HIF-1 α enables endothelial cells to release more inflammatory mediators and adhesion molecules, attract and activate inflammatory cells, and enhance local inflammatory response, which can lead to cardiovascular disease [10].

3.2. Endothelial cell injury and dysfunction

Atherosclerosis begins with damage and dysfunction of vascular endothelial cells (ECs). Abnormal changes of mechanical stress such as blood flow shear and tension are important causes of endothelial cell injury. This damage leads to increased endothelial permeability, infiltration of low-density lipoprotein (LDL) into the artery wall and oxidation to oxidized low-density lipoprotein (oxLDL), causing blood vessels to constrict and further plaque formation [8,10].

3.3. Myocardial ischemia and infarction

Myocardial ischemia occurs when the supply of blood to the coronary arteries cannot meet the metabolic needs of the heart muscle. A short period of ischemia may be reversible, but if the ischemia continues, irreversible damage to the heart muscle cells can occur, eventually leading to myocardial infarction.

4. Pathological mechanisms of coronary heart disease under mechanical forces

Coronary heart disease (CHD) is a kind of heart disease that causes myocardial ischemia, hypoxia or necrosis due to atherosclerosis of the coronary arteries [8]. The mechanism of mechanical stress-induced coronary heart disease (CAD) is realized through a series of complex biological processes, in which mechanical stress and inflammatory response are key factors

4.1. Tensile stress

After feeling tensile stress, cardiomyocytes regulate the occurrence of cardiac hypertrophy by activating MAPK signaling pathways (ERK, JNK, p38 MAPK) and JAK/STAT signaling pathways. These pathways play an important role in the thickening of myocardial fibers and the thickening of myocardial walls, and long-term pathological tensile stress can lead to cardiac dysfunction and heart failure.

4.2. Shear stress effects

Low shear stress and oscillatory shear stress increase oxidative stress levels, decrease nitric oxide (NO) generation, and activate nuclear factor kappa B (NF- κ B) to promote endothelial cells' inflammatory response and the development of atherosclerotic plaques. It also promotes the development of plaques and the occurrence of coronary heart disease by regulating the c-Jun N-terminal kinase (JNK)/p38 MAPK signaling pathway, increasing the expression of vascular cell adhesion molecule (VCAM-1) and intercellular adhesion molecule (ICAM-1).

High shear stress is associated with the degeneration of fibrous and fibrofatty areas of arterial plaque. This degeneration causes plaques to become more susceptible to rupture, increasing the risk of acute coronary events such as myocardial infarction. High shear stress promotes an increase in the necrotic core area, making plaques more susceptible to rupture and triggering acute coronary events [11,12].

The shear force of blood flow can also lead to the damage of vascular endothelial cells, which can trigger local inflammatory responses. This inflammatory response further leads to the recruitment of monocytes, activation of endothelial cells, and deposition of lipids in the artery wall, eventually forming atherosclerotic plaques [13-15].

4.3. Blood pressure

The role of mechanical tension in vascular smooth muscle cells (VSMCs) must be emphasized when studying the effect of mechanical force signal on coronary heart disease. Mechanical tension induced by hypertension significantly promotes the proliferation and apoptosis of VSMCs by activating PKC α (protein kinase C α) and MAPK (mitogen-activated protein kinase) signaling pathways, which play a key role in the occurrence and development of atherosclerosis (As). These changes in cell behavior not only drive vascular remodeling, but also exacerbate atherosclerotic plaque instability and increase the risk of acute coronary events [4,14].

4.4. Vulnerability and rupture of plaques

Mechanical stress can lead to increased vulnerability to atherosclerotic plaques through a variety of mechanisms. Inflammatory cells within the plaque, such as macrophages and T cells, release enzymes (such as matrix metalloproteinases) that degrade the plaque's fibrous cap, making it more likely to rupture. Once the plaque ruptures, the exposed lipid core can trigger acute thrombosis, leading to a heart failure.

5. Future research directions and applications

5.1. Understanding complex mechanism

The specific molecular mechanisms of mechanical force signaling in the occurrence and progression of coronary heart disease are still not fully understood. Future research should focus on unraveling the specific molecular mechanisms of mechanical force signaling in coronary heart disease, particularly how high shear stress affects plaque degradation and rupture by altering endothelial and smooth muscle cell function

5.2. The need for multidisciplinary research

Numerous academic fields, including biomechanics, molecular biology, and clinical medicine, are involved in the research of coronary heart disease. A thorough knowledge of the function of mechanical force signals in coronary heart disease can be achieved through multidisciplinary study. For instance, by merging molecular biology research with biomechanical models, the effects of blood flow shear stress on atherosclerosis may be more properly reproduced. Furthermore, the therapeutic applicability of laboratory results may be confirmed with the support of a mix of animal model studies and clinical research.

5.3. Applications

Understanding the role of mechanical force in atherosclerosis provides a new approach for therapeutic intervention. Pathways that target mechanical stress activation, such as those involved in HIF-1 α , offer the potential to develop treatments that prevent plaque formation or reduce plaque susceptibility. For example, interventions that regulate shear stress or inhibit HIF-1 α activation can reduce inflammatory responses and endothelial dysfunction, thereby slowing the progression of atherosclerosis.

6. Conclusion

Through the regulation of gene expression and cellular function, mechanical force signaling plays a significant role in the advancement of atherosclerosis and coronary heart disease. The inflammatory response and endothelial cell function are influenced by several mechanical stress sensors and signaling pathways, which facilitate the development, stabilization, and rupture of atherosclerotic plaques.

Shear stress promote endothelial inflammatory response and atherosclerotic plaque formation by enhancing NF- κ B activity, increasing oxidative stress levels and reducing nitric oxide (NO) production. High shear is associated with degeneration of the fibrotic areas of plaque, making plaque more likely to rupture and increasing the risk of acute coronary events.

This study highlights the importance of mechanical force signaling in the development of atherosclerosis and coronary heart disease (CHD). Mechanical forces, such as shear stress and tensile stress, significantly influence endothelial cell function, inflammatory responses, and the stability of atherosclerotic plaques. These forces contribute to the formation, vulnerability, and potential rupture of plaques, thereby increasing the risk of acute coronary events. The research underscores the importance of understanding these mechanisms to develop targeted therapies that address the underlying causes of CHD, rather than merely treating its symptoms.

Future studies should further reveal the specific mechanisms of different types of mechanical forces in atherosclerotic plaque formation, vascular remodeling and plaque vulnerability, especially how high

shear forces promote plaque degradation and rupture by affecting endothelial and smooth muscle cell function.

References

- [1] Herrington, W., Lacey, B., Sherliker, P., Armitage, J., & Lewington, S. (2016). Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease. *Circulation Research*, 118(4), 535–546.
- [2] Zhu Y, Xian X, Wang Z, Bi Y, Chen Q, Han X, Tang D, Chen R. Research Progress on the Relationship between Atherosclerosis and Inflammation. *Biomolecules*. 2018 Aug 23;8(3):80.
- [3] Fioranelli, M., Bottaccioli, A. G., Bottaccioli, F., Bianchi, M., Rovesti, M., & Rocchia, M. G. (2018). Stress and Inflammation in Coronary Artery Disease: A Review Psychoneuroendocrineimmunology-Based. *Frontiers in Immunology*, 9(1). <https://doi.org/10.3389/fimmu.2018.02031>
- [4] Jebari-Benslaïman, S., Galicia-García, U., Larrea-Sebal, A., Olaetxea, J. R., Alloza, I., Vandenbroeck, K., Benito-Vicente, A., & Martín, C. (2022). Pathophysiology of Atherosclerosis. *International Journal of Molecular Sciences*, 23(6), 3346.
- [5] Mu Jie Semu Kade. (2023). Research Progress of the Effect of Shear Stress on Vascular Endothelial Cells Function. *Advances in Clinical Medicine*, 13(05), 7227–7231.
- [6] Theofilis, P., Sagris, M., Oikonomou, E., Antonopoulos, A. S., Siasos, G., Tsioufis, C., & Tousoulis, D. (2021). Inflammatory Mechanisms Contributing to Endothelial Dysfunction. *Biomedicines*, 9(7), 781.
- [7] Lai, A., Cox, C. D., Chandra Sekar, N., Thurgood, P., Jaworowski, A., Peter, K., & Baratchi, S. (2021). Mechanosensing by Piezo1 and its implications for physiology and various pathologies. *Biological Reviews*, 97(2), 604–614. 4
- [8] van der Flier, A., & Sonnenberg, A. (2001). Function and interactions of integrins. *Cell and Tissue Research*, 305(3), 285–298.
- [9] Feng, S., Bowden, N., Fragiadaki, M., Souilhol, C., Hsiao, S., Mahmoud, M., Allen, S. T., Pirri, D., Blanca Tardajos Ayllon, Akhtar, S., Thompson, A. S., Jo, H., Weber, C., Ridger, V., Schober, A., & Evans, P. G. (2017). Mechanical Activation of Hypoxia-Inducible Factor 1 α Drives Endothelial Dysfunction at Atheroprone Sites. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 37(11), 2087–2101.
- [10] Conway, D. E., & Schwartz, M. A. (2014). Mechanotransduction of shear stress occurs through changes in VE-cadherin and PECAM-1 tension: Implications for cell migration. *Cell Adhesion & Migration*, 9(5), 335–339.
- [11] Henderson, A. (1996). Coronary heart disease: Overview. *The Lancet*, 348, S1–S4.
- [12] Mahmoudi, M., Farghadan, A., McConnell, D. R., Barker, A. J., Wentzel, J. J., Budoff, M. J., & Arzani, A. (2020). The Story of Wall Shear Stress in Coronary Artery Atherosclerosis: Biochemical Transport and Mechanotransduction. *Journal of Biomechanical Engineering*, 143(4).
- [13] Theofilis, P., Sagris, M., Oikonomou, E., Antonopoulos, A. S., Siasos, G., Tsioufis, C., & Tousoulis, D. (2021). Inflammatory Mechanisms Contributing to Endothelial Dysfunction. *Biomedicines*, 9(7), 781.
- [14] Liu Shuying, Li Chaohong, & Chaohong, L. (2023). Structural and functional changes of vascular smooth muscle cells induced by hypertensive mechanical force and their role in vascular diseases. *Chinese Journal of Arteriosclerosis*, 31(7), 553-563.
- [15] Bajraktari, A., Bytyçi, I., & Henein, M. Y. (2021). High Coronary Wall Shear Stress Worsens Plaque Vulnerability: A Systematic Review and Meta-Analysis. *Angiology*, 72(8), 706–714.