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INFLAMMATORY-IMMUNE AND METABOLIC PREDICTORS OF STRUCTURAL AND FUNCTIONAL CHANGES IN THE MYOCARDIUM AND DAILY PRESSURE PROFILE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Cardiovascular diseases continue to occupy leading positions in the structure of general mortality and disability of the population, while arterial hypertension is considered one of the main modifiable risk factors for the development of adverse cardiovascular outcomes [5, 15]. Modern understanding of the pathogenesis of arterial hypertension extends beyond isolated hemodynamic disorders and increasingly emphasizes the role of systemic inflammation, immune dysfunction, and metabolic disorders in the formation of target organ damage, including the heart [2].

Rheumatoid arthritis is a model of a chronic systemic inflammatory disease accompanied by persistent immune activation and pronounced extra-articular manifestations. According to domestic and foreign authors, the presence of rheumatoid arthritis is associated with a significant increase in cardiovascular risk comparable to that of type 2 diabetes mellitus [3, 6, 11]. Meta-analytical studies indicate an increase in cardiovascular mortality and the frequency of fatal complications in patients with rheumatoid arthritis, which cannot be explained solely by traditional risk factors [7, 13].

One of the main pathogenetic mechanisms of cardiovascular disorders in rheumatoid arthritis is chronic inflammation of low intensity. C-reactive protein is considered a universal marker of systemic inflammation and an independent predictor of cardiovascular events, reflecting the activation of the innate immune response [14]. Rheumatoid factor, in turn, characterizes the autoimmune component of the disease and, according to several studies, is associated with more pronounced cardiovascular system damage and an unfavorable prognosis [3, 4, 11].

Dyslipidemia, which occurs against a background of inflammatory activity, plays an important role in the formation of cardiovascular complications in patients with rheumatoid arthritis. It has been shown that inflammation contributes to

atherogenic changes in the lipid spectrum, the formation of endothelial dysfunction, and accelerated myocardial remodeling, even in the absence of pronounced traditional lipid disorders [9]. The combination of arterial hypertension, systemic inflammation, and dyslipidemia forms an unfavorable metabolic-inflammatory background that contributes to the progression of structural and functional changes in the myocardium.

Echocardiography is the main non-invasive method for assessing the structural and functional state of the myocardium and allows for the detection of early signs of pathological remodeling of the left ventricle, which have independent prognostic significance [10]. It has been established that myocardial hypertrophy and diastolic dysfunction are significantly more frequently detected in patients with systemic inflammatory diseases, including rheumatoid arthritis, especially with concomitant arterial hypertension [2, 6].

Daily blood pressure monitoring allows for the assessment of not only blood pressure levels but also its circadian profile, variability, and pressure load, disorders of which are associated with increased risk of cardiovascular complications and progressive myocardial remodeling [1, 12]. According to Kario K. (2020), unfavorable types of daily blood pressure profile, particularly non-dipper and night-peaker, are more commonly detected in patients with chronic inflammation and autoimmune pathology [8].

Despite the existence of studies devoted to individual aspects of cardiovascular risk in rheumatoid arthritis, a comprehensive assessment of the relationship between inflammatory-immune markers (C-reactive protein, rheumatoid factor), lipid spectrum indicators with parameters of the structural and functional state of the myocardium, and the daily blood pressure profile in patients with arterial hypertension remains insufficiently studied. Comparative data involving patients with arterial hypertension without autoimmune pathology are especially limited, which emphasizes the relevance of conducting this study.

The purpose of the study: to assess the relationship between inflammatory-immune and metabolic markers with indicators of the structural and functional state of the myocardium and the daily blood pressure profile in patients with arterial hypertension against the background of rheumatoid arthritis.

Materials and Research Methods:

The research was conducted as a comparative observation study. The study included 80 patients with arterial hypertension aged 40 to 50 years. All patients were divided into two comparable age and sex groups. The first group consisted of 40 patients with rheumatoid arthritis and arterial hypertension. The second

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comparison group included 40 patients with rheumatoid arthritis without arterial hypertension.

Analysis of the basic clinical and demographic characteristics of the examined patients showed a high degree of comparability between the main group and the comparison group. The average age of patients in the main group was 45.3±2.8 years, in the comparison group - 44.9±3.1 years, the differences did not reach statistical significance (p>0.05), which made it possible to exclude the influence of the age factor on the studied indicators (Table. 1).

The gender structure of the sample in both groups was comparable: in the main group, the proportion of men was 45.0% (n=18), women - 55.0% (n=22), while in the comparison group - 42.5% (n=17) and 57.5% (n=23) respectively (p>0.05). Body mass index also did not differ between the groups and was 28.1±3.4 kg/m2 in patients with arterial hypertension against the background of rheumatoid arthritis and 27.6±3.1 kg/m2 in patients with isolated arterial hypertension (p>0.05).

Table 1

Basic clinical and demographic characteristics of the examined patients

Indicator	Main group, n=40	Comparison group, n=40	p.
Age, years	45.3±2.8	44.9±3.1	>0.05
Men / Women, n (%)	18 (45%) / 22 (55%)	17 (42.5%) / 23 (57.5%)	>0.05
Body mass index, kg/m2	28.1±3.4	27.6±3.1	>0.05
Duration of AH, years	6.2±2.1	5.9±2.4	>0.05
Degree of AH I n (%)	12.	14.	>0.05
Degree of AH II n (%)	18.	17.	>0.05
Degree of hypertension III n (%)	10.	9.	>0.05
Smoking, n (%)	11 (27.5%)	10 (25.0%)	>0.05
Weighted heredity for cardiovascular disease, n (%)	16 (40.0%)	15 (37.5%)	>0.05
Type 2 diabetes mellitus, n (%)	6 (15.0%)	5 (12.5%)	>0.05
Dylipidemia, n (%)	24 (60.0%)	22 (55.0%)	>0.05
Antihypertensive therapy, n (%)			
- IAPF / BRA	30 (75.0%)	31 (77.5%)	>0.05
- β-blockers	18 (45.0%)	17 (42.5%)	>0.05
- Calcium antagonists	14 (35.0%)	13 (32.5%)	>0.05
- Diuretics	20 (50.0%)	19 (47.5%)	>0.05

The average duration of arterial hypertension in the main group was 6.2±2.1 years, in the comparison group - 5.9±2.4 years, without significant intergroup differences (p>0.05). The distribution of patients by the degree of arterial

hypertension was also comparable: in the main group, I, II, and III degrees of arterial hypertension were registered in 30.0%, 45.0%, and 25.0% of patients, respectively, while in the comparison group - in 35.0%, 42.5%, and 22.5% of patients ($p>0.05$).

The frequency of smoking in the main group was 27.5% (n=11), in the comparison group - 25.0% (n=10), and a complicated heredity for cardiovascular diseases was noted in 40.0% and 37.5% of patients, respectively ($p>0.05$). Type 2 diabetes mellitus was detected in 15.0% of patients in the main group and in 12.5% of patients in the comparison group, the differences were also not statistically significant. Dyslipidemia was diagnosed in 60.0% of patients with combined arterial hypertension and rheumatoid arthritis, and in 55.0% of patients with isolated arterial hypertension ($p>0.05$).

Analysis of antihypertensive therapy showed comparable use of the main classes of drugs. ACE inhibitors or angiotensin II receptor blockers were administered to 75.0% of patients in the main group and 77.5% in the comparison group, β-blockers to 45.0% and 42.5%, calcium antagonists to 35.0% and 32.5%, and diuretics to 50.0% and 47.5% of patients, respectively ($p>0.05$).

The diagnosis of arterial hypertension was made in accordance with the recommendations of the European Society of Cardiologists and the European Society for Arterial Hypertension. The diagnosis of rheumatoid arthritis was confirmed based on clinical, laboratory, and instrumental criteria in accordance with the current ACR/EULAR classification criteria. The study included patients with a confirmed diagnosis of I-III-degree arterial hypertension. Exclusion criteria were secondary forms of arterial hypertension, ischemic heart disease in the instability stage, a history of myocardial infarction or stroke within the last 6 months, chronic heart failure of the III-IV functional class, diabetes mellitus with decompensation, chronic kidney diseases of the IV-V stages, acute inflammatory and infectious diseases, as well as other systemic autoimmune diseases.

All patients underwent a comprehensive clinical, laboratory, and instrumental examination. Laboratory evaluation included determining the level of C-reactive protein as a marker of systemic inflammation, rheumatoid factor as an indicator of autoimmune activation, as well as blood lipid profile indicators: total cholesterol, low- and high-density lipoproteins, triglycerides, and the atherogenicity index. Venous blood collection was performed on an empty stomach in the morning hours using standard methods.

The structural and functional state of the myocardium was assessed using echocardiography using an expert-class ultrasound device. During the study, the linear dimensions of the left ventricle, the thickness of the interventricular septum

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and the posterior wall of the left ventricle were determined, myocardial mass and myocardial mass index of the left ventricle, relative wall thickness, left ventricular ejection fraction, as well as the main indicators of diastolic function were calculated. The left ventricular geometry type was classified according to generally accepted echocardiographic criteria.

Daily blood pressure monitoring was carried out using an automated monitoring system. The average daily, daytime, and nighttime values of systolic and diastolic blood pressure, blood pressure variability, pressure load index, and the degree of nighttime blood pressure decline were analyzed, with subsequent classification of the daily profile into dipper, non-dipper, over-dipper, and night-peaker.

Statistical processing of data was carried out using standard statistical analysis packages. Quantitative indicators are presented as an average and standard deviation or as a median and interquartile range depending on the nature of the distribution. Parametric and non-parametric methods were used for intergroup comparison. The relationship between laboratory parameters, echocardiography parameters, and daily blood pressure monitoring was assessed using correlation analysis. Multifactorial regression analysis was used to identify independent predictors of structural and functional changes in the myocardium. Differences were considered statistically significant at $p<0.05$.

Research results. Analysis of inflammatory-immune and metabolic indicators revealed significant differences between the examined groups. (table. 2)

Table 2

Inflammatory-immune and metabolic indicators in the examined patients

Indicator	Main group, n=40	Comparison group, n=40	p.
C-reactive protein, mg/l	9.6±2.4	3.8±1.6	<0.001
Rheumatoid factor, IU/ml	84.2±26.5	11.3±4.7	<0.001
Total cholesterol, mmol/l	6.1±0.9	5.4±0.8	<0.05
LDL, mmol/l	3.9±0.7	3.2±0.6	<0.05
HDL, mmol/l	1.02±0.18	1.24±0.21	<0.05
Triglycerides, mmol/l	2.1±0.5	1.7±0.4	<0.05
Atherogenicity index	4.9±1.2	3.4±0.9	<0.01

In patients with arterial hypertension against a background of rheumatoid arthritis, the level of C-reactive protein was significantly higher and amounted to 9.6±2.4 mg/l, while in the comparison group, this indicator was 3.8±1.6 mg/l ($p<0.001$), which indicated the presence of chronic systemic inflammation in patients of the main group.

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The concentration of the rheumatoid factor in the main group reached 84.2±26.5 IU/ml, which was several times higher than the values of patients with isolated arterial hypertension (11.3±4.7 IU/ml, p<0.001), confirming pronounced autoimmune activation in patients with rheumatoid arthritis.

Correlation between cardiovascular system indicators and markers of inflammatory activity

Indicator SSS	Replenishment marker	Correlation method analysis	Coefficient correlations (r)	P.
LV EF	C-reactive protein	Spirman	-0.45	<0.05
LV EF	Interleukin-6	Spirman	-0.57	<0.01
LV myocardial mass index	C-reactive protein	Pearson	+0.52	<0.01
Systolic BP	Leukocytes	Pearson	+0.38	<0.05
Diastolic BP	Neutrophil-lymphocyte ratio	Spirman	+0.41	<0.05

FV- emission fraction

Left ventricle

BP- blood pressure

Lipid spectrum analysis in patients of the main group revealed more pronounced atherogenic changes. Thus, the level of total cholesterol was 6.1±0.9 mmol/l versus 5.4±0.8 mmol/l in the comparison group (p<0.05), and the concentration of low-density lipoproteins was 3.9±0.7 mmol/l versus 3.2±0.6 mmol/l, respectively (p<0.05). Simultaneously, in patients with combined arterial hypertension and rheumatoid arthritis, a decrease in the level of high-density lipoproteins to 1.02±0.18 mmol/l was noted, while in the comparison group, this indicator was 1.24±0.21 mmol/l (p<0.05).

Triglyceride levels in the main group were significantly higher (2.1±0.5 mmol/l) compared to the group of patients without autoimmune pathology (1.7±0.4 mmol/l, p<0.05). As a result of the combined changes in the lipid spectrum, the atherogenicity index in patients of the main group reached 4.9±1.2 and significantly exceeded the similar indicator of the comparison group (3.4±0.9, p<0.01).

Thus, the obtained data indicate the formation of a pronounced inflammatory-immune and atherogenic metabolic profile in patients with arterial hypertension against the background of rheumatoid arthritis, which can be considered one of the

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key factors of adverse structural and functional remodeling of the myocardium and daily blood pressure profile disorders.

Analysis of daily blood pressure monitoring data revealed more pronounced daily blood pressure profile disorders in patients with arterial hypertension with rheumatoid arthritis (Table. 4).

Table 4

Daily blood pressure monitoring indicators in the examined patients

Indicator	Main group, n=40	Comparison group, n=40	p.
САДср, mm Hg.	138.6±9.8	132.4±8.6	<0.05
DADsr, mm Hg.	86.9±6.7	83.2±6.1	<0.05
SDD, mm Hg.	142.8±10.4	136.1±9.2	<0.05
DADdn, mm Hg.	89.4±7.1	85.6±6.4	<0.05
SADn, mm Hg.	131.2±9.6	121.8±8.7	<0.01
DADN, mm Hg.	80.1±6.3	73.9±5.8	<0.01
SBP variability, mm Hg.	16.8±3.2	13.9±2.8	<0.01
DAB variability, mm Hg.	13.6±2.7	11.2±2.4	<0.01
SAD load index, %	38.5±9.6	27.8±8.4	<0.01
DAD load index, %	32.4±8.7	23.6±7.9	<0.01
Nighttime decrease in SBP, %	7.9±3.6	12.4±4.1	<0.001
Types of daily blood pressure profile, n (%)			
- dipper	14 (35.0%)	25 (62.5%)	<0.05
- non-dipper	20 (50.0%)	13 (32.5%)	<0.05
- night-peaker	6 (15.0%)	2 (5.0%)	<0.05

SADn - systolic blood pressure at night

DADn - diastolic blood pressure at night

DADdn - diastolic blood pressure (day)

САДср - average blood pressure (average hemodynamic pressure)

In the main group, the average daily values of systolic and diastolic blood pressure were significantly higher and amounted to 138.6±9.8 mm Hg and 86.9±6.7 mm Hg, while in the comparison group - 132.4±8.6 mm Hg and 83.2±6.1 mm Hg, respectively ($p<0.05$).

The most pronounced differences were revealed in the night period. Thus, the nighttime values of systolic blood pressure in patients of the main group reached 131.2±9.6 mm Hg, which significantly exceeded the similar indicator of the comparison group (121.8±8.7 mm Hg, $p<0.01$). A similar trend was observed for nocturnal diastolic pressure (80.1±6.3 mm Hg versus 73.9±5.8 mm Hg, $p<0.01$), which indicated a disruption in the physiological nocturnal decrease in blood pressure in patients with rheumatoid arthritis.

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The variability of arterial pressure in patients of the main group was significantly higher: the variability of systolic pressure was 16.8±3.2 mm Hg, diastolic - 13.6±2.7 mm Hg, while in the comparison group, the corresponding indicators did not exceed 13.9±2.8 mm Hg and 11.2±2.4 mm Hg ($p<0.01$). The pressure load index was also significantly higher in patients with combined arterial hypertension and rheumatoid arthritis, indicating a more pronounced chronic effect of elevated arterial pressure on target organs.

The degree of nighttime systolic blood pressure decrease in the main group was significantly lower and amounted to 7.9±3.6%, while in patients with isolated arterial hypertension, this indicator reached 12.4±4.1% ($p<0.001$). As a result of analyzing the types of daily blood pressure profile, it was established that the physiological dipper-type was significantly more common in the comparison group (62.5% versus 35.0%, $p<0.05$), while in patients of the main group, unfavorable profile types prevailed, primarily non-dipper (50.0% versus 32.5%, $p<0.05$) and night-peaker (15.0% versus 5.0%, $p<0.05$).

Thus, the results of daily blood pressure monitoring indicate more pronounced disorders of circadian regulation, increased variability, and pressure load in patients with arterial hypertension against the background of rheumatoid arthritis, which, in combination with the identified inflammatory-immune and echocardiographic changes, emphasizes a high cardiovascular risk for this category of patients.

The correlation analysis revealed moderate and pronounced positive relationships between inflammatory-immune and metabolic markers and indicators of the structural and functional state of the myocardium, as well as the daily blood pressure profile. The most close correlation with the left ventricular myocardial mass index was established for the rheumatoid factor ($r=0.61$; $p<0.001$) and the level of C-reactive protein ($r=0.58$; $p<0.001$), which indicates a significant role of immune-inflammatory activity in the formation of myocardial hypertrophy (Table. 5).

Table 5

Correlations of inflammatory-immune and metabolic markers with myocardial remodeling indicators and daily blood pressure profile

Indicator	LVMI, g/m2	Non-dipper (r)
C-reactive protein	r=0.58; p<0.001.	r=0.46; p<0.01.
Rheumatoid factor	r=0.61; p<0.001.	r=0.49; p<0.01.
Atherogenicity index	r=0.47; p<0.01.	r=0.44; p<0.01.

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The presence of an unfavorable non-dipper-type daily blood pressure profile demonstrated a significant positive correlation with the level of the rheumatoid factor (r=0.49; p<0.01), C-reactive protein (r=0.46; p<0.01), and the atherogenicity index (r=0.44; p<0.01), which emphasizes the contribution of inflammatory-immune and metabolic factors to the circulatory regulation of blood pressure.

Multifactorial logistic regression analysis showed that the level of C-reactive protein, rheumatoid factor, and atherogenicity index were independent predictors of left ventricular hypertrophy formation. Thus, an increase in the concentration of C-reactive protein was associated with a 1.38-fold increase in the likelihood of myocardial hypertrophy (95% CI 1.14-1.68; p=0.001), while an increase in the level of the rheumatoid factor was 1.47 times (95% CI 1.20-1.80; p<0.001). The atherogenicity index also maintained independent prognostic significance (OR 1.29; p=0.009).

Similar patterns were identified in relation to the unfavorable non-dipper-type daily blood pressure profile, indicating the universal role of inflammatory-immune and metabolic factors in the formation of both structural changes in the myocardium and circulatory blood pressure disorders. Age and body mass index did not have a statistically significant effect in the presented models.

Table 6

Multifactorial regression analysis of myocardial remodeling predictors and adverse daily blood pressure profile

Variable	LVH (according to LVMI)		Non-dipper	
	OR (95% CI)	p.	OR (95% CI)	p.
C-reactive protein, mg/l	1.38 (1.14-1.68)	0.001	1.42 (1.15-1.76)	0.002
Rheumatoid factor, IU/ml	1.47 (1.20-1.80)	<0.001	1.53 (1.21-1.94)	<0.001
Atherogenicity index	1.29 (1.06-1.57)	0.009	1.31 (1.08-1.59).	0.006
Age, years	1.06 (0.98-1.15).	>0.05	1.07 (0.98-1.17).	>0.05
Body mass index, kg/m2	1.08 (0.99-1.18)	>0.05	1.09 (0.99-1.20)	>0.05

Note. Left ventricular hypertrophy was diagnosed when LVMI exceeded the threshold values according to echocardiographic recommendations. OR - odds ratio; CI - 95% confidence interval. The model includes age and body mass index as potential mixing factors.

The conducted ROC analysis showed high diagnostic and prognostic significance of inflammatory-immune and metabolic markers in the detection of left ventricular hypertrophy in patients with arterial hypertension (Table. 7).

Table 7

ROC analysis of inflammatory-immune and metabolic markers in predicting left ventricular hypertrophy

Indicator	Threshold value	AUC	95% CI	Sensitivity, %	Specificity, %	p.
CRP, mg/l	≥ 6.5	0.81	0.72-0.90	78.4	75.0	<0.001
RF, IU/ml	≥ 48.0	0.84	0.76-0.92	81.6	77.3	<0.001
AA	≥ 4.0	0.76	0.66-0.86	72.1	70.5	0.002
CRP + RF + IA	-	0.89	0.82-0.96	86.8	83.3	<0.001

Rheumatoid factor had the greatest individual prognostic value, for which the area under the ROC curve was AUC = 0.84 (95% CI 0.76-0.92; p<0.001), with a threshold value of ≥48.0 IU/ml, providing sensitivity of 81.6% and specificity of 77.3%.

C-reactive protein also demonstrated high diagnostic effectiveness (AUC = 0.81; 95% CI 0.72-0.90; p<0.001). At a threshold level of ≥6.5 mg/l, the sensitivity of the method was 78.4%, and the specificity was 75.0%, which confirms the significant role of systemic inflammation in the formation of myocardial hypertrophy.

The atherogenicity index was characterized by a moderate prognostic ability (AUC = 0.76; 95% CI 0.66-0.86; p=0.002), however, when used as part of the combined model, the diagnostic accuracy increased significantly. Thus, the integral model, including C-reactive protein, rheumatoid factor, and atherogenicity index, provided AUC = 0.89 (95% CI 0.82-0.96; p<0.001), which corresponded to high prognostic effectiveness, with a sensitivity of 86.8% and a specificity of 83.3%.

Thus, the results of ROC analysis confirm that inflammatory-immune and metabolic markers, especially in the combined model, have high diagnostic value for early detection of left ventricular hypertrophy in patients with arterial hypertension against the background of rheumatoid arthritis.

Conclusions:

1. In patients with arterial hypertension with rheumatoid arthritis, the formation of a pronounced inflammatory-immune and atherogenic metabolic profile was revealed, characterized by a significant increase in the level of C-reactive protein, rheumatoid factor, and atherogenicity index, which is accompanied by more pronounced structural and functional changes in the myocardium, primarily left ventricular hypertrophy and impaired diastolic function.

2. Disorders of the daily blood pressure profile in patients with combined arterial hypertension and rheumatoid arthritis are characterized by a decrease in the degree of nighttime blood pressure decrease, increased variability, and the

predominance of unfavorable non-dipper and night-peaker types, which are reliably associated with the level of inflammatory-immune and metabolic markers.

3. C-reactive protein, rheumatoid factor, and atherogenicity index are independent predictors of left ventricular hypertrophy and adverse daily blood pressure profile, and their combined use has high prognostic significance, justifying the inclusion of these indicators in the algorithms for early stratification of cardiovascular risk in patients with rheumatoid arthritis and arterial hypertension.

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Abstract

Goal. Evaluate the relationship between inflammatory-immune and metabolic markers and indicators of the structural and functional state of the myocardium and the daily blood pressure profile in patients with arterial hypertension against the background of rheumatoid arthritis.

Materials and methods. A comparative observation study included 80 patients aged 40-50 with arterial hypertension, of which 40 patients had concomitant rheumatoid arthritis and 40 had arterial hypertension without autoimmune pathology. All patients underwent a comprehensive examination, including the determination of C-reactive protein levels, rheumatoid factor, and lipid profile indicators, echocardiographic examination, and daily blood pressure monitoring. Correlation, multi-factor logistics, and ROC analysis methods were used.

Results. In patients with rheumatoid arthritis, higher levels of C-reactive protein, rheumatoid factor, and atherogenicity index were found, associated with increased frequency of left ventricular hypertrophy and unfavorable blood pressure non-dipper profile ($p<0.05$). These markers were independent predictors

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of these violations. The combined model demonstrated high predictive value (AUC=0.89).

Conclusion. Inflammatory-immune and metabolic markers are important for the early stratification of cardiovascular risk in patients with rheumatoid arthritis and arterial hypertension.

Keywords: arterial hypertension; rheumatoid arthritis; C-reactive protein; rheumatoid factor; left ventricular hypertrophy.