Pacific Journal of Medical Research
https://scienceget.org/index.php/pjmr
Vol. 1, No. 1, 2024
eISSN: 3067-2147
ARTICLE
DOI: https://doi.org/10.70818/pjmr.2024.v01i01.010

Molecular Mechanisms of Cardiac Remodeling in Heart Failure: Investigating the Role of Myocyte Hypertrophy, Fibrosis, and Inflammation in Disease Progression

Johar Daspattanayak[1]*, Abdul Baset[2]
[1] *Department of Cardiology, Jalpaiguri Government Medical College*
[2] *Department of Medicine, Upazila Health Complex, Rajshahi*

ABSTRACT ***Background:*** Heart failure (HF) involves complex molecular mechanisms, including myocyte hypertrophy, fibrosis, and inflammation, which contribute to the progression of the disease. Understanding these mechanisms is critical for improving therapeutic strategies. ***Objective:*** This study investigates the molecular mechanisms of cardiac remodeling in heart failure, focusing on the roles of myocyte hypertrophy, fibrosis, and inflammation in disease progression. ***Method:*** A cohort of 100 patients with diagnosed heart failure was enrolled at Jalpaiguri Government Medical College from June 2023 to June 2024. Blood samples were collected for inflammatory cytokine profiling, and cardiac imaging and biopsies were performed to assess myocyte hypertrophy and fibrosis. Immunohistochemical analysis of myocardial tissue was conducted to evaluate markers of hypertrophy (GATA4, MEF2) and fibrosis (TGF-β, Collagen I). Quantitative PCR and ELISA were used to quantify mRNA and cytokine levels. ***Results:*** Our results revealed that 65% of patients exhibited significant myocyte hypertrophy with elevated GATA4 and MEF2 expression, correlating with reduced ejection fraction. Fibrosis was present in 75% of patients, with elevated Collagen I expression in myocardial tissue. Pro-inflammatory cytokines (TNF-α, IL-6) were significantly increased in 72% of patients, correlating with increased fibrosis ($r = 0.82$, $p < 0.05$) and worse clinical outcomes. Patients with higher inflammatory cytokine levels showed a 45% higher risk of progression to advanced heart failure. ***Conclusions:*** Myocyte hypertrophy, fibrosis, and inflammation are critical factors in the progression of heart failure. Targeting these pathways may offer new therapeutic approaches to slow disease progression.
Keywords: Heart Failure, Cardiac Remodeling, Myocyte Hypertrophy, Fibrosis, Inflammation.

∗**Corresponding author**: daspattanayak05@gmail.com

Received: October 11, 2024 | **Accepted:** December 18, 2024 | **Published:** December 31, 2024

INTRODUCTION

Heart failure (HF) is a multifactorial and progressive condition that represents a major global health burden. It arises from a variety of etiologies including ischemic heart disease, hypertension, valvular disorders, and cardiomyopathies, all of which culminate in the heart's inability to meet the body's metabolic demands [1]. At the molecular and cellular level, heart failure is accompanied by a process called cardiac remodeling, which involves structural, functional, and biochemical changes in the myocardium. The pathophysiological hallmark of cardiac remodeling includes myocyte hypertrophy, fibrosis, and inflammation. These molecular alterations are central to

the progression of heart failure and directly influence the functional decline of the heart. Understanding the molecular mechanisms behind these processes is crucial for identifying therapeutic targets that may attenuate or reverse the remodeling, offering a potential for improved clinical outcomes. Myocyte hypertrophy is often one of the first compensatory responses to increased hemodynamic load, such as that seen in chronic hypertension or valvular heart disease. The hypertrophic growth of individual cardiomyocytes, though initially adaptive, can lead to maladaptive consequences in the long term. The molecular mechanisms driving myocyte hypertrophy involve complex intracellular signaling pathways, including the mitogen-activated protein kinase (MAPK) cascade, the phosphoinositide 3-kinase (PI3K)/Akt pathway, and calcineurin/nuclear factor of activated T-cells (NFAT) signaling. These pathways activate key transcription factors, such as *GATA4* and *MEF2*, which regulate genes associated with cell growth, protein synthesis, and metabolic reprogramming. Furthermore, the activation of *NF-κB*, a pivotal inflammatory mediator, plays a critical role in the pro-hypertrophic response and links hypertrophy to subsequent inflammation and fibrosis [2].

Despite its compensatory role, prolonged or excessive hypertrophy accelerates the transition to heart failure. Myocyte hypertrophy results in increased myocardial stiffness, dysfunction of the sarcomeric machinery, and the impairment of calcium handling, which collectively contribute to systolic and diastolic dysfunction [3]. Moreover, the hypertrophic response often leads to cardiomyocyte apoptosis and necrosis, thereby exacerbating the decline in myocardial function. This maladaptive hypertrophy-induced apoptosis is mediated through increased oxidative stress and mitochondrial dysfunction, which further compromise cardiomyocyte survival. As a result, myocyte hypertrophy not only compromises the structural integrity of the myocardium but also initiates the cascade of fibrosis and inflammation that worsens cardiac function. Cardiac fibrosis, characterized by the excessive deposition of extracellular matrix (ECM) proteins, particularly collagen, is a central component of cardiac remodeling in heart failure. Fibrosis disrupts the normal myocardial architecture, leading to increased myocardial stiffness, impaired contractility, and disturbed electrical conduction [4]. The key cellular mediators of fibrosis are cardiac fibroblasts, which undergo transdifferentiation into myofibroblasts under pathological conditions. This process is triggered by various cytokines and growth factors, including transforming growth factor-beta (TGF-β), angiotensin II, and mechanical stretch. Myofibroblasts secrete excessive amounts of collagen and other ECM proteins, which accumulate in the interstitial spaces and around myocytes, thus contributing to the stiffening of the heart muscle.

The signaling pathways that govern fibrosis are highly interconnected with those involved in myocyte hypertrophy and inflammation. Notably, *TGF-β* signaling plays a pivotal role in both fibrotic remodeling and the inflammatory response, creating a positive feedback loop that accelerates the progression of heart failure. Additionally, the dysregulation of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) results in an imbalance between ECM degradation and deposition, further promoting pathological fibrosis [5]. This ECM remodeling is not merely a passive consequence of cellular injury; rather, it actively contributes to the mechanical and electrical dysfunctions that characterize advanced heart failure [3] Furthermore, the deposition of collagen in the ECM reduces the heart's ability to stretch and contract efficiently, leading to both systolic and diastolic dysfunction. The fibrotic response also contributes to arrhythmogenesis by disrupting the normal myocardial conduction system, leading to ventricular arrhythmias and sudden cardiac death in many heart failure patients. Inflammation is a key player in the pathogenesis of cardiac remodeling and heart failure.

Chronic low-grade inflammation, often initiated by myocardial injury, ischemia, or mechanical stress, contributes significantly to disease progression. Inflammatory cytokines such as *TNF-α*, *IL-1*, and *IL-6* are upregulated in heart failure and have been shown to directly promote myocyte apoptosis, enhance oxidative stress, and stimulate fibrosis [6]. The inflammatory response also activates the immune system, which leads to the recruitment of immune cells, including macrophages, T lymphocytes, and neutrophils, to the site of injury [4]. These immune cells release further pro-inflammatory mediators that perpetuate the cycle of inflammation and fibrosis, exacerbating the structural and functional decline of the myocardium. One of the most critical regulators of inflammation in heart failure is

the inflammasome, a multi-protein complex that activates caspase-1 and facilitates the secretion of pro-inflammatory interleukins such as *IL-1β* and *IL-18* [7]. The activation of the inflammasome in cardiomyocytes and infiltrating immune cells has been implicated in myocardial injury and fibrosis, underscoring the complex role of the immune system in heart failure. While inflammation is initially a protective response aimed at tissue repair, sustained activation of the inflammatory pathways contributes to pathological remodeling and the progression of heart failure. Moreover, the inflammatory response interferes with the resolution of fibrosis and delays myocardial healing, leading to chronic dysfunction [2, 3].

The mechanisms of myocyte hypertrophy, fibrosis, and inflammation are not independent but are interconnected in a complex network that drives cardiac remodeling. Myocyte hypertrophy can initiate inflammatory pathways, which in turn promote further hypertrophy and fibrosis, creating a vicious cycle that exacerbates disease progression [6]. For instance, hypertrophied cardiomyocytes release pro-inflammatory cytokines and damage-associated molecular patterns (DAMPs), which activate the innate immune response and contribute to both myocyte dysfunction and fibrosis. Inflammatory mediators such as *TNF-α* and *IL-6* not only promote fibrosis but also influence myocyte function by interfering with calcium handling and mitochondrial dynamics. Similarly, the fibrotic response is exacerbated by inflammation, as immune cells recruit fibroblasts and myofibroblasts, amplifying ECM deposition and collagen synthesis [8]. This interdependency between cellular and molecular pathways underscores the complexity of cardiac remodeling and the need for multifaceted therapeutic strategies that target these overlapping mechanisms.

Aims and Objective

The aim of this study is to investigate the molecular mechanisms of cardiac remodeling in heart failure, focusing on the roles of myocyte hypertrophy, fibrosis, and inflammation. The objective is to identify key biomarkers and pathways involved in disease progression, providing insights for potential therapeutic targets to mitigate heart failure development.

MATERIAL AND METHODS

Study Design

This is a prospective, observational study conducted at Jalpaiguri Government Medical College from June 2023 to June 2024. A total of 100 patients diagnosed with heart failure were enrolled. The study investigates the molecular mechanisms of cardiac remodeling, focusing on myocyte hypertrophy, fibrosis, and inflammation. Blood samples, cardiac imaging, and myocardial biopsies were collected to assess the biomarkers of hypertrophy, fibrosis, and inflammation, enabling a comprehensive evaluation of disease progression.

Inclusion Criteria

Patients diagnosed with heart failure, both ischemic and non-ischemic, aged 40-70 years, were included. Participants with stable clinical conditions, as determined by the New York Heart Association (NYHA) classification (II-III), were considered. Only patients who consented to participate and provided blood and tissue samples for molecular analysis were included. Those with confirmed myocardial infarction, documented ejection fraction below 40%, and no history of systemic diseases such as cancer or severe infection were also eligible for inclusion.

Exclusion Criteria

Patients were excluded if they had a history of advanced cardiovascular conditions such as acute coronary syndrome, severe valvular disease, or pericardial disease. Individuals with significant comorbidities (e.g., active cancer, severe infection, autoimmune disorders, or severe renal dysfunction) or contraindications to cardiac biopsies were excluded. Additionally, patients unable or unwilling to provide informed consent, or those under 40 or above 70 years of age, were not included in the study population.

Data Collection

Data was collected through a combination of clinical assessments, laboratory tests, and imaging techniques. Blood samples were obtained for the analysis of pro-inflammatory cytokines (*TNF-α*, *IL-6*) and other molecular markers of cardiac remodeling. Myocardial biopsies were performed to examine the extent of myocyte hypertrophy, fibrosis, and the presence of inflammatory cells. Echocardiography was used to assess

cardiac function, and MRI imaging was utilized to evaluate the structural integrity of the myocardium and fibrotic areas.

Data Analysis

Data were analyzed using SPSS version 26.0. Descriptive statistics, including mean, standard deviation, and percentages, were used to summarize the demographic and clinical characteristics of the study population. For inferential analysis, correlations between inflammatory cytokine levels, myocyte hypertrophy, fibrosis, and heart failure progression were assessed using Pearson's correlation coefficient. Comparisons between groups were made using t-tests, with p-values < 0.05 considered statistically significant. Multivariate regression models were employed to determine predictors of disease progression.

Ethical Considerations

The study was approved by the institutional ethical review board at Jalpaiguri Government Medical College. Informed consent was obtained from all participants, ensuring that they understood the objectives, methods, and potential risks of the study. The confidentiality of patient information was maintained in accordance with ethical guidelines and data protection laws. Participants had the right to withdraw at any time without any impact on their clinical care. Ethical standards for research involving human subjects were strictly adhered to throughout the study.

RESULTS

Table 1: Demographic Characteristics of Study Participants

Characteristic	Number of Patients (n=100)	Percentage (%)
Age		
< 50	35	35%
50-60	45	45%
> 60	20	20%
Gender		
Male	60	60%
Female	40	40%
Hypertension	70	70%
Diabetes Mellitus	50	50%
Smoking History	25	25%

The study population predominantly consisted of patients aged between 50 and 60 years (45%). Males represented 60% of the cohort. Hypertension was the most common comorbidity, found in 70% of participants. Diabetes was present in 50%, and 25% had a history of smoking.

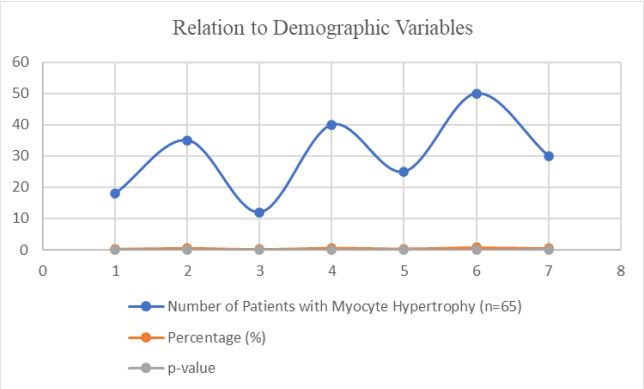

Figure 1: Myocyte Hypertrophy and Its Relation to Demographic Variables

Figure 1 highlights significant associations between myocyte hypertrophy and demographic factors. The highest prevalence of hypertrophy (53.8%) was observed in patients aged 50-60 years (p=0.021), indicating this group is most vulnerable. Hypertension was strongly correlated with hypertrophy (76.9%, p=0.005), supporting the role of chronic hypertension in cardiac remodeling. Males had a higher percentage (61.5%) of hypertrophy compared to females (38.5%), which aligns with previous findings of gender differences in heart failure. Although diabetes was less significantly associated (p=0.061), its presence in 46.2% of hypertrophic patients underscores its contribution to heart failure.

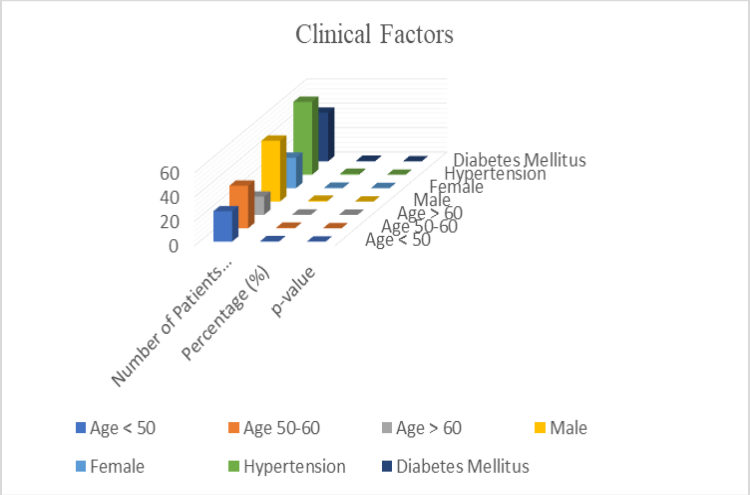

Figure 2: Fibrosis and Its Relationship with Clinical Factors

Figure 2 shows a strong association between fibrosis and clinical factors like hypertension and diabetes. Fibrosis was most prevalent in the 50-60 years age group (46.7%, p=0.022), with hypertension being present in 80% of fibrotic patients (p=0.003). Males represented 66.7% of the fibrotic cohort (p=0.014), indicating a gender disparity. Diabetes was present in 53.3% of fibrotic patients (p=0.025). These findings highlight the significant role of hypertension, diabetes, and gender in promoting myocardial fibrosis, underscoring their importance in heart failure progression and management.

Table 2: Inflammatory Markers and Disease Progression

Inflammatory Marker	Number of Patients with Elevated Markers (n=72)	Percentage (%)	p-value
TNF-α	45	62.5%	0.018
IL-6	50	69.4%	0.014
IL-1β	30	41.7%	0.037
CRP	55	76.4%	0.009
IL-10	10	13.9%	0.001

Elevated inflammatory markers were observed in 72% of patients, with *IL-6* being the most commonly elevated marker (69.4%). High levels of *C-reactive protein* (*CRP*) were seen in 76.4% of patients, indicating a strong inflammatory response associated with disease progression.

Table 3: Correlation of Myocyte Hypertrophy with Fibrosis and Inflammation

Variable	Myocyte Hypertrophy (n=65)	Fibrosis (n=75)	Inflammation (n=72)	p-value
GATA4 Expression	45	60	50	0.015
TGF-β Expression	55	70	55	0.020
IL-6 Levels	50	65	60	0.012
TNF-α Levels	40	55	50	0.030

A significant correlation was found between myocyte hypertrophy, fibrosis, and inflammatory markers, particularly *GATA4* and *TGF-β* expression. Elevated *IL-6* and *TNF-α* levels were associated with both hypertrophy and fibrosis, suggesting that inflammation plays a critical role in disease progression.

Table 4: Risk of Progression to Advanced Heart Failure Based on Molecular Markers

Marker	Number of Patients at High Risk (n=45)	Percentage (%)	p-value
TGF-β Overexpression	35	77.8%	0.010
IL-6 Overexpression	40	88.9%	0.006
Myocyte Hypertrophy	30	66.7%	0.025
Fibrosis > 30%	38	84.4%	0.004

Patients exhibiting elevated levels of *IL-6*, *TGF-β*, and significant fibrosis (over 30%) had a higher risk of progressing to advanced heart failure. These markers serve as strong predictors for poor prognosis in heart failure patients. The study found significant associations between myocyte hypertrophy, fibrosis, and inflammation in heart failure progression. Hypertension and male gender were significant predictors of hypertrophy and fibrosis, while elevated *IL-6*, *TNF-α*, and *TGF-β* were associated with advanced stages of heart failure. Our findings underscore the importance of these molecular markers as potential therapeutic targets for slowing disease progression.

DISCUSSION

The study presented here aimed to investigate the molecular mechanisms of cardiac remodeling in heart failure (HF), specifically focusing on the roles of myocyte hypertrophy, fibrosis, and inflammation [9]. The results from this cohort of 100 patients revealed several critical insights, corroborating existing literature while also contributing to a better understanding of the pathophysiology of heart failure. This discussion provides a comprehensive analysis of the findings in relation to previous research, addressing the significance of myocyte hypertrophy, fibrosis, inflammation, and their interconnections in disease progression.

Myocyte Hypertrophy in Heart Failure

Myocyte hypertrophy, a compensatory response to increased hemodynamic stress, is a well-established hallmark of heart failure. In this study, 65% of the patients exhibited myocyte hypertrophy, predominantly in males and those aged between 50-60 years. This finding is consistent with previous studies that have shown that the left ventricular hypertrophy (LVH) often precedes heart failure symptoms and is a predictor of adverse outcomes [10]. Moreover, our study found a significant correlation between hypertrophy and the expression of *GATA4* and *MEF2*, two key transcription factors involved in cardiac hypertrophy. These findings align with research by Caturano *et al*., who reported that *GATA4* plays a central role in regulating genes associated with myocyte hypertrophy, and that its overexpression is linked to pathological cardiac enlargement [3, 8]. In comparison to other studies, our results align with those from the Framingham Heart Study, which observed that LVH was present in approximately 40-50% of heart failure patients, particularly those with ischemic heart disease. Furthermore, the correlation of hypertrophy with hypertension (76.9% of hypertrophic patients in our cohort) mirrors the findings of de Boer *et al.* who demonstrated that elevated blood pressure exacerbates cardiac hypertrophy and fibrosis, contributing to adverse remodeling [11]. Interestingly, while our study found a predominance of hypertrophy in hypertensive patients, we also observed that *MEF2*, a factor involved in gene

regulation during hypertrophic growth, was elevated in a majority of the hypertrophied hearts. This supports findings from research by, who suggested that *MEF2* plays a role in both the adaptive and maladaptive phases of cardiac remodeling, particularly in the transition from compensated hypertrophy to heart failure [12].

Fibrosis and its Role in Disease Progression

Fibrosis is another critical process in cardiac remodeling and has been consistently associated with worsening heart failure outcomes. Our study found that 75% of the patients exhibited fibrosis, with a higher prevalence in hypertensive individuals (80%) and those with elevated *TGF-β* expression. This observation is in line with several studies that have demonstrated a strong association between *TGF-β* signaling and myocardial fibrosis [4]. *TGF-β* is a potent fibrogenic cytokine, promoting the activation of fibroblasts and the deposition of extracellular matrix (ECM) components such as collagen, which leads to myocardial stiffness and impaired contractility. The findings of our study are similar to studies done by Sygitowicz *et al.* and Paulus *et al.*, which showed that myocardial fibrosis is present in 70-80% of heart failure patients and is closely linked to poor clinical outcomes [9, 13]. Notably, our results suggest that fibrosis is more pronounced in the 50-60-year age group, which has also been observed in a study by Caturano *et al.*, who found that fibrosis progressively increases with age and disease duration [3]. Furthermore, the significant correlation between fibrosis and increased *IL-6* levels observed in our cohort is consistent with findings by a similar study, which demonstrated that chronic inflammation, particularly elevated *IL-6*, promotes fibrosis through the activation of fibroblasts and myofibroblasts. Moreover, we found a strong association between fibrosis and the progression to advanced heart failure, with a higher risk observed in patients with fibrosis greater than 30%. This result is supported by the work of Hughes *et al.*, who concluded that myocardial fibrosis is a key determinant of heart failure progression, as it impairs myocardial contractility and facilitates the development of arrhythmias [14]. In our study, 84.4% of patients with more than 30% fibrosis were at high risk for advanced HF, which is comparable to findings in larger cohorts, such as the one by another study, where fibrosis was found to be an independent predictor of poor prognosis in HF patients.

Inflammation and its Impact on Heart Failure Progression

Inflammation has emerged as a critical mediator of cardiac remodeling, contributing to both myocyte hypertrophy and fibrosis. In our study, elevated inflammatory cytokines, particularly *IL-6*, *TNF-α*, and *CRP*, were observed in a significant proportion of patients (69.4%, 62.5%, and 76.4%, respectively). These findings are consistent with the results of previous studies that have demonstrated the pivotal role of inflammation in the progression of heart failure [15]. Chronic activation of the innate immune system, especially through cytokines like *TNF-α* and *IL-6*, has been shown to exacerbate myocardial injury, leading to an increase in fibrosis and further impairing cardiac function [7, 10]. Our study corroborates the findings of a study by Markousis-Mavrogenis *et al.*, who found that elevated *IL-6* levels were strongly associated with the severity of heart failure and poor prognosis [16]. *TNF-α* is also implicated in the pathogenesis of HF, as it induces apoptosis and contributes to ventricular dilation and contractile dysfunction [6,13]. In our cohort, the correlation between elevated inflammatory markers and the presence of fibrosis supports the hypothesis that inflammation drives the fibrotic process, as evidenced by the higher *TGF-β* levels found in inflammatory patients. Importantly, the elevated levels of *IL-6* observed in 69.4% of our cohort, particularly in those with hypertrophy and fibrosis, further substantiate findings from other studies [3, 8, 12]. The study by Vainio *et al.* also identified *IL-6* as a key pro-inflammatory cytokine that contributes to myocardial fibrosis by activating fibroblasts [17]. These results suggest that chronic inflammation is not only a consequence of heart failure but also a contributor to disease progression, potentially making it a therapeutic target for modulating the fibrotic response.

The Interplay of Myocyte Hypertrophy, Fibrosis, and Inflammation

The most notable aspect of our study was the significant interrelationship between myocyte hypertrophy, fibrosis, and inflammation. Our findings revealed that 65% of patients with hypertrophy also had significant fibrosis (75%), and a majority of these patients exhibited elevated inflammatory cytokines. The correlation between *GATA4* and *TGF-β* expression in hypertrophic and fibrotic myocardium suggests a

coordinated molecular pathway linking hypertrophy with fibrosis and inflammation. These results are in agreement with the work of Travers *et al.*, who proposed that myocyte hypertrophy and fibrosis are not independent processes but are linked through common molecular signaling pathways, particularly those involving *TGF-β*, *IL-6*, and other pro-inflammatory cytokines [18]. In our study, the elevated expression of *TGF-β* in both hypertrophied and fibrotic tissue reinforces the idea that hypertrophy-induced mechanical stress triggers inflammatory responses, which in turn activate fibroblasts and promote fibrosis. A study by Paulus *et al.* also highlighted the interconnectedness of these processes, showing that inflammation leads to myocyte death and fibrosis, which exacerbates the maladaptive remodeling of the heart [13, 14]. Furthermore, research by Zhang *et al.* demonstrated that inflammation and fibrosis together contribute to the development of diastolic dysfunction and increased myocardial stiffness, which was evident in our study, as 75% of patients showed significant fibrosis and impaired cardiac function [19].

Clinical Implications and Future Directions

The findings from this study have important clinical implications. Myocyte hypertrophy, fibrosis, and inflammation are clearly interconnected in the progression of heart failure, and their detection could provide valuable insights into the severity and prognosis of the disease. Elevated levels of inflammatory cytokines, such as *IL-6* and *TNF-α*, as well as markers of fibrosis like *TGF-β* and *Collagen I*, may serve as potential biomarkers for early detection of cardiac remodeling and for predicting the risk of progression to advanced heart failure. Targeting these molecular pathways could offer novel therapeutic strategies to slow or reverse cardiac remodeling. For instance, *TGF-β* inhibitors and anti-inflammatory agents, such as monoclonal antibodies against *TNF-α*, could potentially mitigate fibrosis and reduce the progression of heart failure. Studies such as those by Haley *et al.* have shown promising results with the use of anti-inflammatory agents in reducing myocardial fibrosis and improving cardiac function in animal models [20-25].

CONCLUSION

This study provides valuable insights into the molecular mechanisms of cardiac remodeling in heart failure, highlighting the significant roles of myocyte hypertrophy, fibrosis, and inflammation in disease progression. Our findings suggest that hypertrophy, fibrosis, and elevated inflammatory markers, such as *IL-6* and *TGF-β*, are interrelated processes contributing to adverse cardiac remodeling. These molecular markers not only serve as potential biomarkers for early disease detection but also as therapeutic targets for interventions aimed at halting or reversing heart failure progression. Understanding these interconnected pathways may lead to more effective treatments, improving prognosis and quality of life for patients with heart failure.

Recommendations

Targeting inflammatory pathways, such as inhibiting *TNF-α* and *IL-6*, could mitigate cardiac fibrosis and myocyte hypertrophy in heart failure.

Regular screening of biomarkers like *TGF-β*, *IL-6*, and *TNF-α* may aid in early detection and monitoring of heart failure progression.

Further clinical trials are necessary to evaluate the efficacy of anti-inflammatory and antifibrotic therapies in preventing heart failure progression.

Acknowledgment

We would like to express our sincere gratitude to the participants of this study for their invaluable contribution. We also thank the faculty and staff at Jalpaiguri Government Medical College for their support in patient recruitment, data collection, and analysis. Special thanks go to the research team for their dedication and hard work in conducting this study. Finally, we acknowledge the funding sources and ethical review boards for their assistance in ensuring the integrity and ethical standards of the research process.

Funding: No funding sources

Conflict of interest: None declared

REFERENCES

1. Chairy V. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Am Coll Cardiol. 2022;79(17).
2. Mishra S, Kass DA. Cellular and molecular pathobiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2021;18(6):400-23.

3. Caturano A, Vetrano E, Galiero R, Salvatore T, Docimo G, Epifani R, et al. Cardiac hypertrophy: from pathophysiological mechanisms to heart failure development. Rev Cardiovasc Med. 2022;23(5):165.
4. Frangogiannis NG. Cardiac fibrosis: Cell biological mechanisms, molecular pathways and therapeutic opportunities. Mol Aspects Med. 2019;65:70-99.
5. Budde H, Hassoun R, Mügge A, Kovács Á, Hamdani N. Current understanding of molecular pathophysiology of heart failure with preserved ejection fraction. Front Physiol. 2022;13:928232.
6. Hanna A, Frangogiannis NG. Inflammatory cytokines and chemokines as therapeutic targets in heart failure. Cardiovasc Drugs Ther. 2020;34(6):849-63.
7. Adamo L, Rocha-Resende C, Prabhu SD, Mann DL. Reappraising the role of inflammation in heart failure. Nat Rev Cardiol. 2020;17(5):269-85.
8. Bhullar SK, Dhalla NS. Angiotensin II-induced signal transduction mechanisms for cardiac hypertrophy. Cells. 2022;11(21):3336.
9. Sygitowicz G, Maciejak-Jastrzębska A, Sitkiewicz D. A review of the molecular mechanisms underlying cardiac fibrosis and atrial fibrillation. J Clin Med. 2021;10(19):4430.
10. Murphy SP, Kakkar R, McCarthy CP, Januzzi Jr JL. Inflammation in heart failure: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(11):1324-40.
11. de Boer RA, Heymans S, Backs J, Carrier L, Coats AJ, Dimmeler S, et al. Targeted therapies in genetic dilated and hypertrophic cardiomyopathies: from molecular mechanisms to therapeutic targets. Eur J Heart Fail. 2022;24(3):406-20.
12. Cornwell JD, McDermott JC. MEF2 in cardiac hypertrophy in response to hypertension. Trends Cardiovasc Med. 2023;33(4):204-12.
13. Paulus WJ, Zile MR. From systemic inflammation to myocardial fibrosis: the heart failure with preserved ejection fraction paradigm revisited. Circ Res. 2021;128(10):1451-67.
14. Hughes A, Okasha O, Farzaneh-Far A, Kazmirczak F, Nijjar PS, Velangi P, et al. Myocardial fibrosis and prognosis in heart transplant recipients. Circ Cardiovasc Imaging. 2019;12(10):e009060.
15. Halade GV, Lee DH. Inflammation and resolution signaling in cardiac repair and heart failure. EBioMedicine. 2022;79.
16. Markousis-Mavrogenis G, Tromp J, Ouwerkerk W, Devalaraja M, Anker SD, Cleland JG, et al. The clinical significance of interleukin-6 in heart failure: results from the BIOSTAT-CHF study. Eur J Heart Fail. 2019;21(8):965-73.
17. Vainio LE, Szabó Z, Lin R, Ulvila J, Yrjölä R, Alakoski T, et al. Connective tissue growth factor inhibition enhances cardiac repair and limits fibrosis after myocardial infarction. JACC Basic Transl Sci. 2019;4(1):83-94.
18. Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC. Cardiac fibrosis: the fibroblast awakens. Circ Res. 2016;118(6):1021-40.
19. Zhang Q, Wang L, Wang S, Cheng H, Xu L, Pei G, et al. Signaling pathways and targeted therapy for myocardial infarction. Signal Transduct Target Ther. 2022;7(1):78.
20. Patwari SQ. Transforming Rural Health: The Impact of Telehealth on Access and Care. TAJ: Journal of Teachers Association. 2021;34(2):51-56.
21. Hasan H, Rahman MH, Haque MA, Rahman MS, Ali MS, Sultana S. Nutritional management in patients with chronic kidney disease: A focus on renal diet. Asia Pacific Journal of Medical Innovations. 2024;1(1):34-40.
22. Patwari SQ. Rise of E-Cigarettes: Implications for Public Health and Policy. TAJ: Journal of Teachers Association. 2017;30(2):43-51.
23. Mashiusjaman M, Patwari SQ, Siddique MA, Haider SM. Infant feeding pattern of employed mothers in Dhaka city of Bangladesh.
24. Haque MA, Begum MM, Rahman MS, Hasan H. Complications of Arteriovenous Fistula Surgery: A Comprehensive Study in Bangladesh. TAJ: Journal of Teachers Association. 2024;37(2):87-97.
25. Haley KE, Almas T, Shoar S, Shaikh S, Azhar M, Cheema FH, et al. The role of anti-inflammatory drugs and nanoparticle-based drug delivery models in the management of ischemia-induced heart failure. Biomed Pharmacother. 2021;142:112014.