



## Assessment of the Immune-Inflammatory Relationship in Patients with Chronic Heart Failure with Rheumatoid Arthritis

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**Abstract:** The aim of the study was to assess the relationship between manifestations of immune inflammation and dyslipidaemia and myocardial morphofunctional parameters in patients with chronic heart failure (CHF) with preserved left ventricular ejection fraction (CHF-EFV) in seropositive rheumatoid arthritis (RA).

**Material and methods.** The study included 57 women with CHF as a result of coronary heart disease and/or arterial hypertension. All patients had NYHA functional class I and II. All patients were divided into comparable groups: the first included 31 patients with a combination of CHF and seropositive RA, the second included 26 patients without RA. Patients with RA had low to moderate DAS28 activity. The diagnosis of CHF was verified according to ESC criteria, the diagnosis of RA according to EULAR/ACR criteria (2010). In patients with RA the baseline anti-inflammatory drug used was methotrexate in an average dose ( $12.9 \pm 2.5$  mg/week). Comparative analysis of basic laboratory and instrumental parameters used at diagnosis and monitoring of CHF, as well as the correlation of manifestations of immunoinflammatory process with dyslipidemia, was carried out in the studied groups. and indicators of diastolic myocardial dysfunction.

**Key words:** chronic heart failure; rheumatoid arthritis; dyslipidaemia; diastolic dysfunction.

**Results.** Total cholesterol levels averaged  $4.4 \pm 0.9$  mmol/l in the CHF group without RA and  $5.2 \pm 2.2$  mmol/l in the CHF and RA group ( $p=0.09$ ); triglycerides,  $1.9 \pm 0.7$  and  $1.5 \pm 0.9$  mmol/l ( $p=0.3$ ); low density lipoproteins (LDL-C) -  $2.6 \pm 0.8$  and  $3.1 \pm 1.1$  mmol/l ( $p=0.04$ ); high density lipoproteins (HDL-C) -  $1.3 \pm 0.2$  and  $1.3 \pm 0.1$  mmol/l respectively ( $p=0.7$ ). A direct correlation between methotrexate intake (mean dose was  $12.9 \pm 2.5$  mg/week) and HDL-C levels was found in RA CHF group:  $R=0.3$ ;  $R^2=0.1$ ;  $F=0.9$ ; ( $p=0.01$ ). In the CHF and RA group, there was a statistically significant correlation

between the ratio of transmitral flow parameters with DAS28 and RF level:  $R=0.5$ ;  $R^2=0.3$ ;  $F=2.6$  ( $p=0.04$ ).

**Conclusions.** Against the background of the immune inflammatory process caused by RA, a significant increase in LDL level, which may negatively influence the course of dyslipidemia in CHF patients. There was an increase of HDL concentration on the background of methotrexate treatment in CHF-HF and RA group. A direct correlation between the ratio of transmittent flow parameters and RF and DAS28 levels was found. It is possible that this relationship influences the progression of diastolic left ventricular myocardial dysfunction in the CHF CHF and RA, but prospective studies are needed to clarify its role.

One of the most discussed and topical areas of modern clinical medicine is the study of the course of cardiovascular disease (CVD) against the background of comorbid pathology.

In particular, much attention is now being paid to the clinical and pathogenetic relationships with systemic inflammatory diseases, which are among the most severe chronic pathological conditions with serious consequences for the patient.

Of particular importance may be increased levels of proinflammatory factors such as interleukins (IL)1, IL6, tumour necrosis factor (TNF)- $\alpha$ , and C-reactive protein (CRP) in rheumatoid arthritis (RA). Patients with RA are at high risk of premature mortality due to various complications, including cardiovascular complications. One of the most relevant comorbid associations in RA is chronic heart failure (CHF), which is an outcome of many CVD.

The association of chronic non-infectious inflammatory process with myocardial morphofunctional parameters has been established. The authors have determined the association of chronic non-infectious inflammatory process with myocardial morphofunctional parameters, endothelial dysfunction and dyslipidemia, coronary artery status and prognosis, and discussed the effect of anti-inflammatory therapy on the course of both CHF in general and CHF in particular.

The aim of the study was to assess the association of immune inflammatory process manifestations with dyslipidaemia and myocardial morphofunctional parameters in patients with CHF with preserved ejection fraction (CHF-EFV) against seropositive RA.

### Material and methods

A cohort comparative single-study was conducted in 57 women with CHF-associated coronary heart disease (CHD) and/or essential arterial hypertension (AH). The diagnosis of CHF was based on the current ESC and Society of Cardiovascular Specialists criteria (2018), and all patients had NYHA functional class I-II. Evaluation of morphofunctional parameters were assessed by transthoracic echocardiography, with determination of left ventricular ejection fraction according to Simpson. The diagnosis of RA was made according to EULAR/ACR criteria (2010) and national clinical guidelines. Patients with RA had low and moderate activity according to DAS28, radiological stage of RA I-III according to Steinbroker classification [14].  $\beta$ -adrenoblockers and angiotensin-converting enzyme inhibitors (ACEIs) were used to treat CHF. All patients with RA received methotrexate (MT) at an average dose of  $12.9 \pm 2.5$  mg/week.

Non-steroidal anti-inflammatory drugs (NSAIDs) were used for symptomatic treatment of RA.

The patients were divided into two comparable groups: The first group included 31 patients with CHF against RA and the second group included 26 patients without RA. The general characteristics are presented in Table 1. It shows that the groups of patients did not differ significantly according to the initial parameters - gender, age, duration of CHF, as well as the spectrum of causes leading to CHF.

General blood count with determination of Erythrocyte sedimentation rate (ESR); first level lipidogram Blood count: total cholesterol (GC), low-density lipoproteins low density lipoproteins (LDL-C), high Density lipoproteins (HDL), triglycerides (TG) and glomerular filtration rate (GFR), rheumatoid factor (RRF) Rheumatoid Factor (RF), C-reactive protein (CRP) and antibodies to cyclic citrullinated peptide (ADCP).

Statistical analysis of the data presented was performed using STATISTICA 10.0 software. All of the raw data used in the work had a Gaussian distribution. The nature of the distribution was assessed using the Shapiro-Wilk test. Results of the comparative analysis are presented as  $M \pm SD$ , where M is the mean and SD is the standard deviation. Data deviating from the Gaussian distribution are presented as Me (min; max), where Me is the median, min and max are the minimum and maximum values of the index respectively.

## Results

The combination of CHF and RA was associated with higher CRP, sedimentation rate and LDL-C levels, but lower haemoglobin and more severe impairment of FFR than in CHF without RA. The median ADCP level in RA patients was 172 [0; 100] IU/ml, pain was 53 [30; 60] mm and RF was 31.1[0; 192] IU/ml. Logistic regression analysis revealed a significant association between MT treatment and HDL cholesterol levels.

The next stage of the study involved a comparative analysis of myocardial morphofunctional parameters in the study groups.

At the final stage of the study there was carried out analysis of parameters reflecting the characteristics of RA and their possible relationship with one of the indicators of diastolic dysfunction - the ratio of left ventricular transmitral flow (E/A) parameters. A significant association between E/A and RF levels has been found. a significant association of E/A with RF and DAS28 levels.

## Discussion

The role of inflammation in CHF has been widely discussed in the literature. The most significant comorbid pathology in RA are CVDs, the presence of which increases the risk of vascular events. These associations are mainly represented by AH, atherosclerosis, CHD and IHD. Of particular interest is the effect of MI on outcomes The effect of MI on CVD outcomes with RA is of particular interest. RA in CHF is considered to be a factor destabilizing its course. The analysis of the data revealed differences in CRP, CRP and haemoglobin levels, which may be associated with the effect of chronic systemic inflammation, the pharmacological effect of MT, and impaired renal function, in turn, caused by caused both by regular intake of NSAIDs and by the influence of chronic inflammation. These results are consistent with those of other authors.

The phenomenon of destabilisation of the course of CHF is supported by data on the high mortality rate in this category patients. According to a prospective study of patients with RA admitted to the intensive care unit, the mortality rate was 34.9% within 30 days of destabilisation of CHF.

The present study found a statistically significant increase in HDL concentrations in patients with CHF and RA on MT. This phenomenon is consistent with the current understanding of the positive effect of basal anti-inflammatory drugs on lipidogram parameters. Some authors consider it advisable to increase the dosage of statins in this group of patients and to monitor lipidograms more frequently. Effective immunoinflammatory suppression appears to be able to reduce the likelihood of acute cardiovascular complications. Complementary therapies may also be used to improve prognosis in CHF. One experimental study showed a statistically significant positive effect of hydroxychloroquine (HC) on serum concentrations of LDL-C, triglycerides and total cholesterol. Thus, our results are complementary to the available data. It is also worth noting the statistically significant relationship

between RF and DAS28 levels and left ventricular E/A. This relationship could be considered as a destabilising factor or risk factor for exacerbation of CHF in RA. An earlier study by B. Logstrup, RA patients with CHF showed an improvement in left ventricular ejection fraction, a reduction in left ventricular end-systolic and diastolic volumes. In patients with RA with chronic heart failure there was an improvement in left ventricular end-diastolic volume against the background of MT combined with GC. B Targońska-Stepniak et al. found that diastolic dysfunction parameters in the groups with and without RA did not differ statistically significantly, which is consistent with our study data. However, the manifestations of dysfunction (E/A), despite the low activity of RA, worsen as the bone-articular destruction increases. Analysing the available literature data and comparing them with the results of our own studies, a preliminary conclusion can be made that the evaluation of morphofunctional parameters of myocardium in patients with RA can be of interest both for the prognosis of CHF and for the evaluation of myocardial function. to predict prognosis of CHF and choose the appropriate therapy, However, prospective studies are needed to confirm this assumption.

The results of this study and the literature suggest a need for more research into the management of chronic heart failure (CHF) in RA patients.

### Conclusion

The immune inflammatory process caused by RA revealed a significant increase in LDL level, which may negatively influence the course of dyslipidemia in CHF patients. Significant increase of HDL-C concentration during methotrexate treatment in CHF-HF and RA group was noted. It is possible that this relationship influences the progression of diastolic left ventricular myocardial dysfunction in CHF and RA, but prospective studies are needed to clarify its significance.

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