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Research on the Relationship Between Heart Failure and Calcium Cycling Proteins

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Abstract. Heart failure, defined as the inability of the heart to pump blood efficiently, involves various pathophysiological mechanisms, including disruptions in calcium cycling. Calcium cycling proteins, including calcium pumps and channels, are essential for the optimal contraction and relaxation of cardiac muscle. In patients with heart failure, the dysfunction of these proteins results in impaired calcium regulation, which serves to exacerbate the condition. This study explores the relationship between heart failure and calcium cycling proteins, which play a crucial role in the regulation of heart function. Through a review of recent experimental studies, this research reveals the significant changes in calcium cycling proteins observed in heart failure and discusses potential treatment strategies aimed at restoring calcium homeostasis. The findings indicate that the targeting of calcium cycling proteins may provide novel therapeutic avenues to improve cardiac function in patients with heart failure.

Keywords: Heart failure, Calcium cycling proteins, Pathophysiology, Calcium regulation, Cardiac function.

1. Introduction

Heart failure is a complex and prevalent clinical syndrome, with its global incidence increasing year by year, particularly among the elderly population. In recent years, although clinical research and treatment methods for heart failure have made certain progress, several unresolved issues remain. Calcium cycling plays a crucial role in regulating the contraction and relaxation of cardiomyocytes, and the dysfunction of calcium cycling proteins is considered one of the key factors in the development and progression of heart failure. However, current research on the specific mechanisms of calcium cycling protein dysfunction in heart failure remains insufficient, especially in terms of how targeting these proteins might improve cardiac function. Therefore, it is of significant importance to further investigate the role of calcium cycling proteins in heart failure.

The primary focus of this study is to explore the dysfunction of calcium cycling proteins in heart failure and their impact on myocardial function. Specifically, the research seeks to answer how abnormalities in calcium cycling proteins, such as sarcoplasmic reticulum calcium ATPase (SERCA) and ryanodine receptors, affect the contraction and relaxation processes of the myocardium in heart failure patients. Additionally, the study aims to investigate whether targeting these proteins could offer an effective therapeutic approach to alleviate heart failure symptoms.

To address these questions, this study employs a literature review approach, systematically analyzing recent research related to the functions of calcium cycling proteins and their role in heart failure. By

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synthesizing existing experimental data, this research provides new insights into the potential therapeutic strategies targeting calcium cycling proteins.

The significance of this research lies in its contribution to a deeper understanding of how calcium cycling proteins are involved in the pathophysiology of heart failure, which could serve as a theoretical foundation for the development of new treatment methods. Future research, building on the hypotheses proposed in this study, could further explore the therapeutic potential of targeting calcium cycling proteins and optimize relevant clinical applications, providing more effective treatment options for heart failure patients.

2. Pathophysiological Mechanisms of Heart Failure

2.1. Types and characteristics of heart failure

Heart failure is a complex clinical syndrome where the heart cannot meet the body's metabolic needs, leading to poor circulation and organ dysfunction. It is classified into several types based on cardiac function, including heart failure with reduced ejection fraction (HFrEF), preserved ejection fraction (HFpEF), and mildly reduced ejection fraction (HFmrEF). HFrEF, with an ejection fraction (EF) below 40%, is often due to myocardial damage, while HFpEF, defined as EF above 50%, involves diastolic dysfunction, fibrosis, and inflammation. HFmrEF, with EF between 40-50%, shares traits of both. These types differ in clinical manifestations and causes, affecting treatment strategies. HFrEF treatment focuses on enhancing contractility, whereas HFpEF therapy aims to improve diastolic function and manage comorbidities[1].

2.2. Pathological changes and mechanisms of heart failure

The pathological changes in heart failure primarily include myocardial cell damage, energy metabolism disorders, and inflammatory responses. Firstly, under prolonged stress, myocardial cells undergo remodeling, leading to hypertrophy and fibrosis, which further impair the heart's ability to contract and relax. Additionally, heart failure patients often exhibit metabolic disturbances, particularly changes in energy metabolism. Adenosine monophosphate-activated protein kinase (AMPK) plays a crucial role in regulating cardiac energy balance, and its dysregulation exacerbates the progression of heart failure. Moreover, sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently been found to affect skeletal muscle pathology in heart failure patients, with potential therapeutic effects on myocardial energy metabolism and sodium-calcium exchange.

At the same time, the inflammatory response also plays an important role in the pathogenesis of heart failure. Inflammation triggered by myocardial damage not only accelerates myocardial fibrosis but also further deteriorates cardiac function. In rare cases, such as neonatal venous malformations, high-output heart failure may occur. Thus, the pathophysiology of heart failure is the result of multiple interacting factors, and understanding these mechanisms is critical for developing new treatment approaches.

3. Overview of Calcium Cycling Proteins

3.1. Definition and process of calcium cycling

Calcium cycling refers to a mechanism involving the repeated use and recycling of calcium ions in biological and chemical processes, playing an important role in both nature and industrial applications. In myocardial cells, calcium cycling involves the movement of calcium ions between intracellular and extracellular spaces and different intracellular storage compartments, such as the sarcoplasmic reticulum (SR), to regulate the contraction and relaxation of the myocardium. The process generally includes the uptake, release, and reuptake of calcium ions, each regulated by specific proteins like calcium pumps, calcium channels, and calcium-binding proteins[2].

In industrial applications, calcium cycling is widely used in carbon dioxide capture technology, especially in the processes of calcium carbonate (CaCO3) decomposition and calcium oxide (CaO) sintering. The calcium looping CO2 capture technology uses the decomposition reaction of CaCO3 to

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capture CO2 and convert it to CaO, followed by CO2 release through CaO recarbonation at high temperatures, thus achieving CO2 capture and reuse. The cycling performance of this process is influenced by the pore evolution during CaCO3 decomposition and CaO sintering, and improved pore evolution models can optimize reaction kinetics and thermal efficiency.

Calcium cycling is also considered a potential technology for achieving carbon neutrality, as it can be used for both CO2 capture and thermochemical energy storage. The reaction heat storage from calcium cycling can help balance energy supply during intermittent renewable energy generation, thereby enhancing the stability of energy systems[3]. Additionally, integrating calcium cycling with other processes, such as methane reforming, can simultaneously achieve CO2 capture and energy conversion, thereby improving overall efficiency and economic viability. This integrated approach combines thermodynamic and exothermic processes, which can reduce energy consumption while increasing CO2 utilization efficiency[4].

Overall, calcium cycling has significant applications in both biological and industrial processes. Whether as a core process in cardiac calcium regulation or as a key technology in CO2 capture and utilization, calcium cycling demonstrates great potential and diverse application scenarios.

3.2. Functions of major calcium cycling proteins

Calcium cycling proteins play a crucial role in regulating calcium ions in the heart, essential for maintaining normal myocardial contraction and relaxation. The main calcium cycling proteins include sarcoplasmic reticulum Ca2+-ATPase (SERCA), ryanodine receptor (RyR), and calcium/ calmodulin -dependent protein kinase II (CaMKII), which together participate in the transport, release, and reuptake of calcium ions, thus regulating the cardiac contraction and relaxation cycle[5].

SERCA is responsible for pumping calcium ions from the cytoplasm of myocardial cells back into the sarcoplasmic reticulum, a process vital for myocardial relaxation. Driven by ATP, SERCA efficiently stores calcium ions in the sarcoplasmic reticulum, allowing the heart to rapidly release calcium ions in the next contraction cycle to promote myocardial contraction. If SERCA function is impaired, the efficiency of calcium reuptake decreases, leading to diastolic dysfunction and elevated intracellular calcium levels, a common condition in heart failure patients.

The ryanodine receptor (RyR), located on the sarcoplasmic reticulum membrane, is the main channel regulating calcium release from the sarcoplasmic reticulum. At the onset of myocardial contraction, an action potential triggers a significant release of calcium ions through the RyR into the cytoplasm, activating the sliding of myofilaments and myocardial contraction. RyR dysfunction, particularly prolonged channel opening or calcium leakage, can lead to abnormal calcium accumulation within cells, which not only reduces the heart's contractile ability but may also cause arrhythmias[6].

Additionally, calcium/calmodulin-dependent protein kinase II (CaMKII) plays an important role in regulating the function of calcium cycling proteins. CaMKII modulates the activity of SERCA and RyR through phosphorylation, indirectly controlling the speed of calcium transport and release. In cases of elevated calcium levels, persistent activation of CaMKII can lead to excessive phosphorylation of calcium cycling proteins, further aggravating calcium overload in myocardial cells and eventually causing cell damage and heart failure.

Thus, the interaction between these calcium cycling proteins is essential for maintaining normal myocardial function, and abnormalities in any of these processes can lead to pathological changes in the heart. Studies have shown that triiodothyronine (T3) supplementation can protect calcium cycling proteins, exerting cardioprotective effects during ischemia-reperfusion injury.

4. Research Progress on the Relationship Between Heart Failure and Calcium Cycling Proteins

4.1. Changes in calcium cycling proteins in heart failure

The dysfunction of calcium cycling proteins is considered a key pathological factor in the development of heart failure. These proteins, including sarcoplasmic reticulum Ca2+-ATPase (SERCA), ryanodine receptor (RyR), and sodium-calcium exchanger (NCX), exhibit altered expression and activity,

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affecting the influx, storage, and efflux of calcium ions. Lu Qun et al.pointed out that in heart failure patients, SERCA expression is usually decreased, leading to reduced efficiency of calcium reuptake into the sarcoplasmic reticulum, impairing myocardial relaxation[7]. This reuptake deficiency results in intracellular calcium accumulation, causing dysfunction in myocardial contractility.

In addition, calcium leakage is a common phenomenon in heart failure. Liu Lan and Zou Caoreported that RyR dysfunction, particularly abnormal channel opening due to excessive phosphorylation or oxidative modifications, leads to calcium leakage, further aggravating the pathological progression of heart failure[8]. This not only affects cardiac contractility but may also cause arrhythmias due to calcium overload. Zhang Wei et al.also demonstrated that SUMOylation of RyR undergoes significant changes during heart failure, which may be a crucial factor contributing to calcium regulation disorders[9].

In studies of right heart failure models, J A R et al. found that the regulation of calcium cycling-related gene expression differs from that in left heart failure. Although dysregulation of calcium cycling genes does not directly drive right heart dysfunction, it still significantly impacts adaptive regulation of the heart[10]. Kifle and Abdelwuh further suggested that targeting calcium cycling proteins, particularly enhancing SERCA activity and stabilizing RyR function, may be an effective strategy for treating heart failure[11].

Overall, changes in calcium cycling proteins play a vital role in the development and progression of heart failure. Targeted therapies for these proteins may improve clinical management of heart failure in the future.

4.2. Calcium dysregulation and the pathological process of heart failure

Calcium dysregulation plays a crucial role in the development and progression of heart failure, characterized mainly by abnormalities in calcium cycling proteins and imbalanced intracellular calcium levels. Changwon noted that the sarcoplasmic reticulum Ca2+-ATPase (SERCA) pump is responsible for transporting calcium ions back into the sarcoplasmic reticulum in myocardial cells, maintaining normal intracellular calcium balance. However, in heart failure, SERCA function is significantly reduced, leading to decreased calcium reuptake efficiency and resulting in calcium overload and diastolic dysfunction in myocardial cells[12]. This impaired calcium reuptake not only affects cardiac contraction and relaxation but also exacerbates intracellular calcium accumulation, ultimately causing myocardial cell damage and apoptosis.

Chen et al. demonstrated that electroacupuncture combined with traditional Chinese medicine can synergistically improve heart failure symptoms, partly by regulating calcium cycling. They found that electroacupuncture increased SERCA expression, alleviating calcium overload in heart failure rats and improving cardiac function[13]. H S A et al. further explored the role of calcium-regulating hormones in heart failure, suggesting that these hormones may mitigate myocardial damage from inflammatory molecules by regulating calcium cycling protein expression. Hormonal interventions can reduce myocardial inflammation and slow the pathological progression of heart failure[14].

Moreover, Zhao Meiying found in a study of chronic heart failure rat models that the traditional Chinese medicine formula Shenqi Jianxin Fang improved cardiac function by increasing calcium regulatory protein expression, providing new evidence for its use in heart failure treatment, especially through intervention in calcium regulatory pathways[15]. Xiang et al. indicated that Yixinshu Capsules had a significant effect on calcium regulatory proteins in cardiac myocytes of heart failure rats, with mechanisms involving regulation of SERCA and other calcium cycling proteins to restore normal calcium regulation[16].

In conclusion, calcium dysregulation is a significant factor in the pathological process of heart failure, and targeted interventions for calcium cycling proteins may offer effective strategies for treating the condition.

5. Current Treatment Strategies and Prospects

Currently, treatment strategies for heart failure primarily focus on alleviating symptoms, slowing disease progression, and improving quality of life. Common pharmacological treatments include

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diuretics, angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, and mineralocorticoid receptor antagonists, which help reduce cardiac workload and relieve symptoms by modulating neurohormonal systems. However, these therapies mainly address symptoms and do not completely reverse pathological changes. As research on heart failure mechanisms advances, calcium cycling proteins have emerged as potential therapeutic targets, with strategies aimed at restoring calcium regulation to improve myocardial function gaining attention.

Treatments targeting calcium regulation, such as drugs that enhance sarcoplasmic reticulum Ca2+-ATPase (SERCA) function, are currently under investigation and have shown potential to improve myocardial relaxation and reduce calcium overload. Additionally, sodium-glucose cotransporter 2 (SGLT2) inhibitors, initially used for diabetes, have demonstrated potential benefits in heart failure, possibly related to their effects on intracellular calcium regulation. Complementary therapies, such as traditional Chinese medicine and electroacupuncture, have also shown efficacy in some studies by improving cardiac function through the modulation of calcium cycling proteins.

Future treatment prospects focus on precision medicine and personalized therapy, utilizing genetic testing and biomarker analysis to develop optimal treatment plans for each patient. Moreover, gene therapy and stem cell therapies targeting calcium regulation may bring new hope to heart failure patients, providing more effective therapeutic options in the future.

6. Conclusion

This paper examines the relationship between heart failure and calcium cycling proteins, focusing on their role in the regulation of cardiac function. The research highlights the crucial impact of calcium cycling proteins such as SERCA and ryanodine receptors in heart muscle contraction and relaxation. It was found that dysfunctions in these proteins can lead to impaired calcium regulation, which exacerbates the pathological process of heart failure. The study presents an overview of the types and characteristics of heart failure, exploring how these proteins play a role in the progression of the disease. Additionally, it emphasizes the importance of targeting calcium cycling proteins as a potential therapeutic strategy for improving the prognosis of heart failure patients.

However, this paper has certain limitations. The scope of the literature reviewed could be expanded to include more recent and diverse studies that examine the role of other calcium-related proteins beyond SERCA and ryanodine receptors. Moreover, the methods discussed in this research, particularly those used in experimental studies, could benefit from more in-depth analysis. Future studies could enhance the current findings by incorporating more advanced techniques, such as gene editing or new molecular imaging technologies, to further explore the precise mechanisms by which calcium cycling proteins contribute to heart failure.

In the future, research could focus on developing more specific therapies that directly target calcium cycling protein dysfunctions. One promising direction might be to explore gene therapy approaches aimed at restoring normal calcium protein function in heart failure patients. Furthermore, additional research is required to elucidate the interactions between calcium cycling proteins and other molecular pathways implicated in heart failure, with the potential to identify novel therapeutic targets. The integration of personalized medicine approaches, based on genetic or molecular profiling of heart failure patients, could also open up new possibilities for more effective treatments in the future.

References

[1] Ren, K., Luan, Y., Sun, Y., et al. (2024). NPLOC4 aggravates heart failure by regulating ROS and mitochondrial function [J]. International Immunopharmacology, 142(PB): 113199-113199.

[2] Shi, Z., Luo, C., Lai, D., et al. (2025). A modified pore evolution particle model applied to CaCO3 decomposition and CaO sintering during calcium looping CO2 cycles [J]. Separation and Purification Technology, 355(PB): 129733-129733.

[3] Zhang, Y., Wang, Y., Han, K., et al. (2024). Calcium looping for CO2 capture and thermochemical heat storage, a potential technology for carbon neutrality: A review [J]. Green Energy and Resources, 2(3): 100078-100078.

[4] Papalas, T., Antzaras, N.A., & Lemonidou, A.A. (2024). Integrated CO2 Capture and Utilization by Combining Calcium Looping with CH4 Reforming Processes: A Thermodynamic and Exergetic Approach [J]. Energy & Fuels: An American Chemical Society Journal, 38(13): 11966-11979.

[5] Lichao, F., Zhiping, X., Jian, L., et al. (2021). [Corrigendum] Cardioprotective effects of triiodothyronine supplementation against ischemia reperfusion injury by preserving calcium cycling proteins in isolated rat hearts [J]. Experimental and Therapeutic Medicine, 21(2): 1-1.

[6] Lichao, F., Zhiping, X., Jian, L., et al. (2019). Cardioprotective effects of triiodothyronine supplementation against ischemia reperfusion injury by preserving calcium cycling proteins in isolated rat hearts [J]. Experimental and Therapeutic Medicine, 18(6): 4935-4941.

[7] Lu, Q., Liang, X., Bai, L., et al. (2024). Mechanism and Clinical Research of Inotropic Agents for Heart Failure [J]. Chinese Journal of Interventional Cardiology, 32(08): 457-462.

[8] Liu, L., & Zou, C. (2024). Research Progress on the Relationship Between Heart Failure and Calcium Cycling Proteins [J]. Modern Medicine & Health, 40(13): 2287-2292.

[9] Zhang, W., Qiu, Z., Gu, N., et al. (2024). Progress in Research on the Role and Mechanism of SUMO Modification in Heart Failure [J/OL]. Advances in Anatomy, 1-7. [2024-10-09].

[10] J.A.R., Renata, M., Spyros, M., et al. (2023). Abstract 18817: Dysregulation of Key Calcium Cycling Genes Does Not Drive Right Heart Maladaptation in a Porcine PH Model [J]. Circulation, 148(Suppl_1): A18817-A18817.

[11] Zhang, W., Qiu, Z., Gu, N., et al. (2024). Progress in Research on the Role and Mechanism of SUMO Modification in Heart Failure [J/OL]. Advances in Anatomy, 1-7. [2024-10-09].

[12] Changwon, K. (2023). Targeting Calcium Regulators as Therapy for Heart Failure: Focus on the Sarcoplasmic Reticulum Ca-ATPase Pump [J]. Frontiers in Cardiovascular Medicine, 10: 1185261-1185261.

[13] Chen, Z., Zheng, M.W., Qun, L., et al. (2022). Synergistic and Attenuating Effect of Electroacupuncture on Aconitine in Improving Heart Failure and Its Calcium Regulation Mechanism [J]. Evidence-Based Complementary and Alternative Medicine, 2022: 4940745-4940745.

[14] H.S.A., R.K.H., T.H.A., et al. (2021). Can the Calcium-Regulating Hormones Counteract the Detrimental Impact of Pro-Inflammatory Damage-Associated Molecular Patterns in the Development of Heart Failure? [J]. Journal of Investigative Medicine: The Official Publication of the American Federation for Clinical Research, 69(6).

[15] Zhao, M. (2021). Effect of Shenqi Jianxin Formula on Cardiac Function and Calcium Regulatory Protein Levels in Chronic Heart Failure Rat Models [D]. Anhui University of Traditional Chinese Medicine.

[16] Xiang, C., Zhou, R., Zhang, J., et al. (2020). Effect of Yixinshu Capsules on Calcium Regulatory Protein in Cardiac Myocytes of Rats with Heart Failure [J]. Zhongguo Zhong Yao Za Zhi = China Journal of Chinese Materia Medica, 45(20): 4984-4990.