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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
ORIGINAL RESEARCH

Aortic-brachial stiffness mismatch as potential marker of subclinical arterial damage in patients with rheumatoid arthritis

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Abstract. Aortic-brachial stiffness mismatch is a potential new marker of a subclinical vascular damage that has never been studied in patients with rheumatic diseases. *The aim of the study* was to assess the frequency of arterial stiffness mismatch in rheumatoid arthritis (RA) and to evaluate its clinical associations. *Materials and Methods.* The study group included 85 patients with RA (males 22.4 %, aged 59.7 ± 14.3 years, hypertension in 65 %, mean disease activity score (DAS-28 (C-reactive protein) 3.7 ± 1.1), and the control group included 40 subjects matched by gender, age and risk factors. The study methods included measurements of clinical and ambulatory brachial and aortic blood pressure (BP) (BPLab-Vasotens), arterial stiffness parameters parameters (applanation tonometry, SphygmoCorAtCor), cardio-ankle vascular index (VaSera) and cardio-vascular risk assessments using the SCORE, American College of Cardiology/American Heart Association (ACC/AHA) 2013 pooled cohort equations and QRisk2 scoring systems. The arterial stiffness gradient was calculated as a ratio between carotid-femoral (cf) and carotid-radial (cr) pulse wave velocity, and its elevation of ≥ 1 was considered as arterial stiffness mismatch. A p-value of < 0.05 was considered significant. *Results and Discussion.* The mean stiffness gradient in RA patients without and with hypertension was 1.1 ± 0.1 and 1.4 ± 0.4, respectively ($p < 0.001$); in controls, 0.99 ± 0.2 and 1.3 ± 0.3, respectively ($p < 0.001$). The frequency of stiffness mismatch in the RA group was significantly higher compared to the controls in the whole study population (88.2 % vs 65 % ($p = 0.002$)) and in both normotensive and hypertensive subgroups (76.7 % vs 43.8 % ($p = 0.03$), and 94.5 % vs 79.2 % ($p = 0.04$), respectively). The same trend was observed in the subgroups with normal carotid-femoral pulse wave velocity: arterial stiffness mismatch was present in 82.1 % of RA patients vs. 51.9 % control subjects ($p = 0.004$). The stiffness gradient was associated with age ($r = 0.63$), hypertension duration ($r = 0.56$), cardio-vascular risk by the ACC/AHA 2013 ($r = 0.69$) and Qrisk2 ($r = 0.7$) scoring systems, nocturnal aortic systolic BP ($r = 0.53$), cardio-ankle vascular index ($r = 0.60$) and diurnal index of brachial systolic BP ($r = –0.4$). Significant differences in stiffness gradient values were observed in the subgroups based on elevation of aortic systolic BP and pulse wave velocity above individual reference values, aortic pulse pressure > 50 mmHg, cardio-ankle vascular index > 9, presence of high cardio-vascular risk, masked and nocturnal hypertension, and non-dipping. *Conclusion.* Patients with RA are characterized by higher frequency of arterial stiffness mismatch compared to controls, irrespective of the history of hypertension or the values of carotid-femoral pulse wave velocity. Arterial stiffness mismatch is associated with unfavorable 24-h BP profile, higher frequency of nocturnal hypertension and cardio-vascular risk.

Key words: rheumatoid arthritis, arterial stiffness, arterial stiffness gradient, aortic-brachial stiffness mismatch

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Introduction

Cardiovascular diseases (CVD) are the main cause of death in patients with rheumatoid arthritis (RA). Studies show a 10-year earlier onset of CVD in RA patients. The risk of cardiovascular (CV) disease in patients with arthritis is 60 percent higher than in general population [1]. RA, which is an active chronic inflammatory condition, is considered as a model of early vascular aging, same as arterial hypertension (HTN), diabetes mellitus (DM), and chronic kidney disease (CKD) [2, 3]. Therefore, markers of arterial wall changes may play an equally important role in this disease. Much attention has been recently paid to the search for new markers of arteriolosclerosis, independent of blood pressure (BP) levels and suitable for detecting changes at earlier stages of disease. One of the promising markers is the arterial stiffness (AS) gradient between the aorta and brachial artery.

Since it is the stiffness of the arterial system that determines the pulse wave propagation velocity (PWV) in the carotid-femoral segment is a reliable parameter of the aortic stiffness. PWV can be also measured in other segments — carotid-radial, femoral-plantar, shoulder-ankle — but the measurements should be interpreted differently. Peripheral muscular arteries are originally stiffer than elastic arteries, and their stiffness almost does not change with age [4–7]. While the contribution of aortic stiffness to CV risk is indisputable, there are limited data regarding peripheral stiffness. Studies in the general population [8–10], elderly [11], and patients with terminal CKD [12] give contradictory results [13].

Regardless of the prognostic significance of peripheral arterial stiffness, the increasing stiffness of the aortic arteries with the advancing age leads to cfPWV becoming equal to or even exceeding peripheral PWV. Some researchers suggest that the aortic-brachial PWV ratio (the so-called the AS gradient) [14] may potentially be an important outcome marker since the reversal of physiological stiffness gradient is associated with a number of adverse effects due to increased transmission of pulsatile forces to the peripheral vascular bed and target organs, as well as more pronounced pulse fluctuations of the microcirculatory bed [15]. There have been suggestions that this parameter may be a more accurate mortality predictor than increase in cfPWV, but the available studies of the effect of AS gradient on the outcomes in patients on hemodialysis [16, 17], peritoneal dialysis [18], in the Framingham study cohort [15], and in a small group

of patients with HTN and type 2 DM without a history of atherosclerotic CVD [19–21] report contradicting results. Thus, the significance of this parameter for CV risk assessment is ambiguous, and the expediency of its measurement is not obvious. The indicator has not been studied before in patients with rheumatic diseases. Yet, as chronic inflammation leads to early changes in the vascular wall, AS mismatch may be a promising marker of the risk of CV events and a predictor of their outcomes.

The aim of the study was to evaluate the prevalence of AS mismatch in the carotid-femoral and carotid-radial segments in patients with RA and to establish its clinical associations.

Materials and methods

We present a cross-sectional study in 85 patients with verified RA (ACR/EULAR, 2010) [22] and 40 control subjects. Written consent was obtained from all participants for the investigation and publication of relevant medical information according to WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013. The study was approved by the ethics committee of the Peoples' Friendship University of Russia. The RA group included patients aged 18 years and older, without known complications (patients with uncomplicated HTN with risk factors could be included), who received disease-modifying antirheumatic drugs (DMARDs). The control group consisted of 40 subjects selected to match the patient group in a ratio of approximately 1:2 in terms of age, gender, smoking history, presence or absence of HTN, obesity, and type 2 DM. All subjects provided informed consent to participate in the study. The study did not include subjects with other autoimmune diseases, active infection, grade 3 HTN, atrial fibrillation, history of atherosclerotic CVD, chronic heart failure NYHA II to IV, CKD-EPI with GFR < 30 ml/min/1.73 m^2.

The assessment protocol included clinical history, standard physical examination, laboratory assessments, RA activity assessment by the modified Disease Activity Score in 28 joints with C-reactive protein (DAS28-CRP) in accordance with the guidelines of the Association of Rheumatologists of Russia (ARR) [23].

Clinical measurement of BP in the brachial artery (peripheral BP) was performed using a validated oscillometric device with an individually selected cuff for each patient; aortic BP was measured by applanation tonometry (Sphygmocor, AtCor, Australia). Aortic BP data were interpreted using reference values for healthy population [24]. Parallel 24-hour peripheral and aortic BP monitoring was carried out according to a standard technique using BPLab Vasotens (OOO "Petr Telegin"). BP phenotypes were determined based on clinical BP measurements and results of 24-hour monitoring [25, 26].

Assessment of the arterial bed was based on direct (cfPWV) and indirect (aortic pulse pressure (PP), AS gradient, cardio-ankle vascular index (CAVI)) markers of AS. PWV, aortic PP, AS gradient were assessed by applanation tonometry. Increased AS was defined as cfPWV > 10 m/s [25, 26] and aortic PP ≥ 50 mmHg [27, 28]. In addition, reference values obtained for healthy population and depending on age and systolic BP (SBP) were used as the cfPWV reference values [29]. The AS gradient was assessed by measuring PWV in the carotid-radial segment (crPWV) and calculating the cfPWV to crPWV ratio. The AS gradient of ≥ 1 was defined as AS mismatch. CAVI was measured by volumetric sphygmography using a VaSera VS-1500N (Fukuda Denshi, Japan). CAVI values ≥ 9.0 were considered elevated.

For the estimation of CV risk we used the following scales: SCORE [30], the Pooled Cohort 10-year atherosclerotic cardiovascular disease (ASCVD) risk equations (hereinafter referred to as "ACC/AHA risk) [31] and QRisk2 [32]. Modified versions of the first two scoring systems were also used, multiplying the obtained values by 1.5 [33].

Statistical analyses of data were performed using the Statistica Version 8 software package. Parametric variables were summarized as a mean with a standard deviation (M ± SD). Non-parametric variables were summarized and analyzed using medians and interquartile ranges (IQR). The data distribution normality was tested using the Kolmogorov-Smirnov test. Comparative analyses of quantitative variables

between the two groups were performed using the Student's t-test or Mann-Whitney test, for normally distributed or abnormally distributed variables, respectively. Categorical variables were compared using the χ^2-test and Fisher's exact test. Inter-variable relationships were studied using Spearman's correlation analysis and multivariate regression analysis. Differences in mean values and correlations were considered significant at $p < 0.05$.

Results and discussion

General characteristics of study subjects

The clinical and demographic characteristics of study subjects are presented in Table 1. Conventional CV risk factors (sex, age, dyslipidemia, HTN, obesity, DM) were absent in as little as 10 (11.8 %) subjects; 18 (21.2 %) subjects had 1, 12 (14.1 %) had 2, 28 (32.9 %) had 3, 11 (12.9 %) had 4, 5 (5.9 %) had 5, and 1 (1.2 %) subject had 6 risk factors. A decrease in GFR < 60 ml/min/1.73 m^2 was found in 13 (15.3 %) RA patients.

Table 1.

Clinical and demographic characteristics of study subjects

Parameter	RA (n = 85)	Control (n = 40)	p
Males, n (%)	19 (22.4)	9 (22.5)	0.99
Age, yrs	59.7 ± 14.3	58.9 ± 15.5	0.27
BMI, kg/m^2	26.4 ± 5.6	26.9 ± 4	0.81
Abdominal obesity, n (%)	37 (43.5)	20 (50)	0.50
Smoking, n (%)	10 (11.8)	9 (22.5)	0.24
Dyslipidemia, n (%)	48 (56.5)	26 (65)	0.09
Type 2 DM, n (%)	5 (5.9)	3 (7.5)	0.73
HTN, n (%)	55 (64.7)	24 (60)	0.61
HTN duration, yrs*	6.6 (0;10)	5 (4;7.5)	0.10
Creatinine, μmol/L	80.8 ± 18.8	79.2 ± 17.3	0.80
GFR_{CKDEPI}, mL/min/1.73 m^2	77.3 ± 19.8	78.9 ± 20.1	0.87
TC, μmol/L	5.2 ± 1.2	6.0 ± 1.2	0.01
LDL cholesterol, μmol/L	3.2 ± 1.0	3.4 ± 0.9	0.08
TG, μmol/L	1.6 ± 0.8	1.6 ± 0.9	0.14
HDL cholesterol, μmol/L	1.4 ± 0.4	1.6 ± 0.3	0.12
Plasma glucose, μmol/L	5.2 ± 0.9	5.2 ± 0.6	0.84

Note: Data are expressed as M ± SD with the exception of *data presented as median (IQR). *Abbreviations:* BMI = body mass index; DM = diabetes mellitus; GFR = glomerular filtration rate; HDL = high density lipoproteins; HTN = hypertension; LDL = low density lipoproteins; RA = rheumatoid arthritis; TC = total cholesterol; TG = triglycerides.

Clinical characteristics of RA course

Seropositive were 64.7 % of the patients, median disease duration was 7 yrs (IQR 3;16 yrs), median erythrocyte sedimentation rate (ESR) was 35 mm/h (IQR 22;55 mm/h), high-sensitivity (hs) CRP was 10 mg/dl (2.2;22 mg/dl), rheumatoid factor (RF) 51.3 IU/ml (12.2;165 IU/ml), mean DAS28 (CRP) 3.7 ± 1.1. Systemic RA manifestations were not found. The swollen joint count (SJC) ranged 0 (n = 22) to 12 (n = 1); the tender joint count (TJC) was 0 (n = 11) to 16 (n = 1). The visual analogue scale patient global assessments (PGA-VAS) ranged from 10 to 90 mm (mean = 31 mm).

Remission was observed in 12.1 % of patients; the RA activity was mild in 18.2 %, moderate in 59.1 %, and severe in 12.1 % of patients. An RA duration of less than 1 year was observed in 10 (11.8 %) patients, with their disease activity being significantly higher (DAS28: 5.2 ± 1.6 vs. 3.4 ± 0.9, p = 0.005). Based on the radiographic staging the patients were distributed as follows: stage I in 25 (29.4 %); stage II in 29 (34.1 %), stage III in 25 (29.4 %), and stage IV in 6 (7.1 %). Functional incompetence of the 1st, 2nd and 3rd classes was found in 31 (36.5 %), 45 (52.9 %) and 9 (10.6 %) patients, respectively. All patients received DMARDs: 96.7 %, 2.8 %, and 0.5 % of the patients received methotrexate (average dose 12.5 mg), leflunomide, or sulfasalazine, respectively. Nonsteroidal anti-inflammatory drugs (NSAIDs) were taken by 27 (31.8 %) patients; glucocorticoids (GC) by 22 (25.9 %) (maximum dose was equivalent to 10 mg of prednisone). A history of biologics was found in 12 (14.1 %) patients; more than 2 years had passed since the last dose in all patients.

Blood pressure in the study population

Data on clinical and 24-h BP are presented in Table 2. HTN was found in 64.7 % of patients, all received antihypertensive therapy (AHT). In the RA group, 85 % of patients received monotherapy and 15 % of patients received dual therapy (a renin-angiotensin system (RAS) inhibitor combined with a diuretic (82 %) or a calcium channel blocker (18 %)).

Table 2.

Clinical BP and 24-h BP data in study groups, depending on the presence of HTN

Parameter	RA		Control	
	No HTN (n = 30)	HTN (n = 55)	No HTN (n = 16)	HTN (n = 24)
brSBP	117 ± 13	138 ± 18*ˆˆ	117 ± 7	130 ± 16*
brDBP	73 ± 9	82 ± 10*ˆˆ	68 ± 8	74 ± 11
aoSBP	108 ± 13	132 ± 20*ˆˆ	106 ± 10	120 ± 17*
aoDBP	74 ± 10	82 ± 10*ˆˆ	71 ± 8	74 ± 12
Outpatient peripheral BP				
Diurnal SBP	120 ± 9	134 ± 16ˆˆ	115 ± 11	125 ± 9
Diurnal DBP	71 ± 7	77 ± 10	68 ± 7	73 ± 8
Nocturnal SBP	113 ± 10ˆˆ	128 ± 17ˆˆ	105 ± 9	116 ± 9
Nocturnal DBP	65 ± 9	71 ± 11ˆˆ	61 ± 6	65 ± 10
24-h SBP	118 ± 8	133 ± 15ˆˆ	113 ± 9	123 ± 9
24-h DBP	69 ± 8	75 ± 10	67 ± 6	71 ± 9
Outpatient aortic BP				
Diurnal SBP	110 ± 8	124 ± 14ˆˆ	104 ± 9	115 ± 14
Diurnal DBP	73 ± 8	78 ± 10	70 ± 7	77 ± 11
Nocturnal SBP	105 ± 10	121 ± 16ˆˆ	100 ± 8	111 ± 10
Nocturnal DBP	67 ± 10	72 ± 10	65 ± 7	69 ± 12
24-h SBP	109 ± 8	123 ± 14ˆˆ	103 ± 8	115 ± 8
24-h DBP	72 ± 8	77 ± 9	68 ± 7	74 ± 10

Note: All data are expressed in mmHg. *Note*: Data are expressed as M ± SD. *p < 0.05, compared with normotensive subgroup (No-HTN) based on Mann-Whitney test; ˆˆ p < 0.05, compared with control group based on Mann-Whitney test.
Abbreviations: ao — aortic; br — brachial; DBP — diastolic blood pressure; HTN — hypertension; RA — rheumatoid arthritis; SBP — systolic blood pressure.

Masked HTN was detected in 28.2 % of RA patients vs 7.5 % control subjects (p = 0.009). Nocturnal increase in BP was detected in 56.5 % of RA patients vs 17.5 % of control subjects ($\chi^2 = 16.7$, p < 0.001). RA patients had a lower diurnal index (DI) compared to controls (median 4.6 % (0;9 %) vs 7.5 % (5;11.5 %), p = 0.006), and there were more non-dippers (SBP DI < 10 %) among RA patients: 83.5 % vs 62.5 % in control ($\chi^2 = 7.4$, p = 0.02). There were no significant differences in the frequency of individual phenotypes of nocturnal BP decrease [34].

Arterial stiffness

The RA and control groups were comparable in terms of most stiffness parameters. HTN was the main factor driving the increase in the AS markers (Table. 3) [35].

Table 3.

Arterial stiffness in study groups

Parameter	RA		Control	
	No HTN (n = 30)	HTN (n = 55)	No HTN (n = 16)	HTN (n = 24)
cfPWV, m/s	7.3 ± 1.5	10.3 ± 3.1^	6.7 ± 1.4	9.6 ± 1.9^
aoPP, mmHg*	33 (28;38)	47 (38;59)^	34 (30;40)	44 (38.5;56)^
Augmentation index,%*	25.5 (9.5;33.5)	33 (25;38)^	24 (4;31)	29 (22.5;35.5)
RWTT, ms	135.8 ± 14.2	132.2 ± 18.7	153.5 ± 31.4	131.1 ± 13.5^
Arterial stiffness gradient	1.1 ± 0.1	1.4 ± 0.4^	0.99 ± 0.2	1.3 ± 0.3^
CAVI	7.2 ± 1.1	9.0 ± 1.6^	7 ± 1.2	9.2 ± 1.5^

Note: The data are presented as M ± SD with the exception of *data presented as median (IQR). Augmentation index normalized to a heart rate of 75 bpm.^p < 0.001 compared to normotensive (No HTN) subgroup, based on Mann-Whitney test.
Abbreviations: ao — aortic; CAVI — cardio-ankle vascular index; cf — carotid-femoral; HTN — hypertension; PP — pulse pressure; PWV — pulse wave velocity; RA — rheumatoid arthritis; RWTT — reflected wave transit time.

AS mismatch in carotid-femoral and carotid-radial segments

The RA group was comparable with the control group in terms of AS gradient means (see Table 3). As shown by age-related analysis in the RA group, AS gradient had a clear tendency to increase with age: 0.84 ± 0.11 in patients under 20; 0.92 ± 0.12 at the age of 20–29, 0.94 ± 0.16 at 30–39, 1.09 ± 0.10 at 40–49, 1.11 ± 0.14 at 50–59, 1.26 ± 0.13 at 60–69, 1.60 ± 0.19 at 70–79, and 1.65 ± 0.25 in patients over 80.

RA patients without HTN tended to have a higher stiffness gradient compared with the similar control subgroup, p = 0.06. The presence of HTN, both in the RA group and in the control group, was associated with significantly higher AS gradients than in the respective subgroups without HTN. The frequency of AS mismatch was significantly higher in the RA group, regardless of HTN (Fig. 1).

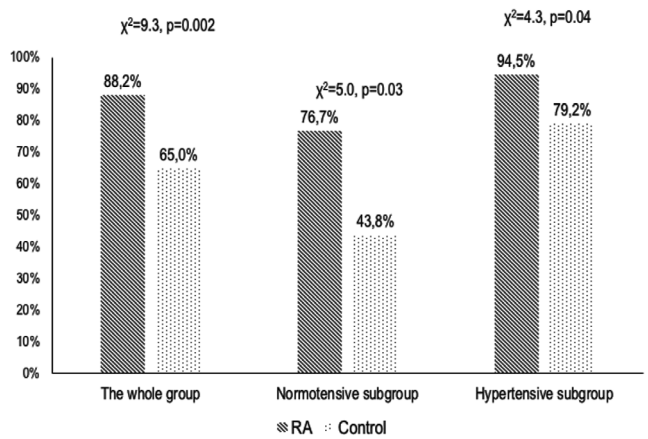

Fig. 1. Frequency of AS mismatch in the study population. ***Note:*** the significance of differences between RA and control groups was tested using χ^2-test. *Abbreviations:* HTN — hypertension; RA — rheumatoid arthritis

Characteristics of patients with RA based on the presence or absence of AS mismatch

Compared to RA patients with a normal AS gradient, patients with RA and AS mismatch were older, had longer duration of HTN, higher body mass index (BMI), higher clinical SBP in the brachial artery and diastolic BP (DBP) in the aorta, as well as nocturnal peripheral and aortic SBP, higher CAVI and lower DI, as well as a higher CV risk. The frequency of nocturnal HTN and non-dipping was significantly higher in this subgroup (Table 4). There were no differences in the RA activity, radiographic stage, or the type of anti-inflammatory therapy. It should be noted that a similar analysis within the control group has revealed significant differences only in age, frequency of HTN, dyslipidemia and the magnitude of CAVI.

Table 4.

Characteristics of RA patients based on AS mismatch

Parameter	AS gradient < 1 (n = 10)	AS gradient ≥ 1 (n = 75)	p
Age, yrs	44.7 ± 17.9	61.7 ± 12.6	0.004
Duration of HTN, yrs*	0 (0;0.5)	5 (0;12)	0.02
BMI, kg/m^2	23 ± 4.5	26.8 ± 5.6	0.04
Dyslipidemia, n (%)	2 (20)	38 (50.7)	0.06
brSBP, mmHg	120 ± 19	132 ± 18	0.03
brDBP, mmHg	73 ± 9	80 ± 10	0.06
aoSBP, mmHg	114 ± 24	125 ± 20	0.08
aoDBP, mmHg	73 ± 8	80 ± 11	0.03
Nocturnal brSBP, mmHg	109 ± 14	124 ± 16	0.01
Nocturnal aoSBP, mmHg	101 ± 14	117 ± 15	0.009
Nocturnal HTN, n (%)	1 (10)	44 (59)	0.004
SBP DI,%*	11 (9;16)	3 (−2;7.5)	0.001
Non-dippers, n (%)	5 (50)	66 (88)	0.002
CAVI	6.5 ± 1.0	8.6 ± 1.6	< 0.001
SCORE,%*	0.1 (0.03;2.1)	3.0 (1.2;5.8)	< 0.001
mSCORE,%*	0.2 (0.05;3.3)	4.5 (1.7;8.7)	< 0.001
ACC/AHA risk,%*	0.8 (0.4;4.4)	8.3 (2.5;17.9)	< 0.001
ACC/AHA risk x1.5,%*	1.1 (0.6;6.6)	12.5 (3.8;26.9)	< 0.001
QRisk2*	1.0 (0.7;8.5)	13.3 (5.6;24.7)	< 0.001

Note: Data are expressed as M ± SD with the exception of *data presented as median (IQR). ***Abbreviations:*** ao — aortic; BMI — body mass index; br — brachial; CAVI — cardio-ankle vascular index; DBP — diastolic blood pressure; DI — diurnal index; HTN — hypertension; SBP — systolic blood pressure; mSCORE — total 10-year risk of fatal CVD calculated using the correction factor of 1.5

There were significant differences in AS gradient between subgroups based on increase in aortic SBP or PWV above individual reference values [29], increase in aortic PP ≥ 50 mmHg, increase in CAVI > 9, in CV risk magnitude, the presence of nocturnal HTN, non-dipping, latent HTN (in the clinically normotensive subgroup) (Fig. 2). There were no differences in the level of AS gradient in subgroups based on gender, RF positivity, median CRP or ESR, RA activity by DAS28, radiographic stage, functional class, use of NSAIDs and GC.

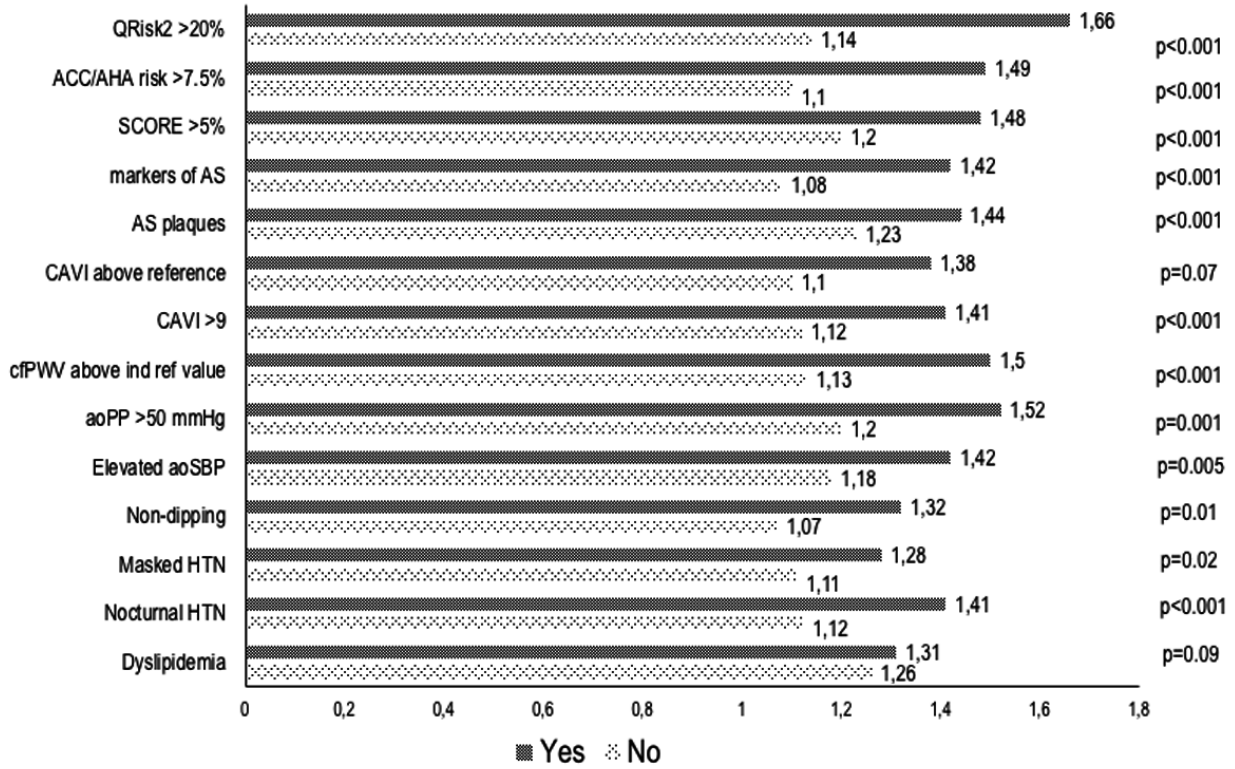

Fig. 2. AS gradient in RA patients, depending on various parameters.

Note: the significance of differences was tested using the Mann-Whitney test. ***Abbreviations:*** ao — aortic; AS — atherosclerotic; CAVI — cardio-ankle vascular index; cf — carotid-femoral; HTN — hypertension; PP — pulse pressure; PWV — pulse wave velocity; SBP — systolic blood pressure.

A comparison of test parameters between the AS mismatch subgroups from the RA and control groups showed that patients with RA had increased clinical peripheral and aortic DBP (80 ± 10 vs. 72 ± 8 mmHg, $p < 0.001$ and 80 ± 11 vs. 73 ± 9 mmHg, $p = 0.002$), increased nocturnal peripheral and aortic SBP (124 ± 16 vs. 113 ± 10 mmHg, $p = 0.005$ and 117 ± 15 vs. 108 ± 10 mmHg, $p = 0.02$, respectively) and DBP (69 ± 10 vs. 63 ± 8 mmHg, $p = 0.03$ and 71 ± 11 vs. 66 ± 10 mmHg, $p = 0.04$, respectively), decreased SBP DI (3 % (–2;7.5 %) vs. 6 % (4;12 %), $p = 0.005$), increased frequency of non-dipping (66 (88 %) vs. 16 (61.5 %), $p = 0.003$) and nocturnal HTN (44 (58.7 %) vs. 4 (15.4 %), $p < 0.001$).

Univariate correlation analysis has confirmed associations of the AS gradient with parameters in Table 4: the highest correlation coefficient was noted for age ($r = 0.63$), HTN duration ($r = 0.56$), ACC/AHA risk ($r = 0.69$) and Qrisk2 ($r = 0.7$), nocturnal SBP in the aorta ($r = 0.53$), CAVI ($r = 0.60$), and SBP DI ($r = –0.4$). Inclusion of clinical and nocturnal SBP and CAVI into the regression model revealed independent associations between AS gradient and nocturnal aortic SBP ($\beta = 0.31$, $p = 0.02$) and CAVI ($\beta = 0.45$, $p < 0.001$). These associations disappeared if the model also included HTN duration and CV risk values, although the independent association with Qrisk2 score was confirmed ($\beta = 0.33$, $p = 0.05$). The significance of the above associations was not confirmed when the same model was adjusted by age.

AS gradient in RA patients with normal PWV

In the RA subgroup with cfPWV£10 m/s, AS mismatch was significantly more common than in the control group (Fig. 3). In the subgroup with cfP-

WV > 10 m/s, the frequency of AS mismatch in patients with RA was 97.6 % vs 92.3 % in control. In subjects with normal cfPWV, mean AS gradient was 1.09 ± 0.14 in patients with RA and 1.07 ± 0.25 in the control group (p = 0.24).

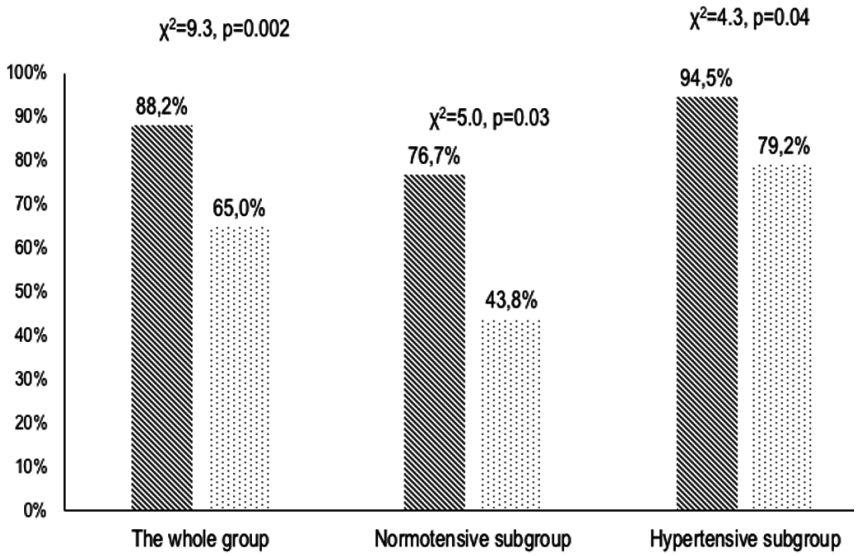

Fig. 3. Frequency of AS mismatch in subjects with PWV ≤10 m/s. ***Note:*** significance of differences RA vs control was tested using χ^2-test. ***Abbreviations:*** HTN — hypertension; RA — rheumatoid arthritis.

In RA patients with normal PWV, AS mismatch was associated with older age, lower SBP DI, higher nocturnal aortic SBP, CAVI, and CV risk (Table 5).

Table 5.

Characteristics of RA patients depending on AS mismatch in the subgroup with cfPWV ≤10 m/s (n = 56)

Parameter	AS gradient < 1 (n = 10)	AS gradient ≥ 1 (n = 46)	p
Age, yrs	44.7 ± 17.9	57.1 ± 12.7	0.04
Dyslipidemia, n (%)	2 (20)	24 (52.2)	0.06
Nocturnal aoSBP, mmHg	101 ± 14	112 ± 11	0.03
Nocturnal HTN, n (%)	1 (10)	21 (45.7)	0.04
SBP DI,%*	11 (9;16)	3.5 (−1;7.5)	0.003
Non-dippers, n (%)	5 (50)	39 (84.8)	0.02
CAVI	6.5 ± 1.0	8.2 ± 1.4	0.006
SCORE,%*	0.1 (0.03;2.1)	1.8 (0.6;4.0)	0.02
mSCORE,%*	0.2 (0.05;3.3)	2.7 (0.8;5.9)	0.02
ACC/AHA risk,%*	0.8 (0.4;4.4)	4.4 (1.3;10.2)	0.005
ACC/AHA risk x1.5,%*	1.1 (0.6;6.6)	6.5 (2.0;15.3)	0.005
QRisk2*	1.0 (0.7;8.5)	8.7 (3.3;14.6)	< 0.01

Note: Data are expressed as M ± SD with the exception of *data expressed as median (IQR). ***Abbreviations:*** ao — aortic; CAVI — cardio-ankle vascular index; DI — diurnal index; HTN — hypertension; SBP — systolic blood pressure; mSCORE — total 10-year risk of fatal CVD calculated using the correction factor of 1.5.

According to a similar analysis in the subgroup with PWV within individual reference ranges, the frequency of AS mismatch was 82 % in RA patients and 51.7 % in control subjects (p = 0.04): 66.7 % vs. 40 % in patients without HTN (p = 0.13) and 90.6 % vs. 64.3 % (p = 0.03) in patients with HTN, respectively. Comparative analysis revealed differences similar to those in Table 5, as well as differences in RF (106.2 (30.8;203.5) IU/ml vs. 25.5 (11;40.5) IU/ml, p = 0.01) and nocturnal peripheral SBP (120 ± 13 vs. 109 ± 15 mmHg, p = 0.04).

Thus, the presence of RA was associated with a high frequency of AS mismatch, including in patients with normal PWV, regardless of their HTN history. At the same time, AS mismatch was associated with nocturnal HTN, non-dipping, increased CAVI, and high CV risk. No independent predictors of AS mismatch have been identified.

The presented study was conducted on a sample of RA patients without a history of CVD. The specific feature of the study was that it included a comprehensive assessment of the condition of the arterial bed using, among routine things, some relatively new indicators or those that hadn`t been studied in this population before (AS gradient), as well as detailed 24-hour profile of peripheral and aortic BP, and analysis of associations between the test variables and CV risk indicators. All key analyses were also performed in the control group.

One of the innovative aspects of this study is the characterization of AS gradient in a population of RA patients. In the last few years, there have been publications studying some controversial issues concerning AS gradient: its normal levels in different age groups [36], dependence on mean BP [37, 38], its clinical associations, and the relationship with adverse outcomes in the general population [15]. However, no previous studies dealt with characterization of AS gradient in patients with inflammatory joint diseases.

In our study, the mean AS gradient was 1.1 and 1.4 in the normotensive and hypertensive RA subgroups, respectively, and 0.99 and 1.3 in the respective control subgroups. The highest values were predictably observed in the whole RA group and in the RA subgroup with HTN. Our control group data are partially consistent with the results of recently published studies. Niiranen et al [15] studied the prognostic value of the AS gradient in the Framingham Heart Study Offspring cohort (n = 3539), where the AS gradient was calculated as the ratio of carotid-radial to carotid-femoral PWV, with its mean values being 1.08 ± 063. Thus, it was noted that this indicator decreased from 1.36 ± 0.19 in subjects under 40 to 0.73 ± 0.21 in those over 80. Upon conversion of the obtained results in the inverse formula we used, the mean value of AS gradient in this study was 0.99, which is consistent with the values we have obtained in the control subgroup without HTN. In Armstrong's study, which examined the independence of AS gradient from mean BP in different cohorts, the mean AS was 0.92 ± 0.21 in healthy subjects, 1.13 ± 0.30 in HTN, 1.11 ± 0.35 in those with T2DM, and 1.21 ± 0.24 in subjects with CKD [38]. Noteworthy is that the mean value for the group with HTN was somewhat lower than in our study, although the groups were comparable by age. This can be due to higher mean BP and PWV values in our study population. Yet another research by Bia D. et al. [36] evaluated consistency among various methods and parameters that characterize arterial stiffness (n = 3619 individuals, aged 3 to 90 yrs, including 1289 healthy individuals without risk factors): the median AS gradient gradually increased from 0.58 in the youngest age group (under 5 yrs) to 1.08 in the group aged 75–80 yrs. Among the 60-year-olds (the age group comparable to our study population), the median AS gradient was 0.81. We have obtained similar data with a clear trend towards the AS gradient increase with older age and with maximum values in patients older than 70 years. In a study by Starostina E.S. et al., the mean AS gradient in subjects with HTN and T2DM was 1.2 ± 0.9 [21], i.e. comparable to our results in RA. As shown by previous studies in patients with T2DM, AS mismatch may be an earlier marker of increased AS than cfPWV [19–21]. Therefore, it was interesting to conduct a similar analysis in patients with RA. We found a high frequency of AS mismatch in patients with normal cfPWV, regardless of the presence of HTN and despite of comparable mean values of this variable (88.2 % vs. 65 % in the whole study population), including in the subgroup with normal cfPWV (82.1 % vs. 51.9 %). This is consistent with the results of Starostina's study, where

the frequency of AS mismatch in hypertensive patients with T2DM was also high (93 % in the whole group and 70 % in the subgroup with a normal cfPWV) [21]. Our data suggest that the AS gradient is an earlier marker of increasing AS in patients with RA than cfPWV is, and hence may be a promising parameter for early diagnosis of changes in the arterial bed.

The associations of AS gradient with age, HTN duration, CV risk scores, and BMI that have been revealed in our study are predictable and consistent with previous studies [15, 16, 38]. In addition, our results do not support independence of AS gradient from BP, as was previously found in patients on hemodialysis [37], which is consistent with the results of Armstrong for a healthy population [38]. Similarly to the Starostina study [19, 21], we have also identified associations of AS gradient with nocturnal SBP and CAVI, as well as with SBP DI, including in patients with cfPWV < 10 m/s, which confirms associations between unfavorable phenotypes of 24-h BP and early changes in the vascular wall.

Conclusion

It has been shown that AS mismatch between the aortic and peripheral arteries is quite common in patients with RA, regardless of their HTN history. The phenomenon is associated with unfavorable 24-hour BP profile, and may be an earlier marker of increased AS than cfPWV. We think that assessment of this parameter can be recommended to RA patients without a history of CV complications for early detection of changes in the arterial bed and appropriate correction of therapy.

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Феномен утраты градиента жесткости — потенциальный маркер субклинического поражения сосудистого русла у пациентов с ревматоидным артритом

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Аннотация. Градиент жесткости между аортой и плечевой артерией — новый перспективный маркер субклинического поражения сосудистого русла, ранее не изучавшийся у пациентов с ревматическими заболеваниями. *Цель исследования* — изучить частоту феномена утраты градиента жесткости на каротидно-феморальном и каротидно-радиальном сегментах у пациентов с ревматоидным артритом (РА) и установить его клинические ассоциации. *Материал и методы.* В одномоментное поперечное исследование включено 85 пациентов с РА (22,4 % мужчин, возраст 59,7 ± 14,3 лет, артериальная гипертония у 65 %, индекс DAS28 (по С-реактивному белку) 3,7 ± 1,1) и 40 пациентов контрольной группы, сопоставимых по основным клинико-демографическим параметрам. Всем проводилось измерение клинического артериального давления (АД), 24-часовое суточное мониторирование периферического и центрального АД (BPLab Vasotens), аппланационная тонометрия (SphygmoCor AtCor) с оценкой скорости распространения пульсовой волны на каротидно-феморальном и каротидно-радиальном сегментах и расчетом градиента жесткости как отношения между ними, оценка сердечно-сосудистого лодыжечного индекса и сердечно-сосудистого риска по шкалам SCORE, 10-летнего риска атеросклеротических сердечно-сосудистых заболеваний (СС3) (ACC/AHA 2013) и QRisk2. Утратой градиента

жесткости считали его значения ≥1. Результаты считали статистически достоверными при p <0,05. *Результаты и обсуждение.* Значения градиента жесткости составили в группе РА 1,1±0,1 и 1,4±0,4 у пациентов без и с артериальной гипертонией соответственно (p<0,001), в контрольной группе — 0,99±0,2 и 1,3±0,3 соответственно (p<0,001). Частота утраты градиента жесткости в целом составила 88,2 % в группе РА и 65 % в группе контроля (p=0,002): у пациентов без гипертонии 76,7 % и 43,8 % (p=0,03); у пациентов с гипертонией 94,5 % и 79,2 % (p=0,04) соответственно. В подгруппе со скоростью распространения пульсовой волны <10 м/с частота утраты градиента жесткости при РА составила 82,1 % против 51,9 % в группе контроля (p=0,004). Установлены ассоциации градиента жесткости с возрастом (r=0,63), продолжительностью артериальной гипертонии (r=0,56), риском по шкалам 10-летнего риска (r=0,69) и Qrisk2 (r=0,7), ночным систолическим АД в аорте (r=0,53), сердечно-лодыжечным сосудистым индексом (r=0,60) и суточным индексом систолического АД (r= –0,4). Выявлены достоверные различия значений градиента жесткости в группах, выделенных в зависимости от повышения центрального систолического АД и скорости распространения пульсовой волны выше индивидуальных нормативов, повышения центрального пульсового давления >50 мм рт. ст., сердечно-лодыжечного сосудистого индекса >9, величины риска, наличия ночной гипертонии, нон-диппинга и скрытой гипертонии. Независимых предикторов утраты градиента жесткости не выявлено. *Выводы.* Утрата градиента жесткости между каротидно-феморальным и каротидно-радиальным сегментом при РА широко распространена, встречается чаще, чем в контрольной группе, в том числе и при нормальных значениях скорости распространения пульсовой волны и ассоциируется с неблагоприятным циркадным профилем АД, высокой частотой ночной гипертонии и повышением сердечно-сосудистого риска.

Ключевые слова: ревматоидный артрит, артериальная ригидность, градиент артериальной жесткости, утрата градиента артериальной жесткости

Информация о финансировании. Авторы заявляют об отсутствии внешнего финансирования.

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