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Pathophysiological Mechanisms and Therapeutic Research Advances in Cardiorenal Syndrome

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Abstract: The quantitative association mechanism between inflammatory response and oxidative stress in cardiorenal syndrome remains unclear. This study investigates the dynamic changes of neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18) in early renal injury and their correlation with myocardial remodeling. It included 45 patients with cardiorenal syndrome meeting the Framingham criteria. Serum NGAL and IL-18 concentrations are quantitatively detected at baseline, week 4, and week 8 using enzyme-linked immunosorbent assay (ELISA). Concurrently, cardiac magnetic resonance imaging (CMR) is used to quantify the left ventricular mass index (LVMI) and global longitudinal strain, and high-performance liquid chromatography-mass spectrometry (HPLC-MS) is employed to determine urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels to assess systemic oxidative stress status. NGAL and IL-18 showed a continuous increase over 8 weeks, and urinary 8-OHdG levels increased by 51.4% in the significant remodeling group. The dynamic changes of NGAL, IL-18, and 8-OHdG sensitively reflect the myocardial remodeling process in CRS patients, providing potential targets for early intervention.

1. Introduction

Cardiorenal Syndrome (CRS) is a clinical syndrome where the heart and kidneys influence each other in pathophysiological processes, leading to the functional deterioration of one or both organs. With global population aging and the prevalence of metabolic diseases (such as diabetes, hypertension), the incidence of CRS continues to rise, and its high mortality rate makes it a significant public health challenge.

This study reveals the quantitative association between the dynamic trajectories of biomarkers and the myocardial remodeling process. The main contributions include: elucidating the temporal association between inflammation and oxidative stress: discovering that NGAL, IL-18, and 8-OHdG continuously increase over 8 weeks and are significantly correlated with left ventricular remodeling, providing sensitive indicators for early intervention; combining ELISA, HPLC-MS/MS, and CMR technologies to achieve synchronous dynamic monitoring of biomarkers and imaging

parameters; proposing new perspectives for targeted therapy: based on the mediating role of oxidative stress, it demonstrates the potential value of drugs such as SGLT2 inhibitors and RAAS blockers in regulating the cardiorenal metabolic axis.

The full structure is as follows: it reviews the classification, mechanisms, and treatment advances of CRS; details the research design, biomarker detection, and statistical methods; analyzes the association between dynamic changes in biomarkers and myocardial remodeling; summarizes the efficacy and mechanisms of treatment strategies; and finally, outlines future research directions.

2. Related Work

As a complex clinical syndrome in which cardiac and renal functions interact, CRS's pathophysiological mechanisms and treatment strategies have always been the focus and difficulty of medical attention. McCallum and Sarnak [1] systematically reviewed the in-hospital clinical manifestations, pathophysiological mechanisms, and diagnosis and treatment strategies of CRS, and explored its management pathways in different clinical scenarios. Zoccali et al. [2] focused on the long-term interaction between chronic cardiovascular and renal diseases, and conducted an in-depth analysis of their impact on cardiac and renal functions during the course of chronic disease. Junho et al. [3] explored the challenges posed by CRS to clinical management based on pathophysiological mechanisms; Prastaro et al. [4] discussed neurohormonal activation, the renin-angiotensin-aldosterone system (RAAS), and inflammatory mechanisms, and analyzed their application value in treatment strategies. Patar et al. [5] further analyzed the role of the neural connection between the heart and kidney in the occurrence and development of CRS.

It is worth noting that there is a close connection between cardiorenal syndrome and heart failure with preserved ejection fraction (HFpEF). Méndez et al. [6] conducted an in-depth analysis of the pathophysiological relationship between the two; León-Román et al. [7] combined clinical practice with literature to explore the actual role of the cardiorenal unit (CRU) in the management of CRS. In terms of complication management, McCullough [8] pointed out that the treatment of anemia needs to take into account the interactive relationship between cardiorenal function and called for future research to improve the prognosis of such patients. Chávez-Iñiguez et al. [9] systematically sorted out the classification, pathophysiological mechanism and diagnosis and treatment strategies of CRS; McCallum and Testani [10] also emphasized that the clinical management of CRS needs to integrate the two major systems of heart and kidney, and pointed out that in the future, efforts should be made to develop new diagnostic tools and treatment methods to improve patient prognosis. Although existing studies have explored the mechanism and treatment of cardiorenal syndrome from multiple perspectives, its complexity and heterogeneity still pose great challenges to clinical practice. This article aims to systematically sort out the research progress on the pathophysiological mechanism and treatment of cardiorenal syndrome, in order to provide reference for clinical work and provide ideas for future research directions.

3. Methods

3.1 Pathophysiological Mechanism Differences among CRS Types

CRS can be divided into five types based on pathophysiological mechanisms and clinical course characteristics, and the core pathological mechanisms of each type are significantly different. Type I is acute cardiorenal syndrome, the core mechanism of which is that a sharp drop in cardiac output leads to insufficient renal perfusion, activates the RAAS and sympathetic nervous system, triggers water and sodium retention and renal vasoconstriction, and then aggravates renal ischemia and oxidative stress. Type II is chronic cardiorenal syndrome, which is caused by the long-term impact

of chronic heart failure on renal function. Pathologically, it is characterized by persistent neurohormonal activation, chronic inflammation and fibrosis. Elevated levels of inflammatory factors such as IL-18 and NGAL in the circulation promote myocardial and renal tissue remodeling. Type III is acute renocardia syndrome, the mechanism of which involves electrolyte imbalance, accumulation of uremic toxins and volume overload, which directly causes myocardial depression, arrhythmias and even acute heart failure. Type IV is chronic renocardia syndrome, the core of which lies in the long-term effects of micro-inflammatory state and endothelial dysfunction. Type V is a secondary cardiorenal syndrome, in which systemic diseases such as sepsis or diabetes damage both the heart and kidneys. Pathologically, systemic inflammation, immune activation, and metabolic disorders predominate, with marked elevations in oxidative stress markers such as 8-OHdG, exacerbating organ damage. The mechanistic differences between these subtypes highlight the complexity of CRS, necessitating individualized interventions tailored to specific pathological components in clinical management [11-12].

3.2 Study Design and Population

This study aims to clarify the association between the dynamic changes of inflammatory and oxidative stress biomarkers and myocardial remodeling in patients with cardiorenal syndrome. Patients are consecutively recruited from the heart failure specialist clinic. Inclusion criteria are: 1) age 18-80 years; 2) diagnosis of chronic heart failure according to the Framingham criteria; 3) New York Heart Association functional class III or IV; 4) estimated glomerular filtration rate between 30 and 60 mL/min/1.73m² [13]. Patients are excluded if they had: 1) acute coronary syndrome or revascularization within 3 months; 2) end-stage renal disease requiring renal replacement therapy; 3) severe liver disease; 4) active autoimmune disease or malignancy; or 5) contraindications to cardiac magnetic resonance scanning. Finally, 45 patients who met all criteria and completed all follow-ups are included in the final analysis.

3.3 Biomarker and Imaging Assessment

All participants were required to obtain 10 ml of fasting cubital venous blood and 10 ml of random midstream urine in the morning at three fixed time points (baseline, week 4 ± 3 days, and week 8 ± 3 days) while resting. Serum separated from the blood samples was aliquoted into EP tubes and immediately stored at -80°C until analysis. All serum samples were batch-tested using enzyme-linked immunosorbent assays (R&D Systems Duoset series for NGAL and MBL kit for IL-18). All samples were assayed in duplicate, and absorbance was read on a BioTek ELx800 microplate reader. Urine samples were protein-precipitated and diluted, and quantitative results were corrected for urine creatinine (expressed as ng/mg creatinine). Cardiac imaging was performed at baseline and week 8 (with a ±5-day window period) using the same 3.0T Siemens Skyra magnetic resonance imaging scanner using a standardized protocol. Left ventricular mass was measured using short-axis cine sequences and automatically calculated using cvi42 post-processing software after manually outlining the endocardial and epicardial borders. The LV mass index was then divided by body surface area. Global longitudinal strain was automatically analyzed and obtained using feature tracking technology on long-axis cine sequences of two-chamber, three-chamber, and four-chamber heart chambers [14-15].

Table 1 summarizes key information on biomarkers and imaging assessments:

Table 1: Summary of Detection Methods and Conditions for Biomarkers and Imaging Parameters

Parameter	Assay Method	Sample Type	Detection Instrument / Software	Time Points

Serum NGAL	Enzyme-linked immunosorbent assay (ELISA)	Serum	BioTek ELx800 microplate reader	Baseline, Week 4, Week 8
Serum IL-18	Enzyme-linked immunosorbent assay (ELISA)	Serum	BioTek ELx800 microplate reader	Baseline, Week 4, Week 8
Urinary 8-OHdG	High-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)	Urine	Agilent 1260 Infinity II + Agilent 6470 mass spectrometer	Baseline, Week 4, Week 8
Left Ventricular Mass Index (LVMI)	Cardiac Magnetic Resonance Imaging (CMR)	Imaging	Siemens Skyra 3.0T scanner + cvi42 software	Baseline, Week 8
Global Longitudinal Strain (GLS)	Feature-tracking technique on cine images	Imaging	cvi42 software	Baseline, Week 8

The table system organizes the testing process of various parameters to ensure the consistency and comparability of experimental data.

3.4 Statistical Analysis Methods

Continuous variables conforming to a normal distribution are expressed as mean ± standard deviation, while non-normally distributed variables are expressed as median (interquartile range). Categorical variables are expressed as frequency (percentage). For the relationship between repeatedly measured biomarkers (NGAL, IL-18, 8-OHdG) and time, linear mixed-effects models (using the lme4 package) are constructed, with time (as a categorical variable), baseline age, gender, and blood pressure as fixed effects, and a random intercept set for each subject to account for correlations within repeated measurements. For internal comparison, patients are divided into a "significant myocardial remodeling group" (ΔLVMI% $\geq$ 15%) and a "stable myocardial remodeling group" (ΔLVMI% < 15%) based on the percentage change in left ventricular mass index at week 8 compared to baseline (ΔLVMI%). Finally, to verify the mediating role of oxidative stress, a structural equation model is constructed using the lavaan package. This model sets the dynamic change indicators of NGAL/IL-18 as independent variables, the average level of urinary 8-OHdG at week 8 as the mediating variable, and ΔLVMI as the dependent variable, while controlling for the influence of baseline LVMI.

4. Results and Discussion

4.1 Association between Dynamic Changes in Biomarkers and Myocardial Remodeling

Through an 8-week longitudinal observation of 45 patients with chronic heart failure and renal insufficiency who met the inclusion criteria, serum and urine samples are systematically collected at three time points: baseline, week 4, and week 8. Patients are divided into significant myocardial remodeling and stable groups based on ΔLVMI%. By comparing the differences in dynamic trajectory parameters of biomarkers between the two groups, the results are shown in Figures 1 and 2:

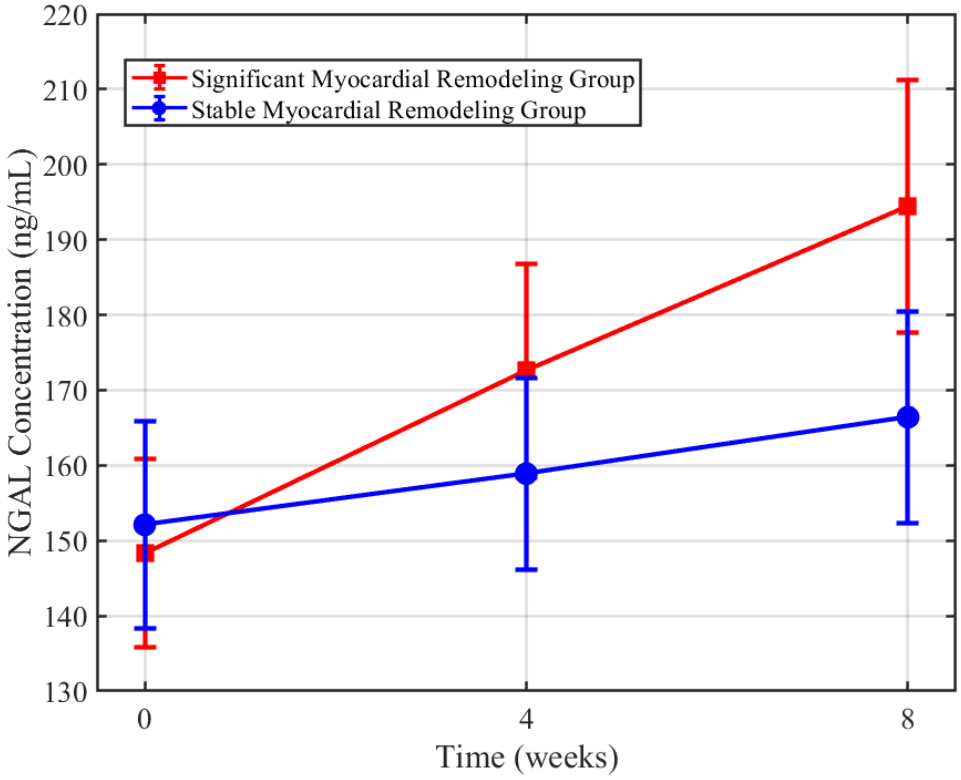

Figure 1 NGAL Dynamic Change Trajectory

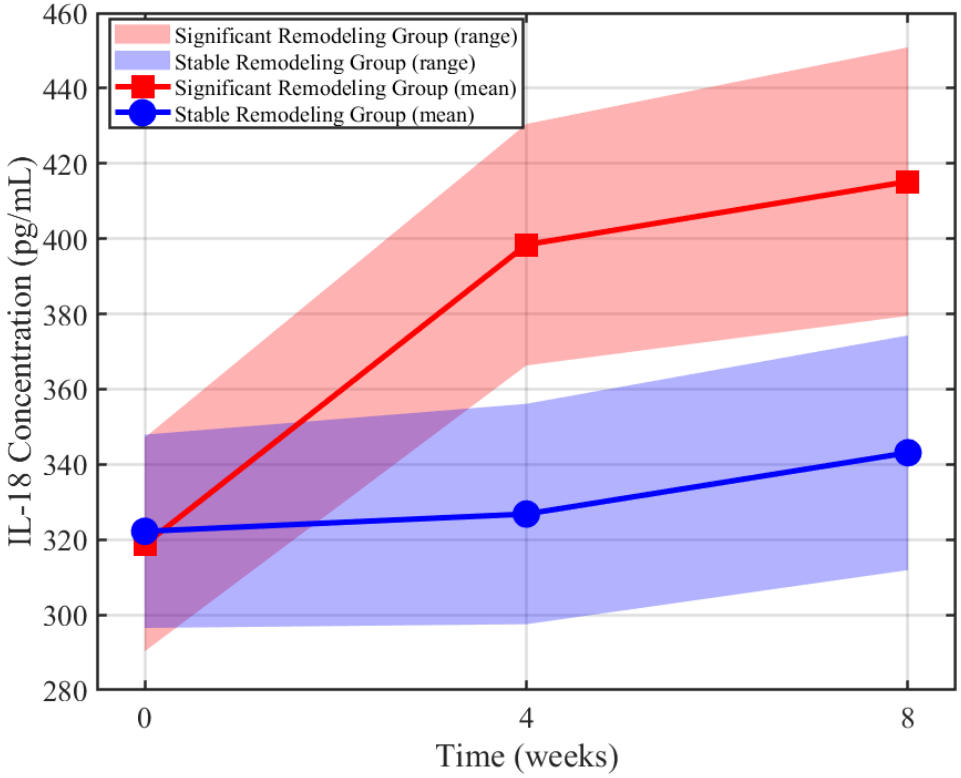

Figure 2 IL-18 Dynamic Change Trajectory

The concentrations of NGAL and IL-18 in the significant remodeling group show a continuous and rapid increasing trend over time, while the increase in the stable group is more gradual. NGAL in the significant remodeling group increases from 148.3 ng/mL at baseline to 194.5 ng/mL at week 8, an increase of 31.2%, significantly higher than the 9.4% increase in the stable group. IL-18 in the significant remodeling group increases from 318.7 pg/mL to 415.2 pg/mL, an increase of 30.3%, while the stable group increases only 6.1%. This differential pattern indicates that the continuous activation of the inflammatory response is closely related to the myocardial remodeling process. Patients in the significant remodeling group exhibit a more intense systemic inflammatory response, and the dynamic changes in inflammatory factor levels can serve as sensitive indicators for predicting the progression of myocardial remodeling. From a pathophysiological mechanism perspective, NGAL, as a marker of neutrophil activation, its rapid increase reflects a state of continuous activation of the innate immune system, while IL-18, as a pro-inflammatory cytokine, its significant elevation indicates the key role of the inflammasome pathway in the myocardial remodeling process of cardiorenal syndrome.

4.2 The Mediating Role of Oxidative Stress

The study uses high-performance liquid chromatography-tandem mass spectrometry to quantitatively detect urinary 8-OHdG levels and precisely assesses changes in the left ventricular mass index using 3.0T cardiac magnetic resonance imaging to explore the expression characteristics of oxidative stress in different remodeling phenotypes and its potential mediating role in the inflammation-myocardial remodeling pathway, as shown in Figure 3 below:

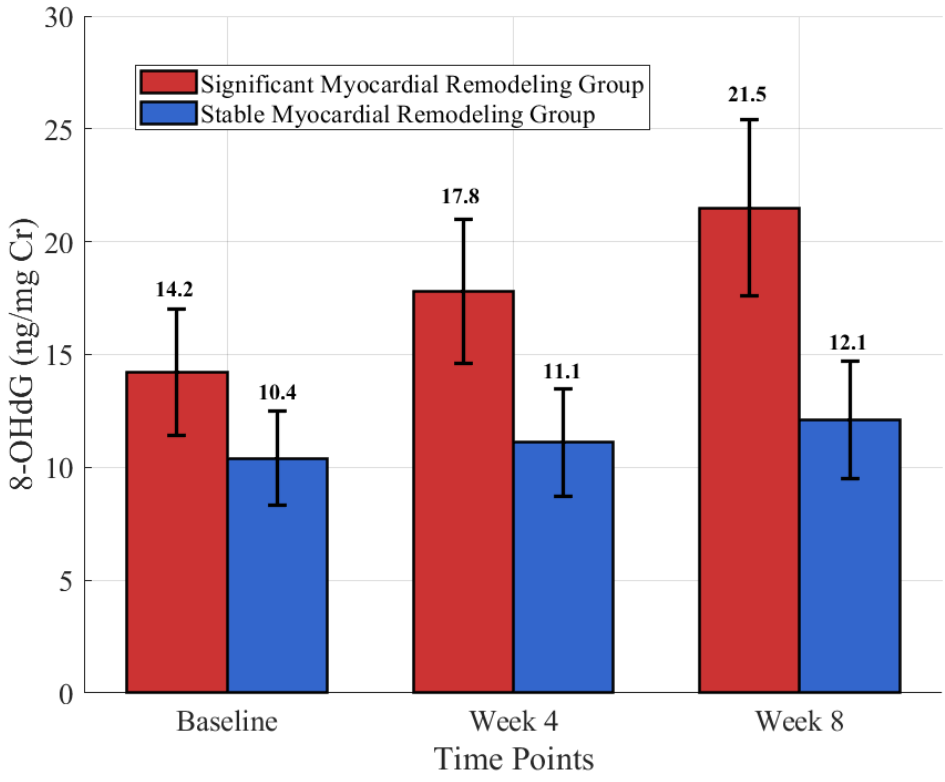

Figure 3 Patient Urinary 8-OHdG Levels

8-OHdG levels in the significant myocardial remodeling group are significantly higher than those in the stable group at all three time points, with a more rapid upward trend over time. A significant difference between the two groups is already present at baseline (14.2 vs 10.4 ng/mg Cr), which widened to 21.5 vs 12.1 ng/mg Cr by week 8. The cumulative increase in 8-OHdG levels in the significant remodeling group reached 51.4%, while it is only 16.3% in the stable group. This dynamic pattern of differences suggests that the degree of oxidative stress activation is closely related to the severity of myocardial remodeling, with patients in the significant remodeling group experiencing a persistent state of greater oxidative damage. From a pathophysiological perspective, the rapid increase in 8-OHdG, a specific marker of DNA oxidative damage, reflects the central role of reactive oxygen species-mediated cellular damage in the course of cardiorenal syndrome, suggesting that oxidative stress is a key factor driving the progression of myocardial remodeling.

4.3 Efficacy and Mechanism Discussion of Treatment Strategies

Based on the complex pathophysiological mechanisms of cardiorenal syndrome, current treatment strategies primarily involve multi-target interventions targeting key pathways such as neurohormonal activation, inflammation, and oxidative stress. The research results show that the continuous increase in inflammatory markers NGAL and IL-18 is significantly correlated with myocardial remodeling, and the sharp increase in the oxidative stress marker 8-OHdG further confirms the core role of oxidative damage in disease progression, suggesting that inhibiting these pathways can improve patient prognosis. In clinical practice, RAAS inhibitors and aldosterone receptor antagonists remain cornerstone treatments, capable of reducing water and sodium retention and vasoconstriction, but require close monitoring of renal function to avoid acute injury. In recent years, the application of SGLT2 inhibitors in heart failure and chronic kidney disease has shown anti-inflammatory and antioxidant benefits, reducing levels of biomarkers such as NGAL and delaying myocardial remodeling. Furthermore, management of anemia, such as using erythropoietin or iron supplements, can improve tissue oxygen supply and reduce the burden on the heart and kidneys. For volume overload, ultrasound-guided decongestion strategies help optimize fluid balance and reduce the risk of renal injury. Future treatment directions should focus on personalized medicine, utilizing dynamic biomarker monitoring to guide the combined application of targeted drugs, in order to break through current management bottlenecks and improve overall efficacy.

5. Conclusion

This article elaborates on the pathophysiological mechanisms of cardiorenal syndrome, focusing on the dynamic association between inflammatory response, oxidative stress, and myocardial remodeling. It validates the predictive value of biomarkers such as NGAL, IL-18, and 8-OHdG for early renal injury and cardiac remodeling in CRS through a prospective study. However, this study has a small sample size and a short follow-up period, unable to fully assess the heterogeneity of different CRS types; furthermore, the causal relationship between biomarkers and imaging parameters still requires verification through larger-scale multicenter studies combined with mechanistic experiments. Future research should focus on developing specific therapies targeting inflammatory and oxidative stress pathways, exploring holistic management strategies for cardiovascular-renal-metabolic syndrome, and integrating multi-omics data with artificial intelligence models to achieve individualized precision prevention and treatment for CRS.

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