COMPLEX PATHOGENESIS OF CHRONIC HEART FAILURE IN RHEUMATIC MITRAL VALVE DISEASE: INTERRELATIONSHIP OF HEMODYNAMIC, NEUROHUMORAL AND INFLAMMATORY COMPONENTS

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https://doi.org/10.5281/zenodo.18888852

ARTICLE INFO

Received: 01st March 2026
Accepted: 04th March 2026
Online: 06th March 2026

KEYWORDS

Hemodynamic disturbances arising from rheumatic mitral valve disease (RMVD) serve as the main mechanism for the development of CHF

ABSTRACT

According to the World Health Organization, nearly 33 million people worldwide suffer from chronic rheumatic heart disease, and annually over 300,000 deaths are associated with this disease. Among rheumatic heart defects, mitral valve involvement is the most common, which, when prolonged, leads to the development of chronic heart failure (CHF). CHF is a pathological condition with a high prevalence rate and adverse outcomes, and an in-depth study of its pathogenesis is a relevant scientific and practical problem.

Introduction. According to the World Health Organization, nearly 33 million people worldwide suffer from chronic rheumatic heart disease, and annually over 300,000 deaths are associated with this disease. Among rheumatic heart defects, mitral valve involvement is the most common, which, when prolonged, leads to the development of chronic heart failure (CHF). CHF is a pathological condition with a high prevalence rate and adverse outcomes, and an in-depth study of its pathogenesis is a relevant scientific and practical problem.

Hemodynamic disturbances arising from rheumatic mitral valve disease (RMVD) serve as the main mechanism for the development of CHF. According to Roitberg and Strunsky, mitral valve defect is considered the first hemodynamic barrier, obstructing blood flow between the left atrium and left ventricle. Consequently, pressure in the left atrium increases, subsequently transmitted through the pulmonary veins to the pulmonary artery, leading to the development of a second hemodynamic barrier — pulmonary hypertension. However, the pathogenesis of CHF is not limited to hemodynamic disturbances alone. According to modern concepts, activation of the neurohumoral system (renin-angiotensin-aldosterone system, sympathoadrenal system, natriuretic peptides) and inflammatory processes (C-reactive protein, cytokines) play an important role in the pathogenesis of heart failure.

Studying the interrelationship between intracardiac hemodynamic parameters, neurohumoral activation and inflammatory markers in mitral valve disease, as well as

assessing the impact of surgical treatment on these indicators, is of great importance for a deeper understanding of CHF pathogenesis and improving treatment strategies.

Objective: To study the relationship between intracardiac hemodynamic parameters, neurohumoral activation and inflammatory markers, as well as the impact of surgical treatment on these indicators, in patients with chronic heart failure developed against the background of rheumatic mitral valve disease.

Materials and methods. The study was conducted at the Namangan branch of the Republican Specialized Scientific-Practical Medical Center of Cardiology during 2022–2025. This prospective, comparative, cross-sectional study involved 90 patients with CHF developed against the background of RMVD.

All patients were divided into two groups based on the morphological status of the mitral valve. Group I included 45 patients who underwent surgical intervention (valve replacement or commissurotomy) for rheumatic mitral valve disease within the last 5 years. Group II consisted of 45 patients with persistent rheumatic mitral valve disease who did not undergo surgical treatment.

Patients aged 33 to 79 years (mean age 58±2.97 years) with CHF developed against the background of RMVD were included in the study. Patients with the following criteria were excluded from the study: non-rheumatic etiology of heart valve disease, acute myocardial infarction or cerebrovascular accident within the last 3 months, severe renal failure (GFR <30 ml/min/1.73 m^2), predicted life expectancy of less than 3 years, acute inflammatory diseases, oncological pathologies.

All patients underwent standard echocardiographic examination (using Mindray I 90 device), electrocardiography (using Schiller D 40/7 device), determination of NT-proBNP (using Finecare-Wondfo device) and C-reactive protein (CRP) levels (using HumaLyzer Primus device) in the blood. Additionally, the clinical status of patients was assessed using the SHOKS scale modified by. B. Y Mareev, the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and the 6-minute walk test (6-MWT).

Statistical analysis was performed using Microsoft Office Excel 2013 and Statistica for Windows v10 software. Mean values (M) and standard errors (±m) were calculated. Student's t-test and Z-test were used to assess differences between groups. Pearson correlation coefficient was calculated to determine correlational relationships between indicators. Differences were considered statistically significant at $p<0.05$.

The study was approved by the Ethics Committee of the Republican Specialized Scientific-Practical Medical Center of Cardiology, and informed consent was obtained from all patients.

Results. Of the 90 patients included in the study, 45 (50%) were in Group I and 45 (50%) in Group II. No statistically significant differences in gender and age were found between the groups. In Group I, there were 29 females (64.4%) and 16 males (35.6%), while in Group II, there were 36 females (80.0%) and 9 males (20.0%) ($p=0.163$). The mean age was 60.2±1.69 years in Group I and 56.1±1.25 years in Group II ($p=0.054$).

The duration of CHF was significantly longer in Group I: 6.7±0.8 years in surgically treated patients versus 4.2±0.7 years in non-surgically treated patients (p=0.02). This indicates a longer disease history in surgically treated patients.

Significant differences were observed in the distribution of heart failure functional class. In Group I, 28 patients (62.2%) were in FC I, while in Group II, FC II (21 patients; 46.7%) and FC III (14 patients; 31.1%) predominated (p<0.001 and p=0.015, respectively). Permanent atrial fibrillation was significantly more common in Group I: 34 patients (75.5%) compared to 15 patients (33.3%) in Group II (p<0.001).

According to echocardiographic examination results, both groups exhibited the phenotype of preserved left ventricular ejection fraction. However, left ventricular ejection fraction was statistically significantly higher in Group II: 60.8±1.56% versus 55.8±0.98% in Group I (p=0.008).

The main hemodynamic differences were as follows. Left atrial size was found to be significantly larger in Group II: 56.7±0.81 mm versus 45.8±0.64 mm in Group I (p<0.001). This indicates ongoing left atrial dilation in patients with persistent mitral valve disease. Mitral valve diastolic pressure gradient was near-normal in Group I (11.2±0.52 mmHg), while remaining elevated in Group II (16.3±1.16 mmHg; p<0.001). This confirms that surgery effectively eliminated the hemodynamic barrier at the mitral valve level.

Systolic pulmonary artery pressure was 29.8±1.2 mmHg in Group I and 42.1±1.76 mmHg in Group II (p<0.001). Patients who underwent surgical treatment showed regression of pulmonary hypertension. Right ventricular systolic pressure was also found to be higher in Group II: 42.5±1.89 mmHg versus 35.1±1.50 mmHg in Group I (p=0.002), indicating persistent load on the right heart chambers. Tricuspid valve regurgitation was slightly higher in Group II: 1.5±0.08 versus 1.2±0.09 in Group I (p=0.01). Other morphometric parameters of the left ventricle (left ventricular end-diastolic dimension, end-diastolic volume, end-systolic volume, left ventricular myocardial mass) did not show statistically significant differences between the groups (p>0.05).

Analysis of neurohumoral activation and inflammatory markers yielded the following results. In non-surgically treated patients of Group II, NT-proBNP level was 1240.91±165.0 pg/ml, which was 54% higher compared to 804.91±115.0 pg/ml in Group I (p=0.031). C-reactive protein level was also statistically significantly higher in Group II: 16.7±1.34 mg/ml versus 12.7±0.87 mg/ml in Group I (p=0.014).

Correlation analysis results demonstrated strong relationships between hemodynamic parameters and biomarkers. A strong positive correlation was found between left atrial size and NT-proBNP (r=0.72; p<0.001). A moderate positive correlation was also present between left atrial size and CRP (r=0.54; p=0.002). A strong positive correlation was observed between systolic pulmonary artery pressure and NT-proBNP (r=0.68; p<0.001), and a moderate positive correlation between systolic pulmonary artery pressure and CRP (r=0.49; p=0.005). A moderate positive correlation was found between mitral valve diastolic pressure gradient and NT-proBNP (r=0.58; p<0.001), and a moderate negative correlation between left ventricular ejection fraction and NT-proBNP (r=-0.46; p=0.008). These correlational relationships confirm the intrinsic connection between the severity of hemodynamic disturbances and the intensity of neurohumoral activation and inflammatory processes.

Analysis of clinical parameters showed that surgically treated patients had significantly better clinical status. The SHOKS scale score was 1.8±0.14 in Group I and 3.6±0.11 in Group II ($p<0.001$). The Minnesota Questionnaire score was 15.6±0.87 in Group I and 32.9±0.98 in Group II ($p<0.001$). The 6-minute walk test distance was 428.9±9.8 m in Group I and 312.1±11.9 m in Group II ($p<0.001$). These data confirm that surgically treated patients have better clinical status and higher quality of life.

Discussion. The results of our study demonstrated the presence of an intrinsic relationship between hemodynamic disturbances, neurohumoral activation and inflammatory processes in patients with chronic heart failure developed against the background of rheumatic mitral valve disease. In non-surgically treated patients, the worst hemodynamic parameters (high pulmonary hypertension, high mitral gradient, enlarged left atrium) were accompanied by the highest values of NT-proBNP and CRP levels.

The elevated NT-proBNP levels in both groups (804.91 pg/ml in Group I, 1240.91 pg/ml in Group II) are noteworthy. This is higher than the average value (986 pg/ml) reported in the REDHOT study for patients hospitalized with dyspnea. According to the 2021 ESC guidelines for CHF, the cut-off value for NT-proBNP is set at 125 pg/ml. The values in our study are several times higher than this threshold, indicating even higher neurohumoral activity in CHF of rheumatic etiology.

The elevated CRP levels (12.7 mg/ml in Group I, 16.7 mg/ml in Group II) confirm the important role of inflammatory processes in the pathogenesis of CHF. This condition is explained by endothelial dysfunction, oxidative stress, and activation of the inflammatory cascade resulting from hemodynamic disturbances against the background of mitral valve disease.

Correlation analysis results demonstrated strong relationships between hemodynamic parameters (left atrial size, systolic pulmonary artery pressure, mitral valve diastolic pressure gradient) and biomarkers (NT-proBNP, CRP). This confirms the close interconnection of hemodynamic, neurohumoral and inflammatory components in CHF pathogenesis and the need to view them not separately, but as an integrated system.

In surgically treated patients, hemodynamic improvement (reduction in pulmonary hypertension and mitral gradient) was accompanied by a relative decrease in NT-proBNP and CRP levels. This indicates that eliminating the hemodynamic barrier reduces neurohumoral and inflammatory activity. However, these indicators did not fully return to normal levels, indicating that the pathological process has not completely stopped.

The persistence of left atrial dilation in both groups (45.8±0.64 mm in Group I, 56.7±0.81 mm in Group II) indicates the continuity and irreversibility of the pathogenetic chain (hemodynamic load → remodeling → neurohumoral/inflammatory → CHF progression). According to the "remodeling begets arrhythmia" concept, prolonged left atrial dilation leads to structural (fibrosis) and electrophysiological remodeling, and these changes do not fully reverse even after the hemodynamic barrier is eliminated.

The study by Estu Rudiktiyo and colleagues showed that RMVD predominantly affects females (84%) and occurs with preserved left ventricular ejection fraction. In our study,

females constituted 71.1%, and left ventricular ejection fraction was preserved — consistent with the heart failure with preserved ejection fraction (HFpEF) phenotype.

Thus, the pathogenesis of CHF against the background of RMVD is a complex, multicomponent process in which, although hemodynamic disturbances play a primary role, neurohumoral activation and inflammatory processes are important in the chronicity and progression of the disease.

Conclusion. In patients with chronic heart failure developed against the background of rheumatic mitral valve disease, there is an intrinsic relationship between hemodynamic disturbances, neurohumoral activation and inflammatory processes. As hemodynamic parameters (left atrial size, systolic pulmonary artery pressure, mitral valve diastolic pressure gradient) worsen, NT-proBNP and CRP levels also increase proportionally.

In non-surgically treated patients, the worst hemodynamic parameters (left atrial size 56.7±0.81 mm, systolic pulmonary artery pressure 42.1±1.76 mmHg, mitral valve diastolic pressure gradient 16.3±1.16 mmHg) were accompanied by the highest values of NT-proBNP (1240.91±165.0 pg/ml) and CRP (16.7±1.34 mg/ml).

In surgically treated patients, hemodynamic improvement (systolic pulmonary artery pressure 29.8±1.2 mmHg, mitral valve diastolic pressure gradient 11.2±0.52 mmHg) was accompanied by a relative decrease in NT-proBNP (804.91±115.0 pg/ml) and CRP (12.7±0.87 mg/ml) levels. However, these indicators remained above normal levels.

The persistence of left atrial dilation in both groups (45.8±0.64 mm in Group I, 56.7±0.81 mm in Group II) indicates the continuity of the pathogenetic chain (hemodynamic load → remodeling → neurohumoral/inflammatory → CHF progression) and the irreversibility of remodeling processes.

The strong correlational relationships between hemodynamic parameters and biomarkers (left atrial size and NT-proBNP $r=0.72$; systolic pulmonary artery pressure and NT-proBNP $r=0.68$; $p<0.001$) confirm the close interconnection of these components in CHF pathogenesis.

References:

1.Watkins, D. A., Johnson, C. O., Colquhoun, S. M., et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. The New England Journal of Medicine. 2017;377(8):713–722.

2.Bursi, F., Enriquez-Sarano, M., Nkomo, V. T., et al. Heart failure after myocardial infarction: A review. European Heart Journal. 2007;28(23):2866–2872.

3.Koelling, T. M., Aaronson, K. D., Cody, R. J., et al. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. American Heart Journal. 2002;144(3):524–529.

4.Agricola, E., Oppizzi, M., Pisani, M., et al. Ischemic mitral regurgitation: Mechanisms and echocardiographic classification. European Journal of Echocardiography. 2008;9(2):207–221.

5.Mirabel, M., Lung, B., Baron, G., et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? European Heart Journal. 2007;28(11):1358–1365.

6.Guazzi, M., & Borlaug, B. A. Pulmonary hypertension due to left heart disease. Circulation. 2012;126(8):975–990.
7.Negi, P. C., Sondhi, S., Rana, V., et al. Prevalence, risk factors and outcomes of atrial fibrillation in rheumatic heart disease: The HP-RF/RHD Registry. Indian Heart Journal. 2018;70(1):68–73.
8.Hugenholtz, P. G., Ryan, T. J., Stein, S. W., & Abelmann, W. H. The spectrum of pure mitral stenosis. Hemodynamic studies in relation to clinical disability. The American Journal of Cardiology. 1962;10:773–784.
9.January, C. T., Wann, L. S., Alpert, J. S., et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. Circulation. 2014;130(23):2071–2104.
10.Obadia, J. F., el Farra, M., Bastien, O. H., et al. Outcome of atrial fibrillation after mitral valve repair. The Journal of Thoracic and Cardiovascular Surgery. 1997;114(2):179–185.
11.Bozkurt, B. 2021 ACC/AHA key data elements and definitions for heart failure. Journal of the American College of Cardiology. 2021;77(16):2053–2150.
12.McDonagh, T. A., Metra, M., Adamo, M., et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021;42(36):3599–3726.
13.Mueller, C., McDonald, K., de Boer, R. A., et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. European Journal of Heart Failure. 2019;21(6):715–731.
14.Maisel, A., Hollander, J. E., Guss, D., et al. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). Journal of the American College of Cardiology. 2004;44(6):1328–1333.
15.Roitberg, G. E., & Strutynsky, A. V. Internal diseases. Cardiovascular system. MEDpress-inform. 2014.
16.Rudiktiyo, E., et al. Left Ventricle Myocardial Work Correlated with Functional Capacity in Severe Rheumatic Mitral Stenosis with Preserved Left Ventricular Ejection Fraction. 2024