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Original Research Article

Levels of inflammatory cytokines in patients with different phenotypes of heart failure

Kalatsei Liudmila, Bihara Rasanjalee Mathotaarachchi*, Sandeepa Abhishek Hewage, J. A. Sudeepa Madhavi Rajakaruna Jayasinghe, Wadu Arachchige Kavinda Nuwan

Department of Internal Studies, Grodno State Medical University, Belarus

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***Correspondence:**
Dr. Bihara Rasanjalee Mathotaarachchi,
E-mail: biharar2@gmail.com

ABSTRACT

Background: The association between HF and inflammation was first recognized in 1990 by Levine et al, who reported elevated levels of TNF in patients with HFrEF. To date, the levels of C-reactive protein, interleukin 6, and interleukin 1-beta are verified to be increased in plasma of HF patients. Current clinical trials are investigating on the effectiveness of IL-1 blockade to reduce inflammation, ventricular remodeling, and improved exercise capacity in patients with HF.
Methods: The study included 76 patients with HF of NYHA functional classes I-IV. 46 (61%) patients had a preserved LVEF (≥50%) and 30 (39%) had reduced LVEF (<50%). All patients underwent clinical, laboratory, and instrumental studies, including determination of CRP and IL-1 levels in venous blood serum using enzyme immunoassay. Statistical analysis was performed using the STATISTICA 12.0 software.
Results: Patients with HFrEF more often suffered from atrial fibrillation than patients with HFpEF. Also, patients with HFrEF were characterized by higher HF NYHA class. Patients with HFrEF had significantly higher levels of BNP and NT-proBNP. When conducting an enzyme immunoassay in patients of the HFrEF group, the CRP level was 3.95 mg/L, and in patients of the HFpEF group -3.52 mg/L, these differences were statistically significant (p=0.011). However, there were no intergroup differences in IL-1 level.
Conclusions: Patients with HFrEF had higher values of CRP ($p<0.05$) in comparison with patients with HFpEF. However, there were no intergroup differences in IL-1 values ($p>0.05$). Reliability of the obtained results should be further checked on larger samples of patients.

Keywords: CRP, Heart failure, Inflammation, IL-1

INTRODUCTION

The American College of Cardiology (ACC) and the American Heart Association defines heart failure (HF) as a clinical syndrome caused by structural or functional abnormalities that impair the heart's ability to fill with or eject blood effectively. According to the ejection fraction HF is classified into, 1) HF with reduced ejection fraction (HFrEF): LVEF ≤40%;2) HF with mildly reduced ejection fraction: LV EF 4-49% and evidence of HF (elevated cardiac biomarkers or elevated filling pressures); 3) HF with preserved ejection fraction (HFpEF): LVEF ≥50% and evidence of HF (elevated cardiac biomarkers or elevated filling pressures); 4) HF with improved ejection fraction: LVEF >40%, with previously documented LVEF ≤40%.[1]

Further the NYHA divides heart failure into;[2] 1) Class I - No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.; 2) Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity; 3) Class III - Marked limitation in activity due to

symptoms, even during less-than-ordinary activity, e.g., walking short distances (20100 m). Comfortable only at rest, 4) Class IV- Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients; 4) No NYHA class listed or unable to determine.

Heart failure induces myocardial cell death and damage and further involves neurohumoral activation, inflammatory responses and renal dysfunction.[3] Although the etiology and pathogenesis of HF is rather complex, it is believed that the myocardium undergoes persistent inflammation across different phenotypes of HF. The association between HF and inflammation was first recognized in 1990 by Levine et al, who reported elevated levels of TNF in patients with reduced ejection fraction.[4]

Both innate and adaptive immune responses are activated in response to injury of cardiac tissue. The adaptive immune system produces a highly specific response through cytokine production, mediated by T and B lymphocytes. Myocardial injury triggers the release of damage-associated molecular patterns (DAMPs). The DAMPs arise from the cytosolic contents of dying cells, and the degradation products of the extracellular matrix, in response to tissue damage.[5] The DAMPs are recognized by pattern recognition receptors (PRRs) located on the cellular and endosomal membranes. A subset of these activated PRRs signals inflammatory cells such as the macrophages, consequently initiating the production of proinflammatory cytokines such as interleukin-1-beta (IL-1) from macrophages. The release of these cytokines is sufficient to induce cardiac inflammation. The PRRs further signals hepatocytes, resulting in the release of inflammatory mediators such as C- reactive protein (CRP). The levels of tumor necrosis factor (TNF-α), interleukin 6 (IL-6), IL-1β, IL-18 are verified to be increased in plasma of HF patients.[2,3]

CRP is one of the best studied acute-phase proteins. Its synthesis occurs mainly in the liver, being induced by raised IL-6 concentrations under conditions of infection, trauma and other inflammatory states. In humans, CRP values markedly increase in the first 72 hours after tissue damage, being a sensitive yet non-specific biomarker of inflammation.

Also, CRP is an established independent cardiovascular risk factor, with higher CRP values being associated with major cardiovascular events and mortality and showing prognostic significance for risk stratification. Increased CRP values appear to be a predictor for HF development in high-risk populations. CRP values higher than 3.23 mg/L are associated with higher HF severity evidenced by lower LVEF, higher NYHA functional classes, higher heart rate and increased prevalence of atrial fibrillation.[4] Elevated CRP is also related with increased risk of death and HF readmissions within 3 months.[3]

The presence of these prototypal proinflammatory cytokines and mediators has been linked to worse prognosis.[6] Experimental research correlates inflammatory processes to ventricular remodeling and dysfunction.[2]

Preclinical studies suggest that blocking IL-1 could be a promising therapeutic strategy. Current clinical trials are investigating on the effectiveness of IL-1 blockade to reduce inflammation, reduction in ventricular remodeling, and improved exercise capacity in patients with HF.[6] In HF, IL-1 can be produced by immune cells, cardiomyocytes, vascular cells and fibroblasts.[4] IL-1 contributes to cardiac dysfunction and remodeling by reducing beta-adrenergic responsiveness of L-type calcium channels and the expression of genes involved in the regulation of calcium homeostasis, by stimulating apoptosis in cardiomyocytes, by inducing the activation of leukocytes and endothelial cells, thus promoting their interaction and increasing the recruitment of inflammatory cells to the myocardium, by favoring fibrosis and by promoting arterial stiffness and microvascular inflammation.[4] IL-1β also decreases energy production and myocardial contractility by directly damaging mitochondria. The objective of the study was to evaluate levels of inflammatory cytokines (IL-1 and CRP) in patients with different phenotypes of chronic HF.

METHODS

This was an analytical observational study using a case-control study design that was conducted at the Grodno Regional Clinical Cardiology Center (Grodno, Belarus) from July 2024 to January 2025.

The study included 76 patients with HF of NYHA functional classes I-IV. 46 (61%) patients had a preserved LVEF (≥50%) and 30 (39%) had reduced LVEF (<50%).

Inclusion criteria

The inclusion criteria were the patients with HF diagnosed based on ESC (2021) guidelines, age >18 years and agreement to participate in the study.[1]

Exclusion criteria

Exclusion criteria for the study were chronic rheumatic heart disease, acute coronary syndrome, acute myocarditis, endocarditis or pericarditis, valvular pathology of the heart requiring surgical correction, prosthetic heart valves, oncological diseases and severe concomitant extracardiac pathology.

All patients underwent clinical, laboratory, and instrumental studies, including transthoracic echocardiography and ELISA test.

Echocardiography was performed on Phillips iE33 device with a multi-frequency sensor (frequency 2.5-5.0 MHz). The examination was performed with the patient lying on his left side with his back to the researcher or on his back.

The study protocol included the following indicators: LA and right atrium (RA) diameter in 2-chamber and 4-chamber mode, end-systolic diameter and end-diastolic diameter (mm) of the left ventricle (LV), LVEF; assessment of the state of the valvular apparatus of the heart, degree of regurgitation on the valves.

Venous blood was collected in compliance with aseptic and antiseptic rules from the cubital vein in the morning on an empty stomach in a state of rest using disposable vacuum tubes with a coagulation activator and a separating gel. The blood in the tube was left to stand for 20-25 minutes at room temperature (18-25 C), after which the collected samples were centrifuged at a speed of 3 thousand revolutions per second for 15 minutes. After centrifugation, blood serum was collected for further analysis.

For quantitative determination of IL-1 and CPR in blood serum, the EH0099 Human CRP (C-Reactive Protein) High sensitive ELISA Kit and EH0185 Human IL-1β (Interleukin 1 Beta) ELISA Kit («FineTest», China) were used. The principle of operation of these kits is based on the double antibody-Sandwich ELISA detection method and takes 4h assay time.

The study was performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki and was approved by the Ethical Committee of the Grodno State Medical University (Grodno, Belarus). Written informed consent was obtained from all participants prior to inclusion in the study.

Statistical analysis

Statistical analysis was performed using the STATISTICA 12.0 software package with a preliminary check for normal distribution using a distribution histogram. Nominal data were described with an indication of absolute values and percentages. Quantitative data, the distribution of which was not normal, were given as a median, 25% and 75% quartiles. Since most of the quantitative characteristics did not obey the normal distribution law, non-parametric methods were used for comparison.

Comparison of numerical indicators between two independent groups was carried out using the nonparametric Mann-Whitney U-test. The statistical significance of differences between qualitative characteristics was assessed using the χ^2-Pearson test. The threshold value of the level of statistical significance was taken to be 0.05. To study the relationship between variables, Spearman's rank correlation coefficient was used.

RESULTS

Clinical characteristics of the patients are presented in Table 1.

Patients with HFrEF and HFpEF were comparable in age (59.4 [51.3; 66.8] vs 63.9 [58.5; 70.3] years, p>0.05) and gender (male gender 61% vs 63%). Also, both groups were comparable in prevalence of obesity (37% vs 37%, p>0.05) hypertension (91% vs 80%, p>0.05) and myocardial infarction history (33% vs 40%), p>0.05). However, patients with HFrEF more often suffered from atrial fibrillation (53% vs 24%, p=0.009) than patients with HFpEF. Also, patients with HFrEF were characterized by higher HF NYHA class (Class 3-4 in 19% of Group 1 and 67% of Group 2, p<0.001).

Table 1: Clinical characteristics of patients.

Parameters	Group 1 HFpEF (n=46)	Group 2 HFrEF (n=30)	P value
Male gender, N (%	28 (61)	19 (63)	0.829
Age in years, (Mean [25%;75%])	59.4 [51.3; 66.8]	63.9 [58.5; 70.3]	0,056
Obesity, N (%)	17 (37)	11 (37)	0.980
Class 1, N (%)	12 (26)	6 (20)	0.542
Class 2, N (%)	4 (9)	3 (10)	0.848
Class 3, N (%)	1 (2)	2 (7)	0.332
Hypertension, N (%)	42 (91)	24 (80)	0.282
Stage 1, N (%)	10 (22)	3 (10)	0.185
Stage 2, N (%)	30 (65)	20 (67)	0.897
Stage 3, N (%)	2 (4)	1 (3)	0.825
Myocardial infarction history, N (%)	15 (33)	12 (40)	0.511
Diabetes mellitus, N (%)	7 (15)	8 (27)	0.221
Atrial fibrillation, N (%)	11 (24)	16 (53)	0.009
Heart failure NYHA Class			
Class 1, N (%)	7 (15)	0 (0)	0.025
Class 2, N (%)	30 (65)	10 (33)	0.007
Class 3, N (%)	8 (17)	18 (60)	<0.001
Class 4, N (%)	1 (2)	2 (7)	0.332

Laboratory parameters of patients are presented in Table 2.

In biochemical blood test patients didn't show significant intergroup differences in values of renal function tests, total cholesterol, triglycerides, sodium and potassium (p>0.05). However, patients with HFrEF had significantly higher levels of BNP (817 (812.5; 821.5) vs 440.68 (164; 728) ng/ml, p=0.04) and NT-proBNP (4304 (1473; 5702) vs 2640 (32; 2126) pg/ml, p=0.02). Surprisingly, the cholesterol levels in HFrEF (5.00 [3.8; 5.83]) was much higher than the HFpEF patients (4.03 [3.1; 4.4], p=0.006).

The values of echocardiographic parameters recorded in patients of both groups are presented in Table 3.

Table 2: Laboratory parameters of patients (Me [25%;75%]).

Parameters	Group 1 HFpEF (n=46)	Group 2 HFrEF (n=30)	P value
RBC, 10^{12}/l	4.64 [4.24; 4.97]	4.74 [4.21;5.22]	0.357
Hemoglobin, g/l	139 [127; 152]	140 [128; 153]	0.773
WBC, 10^9/l	6.66 [5.1; 7.8]	7.47 [5.38; 8.13]	0.394
ESR, mm/h	15.58 [6; 22]	12.57 [5; 16.25]	0.119
Urea, mmol/l	6.41 [5.03; 7.46]	6.91 [5.43;7.99]	0.179
Creatinine, µmol/l	101.1 [83.5; 108.8]	98.05 [79.3; 115.3]	0.696
eGFR, ml/min/1.73m^2	65.45 [50.41; 74.19]	64.88 [48.1; 82.7]	0.853
Cholesterol, mmol/l	5.00 [3.8; 5.83]	4.03 [3.1; 4.4]	0.006
Glucose, mmol/l	6.78 [5.75; 6.92]	6.28 [5.05; 5.84]	0.456
Sodium, mEq/l	143.65 [141.3; 146]	140.22 [136; 143]	0.233
Potassium, mEq/l	4.47 [4.20; 4.70]	4.68 [4.46; 4.90]	0.567
BNP, ng/ml	440.68 [164; 728]	817 [812.5; 821.5]	0.040
NT-proBNP, pg/ml	2640 [32; 2126]	4304 [1473; 5702]	0.020

Abbreviations: RBC-red blood cells; WBC-white blood cells; ESR-erythrocyte sedimentation rate; eGFR-estimated glomerular filtration rate; BNP-brain natriuretic peptide; NT-proBNP-N-terminal pro b-type natriuretic peptide

Table 3: Echocardiographic parameters of patients (Me [25%;75%]).

Parameter	Group 1 HFpEF (n=46)	Group 2 HFrEF (n=30)	P value
LA diameter (2 chamber), mm	37.0 [34.0; 42.0]	44.7 [42.0; 47.0]	<0.001
LA diameter (medial to lateral), mm	39.0 [35.0; 42.0]	44.7 [41.3; 47.8]	<0.001
LA diameter (front to back), mm	53.0 [48.0; 57.8]	62.3 [56.0; 66.5]	<0.001
RA diameter (medial to lateral), mm	36.8 [34.0; 39.8]	43.3 [40.0; 47.8]	<0.001
RA diameter (front to back), mm	49.2 [45.0; 51.8]	61.0 [54.3; 63.8]	<0.001
LV ESD, mm	34.1 [31.3; 36.8]	47.7 [41.3; 56.0]	<0.001
LV EDD, mm	51.7 [49.0; 54.8]	60.1 [54.0; 64.8]	<0.001
M-mode	-	-	
LV ESV, ml	48.9 [40.0; 56.0]	119.3 [83.5; 145.3]	<0.001
LV EDV, ml	130.7 [112.0; 146.0]	192.5 [152.8; 218.5]	<0.001
LVEF, %	62.8 [58.0; 67.0]	39.0 [32.8; 45.3]	<0.001
B-mode	-	-	
LV ESV, ml	65.8 [53.0;92.0]	114.0 [75.0; 150.0]	<0.001
LV EDV, ml	150.6 [109.0;186.5]	178.0 [125.0; 222.0]	0.240
LVEF, %	56.2 [51.5;62.0]	37.5 [33.0;45.0]	<0.001
Septal thickness (systolic), mm	18.1 [16.3; 19.0]	15.1 [13.0; 16.0]	<0.001
Septal thickness (diastolic), mm	13.1 [12.0; 14.0]	12.5 [11.0; 13.0]	0.084
Posterior wall thickness (systolic), mm	17.0 [16.0; 18.0]	15.1 [13.0; 17.0]	0.010
Posterior wall thickness (diastolic), mm	12.0 [11.0;12.8]	11.3 [10.0; 12.0]	0.125
Right ventricle diameter, mm	24.0 [23.0; 25.0]	30.8 [26.3; 34.0]	<0.001
Contractility index	1.04 [1;1]	1.65 [1;2.13]	0.003
MR grade 1, N (%)	25 (54)	3 (10)	<0.001
MR grade 2, N (%)	18 (39)	25 (83)	<0.001
MR grade 3, N (%)	3 (7)	1 (3)	0.543
TR grade 1, N (%)	22 (48)	7 (23)	0.032
TR grade 2, N (%)	23 (50)	14 (47)	0.777
TR grade 3, N (%)	1 (2)	8 (27)	0.002
TR grade 4, N (%)	0 (0)	1 (3)	0.213

Abbreviations: LA-left atrium; RA-right atrium; LV-left ventricle; ESD-end-systolic diameter; EDD-end-diastolic diameter; ESV-end-systolic volume; EDV-end-diastolic volume; LVEF-left ventricular ejection fraction; MR-mitral regurgitation; TR-tricuspid regurgitation.

The LA, RA, RV and both LV diameters were much higher in HFrEF in contrast to the HFpEF (p<0.001), indicating a strong significance. Both volumetric parameters in M-mode and LV end-systolic volume in B-mode showed significant differences also (p<0.001), greater in HFrEF than in HFpEF patients. Both LVEF in M and B mode were both notably lower in HFrEF in contrast to HFpEF. Septal thickness during systole in HFpEF (18.1 [16.3; 19.0]) is significantly lower than in HFrEF (15.1 [13.0;16.0]), with a p<0.001. Posterior wall thickness during systole in HFpEF (17.0 [16.0; 18.0] was relatively lower in HFrEF (15.1 [13.0; 17.0]), with a p<0.010. Contractility index was higher in HFrEF (1.65 [1; 2.13]) than in HFpEF (1.04 [1; 1]). Also, patients with HFrEF had higher grades of mitral and tricuspid regurgitation (p<0.05).

When conducting an enzyme immunoassay in patients of the HFrEF group, the CRP level was 3.95 [3.55; 4.41] mg/l, and in patients of the HFpEF group -3.52 [2.87; 4.16] mg/l, these differences were statistically significant (p=0.011). However, there were no intergroup differences in IL-1 level (8.20 [2.70; 12.75] vs 7.09 [2.87; 9.16] pg/ml, p=0.66) (Figure 1).

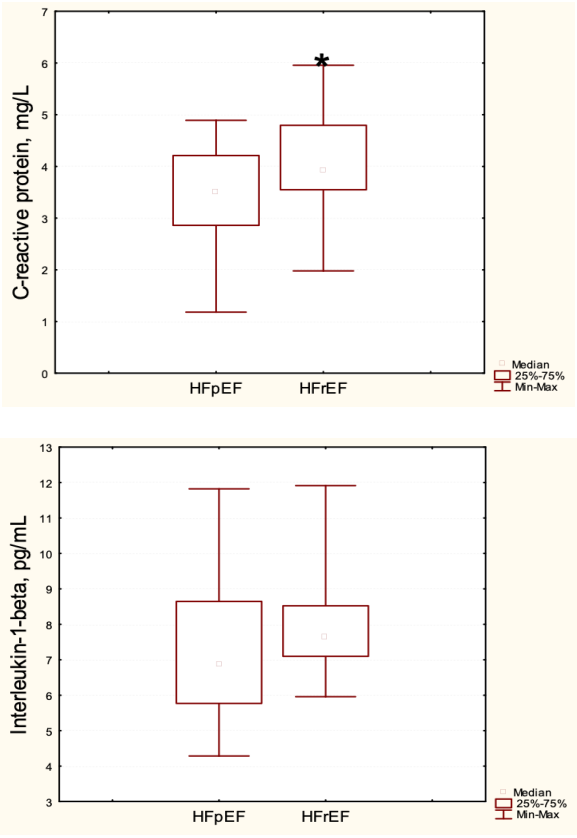

Figure 1: Levels or CRP and IL-1 in patients of both groups.

When conducting a correlation analysis, a statistically significant correlation was revealed between the level of IL-1 and a number of echocardiographic parameters (Figure 2). Positive correlations were established between IL-1 level and LA diameter (R=0.44, p<0.001) and right ventricle diameter (R=0.36, p=0.001). Negative correlation was found between IL-1 level and LVEF (R=-0.33, p<0.05). Also, there was a positive correlation between the level of CRP and LA diameter (R=0.3, p=0.02).

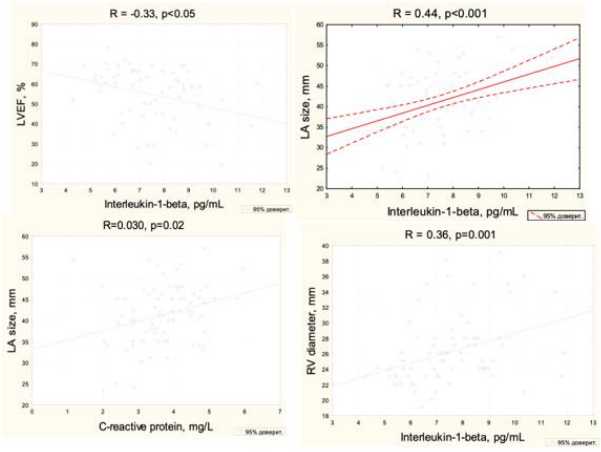

Figure 2: Results of correlation analysis.

DISCUSSION

According to our study we can discuss that HFrEF is more prevalent in male gender and in those with AF, history of myocardial infarction and diabetes mellitus. While these factors appear to be associated with reduced ejection fraction in comparison to preserved ejection fraction the other laboratory parameters do not show any significant variation across the phenotypes of HF.

However, it appears that BNP and pro-BNP levels are significantly high in patients with HFrEF, making it a method to verify HFrEF and enabling us to evaluate prognosis of patients with heart failure. Further, studies show that mortality and morbidity were independently correlated with BNP and CRP.[7]

The echocardiographic parameters depicted in the results shows significant changes across different phenotypes of HF, and can be further evaluated to differentiate the prognosis of phenotypes. The relationship between inflammation and incidence HF may be explained by a number of processes which were elaborated in studies. First, systemic inflammation causes the sympathetic nervous system and the renin-angiotensin system to become activated. This leads to myocyte hypertrophy and apoptosis, increased peripheral vascular resistance, and volume expansion.[8]

Second, CRP causes plasminogen activator inhibitor-1, which encourages platelet aggregation, while also decreasing prostacyclin. Third, CRP causes monocytes to adhere to the endothelium, secrete more proinflammatory cytokines, and absorb oxidised low-density lipoprotein, which results in the development of foam cells.[8]

The role of CRP in promoting endothelial dysfunction was discussed in a previous review, it further elaborates the role of CRP in atherothrombosis that eventually contributes to the development of HF.[9]

It is unclear, nevertheless, if CRP is actually a component of the causal chain between inflammation and incident HF.[10] Increase in CRP may also reflect increased synthesis in the liver under the influence of other cytokines such as IL-6 as discussed in the introduction.

According to a previous assessment, CRP was strongly linked to an elevated risk of all phenotypes of HF.[10]

In another randomized study done on plasma CRP values, the characteristics of more severe heart failure, including a decreased left ventricular ejection fraction, higher heart rate, higher prevalence of atrial fibrillation, third heart sound, and NYHA classes III or IV, worse neurohormonal profile, higher neutrophil counts, and lower quality of life, were observed in patients with plasma CRP above the median. Higher CRP patients were also more likely to be female, take digoxin and diuretics, and be less likely to be taking aspirin, statins, or blockers. The percentages of patients with ischemic or nonischemic etiology, however, were not different.[11] Some other studies suggest a strong correlation found between elevated blood hs-CRP levels and an increased likelihood of HF hospitalization.[12]

Studies show that while levels of IL-5, IL-7 or IL-33 are down-regulated in HF, concentrations of a number of interleukins, including as IL-1β, IL-6, IL-8, IL-9, IL-10, IL-13, IL-17, and IL-18, are elevated. They further show that regardless of the origin of HF, the level of IL-1β was proportionate to the NYHA's functional class.[7] IL-1 stimulates the development of atherosclerotic plaque and aids in its advancement and complications. In a large phase III clinical trial, recurrent atherothrombotic cardiovascular events were avoided by employing a monoclonal antibody to suppress IL-1 activity in stable patients with a history of myocardial infarction.[13]

Pilot clinical trials are now being conducted to assess the potential benefits of IL-1 blockage in reducing inflammation, improving ventricular remodeling, and increasing exercise capacity in patients with heart failure.

Regardless of whether the cause is ischemic, hypertensive, idiopathic dilated cardiomyopathy, or inflammatory, patients with chronic or decompensated HF exhibit a marked increase in a variety of proinflammatory cytokines, including CRP, with levels rising in proportion to the severity of the disease.[13]

Our study had some limitations primarily due to the small size of the sample of patients and the single-center nature of the study, so the results may not be generalizable to other populations and settings. Secondly, a single measurement of CRP and IL-1 was used, while concentrations might fluctuate during follow-up. Measurement biases in CRP and IL-1 levels could also exist.

CONCLUSION

Patients with HFrEF had higher values of CRP ($p<0.05$) in comparison with patients with HFpEF. However, there were no intergroup differences in IL-1 values ($p>0.05$). Statistically significant correlations between the levels of proinflammatory cytokines and echocardiographic parameters were found. However, taking into account the small size of the study sample, the possibility of using these markers requires testing on a larger group of patients, considering ongoing pharmacological therapy and concomitant diseases.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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