RELATIONSHIP BETWEEN ANEMIA AND HEART DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Objective: To determine the impact of anemia on the structural-geometrical condition of the heart in patients with rheumatoid arthritis (RA).

Methods: 154 patients with RA were included in the study: 37 patients with anemia (1st group) and 117 – without systemic manifestations of RA (2nd group). All patients underwent echocardiography.

Results: Both groups were comparable in age, sex, ratio of seropositive and seronegative patients. A comparative analysis of both groups revealed that in 1st group DAS28 was higher than in 2nd group (p<0.05). The left ventricular myocardial mass index was higher in 1st group than in the 2nd group (p<0.05). The same applies to the left ventricular end-diastolic diameter: in patients with anemia, it was more than in patients without it (p<0.05). Our results suggest that patients with anemia often have a violation of diastolic myocardial function, which is accompanied by an increase in myocardial mass. The correlation analysis in both groups revealed a direct relationship between age and left ventricular mass index (r=0.62, p<0.0005), inverse relationship between age and E/a parameter of mitral valve (r=-0.71, p<0.00001). In addition, in 1st group we revealed the inverse relationship between DAS28 and E/a parameter of tricuspid valve (r=-0.43, p<0.05).

Conclusions: Thus, regardless of the presence of anemia, the patients with RA observed dependence of structural and functional changes in the heart of age: a violation of diastolic function of the left ventricle, an increase of the left ventricular myocardial mass index. However, in patients with anemia, an increase in the activity of the disease is accompanied by diastolic dysfunction of the right ventricle that requires correction in patient management process.

Keywords: *Rheumatoid arthritis, anemia, echocardiography, diastolic dysfunction.*

ВЗАИМОСВЯЗЬ МЕЖДУ АНЕМИЕЙ И ПОРАЖЕНИЕМ СЕРДЦА У ПАЦИЕНТОВ С РЕВМАТОИДНЫМ АРТРИТОМ

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Цель: определить влияние анемии на структурно-геометрическое состояние сердца у пациентов с ревматоидным артритом (РА).

Материал и методы: в исследование были включены 154 пациента с РА: 37 больных с анемией (I группа) и 117 – без системных проявлений РА (II группа). Все пациентам проведена эхокардиография.

Результаты: обе группы были сопоставимы по возрасту, полу, соотношению серопозитивных и серонегативных пациентов. Сравнительный анализ обеих групп показал, что в I группе индекс DAS28 был выше, чем во II группе (p<0,05). Индекс массы миокарда левого желудочка был выше в I группе по сравнению со II (p<0,05). То же касалось и конечного диастолического размера левого желудочка: у пациентов с анемией он оказался больше, чем у пациентов без неё (p<0,05). Наши результаты показали, что у пациентов с анемией часто наблюдается нарушение диастолической функции миокарда, которое сопровождается увеличением массы миокарда. Корреляционный анализ в обеих группах выявил прямую связь между возрастом и индексом массы левого желудочка (r=0,62, p<0,0005), обратную связь между возрастом и показателем E/a митрального клапана (r=-0,71, p<0,00001). Кроме того, в I группе мы выявили обратную зависимость между DAS28 и параметром E/a трикуспидального клапана (r=-0,43, p<0,05).

Заключение: таким образом, независимо от наличия анемии, у пациентов с РА наблюдается зависимость структурных и функциональных изменений сердца от возраста: нарушение диастолической функции левого желудочка, увеличение индекса массы миокарда левого желудочка. Однако у пациентов с анемией увеличение активности заболевания сопровождается диастолической дисфункцией правого желудочка, что требует коррекции в тактике ведения пациента.

Ключевые слова: *ревматоидный артрит, анемия, эхокардиография, диастолическая дисфункция.*

INTRODUCTION

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 (EAM). Presence of EAM of RA occurs in more severe disease [1]. EAM of RA can occur at any age after onset [2]. And also, EAM of RA are still a major mortality risk factor for patients [3]. One of these manifestations is anemia. It is important to know hemoglobin level, because using this we can predict disease activity in RA patients which can guide us for proper management to prevent further disease progression [4].

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 anemia of chronic disease (ACD) refers to the impaired

production of erythrocytes associated with chronic inflammatory status, including autoimmune diseases [5, 6]. The actions of several pro- and anti-inflammatory cytokines and hormones produce the suppression of erythropoiesis [7]. This problem is topical, because anemia can independently impact on morbidity and mortality in patients with conditions associated with ACD as well as affecting quality of life [8].

The second most common variant is 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 [9].

It is known that patients with RA have a higher risk of coronary heart disease and sudden cardiac death [10-12]. Chronic inflammation plays a pivotal role in this increased risk [11]. Some authors associate it with the heart failure (HF), however, the real reason of myocardial dysfunction leading to HF in RA described in a few publications [13-15]. RA is associated with increased LV mass [3]. The nature of impairments in left ventricular (LV) function is complex, pathologic LV remodeling in patients with RA may contribute to impaired LV filling, resulting in the subsequent progression of myocardial dysfunction and the ultimate development of HF [11].

The relevance of the study is that in the literature there is a few information regarding the effects of anemia [17, 18] and rheumatoid arthritis [11, 19] on structural-geometric condition of the myocardium, but there is no data about effects of anemia and RA together on the structural-geometric remodeling of myocardium.

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

MATERIALS AND METHODS

154 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.

Inclusion criteria were:

- Patients have 1st degree of arterial hypertension, lasting less than 1 year, or they have not arterial hypertension.
- In the history-cases there are no data on the presence of diseases that could lead to anemia.
- Patients have not coronary artery disease, heart valve defects and other diseases that could lead to structural-

geometric remodeling of the myocardium except anemia and rheumatoid arthritis in their history-cases.

- The group of patients with anemia included only persons with 1st degree of anemia (Hb≥91 g/l).
- Patients have not extraarticular manifestations of rheumatoid arthritis except anemia.
- Patients with curtain duration of rheumatoid arthritis from 5 to 6 years.

RA activity was assessed by the disease activity index DAS28. 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 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 [17].

Using the echocardiography, we performed standard examinations of the left ventricular 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 AND DISCUSSION

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.

In the comparative analysis of both groups, it was found that in the 1st group level of disease activity, determined by DAS28, was higher than in the 2nd group (p<0.05). According to the results of echocardiography, the LVMI was higher in the 1st group than in the group without systemic manifestations of RA (p<0.05). The same applies to the LVED: in patients with anemia, it was higher than in patients without it (p<0.05) (Table 2).

Table 1 Characteristics of the groups of patients with anemia and without systemic manifestations of RA

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 2 3 4	0 16.2 37.8 46.0	0 33.4 33.3 33.3

Table 2 Levels of DAS28 index, CIC, anti-MCV and parameters of echocardiography in patients with anemia and without systemic manifestations of RA

Patients with RA	With anemia	Without systemic manifestations
DAS28	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]*
EF	66 [62; 68]	66 [63; 68]

* – $p < 0.05$

Our results evidence that anemia is more common in patients with late (third to fourth) X-ray stages of RA and is accompanied by increase in the activity of the main disease. According to 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 LVMI ($r=0.62$, $p<0.0005$), between age and the LVED ($r=0.37$, $p<0.05$). We also found a negative correlation between age and E/a parameter of mitral valve ($r=-0.71$, $p<0.00001$), between DAS28 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 LVMI ($r=0.46$, $p<0.0001$), between age and relative wall thickness ($r=0.43$, $p<0.0005$), and also the negative correlation between age and E/a parameters of the mitral and tricuspid valves ($r=-0.55$, $p<0.00001$; $r=-0.27$, $p<0.05$ respectively).

The results of the correlation analysis indicated that, regardless of the anemia presence in patients with RA, the structural-geometric changes of the heart depend on age: LVMI is increased, 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.

In many studies, it has been found that anemia take part in remodeling of the left part of the heart [20, 21], the same results have researches on RA [22-24]. However, in our research, we found that combination of anemia and RA leads to remodeling of the right part of the heart, which has big practical importance in clinical management of patients.

We conclude that increase of the disease activity in patients with RA 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 myocardium condition.

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