

## Chronic Heart Failure in Early Rheumatoid Arthritis Patients Prior to Basic Antirheumatic Therapy

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**Aim.** To study the clinical manifestations and factors associated with the presence of chronic heart failure (CHF) in patients with early rheumatoid arthritis (RA) prior to anti-inflammatory therapy. **Material and methods.** The study included 74 patients with valid diagnosis of RA (criteria ACR/EULAR, 2010), 56 women (74%), median age – 54 [46;61] years, disease duration – 7 [4;8] months; seropositive for IgM rheumatoid factor (87%) and/or antibodies to cyclic citrullinated peptide (100%) prior to taking disease modifying anti-rheumatic drugs and glucocorticoids. CHF was verified in accordance with actual guidelines. The assessment of traditional risk factors for cardiovascular diseases, echocardiography, tissue Doppler imaging, carotid artery ultrasound, were carried out before the start of therapy in all patients with early RA. The concentration of NT-proBNP was determined by electrochemoluminescence. The normal range for NT-proBNP was less than 125 pg/ml.

**Results.** CHF was diagnosed in 24 (33%) patients: in 23 patients – CHF with preserved ejection fraction, in 1 patient – CHF with reduced ejection fraction. 50% of patients with RA under the age of 60 were diagnosed with CHF. NYHA class I was found in 5 (21%) patients, class II – in 15 (63%), class III – in 1 (4%). Positive predictive value of clinical symptoms did not exceed 38%. All patients with early RA were divided into two groups: 1 – with CHF, 2 – without CHF. Patients with RA+CHF compared with patients without CHF were older, had higher body mass index, frequency of carotid atherosclerosis, of ischemic heart disease (IHD), hypertension, C-reactive protein (CRP) levels and intima media thickness. Independent factors associated with the presence of CHF were identified by linear regression analysis: abdominal obesity, CRP level, systolic blood pressure, dyslipidemia, carotid intima thickness, IHD. The multiple coefficient of determination was  $R^2=57.1$  ( $R=0.76$ ,  $p<0.001$ ). Level of NT-proBNP in RA patients with CHF (192.0 [154.9; 255.7] pg/ml) was higher than in RA patients without CHF (77 [41.1; 191.2] pg/ml) and in control (49.0 [33.2; 65.8] pg/ml),  $p<0.0001$  and  $p=0.01$ , respectively. To exclude CHF in patients with early RA, the optimal NT-proBNP level was 150.4 pg / ml (sensitivity – 80%, specificity – 79%), the area under the ROC curve = 0.957 (95% confidence interval 0.913-1.002,  $p<0.001$ ).

**Conclusion.** CHF was detected in a third of RA patients at the early stage of the disease. Factors associated with the presence of CHF were abdominal obesity, CRP level, systolic blood pressure, dyslipidemia, intima media thickness, IHD.

**Keywords:** rheumatoid arthritis, chronic heart failure, NT-proBNP.

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In the last few years, one can often find the evidence of a high prevalence of chronic heart failure (CHF) among patients with rheumatoid arthritis (RA), and an increased mortality rate from CHF decompensation in this cohort of patients [1-5]. In the overall population, the incidence of CHF in people older than 65 years is almost 10 patients per 1000, and in 20% of cases, CHF is the cause of all hospital

admissions [6]. In patients with RA, CHF is two times more common than in patients without RA [7].

The numerous studies have revealed structural and functional changes in the myocardium in patients with RA without known cardiovascular diseases that impair the diastolic function of the myocardium [4, 7-10]. According to the meta-analysis, including 25 studies, 1614 RA patients, and 4222 controls, the

prevalence of the left ventricular (LV) diastolic dysfunction (LVDD), LV myocardial mass index, and mean pulmonary arterial pressure in RA patients is higher than in the control group. The ejection fraction (EF) did not differ significantly in the groups [11]. J. Davis et al. found that patients with RA had a predominance of CHF with a preserved ejection fraction (HFpEF), if compared to the controls. However, their mortality rate was higher, than in patients with CHF without RA [12]. To date, there is no study, which has evaluated a myocardial function in the RA debut. This is an important issue, since the timely detection and treatment of CHF in RA patients can lead to a decrease in their mortality.

Also, there is an insufficient data on the CHF clinical pattern in patients with RA in comparison with the general population. For example, the patients with RA may present fewer complaints of shortness of breath during exercise due to the weakness, caused by the joint syndrome. The swelling in the foot area may be associated with arthritis, rather than with the decompensation of cardiac function [4]. These factors can lead to a late diagnosis of CHF in RA patients.

Therefore, the early detection of CHF in patients with early RA is of an undoubted scientific and practical interest for an active prevention and treatment of this complication.

**Study objectives:** to investigate the clinical manifestations and factors associated with the presence of CHF in patients with early RA before a basic anti-inflammatory therapy order.

## Material and methods

As the part of the REMARCA trial, 74 patients with early RA were included in the study. The inclusion criteria were: a definite diagnosis of RA, the duration of the disease less than 1 year, the positive rheumatoid factor (RF) and/or antibodies to cyclic citrullinated peptide (CCP), a moderate and high inflammatory process, prior to the treatment with basic anti-inflammatory drugs and corticosteroids. The characteristics of patients with early RA are presented in table. 1. The majority of the patients were female. The inflammatory process in patients ranged from moderate to high (Table. 1).

At the time of inclusion in the study, most patients with early RA took non-steroidal anti-inflammatory

drugs (NSAIDs). Cardioprotective drugs were regularly taken by 34 (46%) patients (Table. 2).

All patients were examined by a cardiologist, received 24-hour Holter electrocardiogram (ECG) monitoring, blood pressure (BP) monitoring, echocardiography (EchoCG), and duplex scanning of the carotid arteries. According to the current Guidelines [13], the traditional risk factors for cardiovascular diseases (CVD) were evaluated. The CHF diagnosis was verified according to the National Recommendations on the diagnosis and treatment of CHF (2013) [14], in case the patient had four key criteria: the typical symptoms and/or signs of CHF (shortness of breath, fatigue, decline of physical activity, swelling of the ankles), the objective signs of heart dysfunction according to EchoCG with tissue dopplerography data, and the level of NT-proBNP > 125 pg/ml. ECG and chest radiography were also performed. The 6-minute walk test was eliminated, because of the limited mobility in patients with RA. The control group included healthy individuals (n=27) who had no objective signs of CHF and no rheumatic diseases. The groups were compatible in age and gender.

An EchoCG examination was conducted in compliance with the Recommendations of the American Society of Echocardiography [15,16]. Diastolic dysfunction was determined in accordance with the recommendations for the evaluation of LVDD [17]. Diastolic function was considered normal with a left atrium index not higher than  $34 \text{ cm}^3/\text{m}^2$ ,  $e'$  (the average speed of early movement of the septal and lateral part of the mitral valve ring)  $\geq 9.0 \text{ cm/s}$ . The patients with the  $E/A$  ratio  $< 1.0$ , the left atrium index  $\geq 34 \text{ cm}^3/\text{m}^2$ ,  $E/e' \leq 9.0 \text{ cm/s}$  were assigned to LV diastolic dysfunction by the type of relaxation disorder. Pseudonormal LVDD was identified at  $E/A = 1.0-2.0$ , left atrial index  $\geq 34 \text{ cm}^3/\text{m}^2$ ,  $E/e' = 9-15$ .

The concentration of NT-proBNP was determined by electrochemiluminescence, using the Elecsys proBNP II test system (Roche Diagnostics, Switzerland). The normal range for NT-proBNP is  $< 125 \text{ pg/ml}$  (according to the manufacturer's manual).

Statistical data processing was performed using the SPSS 18.0 software. The results are presented as a median (Me) and an interquartile range (25%;75%). The nonparametric Mann-Whitney test

**Table 1. General characteristics of patients with early rheumatoid arthritis (n=74)**

Parameter	Value
Age, years	56 [46;61]
Women, n (%)	54 (73)
Disease duration, months	7 [4;8]
Systemic symptoms of RA, n (%)	10 (14)
Disease Activity Score DAS28, n (%)	
moderate (3.2-5.1)	32 (43.2)
high (>5.1)	42 (56.8)
IgM RF, n (%)	64 (87)
ACCP, n (%)	74 (100)
ESR, mm/h	30 [16.7;48.5]
CRP, mg/l	22.6 [6.7;46.3]
Therapy, prior to inclusion, n (%)	
NSAIDs, n (%)	46 (63)

Data are presented as Me [25%; 75%], unless otherwise is specified

RA – rheumatoid arthritis, ACCP – antibodies to cyclic citrullinated peptide, RF – rheumatoid factor, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, NSAIDs – non-steroidal anti-inflammatory drugs

**Table 2. Cardiovascular therapy prior to inclusion in the study**

Therapy, prior to inclusion,	n (%)
Nitrates	3(4)
Beta-blockers	18 (24)
Calcium-channel blockers	2 (3)
Angiotensin converting enzyme inhibitors	16 (22)
Angiotensin receptor blockers	4 (6)
Diuretics	9 (12)
I <sub>f</sub> -channel inhibitors	2 (3)
Antiaggregants	8 (11)
Statins	4 (6)
Imidazoline receptor agonists	1 (1)
Antiarrhythmic drugs	1 (1)

was used to compare two independent groups. The relationship between two characteristics was evaluated, using the Spearman's nonparametric correlation analysis. The positive predictive value (PPV) was calculated using the formula:  $PPV = TP / (TP + FP)$  (true positive) / (TP + FP [false positive]). A multiple regression analysis was performed to find the factors, associated with the presence of CHF. The construction of a ROC curve allowed to determine the optimal levels of NT-proBNP in relation to the risk of CHF development. The results were considered statistically significant at  $p < 0.05$ .

## Results

CHF was diagnosed in 24 (33%) patients: in 23 patients with preserved ejection fraction (HFpEF), in

**Table 3. Characteristics of patients with early rheumatoid arthritis depending on the presence of chronic heart failure**

Parameter	RA with CHF (n=24)	RA without CHF (n=50)	p
Age, years	61 [58;65]	51 [38;57]	<0.001
Gender, m/f, n (%)	5 (21)/19 (79)	15 (30)/35 (70)	>0.05
SBP, mm Hg	132 [120;140]	120 [100;132]	<0.01
HT, n (%)	10 (83)	26 (52)	<0.02
Dyslipidemia, n (%)	23 (96)	26 (64)	<0.01
Total cholesterol, mmol/l	5.6 [5.1;6.0]	5.2 [4.5;6.03]	>0.05
LDL-C, mmol/l	3.5 [3.0;4.3]	3.4 [2.8;4.2]	>0.05
HDL-C, mmol/l	1.4 [0.96;1.57]	1.3 [1.03;1.6]	>0.05
Triglycerides, mmol/l	1.3 [0.9;1.8]	0.9 [0.8;1.5]	>0.05
Hemoglobin, g/l	136 [114;139.5]	128 [119.5;136]	>0.05
BMI, kg/m <sup>2</sup>	28 [25;32]	24 [22;29]	<0.001
AO, n (%)	24 (100)	24 (58)	<0.001
Type 2 DM, n (%)	2 (8)	3 (6)	>0.05
CA, n (%)	21 (91)	23 (49)	<0.001
CIMT, mm	0.95 [0.89;1.04]	0.79 [0.68;0.93]	<0.01
IHD, n (%)	9 (38)	3 (6)	<0.001
DAS28	5.3 [4.6;6.4]	5.3 [5.0;6.0]	>0.05
ESR, mm/h	34 [16;56]	27 [16;41]	>0.05
CRP, mg/l	28 [13;91]	20.0 [5.6;43]	<0.04
NSAIDs	8 (33)	24 (48)	>0.05

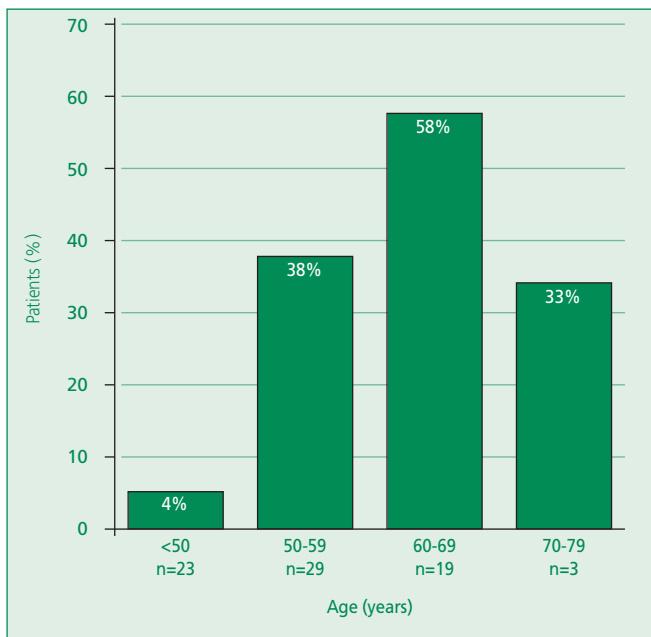
Data are presented as Me [25%;75%], unless otherwise is specified

p – significance of differences between groups (Mann-Whitney)

RA – rheumatoid arthritis, CHF – chronic heart failure, HT – hypertension, AO – abdominal obesity, CA – carotid atherosclerosis, IHD – ischemic heart disease, BMI – body mass index, NSAIDs – non-steroidal anti-inflammatory drugs, TC – total cholesterol, SBP – systolic blood pressure, DM – diabetes mellitus, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein, CIMT – carotid intima-media thickness, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoproteins cholesterol

1 patient – with reduced ejection fraction (HFrEF). CHF was detected mainly in patients aged 60-69 years. However, 50% of RA patients under the age of 60 years were diagnosed with CHF (Figure 1). Among them, 5 (21%) patients had CHF NYHA I functional class (FC); 15 (63%) patients – II FC, and 1 (4%) – III FC. Dyspnea was detected in 21 (87%) person (PPV – 33%), in 6 (25%) – ankle swelling (PPV – 35%), in 24 (100%) patients – fatigue (PPV – 38%).

All patients with early RA were divided into 2 groups depending on the presence of CHF (Table. 3). The patients, suffering both from RA and CHF, were older, had higher body mass index (BMI), were prone to have arterial hypertension (HT), carotid atherosclerosis, ischemic heart disease (IHD),



**Figure 1. Chronic heart failure prevalence in patients with early rheumatoid arthritis depending on age** and significantly higher levels of C-reactive protein (CRP), and carotid intima-media thickness (CIMT).

In order to identify the predictors of CHF, a step-by-step linear regression analysis included the following potential predictors: gender, age, inflammatory markers, activity indexes, traditional risk factors, CVD, cardiovascular drugs, and non-steroidal anti-inflammatory drugs (NSAIDs). The coefficient of multiple determination  $R^2=57.1$  ( $R = 0.76$ ;  $p<0.001$ ). The coefficients of the multi-factor predictive model for the diagnosis of CHF are presented in table 4.

The developed formula for assessing the risk of CHF in patients with early RA is the following:  
 $CHF=0.249 \times \text{abdominal obesity (yes/no)} + 0.004 \times \text{CRP (mg/l)} + 0.255 \times \text{dyslipidemia (yes/no)} + 0.004 \times \text{systolic BP (mm Hg)} + 0.758 \times \text{intima-media thickness (mm)} + 0.227 \times \text{IHD (yes/no)} - 1.294$ .

**Table 4. The regression coefficients for the prediction of chronic heart failure in patients with early rheumatoid arthritis**

Model	Coefficient	p	95%CI
Abdominal obesity, yes/no	0.249	0.025	0.032 0.466
CRP, mg/l	0.004	0.003	0.001 0.006
Dyslipidemia, yes/no	0.255	0.024	0.034 0.476
SBP, mm Hg.	0.004	0.144	0.001 0.010
Carotid intima-media thickness maximum, mm	0.758	0.026	0.091 1.423
IHD, yes/no	0.226	0.073	0.021 0.474

SBP – systolic blood pressure, CRP – C-reactive protein, IHD – ischemic heart disease, CI – confidence interval

If the calculation result is higher than 0.5, the risk of CHF is assumed to be high. The developed predictive model has a high accuracy: the area under the ROC curve is 0.849, (95% confidence interval [95%CI] 0.76-0.94,  $p<0.001$ ) with 88% sensitivity and 88% specificity.

By means of an EchoCG study in the group of patients with early RA with CHF, a statistically significant increase in the size of the LA and in the index of end-systolic volume of the atria (ESV LA) was registered; these indicators were a criterion for dividing into groups (Table 5).

LV myocardial remodeling was observed both in patients with CHF (79%) and without CHF (30%). Patients with RA and CHF are more likely to have concentric LV myocardial remodeling (Figure 2).

The data from a pulse-wave and tissue doppler imaging of transmittal flows differed significantly in the groups. In patients with early RA with CHF, there was a decrease in the E and E' indexes, E/A ratio, and an increase in the A index, E/E' ratio.

**Table 5. Echocardiographic parameters in patients with early rheumatoid arthritis depending on the presence of chronic heart failure**

Parameter	RA with CHF (n=24)	RA without CHF (n=50)	p
LA, mm	38.2 [35.5;39.4]	34.7 [31.9;38.2]	0.01
LA ESVI, cm <sup>3</sup> /m <sup>2</sup>	38.8 [35.9;41.9]	21.2 [19.4;33.0]	<0.0001
EDV LV, cm <sup>3</sup>	74.5 [62.7;87.0]	79.9 [69.3;94.9]	>0.05
IVSTd, mm	10.4 [9.7;11.9]	9.6 [8.4;11.3]	<0.04
LVPWd, mm	10.3 [9.5;10.9]	9.6 [8.2;10.8]	<0.02
LV EF, %	63 [59;68]	67 [61;70]	>0.05
E LV, m/s	0.7 [0.6;0.7]	0.8 [0.7;0.9]	<0.004
A LV, m/s	0.8 [0.7;0.9]	0.6 [0.5;0.7]	<0.0001
E/A LV, m/s	0.9 [0.8;0.9]	1.4 [1.1;1.6]	<0.05
DT LV, ms	220.5 [191.8;252.2]	213.5 [199.1;246.0]	>0.05
LV IVRT, ms	100.2 [81.3;118.3]	90.4 [79.4;103.28]	>0.05
E', m/s	0.09 [0.07;1.0]	0.13 [0.12;0.17]	<0.0001
E/E'	8.2 [6.0;10.7]	5.9 [5.1;7.6]	<0.05
PH, n(%)	3 (13%)	2 (4%)	>0.05

The data are presented as a median with an interquartile range, unless otherwise is specified

p – significance of differences between groups (Mann-Whitney)

RA – rheumatoid arthritis, CHF – chronic heart failure, E – transmitral early diastolic peak velocity, A – transmitral atrial velocity, E/A – ratio of the peak transmitral blood flow velocity during early diastolic filling (E) to the peak transmitral blood flow velocity during atrial systole (A), ESV LA – left atrium end-systolic volume index, LV – left ventricle, CLVH – concentric LV hypertrophy, EDV – end-diastolic volume, CLVR – concentric LV remodelling, PH – pulmonary hypertension, LA – left atrium, LVPWd – left ventricular posterior wall thickness, IVST – interventricular septum thickness, EF – LV ejection fraction, ELVH – eccentric LV hypertrophy, A' – late (atrial) diastolic velocity, DT – deceleration time of early mitral flow velocity, E' – early diastolic velocity, E/E' – ratio of transmitral early diastolic peak velocity to the early diastolic velocity, IVRT – isovolumic relaxation time

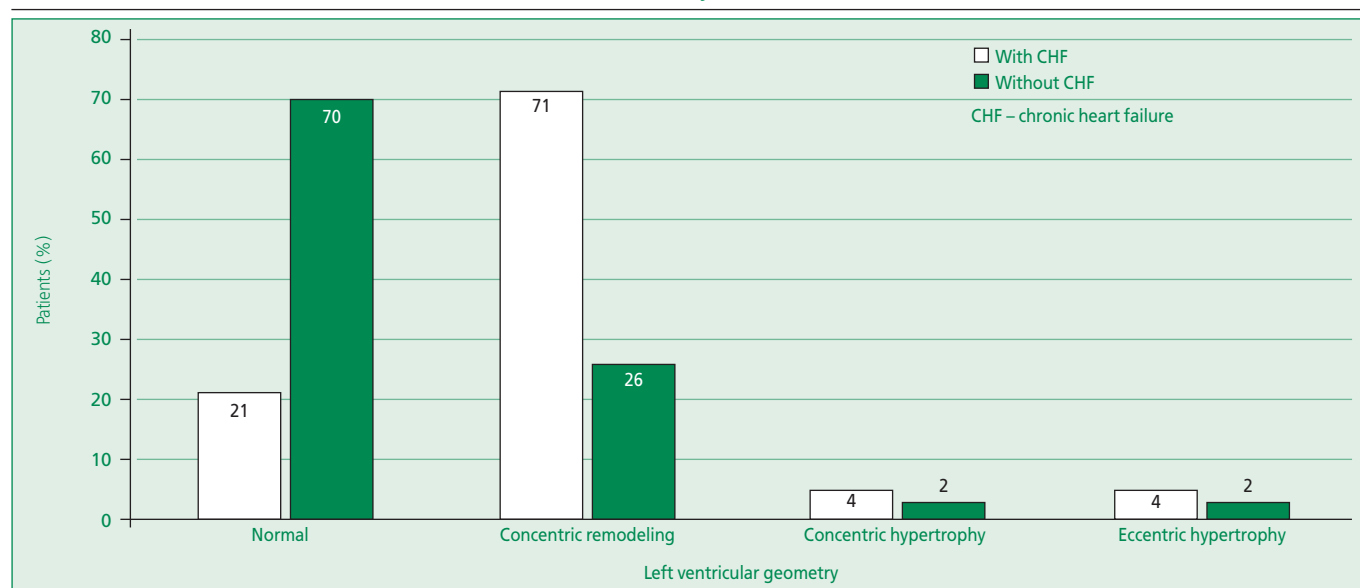


Figure 2. Types of left ventricular geometry changes in patients with early rheumatoid arthritis depending on chronic heart failure

In all RA patients with CHF, the NT-proBNP level was higher (192.0 [154.9; 255.7] pg/ml) than in patients without CHF (77 [41.1;191.2] pg/ml) ( $p<0.001$ ) and in the controls (49.0 [33.2;65.8] pg/ml,  $p<0.0001$ ). In patients with RA without CHF, the level of NT-proBNP was also significantly higher than in the control group ( $p=0.01$ ).

To determine the optimal level of NT-proBNP in RA patients, a ROC curve was constructed to exclude the CHF. The value of NT-proBNP equal to 150.4 pg/ml can be considered as target level to exclude CHF (sensitivity – 80%, specificity – 79%), the area under the ROC curve=0.957 (95%CI 0.913-1.002,  $p<0.001$ ), and the PPV – 75% (Table 6).

## Discussion

Our study is the first one, whose goal is to evaluate the frequency and the risk factors of CHF in patients with early RA, before prescription of the basic anti-inflammatory drugs and corticosteroids. In our cohort of patients with early RA, the clinically expressed CHF was diagnosed in 33% of patients. There is the evidence that in patients with RA, the CHF is diagnosed

in 0.7% of patients at the onset of the disease, and in 15 years it occurs in 10% of patients [18]. A Danish population study demonstrated that the risk of CHF developing is 2.38 times higher in the period from the onset and during the first year of the disease [19]. According to various data, the prevalence of CHF in RA patients ranges from 2.4% to 11.6% [19-22]. Such a significant difference can be explained by the fact, that many researchers took into account only clinically expressed CHF that requires treatment or hospitalization, but did not perform EchoCG with tissue dopplerography and did not register the level of NT-proBNP [22]. In addition, in our cohort, all the patients had moderate or severe pathological process, whereas in the presented studies, there were patients with low or moderate RA. Thus, according to our data, the clinical symptoms of CHF showed a low PPV for verifying the diagnosis (shortness of breath – 33%, ankle swelling – 35%, fatigue – 38%). T. Schau et al., in their study, also registered the low PPV of dyspnea – 42%, oedema – 39%, and pulmonary rales – 38%, while patients with CHF without RA had a higher PPV of edema – 67% [4]. The low PPV of the clinical symptoms in RA patients is explained by the fact, that these manifestations can be observed in RA patients without CHF due to the main disease. These results indicate the problem of diagnosing CHF in RA patients and the need to use the instrumental and laboratory methods to verify the diagnosis.

Table 6. Sensitivity, specificity, and positive predictive value of the NT-proBNP level

NT-proBNP level	Sensitivity	Specificity	PPV
125 pg/ml	100%	75%	41%
150 pg/ml	80%	79%	75%
220 pg/ml	48%	88%	42%
PPV – positive predictive value			

In patients with early RA, the heart failure is mainly presented as HFpEF. Our data are consistent with the results of other researchers. J. Schau et al. detected HFpEF in 23% of RA patients who had already received anti-rheumatic therapy [4], and K. Liang et al. showed that in RA patients with CHF, the EF was higher than in patients with CHF without RA (50% vs 47%;  $p < 0.007$ ) and was represented mainly by the diastolic variant [23].

In our study, we revealed that in patients with early RA, who are younger than 60 years, the CHF occurs in 50% of cases. There is the evidence that CHF in RA patients develops 10 years earlier than in the overall population [1].

By means of the multivariate analysis, we were the first to identify the factors, associated with chronic heart failure in patients with early RA. The prognostic model included the presence of abdominal obesity, dyslipidemia, the level of systolic BP, CIMT, IHD, and the level of CRP. Obesity can lead to the development of CHF through various mechanisms (increase in circulating blood volume, increase in cardiac output, left ventricular hypertrophy (LVH), LVDD, fatty degeneration of the heart) [24,25]. J. Davis et al. mentioned, that RA patients with CHF had higher BMI (23% and 10% [ $p = 0.002$ ]), systolic BP (odds ratio [OR] 0.58; 95%CI 0.38-0.89) and diastolic BP (OR 0.34; 95%CI 0.19-0.60), if compared to patients with CHF without RA [12]. It is important to note that the presence of HT was closely related to the prevalence of CHF in the study of F. Wolf et al. (OR 2.6; 95%CI 2.1-3.2) [1]. An association between HT and the increased risk of CHF development in patients with RA was found during the average 11.8 years of follow-up [2], as well as the HT prevalence in patients with RA and CHF (84%) if compared to the patients without heart failure (47%) [4].

According to the Swedish registry, in the RA debut, there is a significant increase in the risk of heart failure of non-ischemic and ischemic origin (risk ratio 1.22 and 1.27, respectively) [26]. A recent MI (within six months) and a MI in the medical history have statistically significant correlations with CHF in RA patients (OR 16.1; 95%CI 11.0-23.7 and OR 6.6; 95%CI 5.4-8.0, respectively) [1]. In the study, performed by R. Nicola et al., the IHD (including the MI and angina) and the traditional risk factors for CVD were

more common triggers of CHF in RF-negative patients, than in RF-positive RA patients [2]. Subclinical carotid atherosclerosis is more often detected in RA patients than in controls [27].

According to S. Garza-García et al., in patients with RA, dyslipidemia was one of the risk factors for developing LVDD [28]. However, the direct effect of lipid abnormalities and subclinical atherosclerosis on the development of non-ischemic heart disease remains unclear. It was also demonstrated that the increase in the level of CRP  $> 10$  mg/l facilitates the risk of CHF in RA patients (OR 2.6, 95%CI 0.8-8.0) [4].

Thus, the development of CHF in RA patients is influenced by both traditional risk factors for CVD and the inflammation.

We newly demonstrated the changes in echocardiographic parameters in patients with early RA. In our study, the LV EF in patients with early RA and CHF was higher than 60%, and did not differ significantly in patients having CHF and without CHF. In one patient with post-infarction cardiosclerosis and revascularization, EF decreased till 39%. A number of studies also revealed the high LV EF rates in RA patients with CHF [23, 29]. It can be assumed that CHF in RA patients develops mainly due to the impairment of the diastolic function of the myocardium.

The change in LV geometry, according to the EchoCG data in patients with early RA and CHF, was frequently revealed. The concentric remodeling of the LV myocardium was the most frequent variant of LV geometry change in patients with CHF and without CHF (71% and 27%, respectively). According to G.B. Kolotova, the normal LV geometry was changed in 65% of patients with seropositive RA [29]. In a study of T. Schau et al., the concentric LV myocardial remodeling was more common in patients with RA and CHF, if compared to patients without RA (48% vs 17%;  $p = 0.001$ ) [4]. We assume that a change in the geometry of the left ventricle is an early sign of myocardial damage, as well as a trigger for the development of CHF [30]. In patients with CHF in the general population, LV eccentric hypertrophy is most often detected, according to EchoCG data, as opposed to patients with early RA. This trend can be explained by the fact that in RA patients, the LV geometry is mainly affected by inflammation, which leads to myocardial fibrosis, which contributes

to the development of LVDD and CHF. In patients with asymptomatic CHF or IHD, with the increased level of interleukin-6, CRP, and tumor necrosis factor  $\alpha$ , the risk of CHF development is 2-4 times higher than in patients with low levels of these markers and inflammatory mediators [30]. Other researchers revealed a negative correlation between the level of tumor necrosis factor  $\alpha$  and the E/A ratio [31].

In the overall population, the diagnostically significant level of NT-proBNP for detecting the stable CHF is  $>125$  pg/ml with a sensitivity of 88% and a specificity of 92% [32]. In our cohort of patients with early RA, the NT-proBNP level of 125 pg/ml showed a low PPV of 41%. For patients with early RA, a higher NT-proBNP level of 150.4 pg/ml has the optimal sensitivity (80%), specificity (79%), and PPV. Also L. Tomás et al. defined NT-proBNP  $>125$  pg/ml as having low sensitivity/specificity (69%/51%), positive (34%), and negative predictive value (19%) for detecting any heart disease [31]. The causes of elevated level of NT-proBNP for CHF in RA patients require further investigation. Since the increase in NT-proBNP in RA patients is influenced by both the heart muscle damage, underlying the CHF, and the inflammation in RA.

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**Study limitations.** A limitation for our study is associated with a small number of participants with early RA and CHF. Thus, for a statistically significant assessment of CHF prevalence in different age groups of patients, a greater number of persons with early RA should be investigated.

## Conclusion

This study revealed that a third part of RA patients suffers from CHF during the early period of the disease, mainly with HFpEF. The factors, associated with the presence of CHF, are abdominal obesity, CRP level, systolic BP, dyslipidemia, CIMT, and IHD. In patients with early RA, the diagnostically significant NT-proBNP level for excluding CHF is higher (150.4 pg/ml) than in patients without RA (125 pg/ml). The focus of a therapist's attention in patients with severe and moderate RA should include the screening for CVD risk factors and inflammation control, in order to prevent the onset and progression of CHF.

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