Spectrum Journal of Innovation, Reforms and Development
Volume 04, June, 2022 | ISSN (E): 2751-1731
Website: www.sjird.journalspark.org

HEARTS IN RHEUMATOID ARTHRITIS: THE RELATIONSHIP WITH IMMUNOLOGICAL DISORDERS

Ergasheva Ma'mura Toshtemirovna
Khusainova Munira Alisherovna
Yarmatov Suvon Totlibayevich
Ergashova Madina Muxtorovna
Samarkand State Medical University

Abstract

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of connective tissue with progressive damage mainly to peripheral (synovial) joints by the type of symmetrical erosive—destructive polyarthritis with frequent extra-articular manifestations, among which heart damage, according to autopsy data, is noted in 50-60% of cases. Changes in the heart in RA in in the recent past, it was isolated into the articular-cardiac form of the disease. When the joints are affected, when physical activity is noticeably reduced, cardiac pathology is often masked, which requires a more attentive and thorough examination of the patient from the doctor. At the same time, clinical changes on the part of the heart, as a rule, are minimal and rarely come to the fore in the overall picture of the underlying disease. Systemic manifestations of RA, including heart damage, determine the prognosis as a whole, therefore, their early recognition and targeted treatment are important. The frequency of myocardial damage in RA in the form of myocarditis has not been clarified. This is due, on the one hand, to the difficulty of diagnosing myocarditis in people with limited motor activity, on the other — the lag of clinical manifestations from morphological changes of the heart. The pathology of the myocardium is polymorphic in nature due to the presence of various vascular lesions. In some vessels there is vasculitis, in others — hyalinosis, in others — sclerosis. The nature of vasculitis can be proliferative and rarely proliferative-destructive. In the inflammatory infiltrate, lymphohistiocytic elements predominate both in the perivascular space and in the vascular wall. It should be noted that when the main process is activated, a combination of old and fresh vascular changes is observed.

Keywords: heart disease, atherosclerosis, rheumatoid arthritis, cholesterol, daily blood pressure monitoring.

Introduction

Along with this, focal, or diffuse, interstitial myocarditis occurs, ending in the development of small-focal cardiosclerosis. Patients with rheumatoid arthritis often develop brown myocardial atrophy with accumulation of lipofuscin in cardiomyocytes. These changes may be the cause of angina pectoris. A pathogenic sign of rheumatoid arthritis is rheumatoid nodules in the myocardium, pericardium and endocardium at the base of the mitral and aortic valves, in the area of the fibrous ring. At the end of the nodule, sclerosis develops, causing the formation of

valve insufficiency. Myocarditis is manifested and diagnosed, as a rule, at the height of the activity of the main rheumatoid process, that is, with another pronounced exacerbation of the articular syndrome.

A significant number of cases have been described in the literature when cardiac arrhythmia is the only pathological symptom of coronary artery damage. Rhythm and conduction disturbances in active RA are significantly more often detected by daily ECG monitoring and transesophageal electrophysiological examination than with conventional ECG. So, I. B. Vinogradova, in the study of RA patients using the above technique, revealed rhythm and conduction disturbances in 60% of patients, including atrial (18%) and ventricular (10%) extrasystole, paroxysmal tachycardia (4%), atrial fibrillation (6%), passing blockade of the right leg of the Gis bundle (20%) and atrioventricular blockade of the II degree (2%). It has also been suggested that ST depression detected by transesophageal electrophysiological examination is an indirect sign of changes in coronary microcirculation due to rheumatoid vasculitis. Therefore, these patients had high levels of circulating immune complexes, rheumatoid factor, antibodies to cardiolipin Ig M. It is important to note that in the same group of patients there were other signs of vasculitis: digital arteritis, reticular livedo, Raynaud's syndrome and rheumatoid nodules. Consequently, if routine clinical research methods do not reveal sufficiently convincing signs of rheumatoid myocarditis, then modern electrophysiological studies reveal facts of cardiac dysfunction, which indicates the connection of these changes with the activity of the rheumatoid process. This can be confirmed by the positive dynamics of changes under the influence of adequate treatment of the underlying disease, usually noted with the regression of the articular syndrome. Differential diagnosis of myocarditis and myocardiodystrophy, often performed in RA patients receiving massive drug therapy for a long time, is difficult, because clinical manifestations in both cases are close. The presence of myocarditis will be confirmed by the positive dynamics of its manifestations under the influence of properly selected and prescribed anti-rheumatic treatment in adequate doses.

Several epidemiological studies have demonstrated a high incidence of cardiovascular events, including myocardial infarction and sudden death, in RA patients. According to the case-control study, which included more than 34 thousand patients with RA and more than 103 thousand control individuals, the maximum risk of myocardial infarction is observed in women and does not depend on traditional risk factors. It is assumed that the main cause of increased cardiovascular morbidity in RA patients is the accelerated development of atherosclerosis.

Surrogate markers of atherosclerosis, widely used in clinical practice, are being actively studied in RA patients. The largest number of works is devoted to subclinical carotid atherosclerosis (thickness of the intima-media complex, the presence of plaques). A number of studies have studied hypertrophy and remodeling of the left ventricle in RA. In addition to structural markers of atherosclerosis, it is possible to assess functional parameters closely related to the risk of CVD. These include the daily blood pressure profile, a decrease in heart rate variability and the presence of obstructive sleep apnea syndrome. It is of interest to study the relationship of structural and functional markers of atherosclerosis with immunological disorders underlying the pathogenesis of RA.

Goal

To identify instrumental signs of damage to the cardiovascular system (CCC) in patients with rheumatoid arthritis (RA) and to assess their relationship with immunological disorders.

Material and Methods

The study included 25 RA patients who were on inpatient treatment in the rheumatology department 1-clinic of SamSMU. The inclusion criteria were: female gender, age 35-65 years, RA diagnosis (according to the criteria of the 1987 ARA), informed consent of the patient to participate in the study. The exclusion criteria were: angina pectoris, myocardial infarction, a history of revascularization, clinical manifestations of chronic heart failure (CHF) II-IV FC, valvular heart defects, peripheral atherosclerosis (with clinical manifestations), hemodynamically significant arrhythmias, a history of cerebral circulation, polyneuropathy, the presence of risk factors requiring immediate therapy – increase in blood pressure ? 180/110 mmHg. and total cholesterol (OHC) ? 8 mmol/l, already conducted antihypertensive, lipid-lowering therapy, verified diagnosis of type 1 or type 2 diabetes mellitus, clinically significant thyroid diseases (hypothyroidism, diffuse toxic goiter), oncological diseases, acute inflammatory diseases, mental illnesses, alcoholism and drug use, taking psychotropic drugs.

Research protocol. A one-stage study was conducted, which included the collection of complaints and anamnesis to identify CVD risk factors, anthropometric measurements (height, weight, calculation of body mass index - BMI, waist and hip circumference, their ratio - FROM/ABOUT), assessment of articular status (account of swollen, painful joints, Ritchie index), evaluation of extra-articular manifestations and the duration of the disease. Joint pain was assessed using a visual analog scale (VAS). The total activity of RA was assessed using the Disease Activity Score (in the DAS28 modification, which includes the number of painful joints out of 28, the number of swollen joints out of 28, the level of ESR and the general state of health of the patient according to VAS). Fasting blood glucose concentration, total cholesterol level, as well as the number of white blood cells, ESR and C-reactive protein (CRP) levels were determined. RF in blood serum was determined in patients with RA.

All patients underwent daily blood pressure monitoring (ABPM-04 and ABPM-05 oscillometric devices, Meditech, Hungary), daily ECG monitoring with HRV analysis (MT-100 device, Schiller, Switzerland), cardiorespiratory monitoring (ApneaLink device, ResMed, Germany), echocardiography (GE Logic 400, USA). Study of populations and subpopulations of lymphocytes. Examination of the immune status of peripheral blood in RA was carried out according to the following indicators of CD antigens: CD3, CD4, CD8, CD10, CD20, CD25, CD38, CD95, HLA-DR; immunoglobulins: IgG, IgA, IgM. Lymphocytes and their subpopulations were determined by immunofluorescence using monoclonal antibodies. The level of immunoglobulins (Ig) was determined in serum by Mancini in tablets of the company "Reafarm".

Statistical methods. Statistical data processing was carried out using the STATISTICA 6.0 software package (StatSoft, Inc, USA). The normality of the distribution of variables was evaluated using the Shapiro-Wilk criterion. Quantitative variables in the case of a normal distribution are presented in the form of averages and standard deviation, in case of deviation

from normal – in the form of median and quartiles. Qualitative variables are presented in the form of absolute and relative (%) frequencies. Comparison of qualitative features was carried out using the exact Fisher criterion, quantitative – using the Mann-Whitney criterion. A correlation analysis was performed with the calculation of Spearman's rank correlation coefficient. The differences were considered statistically significant at the $p<0.05$ level.

Research Results and Their Discussion

The clinical characteristics of the examined RA patients are presented in Table. 1. All patients received therapy with nonsteroidal anti–inflammatory drugs; 5 patients received glucocorticosteroids (prednisone from 5 to 30 mg / day); 13 received treatment with methotrexate (at a dose of 7.5 – 15 mg / week).

Table 1. Clinical characteristics of RA patients

Indicator	RA patients (n=25)
Age, years	50±7
BMI, kg/m2	26.4±4.6
waist circumference	84 (77; 90)
waist and hip circumferences	0.82±0.07
Smokers, n	7
Postmenopause, n	16
SAD/DAD, mmHg.	121±13/79±9
Total cholesterol, mmol/l	5.0±1.1
Glucose, mmol/l	5,3±0,8
Duration of RA,	8 years (2; 11)
Morning stiffness, min	90 (30; 120)
Pain according to YOUR,	mm 50 (25; 80)
DAS28	4.5±1.2
Extra-articular manifestations, n	7
Seropositivity, n	17
ESR, mm/h	25 (14; 35)
SRB, mg/l	26 (1.5; 72)
Ongoing therapy: Glucocorticosteroids, n	5
Methotrexate, n (%)	13

The data of the instrumental survey are presented in Table. 2. During the SMAD, an increase in the average daily blood pressure (SAD more than 130 and / or DAD more than 80 mmHg) was detected in 7 out of 25 patients (28%), an insufficient decrease in night blood pressure (less than 10%) – in 12 patients for SAD and in 10 for DAD. According to the literature, an increase in the average daily blood pressure has a prognostic value independent of the level of office blood pressure in the general population. Insufficient reduction of blood pressure at night also worsens the prognosis for cardiovascular events.

In the study of HRV the value of SDNN, the main parameter of autonomic dysfunction, below 100 ms was detected in 13 patients (52%). According to studies conducted in patients with postinfarction cardiosclerosis, a decrease in SDNN <100 ms leads to an increased risk of death from cardiovascular complications. The prognostic value of low HRV in a small group of RA patients was also demonstrated.

Table 2. Data of instrumental examination of RA patients (n=25)

Indicator	Value (M+/-SD or Me [25%, 75%])	Range
Daily blood pressure monitoring		
Average daily SAP, mmHg.	122,6+/-12,0	97-150
Average Daily DAP, mmHg.	75,7+/-8,4	60-94
Average daily SAP, mmHg.	125,8+/-12,7	98-158
Average daily DAP, mmHg.	79,4+/-9,0	62-103
Mid – night SAP, mmHg.	116,3+/-12,7	96-137
Mid – night DAP, mmHg.	68,7+/-8,9	56-86
Daily SAP index, %	10 (3; 14)	-4–17
Daily DAP index, %	15 (7;20)	-5–25
Heart rate variability		
SDNN, мs	96,5 (80,5; 121,0)	68-143
SDANN, мs	80,5 (65,5; 103,5)	53-123
rMSSD, мs	26,5 (21,0–40,5)	12-49
Cardiorespiratory monitoring		
Apnea-hypopnea index	6 (3; 11)	1-30
O2 desaturation index	3.5 (1; 7)	0-25
Desaturation (medium), %	95,5 (93; 97)	76-98
Apnea index	1 (1; 3)	0-8
Hypopnea index	5.0 (1.5; 8.5)	1.0–24.0
Episodes of apnea, n	5.0 (3.5; 19.5)	0-80
Episodes of hypopnea, n	30.0 (11.0; 58.5)	5-191
Echocardiography		
Left atrium size, cm	3,46+/-0,36	2,70–4,10
CSSV, cm	3,10+/-0,41	2,40–4,20
CDS LV size, cm	4,60+/-0,40	3,9–5,7
Interventricular septum cm	0,96+/-0,14	0,70–1,25
rear wall of the LV, cm	0,99+/-0,15	0,70–1,25
myocardial mass index LV g/m	2,7 42,3+/-10,2	19,6–66,2
FV, %	62+/-7	51-74

Obstructive sleep apnea syndrome is an independent factor of cardiovascular and general mortality in the general population. According to A. Holman, OSA is an important pathogenetic link of CVD in RA patients. The "gold standard" of OSA diagnostics is polysomnography, but its implementation is fraught with significant difficulties. For screening of OSA, it is possible to use cardiorespiratory monitoring (studies of air flow and pulse oximetry) performed on an outpatient basis. According to our study, OSA (apnea-hypopnea

index greater than 5) during cardiorespiratory monitoring was detected in 14 out of 25 RA patients (56%). The indicators of cardiorespiratory monitoring are presented in Table 2.

The prevalence of OSA in the population has been studied in several studies and is about 20%. According to two small studies conducted in the USA and Japan, OSA was detected in 45% (n=80) and 53.1% (n=96) of cases, respectively. Thus, the data obtained by us are in good agreement with the literature.

EchoCG data in the examined RA patients are also presented in Table. 2. LV hypertrophy (left ventricular myocardial mass index - LVMI > 47 g/m2) was detected in 8 patients (32%); systolic function was preserved in all patients. The data obtained are consistent with the results of a recent study by R.L. Rudomainer et al., which demonstrated an independent association of RA and increased LV myocardial mass.

The results of the study of populations and subpopulations of peripheral blood lymphocytes, as well as the levels of immunoglobulins are presented in Table. 3. The revealed immunological disorders correspond to the clinical manifestations of RA in the examined patients.

Table 3. Populations, subpopulations of lymphocytes and immunoglobulin levels in RA patients (n=25)

Indicator, % or g/l	Value (Me [25%, 75%])	Range
CD3	70 (63; 78)	18–89
CD4	56 (44; 62)	30–75
CD8	30 (22; 36)	10–67
CD4/CD8	1,7 (1,4; 2,5)	0,9–3,5
CD10	10 (4,5; 19,5)	0–44
CD16	28 (23; 35)	13–46
CD20	36 (30; 47)	5–68
CD25	25 (20; 35)	10–61
CD38	27,5 (24,5; 33,5)	15–67
CD95	40 (28; 46)	13–55
HLA-DR	28 (21; 36)	13–64
IgA	4,5 (3,1; 7,8)	2,0–9,4
IgG	28,3 (21,5; 33,0)	15,8–40,9
IgM	2,8 (2,4; 2,9)	0,8–7,9

The interrelation of instrumental signs of damage to the cardiovascular system and immunological parameters in RA patients was analyzed. Statistically significant correlations of CD4/CD8 index with HRV parameters, end-systolic size and LV ejection fraction were found. The data obtained can be explained by the deterioration of the adaptive capabilities of the heart with an increase in the number of helpers and a decrease in suppressors. The negative relationship of the apoptosis marker (CD95) with the indices of OSA (apnea-hypopnea and O2 desaturation) may be due to a decrease in the readiness of lymphocytes for apoptosis under conditions of intermittent hypoxia characteristic of OSA. Similar data were obtained in the work of L. Dyugovskaya et al. in relation to reduced readiness for neutrophil apoptosis in patients with OSA. A similar dependence of CD95 and LV systolic function parameters (CSR and PV) can also be explained by the effect of intermittent hypoxia on the myocardium. Statistically significant negative correlations of HLA-DR (the number of activated T-

lymphocytes) and average SAD indicators (per day, day and night periods) are probably due to blockade of the lymphocyte receptor apparatus in patients with elevated blood pressure.

Conclusions

1. In RA patients with moderate and high activity, signs of damage to the cardiovascular system are observed (an increase in blood pressure according to daily monitoring in 28% of cases, a decrease in HRV - in 52%, OSA – 56%, LV hypertension – 32%).
2. The revealed correlations with immunological indicators indicate the role of systemic inflammation and apoptosis in the pathogenesis of cardiovascular system damage in RA. Given the preliminary nature of the data obtained, further research in this direction is needed.

Literatura

1. Alisherovna, K. M., Tatlibayevich, Y. S., Toshtemirovna, E. M. M., & Nizamitdinovich, H. S. (2021). Diagnostic Significance Daily Monitoring of Blood Pressure in Young Women (Under 40 Years Old) with Arterial Hypertension. CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES, 2(5), 461-465.
2. Alisherovna, K. M., Toshtemirovna, E. M., Jamshedovna, K. D., & Xudoyberdiyevich, G. X. (2022). ASSESSMENT OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC HEART FAILURE. Web of Scientist: International Scientific Research Journal, 3(5), 551-557.
3. Alisherovna, K. M., & Tatlibayevich, Y. S. (2021). ASSESSMENT OF RISK FACTORS FOR ARTERIAL HYPERTENSION HYPERTENSION IN PREGNANT WOMEN. CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES, 2(3), 214-217.
4. Хусаинова, М. (2021). CHRONIC HEART FAILURE IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS. Журнал кардиореспираторных исследований, 2(4), 67-69.
5. Alisherovna, K. M., & Erkinovna, K. Z. (2022). Assessment of the Immune-Inflammatory Relationship in Patients with Chronic Heart Failure with Rheumatoid Arthritis. CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES, 3(2), 373-377.
6. Erkinovna, K. Z., Davranovna, M. K., Toshtemirovna, E. M. M., & Xudoyberdiyevich, G. X. (2022). CORRECTION OF COMPLICATIONS IN CHRONIC HEART FAILURE DEPENDING ON THE FUNCTIONAL STATE OF THE KIDNEYS. Web of Scientist: International Scientific Research Journal, 3(5), 565-575.
7. Totlibayevich, Y. S. (2022). CIRCADIAN RHYTHM BLOOD PRESSURE IN PATIENTS HEART FAILURE IN RENAL DYSFUNCTION. Web of Scientist: International Scientific Research Journal, 3(5), 582-588.
8. Yarmatov, S. T., & Xusainova, M. A. (2021). BRONXIAL ASTMA MAVJUD BO'LGAN BEMORLARDA GASTROEZOFAGIAL REFLYUKS KASALLIGI DIAGNOSTIKASI VA OLIB BORISH ALGORITMI. Scientific progress, 2(2), 208-213.

9. Jamshedovna, K. D., Alisherovna, K. M., Davranovna, M. K., & Xudoyberdiyevich, G. X. (2022). EPIDEMIOLOGY AND FEATURES OF ESSENTIAL THERAPY HYPERTENSION IN PREGNANT WOMEN. Web of Scientist: International Scientific Research Journal, 3(5), 606-611.
10. Zikriyaevna, S. G., & Muhtorovna, E. M. (2019). The features of the early diagnostics of osteoporosis in patients with rheumatoid arthritis. Достижения науки и образования, (12 (53)), 110-112.