ORIGINAL INVESTIGATIONS

Relationship between pro-inflammatory cytokines and subclinical myocardial dysfunction in patients with rheumatoid arthritis

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Objective: *to investigate the association of pro-inflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor α (TNFα), IL-1 receptor antagonist (IL-1Ra), with subclinical left ventricular (LV) dysfunction in patients with rheumatoid arthritis (RA).*

Material and methods. *The study included 61 patients with RA who met the 2010 ACR/EULAR (American College of Rheumatology / European Alliance of Associations for Rheumatology) criteria. In this group, 80% were women, mean age was 47.8±10.1 years, and the median disease duration before initiation of biologics was 120 [54; 165] months. All patients underwent determination of serum N-terminal pro-brain natriuretic peptide (NT-proBNP), IL-6, TNFα, IL-1Ra levels, and echocardiography with assessment of global longitudinal myocardial deformation (GLSLV) of the LV using speckle-tracking.*

Results and discussion. *In patients with RA, IL-6 and TNFα levels were significantly higher than in controls. In RA patients with subclinical myocardial dysfunction, IL-6 levels were significantly higher than in patients with preserved myocardial function (median 14.7 [0.76; 38.5] and 7.8 [0.11; 17.5] pg/ml, respectively; p<0.05). TNFα and IL-1Ra levels did not differ significantly between these groups. RA patients were divided into four groups. Group 1 included patients with elevation of all three cytokines (n=9), group 2 – of two cytokines (n=19), group 3 – of one cytokine (n=23), and group 4 (n=10) had normal cytokine levels. ESR, DAS28 (Disease Activity Score 28), and CRP levels in groups 1–3 were higher than in group 4. All groups differed significantly in ejection fraction (EF) and LV lateral mitral annular velocity (E'). GLSLV was significantly lower in group 1 than in group 4. IL-6 level correlated with GLSLV (r=-0.4); IL-1Ra level– with EF (r=-0.5), LV E' (r=-0.4), and the ratio of early transmitral flow velocity (E)/E' (r=0.3); TNFα level – with LV E' (r=-0.3), p<0.05 for all comparisons.*

Conclusion. *In RA patients with myocardial dysfunction, IL-6 levels are significantly elevated. Simultaneous elevation of IL-6, IL-1Ra, and TNFα leads to more pronounced impairment of systolic and diastolic myocardial function. Inflammation in RA contributes to the deterioration of cardiac myocardial function.*

Keywords: *rheumatoid arthritis; cytokines; echocardiography; speckle-tracking; myocardial dysfunction.*
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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease associated with high cardiovascular risk [1]. In RA patients, the risk of cardiovascular mortality, including through the development of heart failure (HF), is increased due to accumulation of traditional cardiovascular risk factors (TCRFs), systemic inflammation, and the effects of medications such as glucocorticoids (GCs), non-steroidal anti-inflammatory drugs (NSAIDs) and leflunomide. [2. 3]. Mortality from HF in RA patients is twice as high as in the general population [2]. This raises the issue of early identification of subclinical myocardial dysfunction (SMD), characterized by the absence of HF symptoms and signs at present and in the past, but with the evidence of structural and/or functional cardiac involvement and/or elevated natriuretic peptide levels (NT-proBNP) [4].

Echocardiography, including tissue Doppler imaging, plays an important role in diagnosing SMD by enabling assessment of diastolic dysfunction. Speckle-tracking echocardiography provides information on the left ventricle (LV) global longitudinal strain (GLS) based on the displacement of natural ultrasound markers ("speckles") within the myocardium and can detect early impairment of systolic function.

It is known that local up-regulation of pro-inflammatory cytokines—such as IL-1. IL-6 and TNF-α — in the myocardium is important in HF pathogenesis, giving rise to the "cytokine theory" of HF [5. 6]. Cytokines contribute to LV hypertrophy, accelerated apoptosis, endothelial dysfunction and increased fibroblast activity leading to myocardial fibrosis [6]. RA is associated with systemic elevation of pro-inflammatory cytokines, which may further contribute to HF pathogenesis [7].

Data on potential relationships between pro-inflammatory cytokines and echocardiographic manifestations of SMD in RA are limited. It also remains unclear which inflammatory mediators are involved in the increased risk of HF in RA. Therefore, the objective of this study was to investigate associations between pro-inflammatory cytokines (IL-6, TNF-α and IL-1 receptor antagonist (IL-1Ra)) and SMD in RA patients.

Materials and Methods

The study included 70 patients with RA meeting the 2010 ACR/EULAR criteria, with moderate to high disease activity (DAS28-CRP ≥3.2). Patients were hospitalised to V.A. Nasonova Research Institute of Rheumatology in 2024–2025 due to insufficient efficacy or intolerance of prior conventional disease-modifying

antirheumatic therapy. The study was approved by the local ethics committee (protocol No. 18 dated 10 October 2024). All participants provided written informed consent.

Inclusion criteria: age 18–65 years; no prior biologic therapy or interruption of biologic therapy >1 year before inclusion; signed informed consent.

Control group: 30 individuals without rheumatic or cardiovascular diseases, matched by age and sex.

Clinically manifest HF was found in 9 (13%) RA patients, and these were excluded from analyses. The clinical characteristics of RA patients without HF are presented in Table 1 (n=61). Women predominated (80%), mean age 47.8±10.1 years, median disease duration 120 [54; 165] months. Seventy five percent of patients were seropositive for rheumatoid factor (RF) and 74% for anti-cyclic citrullinated peptide antibodies (anti-CCP). The established stage of RA was present in 79% of patients, and late stage in 18%. Extra-articular manifestations were observed in 41% of patients, rheumatoid nodules in 23%, Sjugren's syndrome in 20%, cutaneous vasculitis in 1.6%.

Traditional cardiovascular risk factors were present in 65% of patients: arterial hypertension in 36%, dyslipidaemia in 41%, family history of cardiovascular disease in 74%, and 11% of patients were current smokers.

At the time of inclusion, 92% received medication: conventional DMARDs 83%, methotrexate 35%, leflunomide 43%, sulfasalazine 24%, hydroxychloroquine 13%, NSAIDs 71%. Median GC dose was 5.0 [5.0; 7.5] mg/day; median duration of GC use 7.0 [0.0; 25.0] months.

All patients were examined by a cardiologist according to the Russian Society of Cardiology recommendations [4]. Echocardiography with tissue Doppler imaging was performed in line with the American Society of Echocardiography recommendations [8–10] using a Vivid S70 scanner (USA) and a 3.5-MHz transducer.

LV systolic function was assessed by biplane Simpson EF and GLS using speckle-tracking (Wall Motion Tracing software). Impaired LV systolic function was defined as GLS < −16%. SMD was diagnosed according to chronic HF guidelines [4], which included NT-proBNP elevation and GLS among diagnostic criteria.

LV diastolic function was assessed as recommended [9]. Early (E) and late (A) transmitral flow velocities and the E/A ratio were measured. Tissue Doppler was used to measure lateral mitral annular early diastolic velocity (E′). The E/E′ ratio was calculated.

Table 1. General characteristics of patients with RA (n=61)

Parameters	Values
Sex, n (%): women/men, n (%)	49 (80)/12(20)
Age, years (mean±SD)	47,8±10,1
Disease duration, months (median [25th; 75th]):	120 [54; 165]
BMI, kg/m^2 (median [25th; 75th])	25,3 [21,3; 29,5]
RF positive, n (%)	46 (75)
Anti-CCP positive, n (%)	45 (74)
Clinical stage, n (%):	
early	2 (3)
established	48 (79)
late	11 (18)
Radiographic stage, n (%):	
I	4 (6)
II	35 (58)
III	11 (18)
IV	11 (18)
DAS28, M±SD	5,9±1,2
Activity by DAS28, n (%):	
moderate	12 (20)
high	49 (80)
CDAI, (median [25th; 75th])	31 [24; 39]
Activity by CDAI, n (%):	
moderate	12 (20)
high	49 (80)
SDAI, (median [25th; 75th])	32,6 [25,5; 40,3]
Activity by CDAI, n (%):	
moderate	15 (25)
high	46 (75)
CRP, mg/L (median [25th; 75th])	12,5 [5,4; 28,2]
ESR, mm/h (median [25th; 75th])	36 [19; 57]
HAQ (median [25th; 75th])	1,0 [0,5; 1,8]
Extra-articular manifestations, n (%):	25 (41)
rheumatoid nodules	14 (23)
Sjögren's syndrome	12 (20)
cutaneous vasculitis	1 (1,6)
Traditional cardiovascular risk factors, n (%):	40 (65)
hypertension	22 (36)
current smoking	7 (11)
dyslipidaemia	25 (41)
family history of CVD	45 (74)
sedentary lifestyle	28 (46)

Note. BMI—body mass index; CDAI—Clinical Disease Activity Index; SDAI—Simplified Disease Activity Index; HAQ—Health Assessment Questionnaire.

LV diastolic dysfunction was diagnosed based on: E′<10 cm/s, E/E′>14. left atrial end-systolic volume index >34 mL/mI and peak tricuspid regurgitation velocity (TR V) >2.8 m/s.

Serum IL-6 and TNF-α were measured by ELISA using "Interleukin-6-ELISA-BEST" and "Alpha-TNF-ELISA-BEST" kits (Vector-Best, Russia). IL-1Ra was measured by ELISA using SEA223Hu (Cloud-Clone Corp., USA). In serum analyses of

Table 2. Cytokine levels in patients with RA and in controls, pg/ml, Me [25th; 75th percentiles]

Cytokines	RA (n=61)	Control (n=30)	p
IL-1Ra	0,001 [0,001; 43,95]	0,014 [0,001; 1,62]	>0,05
IL-6	14,7 [0,17; 28,5]	0,001 [0,001; 0,0045]	<0,05
TNF-α	0,12 [0,007; 28,36]	0,006 [0,001; 0,0045]	<0,05

Table 3. Characteristics of patients with RA depending on cytokine levels

Parametres	Cytokines elevated			
	three (n=9)	two (n=19)	one (n=23)	normal (n=10)
Age, years M±SD	48±11,2	46,1±10,8	41,7±10,9	45,5±4,5
TCRFs				
BMI, kg/m², M±SD	28,2±5,2	24,7±5,09	24,7±5,07	23,7±5,5
Hypertension, n (%)	4 (44)	4 (19)	5 (27)	2 (20)
Smoking, n (%)	0 (0)	2 (9)	3 (16)	1 (10)
Total cholesterol, mmol/l, M±SD	5,5±1,5	4,9±1,1	5,3±1,3	5,4±1,3
Triglycerides, mmol/l, M±SD	1,8±0,4	1,3±0,5	1,2±0,4	1,1±0,3
HDL-C; mmol/l, M±SD	1,0±0,2*	1,2±0,3	1,4±0,4	1,5±0,4
LDL-C, mmol/l, M±SD	3,6±1,8	3,1±1,4	2,9±0,9	3,4±1,5
Clinical/laboratory				
DAS28, M±SD	5,7±0,8*	5,7±0,8*	5,9±0,7*	4,6±0,6
CDAI, M±SD	28,5±7,6	32,9±9,9	31,1±10,8	27,8±10,1
SDAI, M±SD	28,1±7,2	34,2±10,2	33,9±11,3	27,0±9,2
CRP, mg/L M±SD	27,7±17,2*	13,3±9,1*	26,0±19,8*	2,8±0,92
ESR, mm/h, M±SD	43,9±16,5*	29,8±14,6*	44,2±20,8*	10,1±3,5
HAQ, M±SD	0,79±0,4	1,11±0,65	1,0±0,62	0,71±0,4
RF, M±SD	509,7±383,5	174±31,7	78±77,0	178,9±4,5
Anti-CCP, M±SD	177,1±104,6	130±116,6	105,5±98,8	145,3±107,2
NT-proBNP, pg/ml, (median [25th; 75th])	86,0 [25,7; 186,2]*	58,1 [25,5; 98]	81,0 [41,9; 122,0]	37,0 [23,2; 42,1]
Echocardiography				
EF LV, %, (median [25th; 75th])	60 [55; 63]*	67 [60; 70]*	63 [59; 66]*	71 [70; 74]
LA end-systolic volume index, ml/m², (median [25th; 75th])	23,9 [21,5; 31,7]	23,3 [17.4; 28.3]	22,4 [20,1; 28]	26,8 [21,4: 27,2]
TR V, m/s (median [25th; 75th])	2,55 [2,4; 2,6]	2,42 [2,37; 2,52]	2,31 [2,24; 2,46]	2,40 [1,8; 2,42]
E/A LV, (median [25th; 75th])	0,95 [0,69; 1,2]	1,35 [1,15; 1,52]	1,24 [1,12; 1,63]	1,42 [1,17; 1,42]
E' LV, m/s, (median [25th; 75th])	0,08 [0,07; 0,09]	0,09 [0,08; 0,10]	0,12 [0,09; 0,13]	0,12 [0,11; 0,12]
E/E' LV, (median [25th; 75th])	9,5 [7,8; 10,8]	8,4 [6,7; 9,5]	7,8 [6,9; 8,8]	7,4 [7,36; 7,5]
LV GLS %, (median [25th; 75th])	-16,0 [-12,9; -18,9]*	-19,7 [-17,4; -23,9]	-18,9 [-17,6; -20,6]	-20,8 [-18,9; -21,6]
impaired GLS, n (%)	6 (85)*	4 (17)	5 (26)	1 (11)

Note. LDL-C — low-density lipoprotein cholesterol; p<0.05 vs group 4.

30 healthy donors, the upper limit of the norm (99th percentile) was 2.66 pg/mL for IL-1Ra, 0.02 pg/mL for IL-6. and 0.01 pg/mL for TNF-α.

NT-proBNP was measured by electrochemiluminescence using Elecsys proBNP II (Roche Diagnostics, Switzerland). The reference range for NT-proBNP is <125 pg/mL (manufacturer's instructions).

Statistical analyses were performed using SPSS Statistics 14.0 (IBM, USA). The Mann–Whitney U test and Student's t-test were used for two-group comparisons. Data are presented as median with interquartile range (Me [25th; 75th percentiles]). Correlations were assessed using Spearman's method. Categorical data were compared using χ^2 or Fisher's exact test. Comparisons among more than two groups were made using Kruskal–Wallis ANOVA (H test). Differences were considered significant at $p<0.05$.

Results

Among all RA patients (n=70), SMD was detected in 28 (40%), myocardial function was preserved in 33 (47%), and clinically manifest HF was present in 9 patients (13%).

In RA patients, IL-6 and TNF-α levels were significantly higher than in controls, whereas IL-1Ra did not differ significantly (Table 2). Elevated IL-1Ra was found in 31% of RA patients, IL-6 in 83%, and TNF-α in 57%.

In RA patients with SMD, IL-6 concentrations were higher than in those with preserved LV function (median 14.7 [0.76; 38.5] vs 7.8 [0.11; 17.5] pg/mL; $p<0.05$). TNF-α (0.06 [0.007; 3.57] vs 0.06 [0.007; 1.3] pg/mL) and IL-1Ra (0.001 [0.007; 58.2] vs 0.001 [0.001; 0.81] pg/mL) did not differ significantly between these groups.

RA patients without HF (n=61) were divided into four groups based on cytokine elevations: group 1—three cytokines elevated (n=9), group 2—two cytokines (n=19), group 3—one cytokine (n=23), and group 4—normal cytokine levels (n=10). Groups were compared by age, TCRFs, clinical and laboratory parameters, and echocardiographic indices of systolic and diastolic function including GLS (Table 3).

Groups were comparable in age, TCRFs, RF, anti-CCP, CDAI, SDAI and HAQ. However, DAS28, ESR and CRP were significantly higher in groups 1–3 than in group 4. A progressive decrease in triglycerides from group 1 to group 4 was observed but was not significant. Group 1 had significantly lower HDL cholesterol and significantly higher NT-proBNP than group 4.

All four groups were comparable in left atrial end-systolic volume index, TR V and E/E′. Groups differed significantly in EF and E′. GLS was significantly lower in group 1 than in group 4.

Correlation analysis showed: IL-6 correlated with GLS (r=−0.4) and peak systolic myocardial velocity S′ (r=−0.3); IL-1Ra correlated with EF (r=−0.5), TR V (r=0.3), E′ (r=−0.4) and E/E′ (r=0.3); TNF-α correlated with E′ (r=−0.3); $p<0.05$ for all.

A ROC analysis was performed to determine the GLS threshold associated with elevation of all three cytokines. GLS ≤ −18% was associated with increased levels of all cytokines (AUC=0.71, 95% CI 0.43–0.98; $p<0.05$), with sensitivity 67% and specificity 74%.

Discussion

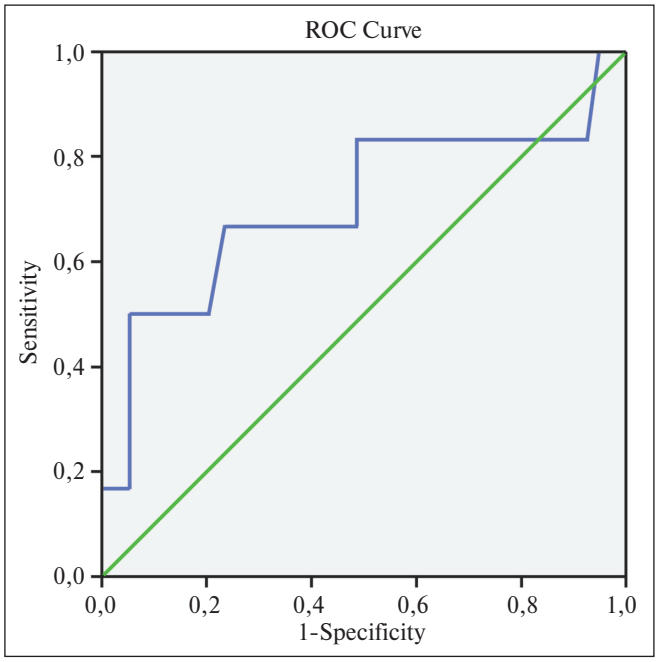
This study is the first to assess IL-6, IL-1Ra and TNF-α levels in RA patients with SMD consistent with the pre-HF stage as defined by current recommendations [4]. The novelty lies in the combined use of speckle-tracking echocardiography for GLS assessment and NT-proBNP measurement when evaluating SMD.

IL-6 and TNF-α were significantly higher in RA patients than in controls, consistent with earlier reports of elevated cytokines in RA [11]. However, in RA patients with SMD, only IL-6 was significantly higher than in those without myocardial dysfunction. These findings are consistent with the data of Liang et al. [12], who reported an association between subclinical LV diastolic dysfunction in RA and increased IL-6, but not TNF-α. We also observed a negative association between IL-6 and echocardiographic indices reflecting systolic function.

IL-6 signaling pathways are known to affect myocardial function. Elevated IL-6 promotes LV hypertrophy by aggravating oxidative stress-related mitochondrial dysfunction, increasing expression of mitophagy-associated proteins and enhancing cardiomyocyte apoptosis, which leads to remodeling, reduced LV contractility and development/progression of HF [13]. In the present study, a negative association between TNF-α and E′ (a marker of diastolic function) was also detected. Persistently elevated TNF-α may induce apoptosis and disrupt the balance between matrix metalloproteinases and their tissue inhibitors, promoting remodeling, LV hypertrophy and diastolic dysfunction [12].

We measured IL-1Ra as a surrogate marker of IL-1β activity; IL-1Ra is considered a more sensitive indicator of immune activation [14]. Increased circulating IL-1Ra predicts atherosclerotic outcomes (coronary artery disease, myocardial infarction) [14. 15] and is also associated with deterioration of myocardial function [15]. High IL-1Ra levels may worsen HF outcomes [14]. This is associated with impaired LV systolic function due to reduced β-adrenergic responsiveness of calcium channels [16] and with the development of diastolic dysfunction. In our study, IL-1Ra showed negative correlations with EF and diastolic function parameters.

Most prior works have focused on single cytokines; fewer studies address cytokine combinations. Recent publications emphasize the prognostic value of combining cardiovascular biomarkers and cytokines [17. 18]. Consistent with this, RA patients with si-



Association of increased cytokine levels with GLSLV

multaneous elevation of all three cytokines had worse GLS, EF and diastolic indices (E/A, E′), as well as higher NT-proBNP, than patients with normal cytokine levels. RA patients with elevated cytokines expectedly have higher disease activity (DAS28, CRP, ESR). This fact supports the adverse impact of systemic inflammation on myocardial function accompanied by increased NT-proBNP. ROC analysis indicated that GLS < −18% is associated with elevation of IL-6, IL-1Ra and TNF-α.

Thus, elevation of all three cytokines—reflecting greater inflammatory activity—was associated with more pronounced myocardial involvement. Previously, we showed that combination therapy with methotrexate and biologics improved myocardial function in early RA compared with methotrexate monotherapy [19].

In this study, groups did not differ significantly in traditional cardiovascular risk factors. Only HDL cholesterol was significantly lower in patients with elevation of all three cytokines compared with those with normal cytokine levels, consistent with inflammation-related changes in lipid profile ("lipid paradox") involving reduced HDL and an increased atherogenic index [20].

Conclusion

RA patients with subclinical myocardial dysfunction have significantly higher IL-6 levels than those without myocardial dysfunction. Simultaneous elevation of IL-6, IL-1Ra and TNF-α is associated with more pronounced impairment of both systolic and diastolic LV function, without affecting the prevalence of traditional cardiovascular risk factors. Inflammation in RA contributes to deterioration of myocardial function.

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