ORIGINAL ARTICLE

FEATURES OF THE DAILY PROFILE OF ARTERIAL BLOOD PRESSURE IN PATIENTS WITH RHEUMATOID ARTHRITIS IN COMBINATION WITH ARTERIAL HYPERTENSION

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ABSTRACT

The aim: To determine the features of daily shifts in blood pressure (BP), the influence of the presence of rheumatoid arthritis (RA) on BP control and identify factors that affect BP among patients with RA in combination with resistant hypertension (RH).

Materials and methods: All material for writing this scientific work were the results of a comprehensive survey of 201 people with RH and RA, hypertension (H) and RA, RA without H, H without RA and relatively healthy individuals. A laboratory study was performed: rheumatoid factor, C-reactive protein (CRP), K+ serum, and creatinine levels. All patients underwent office BP measurement and ambulatory BP monitoring for 24 hours. Statistical processing of the study results was carried out using "IBM SPSS Statistics 22".

Results: Among patients with RA in combination with RH non-dippers (38.7%) are the most common type of BP profile. Patients with RH in combination with RA are characterized by an increase in BP more at night ($p < 0.003$), which corresponds to the high frequency of night-peackers (17.7%). The presence of RA determines worse control of diastolic BP ($p < 0.01$) and more vascular overload on organs and systems during the night ($p < 0.05$).

Conclusions: An increase in BP in patients with RA in combination with RH is more significant at night, characterized by poorer BP control and greater vascular load at night indicating the need for tighter control of BP during sleep. Non-dippers are most often detected among patients with RA in combination with RH, which is prognostically unfavorable for the development of nocturnal "vascular accidents".

KEY WORDS: rheumatoid arthritis, resistant hypertension, ambulatory blood pressure monitoring

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INTRODUCTION

Various epidemiological studies have been conducted, but the reason for the increase in the prevalence of hypertension (H) in patients with rheumatoid arthritis (RA) is still unclear. A direct link between the prevalence of H and inflammation was not detected, but the incidence of H in patients with RA ranges from 52-73% [1-3]. It cannot be ruled out that systemic inflammation plays an important role in the development of H in RA, as the level of C-reactive protein (CRP) in RA varies and this marker may not cover long-term cumulative inflammatory load. The studied populations were well targeted by traditional disease-modifying and immunobiological drugs on endothelial function, arterial stiffness and blood pressure (BP) [4-6]. In addition, certain biological drugs have a beneficial effect on endothelial function and arterial stiffness [5] and, thus, can prevent an increase in the incidence of H. Given the contribution of H in increased risk of premature death from cardiovascular disease (CVD) and insufficient assessment of the impact of these factors in patients with RA are particularly relevant predictors of this comorbidity [7]. The problem of resistant hypertension (RH) attracts special attention, because the development of RH is significantly faster with long-term use of drugs such as glucocorticosteroids (GCs) and nonsteroidal anti-inflammatory drugs (NSAIDs) [8].

THE AIM

The aim of this study is to determine the features of daily shifts in BP, the influence of the presence of RA on BP control and identify factors that affect BP among patients with RA in combination with RH.

MATERIALS AND METHODS

The study was conducted on the basis of the rheumatological and therapeutic departments of the Kyiv City Clinical Hospital No.3, which were the clinical base of the Department of Propedeutics of Internal Medicine No.2 of Bogomolets National Medical University. The

study included a retrospective cohort study, that was based on the medical history data of 560 patients with rheumatoid arthritis or arterial hypertension, who underwent observation in the clinic during 2017-2020. All patients were residents of Kyiv and Kyiv region.

Inclusion criteria for groups 1-4 were following: age 45-59 and 60-74 years, patients with hypertension of the II stage, 1 and 2 degrees and did not receive antihypertensive therapy or received monotherapy with ACE inhibitors or ARBs (except group 3), RA (except group 4), CKD not higher than II stage (GFR 60-89 ml/ min./.73 m^2), LVEF more than 40%, K+ blood serum from 3.0 to 5.0 mmol/l, informed consent to participate in the study. Exclusion criteria were next: 3rd stage hypertension, CKD III-V stages, acute kidney damage in anamnesis, endocrine pathology (diabetes mellitus, Addison's disease, etc.), clinical signs of hypovolemia, office: systolic blood pressure < 115 mm Hg or diastolic < 55 mm Hg, atrial fibrillation and flutter, A-V block II-III on ECG, CHF III-IV according to NYHA, decreased left ventricular ejection fraction (<40%) or valvular heart disease, acute myocardial infarction or other cardiovascular events (Q-myocardial infarction, non-Q-myocardial infarction, unstable angina, myocardial revascularization, stroke, TIA) in the anamnesis, alcohol abuse, drug addiction or mental disorders, infectious diseases, active chronic diarrhea, oncological and hematological diseases, active phases of diseases of the gastrointestinal tract and liver, gout, K+ blood serum > 5.0 mmol/l, Na+ blood serum < 130 mmol/l, current therapy with spironolactone or another mineralocorticoid receptor blocker, use of thiazide or loop diuretics within 6 weeks before the start of the study, inability to provide informed consent for participation in research. Group 5 (the control group) consisted of healthy volunteers of the appropriate age and sex without a previous history of arthritis of any genesis or a stable increase in BP.

201 people were examined in total: 1 group - patients with RH and RA (n = 62), 2 group - patients with H and RA (n = 39), 3 group - patients with RA without H (n = 41), group 4 - patients with H without RA (n = 37), group 5 - healthy individuals (n = 22). All patients with H received the same type of combined antihypertensive therapy ((ARB or ACE inhibitors) + diuretic (hydrochlorothiazide 25 mg or indapamide 1.25 mg) + CCB (amlodipine 10 mg)) and rosuvastatin 20 mg, RA patients - basic therapy with methotrexate 15 mg/week.

Criteria for inclusion in the study: age from 45 to 74 years (middle and old age, according to the WHO classification, 1968); reliable diagnosis of RA and basic therapy according to ACR / EULAR criteria (2010, 2015), glomerular filtration rate (GFR) more than 60 ml/ min/1.73^2, K^+ serum level from 3.0 to 5.0 mmol/l.

A survey of patients with RA and H was conducted, which took into account the duration of both RA and H, specifying the basic therapy in both cases, the duration of GCs use. A laboratory study was performed to determine the content of creatinine, K^+, rheumatoid factor, and CRP levels; GFR was calculated using the formula CKD-EPI, RA activity was measured according to DAS28.

All patients underwent office BP measurement and ambulatory BP monitoring (ABPM) for 24 hours. Office BP was measured according to European Society of Hypertension criteria. ABPM measurements were performed on a non-dominant arm using an automatic ABPM50 monitor, Hubei Province, China. The following parameters were analyzed: average values of systolic BP, diastolic BP per day in the active (day) and passive (night) periods (average day and night (dn), average day (d), average night (n) values for SBP, DBP). The circadian rhythm of BP was calculated according to the night–day ratio (NDR) of SBP and DBP. After assessing NDR of BP, the following groups of patients and types of daily charts of BP curves were identified: Dippers - people with normal nocturnal BP (NDR = 10-20%); Non-dippers - people with insufficient registered BP decrease at night (NDR <10%); Over-dippers - people with considerable decrease of BP at night (NDR > 20%); Night-peackers - people without a recorded increase in BP at night (NDR is negative).

All groups of patients are comparable in age, sex, levels of the glucose and smoker status; groups of patients with RA are comparable in RA variant, duration of RA, RA activity by CRP level, and DAS28-CRP scale, which corresponds to high disease activity in both cases, the need for the use of NSAIDs and GCs; groups of patients with H are comparable in the duration of H (see Table I for details).

The null hypothesis was formed: the dynamics of the daily profile in patients with RA in combination with RH does not differ from the daily changes in BP in people with RH and RA, H and RA, RA without H, H without RA and relatively healthy individuals.

Statistical processing of the obtained results was performed using "IBM SPSS Statistics. Version 22". Under the condition of normal distribution of the studied trait, parametric statistical methods were used in the sample: for descriptive statistics the mean value of the indicator (M), standard deviation (σ), standard error (SE), 95% confidence interval for the mean (95% CI) were determined. The median values (Me), 25 and 75 quartiles (Q25 - Q75) as well as a percentage (%) were used. Comparison of groups on qualitative binary data was performed using Pearson's $\chi 2$-test (corrected by Yates), Fisher's exact test. Odds ratio (OR) and the Pearson correlation coefficient were used for the measurement of relationship between variables.

Table I. General clinical characteristics of the examined groups of patients

	Group 1 (n=62)	Group 2 (n=39)	Group 3 (n=41)	Group 4 (n=37)	Group 5 (n=22)
Age, years, M ± σ	62.9 ± 9.0	61.9 ± 7.0	59.1±8.5	60.6±9.6	50.1±4.94
Women, abs. (%)	52 (83.9)	30 (76.9)	37 (90.2)	31 (83.8)	16 (72.7)
Seropositive RA,n (%)	51 (82.3)	29 (74.4)	31 (75.6)	-	-
CRP, mg / l, Me (25% -75%)	6.9 (2.9-17.0)	6.7 (3.8-23.9)	6.0 (2.6-24.1)	-	-
Rheumatoid factor, U / l, Me (25% -75%)	51.0 (13.1-126.6)ǂ	48.2 (10.4-130.4)	24.1 (11.6-75.4)	-	-
DAS28-CRP, M ± σ	5.4 ± 1.0	5.6 ± 1.0	5.3±1.1	-	-
Duration of RA, years, M ± σ	9.2 ± 8.0	8.7 ± 7.1	8.6±9.2	-	-
Duration of H, years, M ± σ	10.8 ± 7.2	7.0 ± 3.8	-	9.2±6.1	-
Took NSAIDs, abs. (%)	50 (80.6)	33 (84.6)	31 (75.6)	-	-
Took GCs, abs. (%)	21 (33.9)	11 (28.2)	15 (36.6)	-	-
Smoking, abs. (%)	7 (11.3)	5 (12.8)	7 (17.1)	5 (12.2)	3 (13.6)
Body mass index, kg/m2, Me (25%-75%)	29.9 (27.7-31.6)ǂ†	28.6 (24.9-33.7)	23.4 (21.3-26.3)	32.4 (28.9-36.1)	23.8 (21.4-26.4)
Glucose, mmol/l, Me (25%-75%)	4.7 (4.2-5.3)	4.7 (4.4-5.2)	4.7 (4.3-5.0)	4.8 (4.3-5.2)	4.7 (4.3-4.9)

Notes: ǂ - significance of differences with group 4 (p <0.05); † - significance of differences with group 5 (p <0.05).

Table II. Distribution of patients of experimental groups by circadian profile, n (%)

	Group 1 (n=62)	Group 2 (n=39)	Group 3 (n=41)	Group 4 (n=37)	Group 5 (n=22)
Dippers, abs., (%)	22 (35.5)*#ǂ †	18 (46.2) †	20 (48.8) †	18 (48.6) †	22 (100.0)
Non-dippers, abs., (%)	24 (38.7) †	16 (41.0) †	13 (31.7) ǂ †	12 (32.4) †	0
Over-dippers, abs., (%)	5 (8.1)* #†	1 (2.6) #†	6 (14.6) ǂ †	6 (16.2) †	0
Night-peackers, abs., (%)	11 (17.7)*#ǂ †	4 (10.3) #†	2 (4.9) ǂ †	1 (2.7) †	0

Notes: * - p <0.05 compared to group 2, # - p <0.05 compared to group 3, ǂ - p <0.05 compared to group 4, † - p <0.05 compared to group 1 compared to group 1 group 5.

RESULTS

The incidence of H in our study is 71.1% (n = 142) among patients with RA. RH is diagnosed in 61.4% (n = 62) cases of patients with RA in combination with H, which is 6 times higher than in the general population [9]. Unfortunately, there is no data in the literature on the frequency of RH in patients with RA, so this study is quite relevant. Office SBP is higher in patients of group 1 (141.1±8.0 mm Hg) than in patients of groups 2, 3, 4 and 5 by 10.1 mm Hg, 29.3 mm Hg, 9.5 mm Hg and 32.0 mm Hg, respectively (all p <0.01), office DBP (83.7±5.5 mm Hg), in turn, by 12.2 mm Hg and 16.6 mm Hg higher in patients of groups 1 than in patients of groups 3 and 5 (p <0.001), office PBP (57.3±7.8 mm Hg) is higher by 6.7 mm Hg, and 16.9 mm Hg, by 6.1 mm Hg and 15.3 mm Hg in patients of group 1 compared with group 2, 3, 4 and 5, respectively (all p <0.05).

After the analysis of the circadian profile of BP (NDR) in group 1, non-dippers are most often determined, and the prevalence of them does not differ from groups 2, 3 and 4 (p>0.05), on second place in frequency - dippers, which in 1.3 times less often than in groups 2 (χ^2 = 4.3, p <0.05), and 1.4 times less than in groups 3 and 4 (χ^2 = 4.7, p <0.05). Among patients of group 1 the highest frequency of the most unfavorable circadian profile (night-peackers) is found, which is 1.7 times higher than in group 2 (χ^2 = 3.9, p <0.05), 2.4 times higher than in group 3 (χ^2 = 4.2, p <0.05) and 6.6 times than in group 4 (χ^2 = 5.1, p <0.05). The high frequency of non-dippers detection in patients with RA and RH may indicate an increase in cardiovascular risk of this category of patients [10]. It should be noted that the increase in CRP levels and high RA activity by DAS28-CRP are closely associated with the development of night-peackers (OR = 1.32, 95% CI 1.02-2.98, p = 0.005 and OR = 1.38, 95% CI 1.02-3.03, p = 0.004). In the case of NSAIDs and GCs usage, it increases the chances of non-dippers and night-peackers (OR = 1.48, 95% CI 1.06-3.24, p = 0.003 and OR = 1.45, 95% CI 1.04-2.99, p = 0.03). The share of over-dippers` detection in group 1 is 3.1 times higher than in group 2 (χ^2 = 5.2, p <0.05), 2.3 times lower than in group 3 (χ^2 = 3.8, p <0.05), and 2 times than in group 4 (χ^2 = 4.4, p <0.05), in group 5 - 100.0% detection of dippers (see Table II).

We found that patients of group 1 compared with group 2 have higher SBPdn (141.5 (135.7-146.0) mm Hg) by 9.2 mm Hg (p = 0.003), DBPdn (83.4 (78.1-86.6) mm Hg) by 5.4 mm Hg (p = 0.04); SBPd (139.1 (131.9-147.0) mm Hg) by 16.1 mm Hg (p = 0.002); DBPd (84.4 (72.2-86.6) mm Hg) by 9.7 mm Hg (p = 0.04) after analyzing the parame-

ters of ABPM. Compared with group 3, patients in group 1 have higher SBPdn by 28.0 mm Hg (p <0.001), DBPdn by 16.7 mm Hg (p <0.001); SBPd by 23.3 mm Hg (p <0.001), DBPd by 15.2 mm Hg (p <0.001), SBPn by 41.4 mm Hg (p <0.001), DBPn by 22.0 mm Hg (p <0.001). SBP in our patients with RA in combination with H correspond to other studies [11]. When comparing groups 1 and 4, we found that in group 1 SBPdn higher by 10.8 mm Hg (p = 0.002), DBPdn by 7.5 mm Hg (p = 0.008), SBPn by 20.6 mm Hg (p>0.001), DBPn by 6.7 mm Hg (p = 0.009) than in group 4. Summarizing the data obtained, it should be noted that patients with RA and RH have a higher level of SBP and DBP than patients with RA and H and patients with H. These changes are due to higher BP at night, which together with the higher frequency of night-peackers characterizes this category of patients as those at higher risk of severe cardiovascular events, which confirms the importance of monitoring and proper BP managementat night [12-14].

The results of the correlation analysis turned out to be interesting. In group 1 female have higher DBPdn (r = 0.29, p <0.05), with increasing with age. The values of DBPn (r = 0.33, p <0.01), PBPdn (r = 0.31, p <0.05), PBPd (r = 0.31, p <0.05), and PBPn (r = 0.32, p <0.05) are elevated. With a longer duration of RA, a higher number of night-peackers is registered (r = 0.30, p <0.05); patients on NSAIDs use have higher rates of office SBP (r = 0.27, p <0.05) and DBP (r = 0.33, p <0.01). With increasing levels of IL-6, are detected higher values of SBPdn (r = 0.27, p <0.05), DBPn (r = 0.41, p <0.01), PBPn (r = 0.31, p <0,05) and lower levels of SBP and DBP NDR (respectively r = -0.35 and r = -0.32, p <0.05).

DISCUSSION

After comparing our data with the results of a cross-sectional analysis of ABPM, obtained from 26,170 patients, we determined that in patients of group 1 the frequency of dippers is 1.3 times lower than in the general population, with the quantity of non-dippers + night-peackers 56.4% versus 51.3% of group 2, 36.6% of group 3 (p = 0.008) and 35.1% of group 4 (p = 0.006), which shows a significantly worse prognosis of cardiovascular catastrophes in patients with both RA and RH, and RA and H compared with patients with RA and H separately and with the general population [15]. It may also be associated with endothelial and immunological changes leading to premature atherosclerosis, as the presence of macrophages and lymphocytes. Tumor necrosis factor alpha, interleukin (IL) -6, -1 and other factors such as T- and B- cells synthesize in the atheroma [16, 17]. In addition, changes in hemodynamics may also cause higher morbidity and mortality from CVD in these patients (episodes of coronary ischemia during sleep, increased risk of arrhythmia, orthostatic hypotension at night, cerebral ischemia with hypoactive delirium and increased risk of stroke, especially lacunar) [18].

NDR of BP is a physiological response of the body, but a significant increase in BP is the risk of developing hypertensive disorders of target organs and cardiovascular events [19]. Morning increase in SBP is one of the manifestations of changes in the autonomic nervous system, when SBP is increased to a certain value due to sympathetic activity is physiological. At the same time as the activity of the sympathetic nervous system elevates, the levels of blood cortisol and procoagulative activity what leads to the activation of the renin-angiotensin-aldosterone system. Activation of all these factors and a significant increase in SBP (more than 34 mm Hg compared to SBP during sleep) are the cause of increased risk of stroke, myocardial infarction, arrhythmias and sudden cardiac arrest during this period. In our study, SBP NDR in patients of group 1 is lower 1.7 times than in group 2 (p = 0.006), 2.1 times than in group 3 (p = 0.005) and 1.5 times than in group 4 (p = 0.008); DBP NDR in group 1 is 1.4 times lower than in group 3 (p = 0.001). Our data correspond to the analysis of 29 patients with RA and H [18].

Patients with RA are characterized by significant frequency, very low awareness and poorer control of H [20] that leads to the development of adverse cardiovascular events. According to Bartels et al., despite doctors' awareness of the high cardiovascular risk in patients with RA, 22% of the 2,677 outpatient visits to the clinic did not include BP measurements, and 47% were not accompanied by BP management, only 31% cases were accompanied by advice on BP control, of which less than 10% of visits were properly documented and provided the right recommendations [21]. According to other data, by daily monitoring of BP in patients with RA, "masked" H is detected with a frequency of 10-30%, both due to lack of adequate BP control and by increasing BP at night [22]. In addition, the frequency and features of RH in patients with RA have not been studied in depth, which is an important problem for management in these patients.

It was found that 79% and 66% had H (in automatic BP measurement) after analyzing the data of 62 patients with RA according to the criteria of ACC / AHA and ESC / ESH, respectively, according to Bartolini and colleagues [20]. Panoulas et al. studied 400 patients (mean age 63 years) with RA and the prevalence of H in that cohort was 70.5% (282 people). Among those, 60% knew about H and received treatment, 40% were not diagnosed, and only 22% had optimally controlled BP. Multivariate regression analysis showed that the frequency of H was positively correlated with the age of patients (1.054, p = 0.001), body mass index (1.06, p = 0.038) and the use of GCs (2.39, p = 0.045) [1]. At the same time, H can increase morbidity and

mortality from cardiovascular diseases (CVD) in patients with RA who develop H decades earlier than in the general population.

Not only H does increase the overall risk, but also the above-mentioned deterioration of endothelial function and premature atherosclerosis (high levels of CRP and IL-6 are positively correlated with CVD in RA) and other traditional (hyperlipoproteinemia, smoking, diabetes) and non-traditional risk factors (abnormal revascularization function of endothelial progenitor cells in damaged peripheral vessels, gene polymorphism, elevated lipoprotein A, decrease in the level of high-density lipoproteins, insufficient compliance of the arterial wall compared with healthy subjects) [23]. We should not forget about the relationship between RA and H due to common mediators of inflammation, changes in lipoprotein spectrum, immune response, but the features of cardiovascular comorbidity in RA remain unknown [18, 24].

Unfortunately, studies of RH in patients with autoimmune diseases have not attracted the attention of a large number of researchers. The first publications on the relationship between CRP levels and cardiovascular risk in patients with RH appeared in 2016, when data were published that patients with RH have above average CRP levels (3.8 mg / l), there is a twice as high risk of cardiovascular events and a higher risk of cardiovascular death among them [25]. New evidence appeared later that proinflammatory agents such as IL-6, IL-1β, IL-10, and tumor necrosis factor-α may play a significant role in the development of RH by not only increasing the BP but also elevating arterial stiffness, the development of endothelial dysfunction, the occurrence of oxidative stress and target organs damage [26, 27]. It should be noted that such a picture of slightly elevated BP is confirmed in another Czech study and correlated with the age of patients [8]. The high value of BP may correspond to the increase in the thickness of the intima-media complex and the myocardial mass of the left ventricle and characterizes both direct load on blood vessels and mechanical pressure on atherosclerotic plaques [28]. Moreover, important regulatory factors of BP are the sympathetic nervous and renin-angiotensin-aldosterone systems [27].

CONCLUSIONS

Among patients with RA in combination with RH the most common type of the violation of the daily profile of BP is non-dippers (38.7%). These patients are characterized by an increase in BP more at night ($p < 0.003$), that corresponds to an increase in the proportion of night-peackers (17.7%). The presence of RA determines worse control of diastolic BP ($p < 0.01$) and more vascular overload on organs and systems at night ($p < 0.05$). In patients with RA and RH worse BP control is determined by female gender, old age, longer duration and higher RA activity, NSAIDs intake ($p < 0.05$).

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