

# Relationship between anemia and heart disease in patients with rheumatoid arthritis

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**Background.** Rheumatoid arthritis (RA) is often accompanied by anemia. The aim of this study was to determine the effect of anemia on the structural-geometric state of the heart in patients with rheumatoid arthritis. **Material and methods.** 154 patients suffering from RA were involved in our research. Out of them, 37 were diagnosed with mild or moderate anemia (1st group), and 117 did not have systemic manifestations of RA (2nd group). By echocardiography were calculated left ventricular myocardial mass index, relative wall thickness of the left ventricle, left ventricle ejection fraction, left ventricular end-diastolic diameter, and E/a parameters of mitral and tricuspid valves. **Results.** In correlation analysis in the 1st group we found a direct correlation between age and the left ventricular myocardial mass index ( $r=0.62$ ,  $p<0.0005$ ), between age and the left ventricular end-diastolic diameter ( $r=0.37$ ,  $p<0.05$ ). We also found a negative correlation between age and E/a parameter of mitral valve ( $r=-0.71$ ,  $p<0.00001$ ), between DAS-28 index and E/a parameter of tricuspid valve ( $r=-0.43$ ,  $p<0.05$ ), between anti-MCV level and the E/a parameter of mitral valve ( $r=-0.9$ ,  $p<0.05$ ). In the group of patients without systemic manifestations, we found a direct correlation between age and the left ventricular myocardium mass index ( $r=0.46$ ,  $p<0.0001$ ), between age and relative wall thickness ( $r=0.43$ ,  $p<0.0005$ ), and also the negative correlation between age and the E/a parameter of the mitral valve ( $r=-0.55$ ,  $p<0.00001$ ;  $r=-0.27$ ,  $p<0.05$  respectively). **Conclusions.** Regardless of the anemia presence in patients with rheumatoid arthritis, the structural-geometric changes of the heart depend on age, namely, left ventricular myocardium mass index increases, and the diastolic function of the left ventricle is impaired. At the same time, in patients with anemia, increase of the activity of RA entails a worsening in the diastolic function of the right ventricle, and increase of anti-MCV level correlates with diastolic dysfunction of the left ventricle.

**Key words:** Anemia; Rheumatoid arthritis; Diastolic dysfunction; Heart failure.

**Antecedentes.** La artritis reumatoide (AR) a menudo se acompaña de anemia. El objetivo de este estudio fue determinar el efecto de la anemia en el estado geométrico-estructural del corazón en pacientes con AR. **Material y métodos.** 154 pacientes con AR participaron en nuestra investigación. De ellos, 37 fueron diagnosticados con anemia leve o moderada (1er grupo) y 117 no tuvieron manifestaciones sistémicas de AR (2do grupo). Por ecocardiografía, se calcularon índice de masa miocárdica del ventrículo izquierdo, grosor relativo de la pared del ventrículo izquierdo, fracción de eyección del ventrículo izquierdo, diámetro diastólico final del ventrículo izquierdo y relación E/a para las válvulas mitral y tricúspide. **Resultados.** En el análisis de correlación, en el 1er grupo encontramos una correlación directa entre la edad y el índice de masa miocárdica del ventrículo izquierdo ( $r = 0,62$ ,  $p < 0,0005$ ), entre la edad y el diámetro diastólico final del ventrículo izquierdo ( $r = 0,37$ ,  $p < 0,05$ ). También encontramos una correlación negativa entre la edad y la relación E/a de la válvula mitral ( $r = -0,71$ ,  $p < 0,00001$ ), entre el índice DAS-28 y el parámetro E/a de la válvula tricúspide ( $r = -0,43$ ,  $p < 0,05$ ), entre el nivel anti-MCV y relación E/a de la válvula mitral ( $r = -0,9$ ,  $p < 0,05$ ). En el grupo de pacientes sin manifestaciones sistémicas, encontramos una correlación directa entre la edad y el índice de masa del miocardio ventricular izquierdo ( $r = 0,46$ ,  $p < 0,0001$ ), entre la edad y el grosor relativo de la pared ( $r = 0,43$ ,  $p < 0,0005$ ), y también la correlación negativa entre la edad y la relación E/a de la válvula mitral ( $r = -0,55$ ,  $p < 0,00001$ ;  $r = -0,27$ ,  $p < 0,05$ , respectivamente). **Conclusiones.** Independientemente de la presencia de anemia en pacientes con artritis reumatoide, los cambios geométrico-estructurales del corazón dependen de la edad, es decir, el índice de masa del miocardio ventricular izquierdo aumenta y la función diastólica del ventrículo izquierdo se ve afectada. Al mismo tiempo, en pacientes con anemia, el aumento de la actividad de la AR conlleva un empeoramiento de la función diastólica del ventrículo derecho, y el aumento del nivel de anti-MCV se correlaciona con la disfunción diastólica del ventrículo izquierdo.

**Palabras clave:** Anemia; Artritis reumatoide; Disfunción diastólica; Falla cardiaca.

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Rheumatoid arthritis (RA) is a chronic disease characterized by damage of musculoskeletal system and this disease is often accompanied by various systemic, extra-articular manifestations. One of these clinical syndromes is anemia. The most common pathogenetic variant of anemia is anemia of chronic diseases, which can be considered as a systemic manifestation of RA, because it is a consequence of inflammatory process. The second most common variant – iron deficiency anemia, which is widely spread in the world, regardless of the main disease. Aplastic anemia as a result of depression of blood formation when patient uses cytostatic therapy and megaloblastic anemia as a result of vitamin B12 deficiency and/or folic acid deficiency are less common [1].

The aim of our research was to determine the effect of anemia on the structural-geometric state of the heart in patients with RA.

## MATERIAL AND METHODS

One hundred and fifty four patients suffering from RA involved in our research. 37 people were diagnosed with mild or moderate anemia (1st group), and 117 people did not have systemic manifestations of RA (2nd group). The diagnostic criterion for anemia was a decrease of hemoglobin concentration in the blood to less than 130 g/L in men and less than 120 g/L in women.

RA activity was assessed by the disease activity index – DAS-28. In addition to routine laboratory tests, all patients had blood test to determine the level of circulating immune complexes (CIC) and anti-MCV (antibodies to modified citrullinated vimentin) in serum, as well as echocardiography.

It is known that RA is characterized by presence of antibodies, including rheumatoid factor, antibodies to cyclic citrullinated peptide (ACCP) and antibodies to modified citrullinated vimentin (anti-MCV). The specificity of the analysis for anti-MCV is about 98%. In RA, it is comparable to the specificity of ACCP test (specificity is about 92-98%) and much higher than specificity of rheumatoid factor (specificity of 70%). Due to this advantage, this analysis was included in the diagnostic criteria of RA in 2010 [2].

Using the echocardiography, we performed standard examinations of the left ventricular myocardial mass index (LVMI), the relative wall thickness of the left ventricle (RWT), the Simpson ejection fraction (EF), left ventricular end-diastolic diameter (LVED), E/a parameters of mitral and tricuspid valves, where E/a is the ratio of the speeds of early and late filling of the ventricles.

Statistical analysis was performed with Statistica 10.0 for Windows. Taking into account differences of the data distribution from the normal distribution, the non-parametric Mann-Whitney U test, and also Spearman's rank correlation and Fisher's exact test were used to compare the parameters of the studied groups. Differences were considered significant

at a value of  $p < 0.05$ . Descriptive characteristics are given as medians, 25 and 75 percentiles.

## RESULTS

Characteristics of patients are presented in **Table 1**. Both groups were comparable in terms of age, sex, ratio of seropositive and seronegative patients. However, in comparing the percentage of people with different radiological stages of the disease, it turned out that patients with 3-4 stages ( $p < 0.05$ ) predominate in the 1st group.

**TABLE 1. Characteristics of the groups of patients with anemia and without systemic manifestations of rheumatoid arthritis**

Patients with RA*	With Anemia	Without systemic manifestations
Age (years)	54 [45; 62]	54 [47; 59]
Gender (female/male)	91.9/8.1%	81.2/18.8%
Seropositivity (+/-)	81.8/18.2%	77.8/22.2%
X-Ray stages of RA*	1 – 0% 2 – 16.2% 3 – 37.8% 4 – 46%	1 – 0% 2 – 33.4% 3 – 33.3% 4 – 33.3%

\* RA: Rheumatoid arthritis

In the comparative analysis of both groups, it was found that in the 1st group level of disease activity, determined by DAS-28, was higher than in the 2nd group ( $p < 0.05$ ). According to the results of echocardiography, the left ventricular myocardial mass index was higher in the 1st group than in the group without systemic manifestations of RA ( $p < 0.05$ ). The same applies to the left ventricle end-diastolic diameter: in patients with anemia, it was higher than in patients without it ( $p < 0.05$ ) (**Table 2**).

Our results evidence that anemia is more common in patients with late (third to fourth) X-ray stages of rheumatoid arthritis and is accompanied by increase in the activity of the main disease. Talking about the results of echocardiography, it is important to notice that in patients with anemia a violation of the diastolic function of the myocardium, which is accompanied by an increase in myocardial mass, is more often.

In correlation analysis in the 1st group we found a direct correlation between age and the left ventricular myocardial mass index ( $r = 0.62$ ,  $p < 0.0005$ ), between age and the left ventricular end-diastolic diameter ( $r = 0.37$ ,  $p < 0.05$ ). We also found a negative correlation between age and E/a parameter of mitral valve ( $r = -0.71$ ,  $p < 0.00001$ ), between DAS-28 index and E/a parameter of tricuspid valve ( $r = -0.43$ ,  $p < 0.05$ ), between anti-MCV level and the E/a parameter of mitral valve ( $r = -0.9$ ,  $p < 0.05$ ).

In the group of patients without systemic manifestations, we found a direct correlation between age and the left ventricular myocardium mass index ( $r = 0.46$ ,  $p < 0.0001$ ), between

**TABLE 2. Levels of DAS-28 index, CIC, anti-MCV and parameters of echocardiography in patients with anemia and without systemic manifestations of rheumatoid arthritis**

Patients with RA*	With Anemia	Without systemic manifestations
DAS-28	5.88 [5.12; 6.5]*	5,4 [4.84; 5.71]*
CIC	121 [93; 257]	167,5 [109,5; 196]
anti-MCV	3561,9 [359,3; 7000]	671,4 [167,3; 6000]
LVMI	105 [90; 122]*	89,4 [79; 107,2]*
RWT	0.37 [0.35; 0.41]	0.37 [0.34; 0.43]
E/a parameter of mitral valve	1.085 [0.75; 1.25]	0.87 [0.72; 1.25]
E/a parameter of tricuspid valve	1.31 [1.17; 1.41]	1.21 [1.03; 1.36]
LVED	4.8 [4.4; 5.15]*	4.5 [4.2; 4.85]*
LVEF	66 [62; 68]	66 [63; 68]

\* Notice:  $p < 0,05$ . RA: Rheumatoid arthritis.

age and relative wall thickness ( $r=0.43$ ,  $p < 0,0005$ ), and also the negative correlation between age and the E/a parameter of the mitral valve ( $r=-0.55$ ,  $p < 0.00001$ ;  $r=-0.27$ ,  $p < 0.05$  respectively).

## DISCUSSION

The higher the population age, the higher the incidence of heart failure (HF) with normal ejection fraction. Diastolic HF is also called HF with normal ejection fraction. Diastolic HF is characterized by impaired LV relaxation, increased LV stiffness, among many other ones. It represents almost 50% of all cases of HF [3].

Remodeling process of the LV usually begins long before the symptoms appear. This is the main reason to make clear detection must be made by means of subclinical imaging. It

has been detected in a general population as high as 27.3% [4].

Patients with HF and preserved EF have more comorbidities than the patients with HF and reduced EF as hypertension, obesity, and metabolic syndrome [5]. Risk factors associated for HF and preserved EF are hypertension, advanced age, female sex, metabolic syndrome, atrial fibrillation, sleep apnea, chronic obstructive pulmonary disease, renal dysfunction, dyslipidemia, systemic inflammatory diseases, such as rheumatoid arthritis [6,7]. Precipitating factors include ischemia, tachycardia, volume overload, arrhythmias, especially AF, and systemic stressors such as anemia and infection [8].

The results of the correlation analysis indicated that, regardless of the anemia presence in patients with rheumatoid arthritis, the structural-geometric changes of the heart depend on age: left ventricular myocardium mass index increases, and the diastolic function of the left ventricle is impaired. At the same time, in patients with anemia, increase of the activity of RA entails a worsening in the diastolic function of the right ventricle, and increase of anti-MCV level correlates with diastolic dysfunction of the left ventricle.

Thus, increase of the disease activity in patients with rheumatoid arthritis and anemia evidenced a tendency to worsen diastolic myocardial dysfunction, what is more not only of the left ventricle, but also of the right ventricle. Thereby, in this group of patients it is advisable to control the activity of the disease more strictly, using the whole arsenal of modern medicaments, and the frequency of echocardiography to monitor myocardial condition.

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