Research Article

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Ambulatory blood pressure monitoring and hypertension related cardiovascular risk in patients with rheumatoid arthritis

Background: To assess hypertension related cardiovascular risk parameters in patients with rheumatoid arthritis. To determine the effect of long-term treatment with corticosteroids, non-steroid anti-inflammatory drugs, and methotrexate on diurnal BP variability.

Material and methods: 60 patients with clinically stable rheumatoid arthritis and treated hypertension. Casual blood pressure measurement and 24-hour ambulatory blood pressure monitoring.

Results: Mean casual systolic blood pressure 139.0 ± 14.6 mmHg, diastolic blood pressure 85.7 ± 6.5 mmHg, and heart rate 74.9 ± 7.2 beats.min^{-1}. Mean 24-hour systolic blood pressure 129.0 ± 12.7 mmHg, diastolic blood pressure 77.6 ± 7.4 mmHg, and heart rate 73.9 ± 8.7 beats.min^{-1}. Mean casual pulse pressure 54.7 ± 15.6 mmHg, and the mean 24-hour ambulatory pulse pressure 50.1 ± 11.0 mmHg. The mean morning surge of systolic blood pressure 35.3 ± 11.00 mmHg. The number of patients with increased short-term variability of their systolic blood pressure using the coefficient of variation 30 (50%). A number of systolic nondippers in the group were treated with corticosteroids and non-steroidal anti-inflammatory drugs 34% and 35%, respectively, and a number of excessive diastolic dippers in the group were treated with methotrexate 49%.

Conclusions: Certain hypertension characteristics in patients with rheumatoid arthritis can increase cardiovascular risk: Higher pulse pressure, elevated levels of morning surge of systolic blood pressure, increased short-term 24-hour blood pressure variability, higher number of systolic nondippers treated with corticosteroids and non-steroidal anti-inflammatory drugs, and excessive diastolic dippers treated with methotrexate. In addition increased heart rate may contribute to higher cardiovascular risk.

Keywords: hypertension • rheumatoid arthritis • 24-hour ambulatory blood pressure monitoring • pulse pressure • morning surge of blood pressure • blood pressure variability • cardiovascular risk

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that affects about 1% of the world's population. Women are affected two to three times more often than men. Cardiovascular (CV) and cerebrovascular disease accounts for approximately 40% of all US and 46% of all Czech deaths. Hypertension is one of leading risk factors of CV and cerebrovascular disease. 16.5% of all deaths worldwide can be attributed to high blood pressure (BP) [1-3]. When compared with others, patients with RA have increased CV morbidity and mortality that is primarily a result of premature atherosclerosis of coronary and cerebral arteries. For example, the risk of myocardial infarction in female patients with RA is double that of the population of healthy women [4]. RA patients have higher prevalence of hypertension than the unaffected population. Hypertension along with metabolic, inflammatory, and immunological changes including endothelial impairment may play an important role in the pathogenesis of premature atherosclerosis in patients suffering from RA. The specific treatment of RA (non-steroid anti-inflammatory drugs and prednisone) can increase the prevalence of hypertension and some BP related CV risk parameters [5].

- To determine values of clinical (casual) BP and 24-hour ambulatory blood pressure monitoring (ABPM) in patients with RA and treated hypertension.
- To evaluate whether BP target values have been attained in these subjects.

- To determine the short-term 24-hour systolic blood pressure (SBP) variability, diurnal SBP and diastolic blood pressure (DBP) variability, morning surge of SBP and pulse pressure (PP) values.
- To determine the effect of long-term treatment with corticosteroids, non-steroid anti-inflammatory drugs (NSAIDs), and methotrexate on diurnal BP variability.

Material and methods

Sixty patients with clinically stable RA and treated hypertension - 15 men and 45 women with an average age of 57.9 ± 11.3 years. Mean stage of RA was classified as 2.7 ± 0.8, in accordance with Steinbrocker [6] Table 1. Forty one patients were treated with prednisone (68%, mean dose of prednisone below 7.5 mg/day, in all individuals below 10 mg/day), fifty one with NSAIDs (85%) and thirty seven with methotrexate (62%). A total of 24 patients were treated with biological therapy, and 4 patients were previously or simultaneously treated with gold.

Casual BP was measured using the calibrated mercury sphygmomanometer auscultation method in accordance with European Society of Hypertension criteria: Patients were calm and sitting for 10 minutes before dominant arm BP measurement - Korotkoff phaseI for SBP and phaseV for DBP. Average value of these two measurements was included in the analysis. Values were recorded as mean measured values ± standard deviation (SD). A mean BP value more than 140 and/or 90 mmHg was considered as uncontrolled hypertension.

Ambulatory blood pressure (ABPM) was measured on the nondominant arm using automatic SpaceLab 90207, Redmont, Washington, USA, monitor. BP was measured every 15 minutes throughout the day (6a.m.–10p.m.) and every 30 minutes throughout the night (10p.m.–6a.m.). All patients recorded their daily activities (duties, relaxation, sleep time, sleep quality, nocturnal awakening, awakening time). Patients with mean awake BP values ≥ 135/85 mmHg, mean asleep values ≥ 120/70 mmHg, and mean 24-hour ABPM values ≥ 130/80 mmHg were considered to be hypertensive. ABPM values measured in a hospital environment (30 minutes after starting to use the device, and 30 minutes before removing the device) were filtered.

PP was calculated by the formula PP=SBP-DBP. A casual PP value above 50 mmHg and ABPM PP value above 45 mmHg were considered as an increased CV risk factor [7].

Morning surge of SBP was defined as SBP elevation during the first two active hours following awakening after subtraction of the lowest hourly ABPM SBP average recorded during asleep (sleep-trough morning surge of BP).

A sleep–trough morning surge SBP value below 34 mmHg was assessed as a normal CV risk, a value of 34-55 mmHg was considered as an increased CV risk, and a value above 55 mmHg was deemed as a high CV risk factor [8].

Short-term 24-hour SBP variability was measured using the coefficient of the variation (COV) COV=SD/BP × 100. COV value 10% and more was considered as an increased CV risk factor [9].

Patients were divided into 4 groups according to BP diurnal variability - dippers (D), nondippers (ND), excessive dippers (ED), and risers (R). Statistics recorded when patients were either awake or asleep were based on actual times patients fall asleep and subsequently work up in the morning. The BP dropped during asleep compared to the awake period: 10-20% (D), above 20% (ED), 0-10% (ND), and an increase of BP during asleep (R).

Diurnal variability of BP was also assessed according to the RA treatment (prednisone, NSAIDs, methotrexate).

All analysed study participants signed an informed consent form in accordance with the Declaration of Helsinki [10]. The work is part of the grant project focused on gene polymorphisms in a cohort of patients with RA [11,12].

Results

Mean clinical SBP was 139.0 ± 14.6 mmHg, DBP 85.7 ± 6.5 mmHg, and clinical heart rate (HR) 74.9 ± 7.2 beats.min^{-1}. Average 24-hour ambulatory SBP was 129.0 ± 12.7 mmHg, DBP 77.6 ± 7.4 mmHg, and HR 73.9 ± 8.7 beats.min^{-1}. Average SBP during wakefulness was 133.8 ± 12.9 mmHg, DBP 81.5 ± 7.4 mmHg, and HR 76.9 ± 9.8 beats.min^{-1}. Average SBP during sleep was 115.5 ± 12.7 mmHg, DBP 68.0 ± 9.3 mmHg, and HR 66.5 ± 7.4 beats.min^{-1}.

Target casual BP below 140/90 mmHg was achieved in 60% of patients, target 24-hour ABPM below 130/80 mmHg was achieved in 58% of patients, target awake BP below 135/85 mmHg was achieved in 60%, and the target asleep BP was achieved in 70% of treated patients Table 2.

Mean casual PP was 54.7 ± 15.6 mmHg, mean 24-hour ABPM PP 50.1 ± 11.0 mmHg, and mean PP during awake was 50.9 ± 11.6 mmHg. The mean PP during asleep was 47.3 ± 10.3 mmHg Table 3.

Average morning surge of SBP was 35.3 ± 11.00 mmHg. The number of patients with morning surge of SBP below 34 mmHg was 31 (52%), between 34-55 mmHg was 24 (40%) and above 55 mmHg was 5 (8%) Table 4.

Short-term 24-hour SBP variability was 9.95 ± 2.47% determined by COV. The number of patients with elevated SBP variability determined by COV was 30 (50%) Table 5.

24-hour diurnal variability of BP: Number of systolic dippers was 29 (48%), nondippers 17 (28%), excessive dippers 10 (17%), and risers 4 (7%), the number of diastolic dippers was 31 (52%), nondippers 8 (13%), excessive dippers

Table 1. Study population

Number	N=60
Male	N=15
Female	N=45
Smoking	N=9 (15%)
Diabetes	N=11 (18%)
Age (Years ± SD)	57.9 ± 11.3
Body mass index (kg.m-2 ± SD)	26.8 ± 5.0
Stadium of rheumatoid arthritis* ± SD	2.7 ± 0.8

*according to Steinbrocker et al.
SD – standard deviation

Table 2. Mean blood pressure levels and number of patients with target blood pressure

BP mmHg	SBP ± SD	DBP ± SD	HR (min-1) ± SD	Target BP	% (Number)
Casual	139.0 ± 14.6	85.7 ± 6.5	74.9 ± 7.2	<140/90	60 (36)
24-hour	129.0 ± 12.7	77.6 ± 7.4	73.9 ± 8.7	<130/80	58 (35)
Awake	133.8 ± 12.9	81.5 ± 7.4	76.9 ± 9.8	<135/85	60 (36)
Asleep	115.5 ± 12.7	68.0 ± 9.3	66.5 ± 7.4	<120/70	70 (42)

SD – standard deviation
BP – blood pressure
HR – heart rate
SBP – systolic blood pressure
DBP – diastolic blood pressure

Table 3. Pulse pressure, N=60

Casual PP ± SD	54.7 ± 15.6 mmHg
24-hour PP ± SD	50.1 ± 11.0 mmHg
Awake PP ± SD	50.9 ± 11.6 mmHg
Asleep PP ± SD	47.3 ± 10.3 mmHg

SD – standard deviation
PP– pulse pressure

Table 4. The morning surge of blood pressure

N=60 mmHg	Mean morning surge of SBP	Mean SBP max	Mean SBP min
	35.3 ± 11.0	138.6 ± 13.7	103.3 ± 13.4
	Morning surge of SBP	**Number of patients (%)**	
Normal risk*	<34,0	31 (52)	
Increased risk	34-55	24 (40)	
High risk	>55	5 (8)	

SBP – systolic blood pressure
SBP max – SBP during the first two active hours following awakening
SBP min – the lowest hourly mean SBP recorded during sleep* The normal, the increased and the high risk for developing cardiovascular disease

20 (33%), and risers 1 (2%). Total number of systolic dippers (D+ED) was 39 (65%), nondippers (ND+R) 21 (35%); total number of diastolic dippers was 51 (85%) and nondippers 9 (15%) Table 6.

Effects of corticosteroids, NSAIDs and methotrexate on monitored parameters of dipping are shown in Table 7.

Proportion of the various classes of antihypertensive drugs and their combinations are shown in Table 8.

Discussion

Prevalence of hypertension is high in patients with RA. Panoulas et al. studied 400 patients with RA, and the prevalence of hypertension in this cohort was 70.5% (282 individuals). Of these patients, 60% were aware of the disease and were treated, 40% were not diagnosed, and only 22% had optimally controlled BP. Mean age in the cohort was 63 years. Multivariate regression analysis found that hypertension had a positive correlation with age (1.054,

Table 5. Short-term variability of systolic blood pressure according to coefficient of variation

N=60	COV ± SD%
24-hour ABPM SBP variability	9.95 ± 2.47
Number of patients with increased SBP variability*	30 (50%)

SD – standard deviation
CV – coefficient of variation
SBP – blood pressure
ABPM – 24-hour ambulatory blood pressure monitoring
* - increased blood pressure variability (COV >10%)

Table 6. 24-hour diurnal variability of blood pressure

N=60	SBP number (%)	DBP number (%)	Total
Dippers	29 (48%)	31 (52%)	SBP 39 (65%) dippers*
Excessive dippers	10 (17%)	20 (33%)	DBP 51 (85%)
Nondippers	17 (28%)	8 (13%)	SBP 21 (35%) nondippers*
Risers	4 (7%)	1 (2%)	DBP 9 (15%)

Dippers – 10-20% decrease of blood pressure during asleep
Excessive dippers – more than 20% decrease blood pressure during asleep
Nondippers – 0 -10% decrease of blood pressure during asleep
Risers – increase of blood pressure during asleep
* Total dippers/nondippers – ≥ 10% decrease of blood pressure during asleep/< 10% decrease or increase of blood pressure during asleep
SBP – systolic blood pressure
DBP – diastolic blood pressure

Table 7. Impact of treatment with corticosteroids, non-steroidal anti-inflammatory drugs and methotrexate on short-term diurnal variability of blood pressure

	SBP Dipper	SBP Exdipper	SBP Ndipper	SBP Riser	DBP Dipper	DBP Exdipper	DBP Ndipper	DBP Riser
Prednison N=41	20(49%)	7 (17%)	12 (29%)	2 (5%)	18(44%)	15 (37%)	7 (17%)	1 (2%)
	In total 27 (66%)		**In total 14 (34%)**		**In total 33 (81%)**		**In total (19%)**	
NSAID N=51	25(49%)	8 (16%)	15 (29%)	3 (6%)	19(37%)	22 (43%)	8 (16%)	2 (4%)
	In total 33 (55%)		**In total 18 (35%)**		**In total 41 (80%)**		**In total 10 (20%)**	
Methotrexate N=37	20(54%)	9 (24%)	7 (19%)	1 (3%)	16(43%)	18 (49%)	3 (8%)	0 (0%)
	In total 29 (78%)		**In total 8 (22%)**		**In total 34(92%)**		**In total 3 (8%)**	
Together N=60	29(48%)	10 (17%)	17 (28%)	4 (7%)	27(45%)	22 (37%)	9 (15%)	2 (3%)
	In total 39 (65%)		**In total 21 (35%)**		**In total 49 (82%)**		**In total 11 (18%)**	

SBP – systolic blood pressure
DBP – diastolic blood pressure
Exdipper – excessive dippers
Ndipper – nondippers
NSAID – non-steroidal anti-inflammatory drugs
In total – dipper + excessive dipper or nondippers + riser

Table 8. Treatment of hypertension according to classes and combinations of the drugs

	Total N=60	1 Drug N=20	2 Drugs N=24	3 Drugs N=11	4 Drugs N=4	5 Drugs N=1
Beta-blocker	38 (63%)	6 (30%)	17 (71%)	10 (91%)	4 (100%)	1 (100%)
ACE-I	38 (63%)	5 (25%)	17 (71%)	11 (100%)	4 (100%)	1 (100%)
Ca-blocker	19 (32%)	4 (20%)	4 (17%)	6 (55%)	4 (100%)	1 (100%)
Diuretic	18 (30%)	3 (15%)	7 (29%)	5 (45%)	2 (50%)	1 (100%)
Sartan	8 (13%)	2 (10%)	3 (13%)	1 (9%)	2 (50%)	0
Rilmenidin	1 (2%)	0	0	0	0	1 (100%)

ACE-I – angiotensin convertase inhibitor
Ca-blocker – calcium channel blocker
Rilmenidin – central imidazolin 1 receptor agonist

P=0.001), body mass index (1.06, P=0.038), and the use of corticosteroids (2.39, P=0.045) [5]. Hypertension prevalence in the Caucasian population at the age of 60 years is in the range of 40% to 60% [13]. Thus, RA patients have a hypertension prevalence of 10-20% higher than the normal population. Why this prevalence of hypertension is so high was not clearly answered, yet many factors seem to be involved. High inflammatory activity with changes in immunological parameters leads to endothelial dysfunction and dominance of vasoconstrictors. Polypharmacotherapy and in particular the use of NSAIDs and corticosteroids may increase BP. Pain and decreased physical activity contribute to obesity, increased sympathetic activation, and hypertension.

Simultaneously, hypertension may contribute to increased CV morbidity and mortality in patients with RA. Cardiovascular events among patients with RA, as well as diabetic patients, occur a decade earlier than in the general population. Not only does hypertension contribute to an increased risk but also to the aforementioned impairment of endothelial function with premature atherosclerosis (high C reactive protein and interleukin-6 have positive correlation with CV diseases in RA) and other traditional (hyperlipoproteinemia, smoking, diabetes) and non-traditional risk factors (abnormal revascularization function of endothelial progenitor cells in damaged peripheral vessels, genetic polymorphism, elevated lipoprotein A, decreased levels of high density cholesterol, arterial wall compliance failure compared to age-matched healthy subjects) [4].

There is still unsatisfactory BP control in terms of CV prevention. In the Czech Republic, only about 40-50% of patients with hypertension achieve target values. With our cohort, BP control was significantly better (60%) even with casual BP measurement and during ABPM Table 2. This is probably a result of more frequent visits (4 times per year) and better compliance among patients who are monitored regularly.

In our study, we focused on the character of hypertension in patients with RA and in particular on parameters that may increase CV risk. It is given that patients with RA have a risk of premature atherosclerosis, which is probably caused by impaired endothelial function, yet metabolic disorder, increased sympathetic activation, increased short term variability of 24-hour BP, and diurnal rhythm disorder can also be contributing factors. Chronic treatment with NSAIDs and corticosteroids in susceptible individuals may lead to secondary hypertension and eventual failure of normal diurnal rhythm - dipping. Impaired endothelial function and incipient atherosclerotic changes can induce rigidity of elastic artery e walls increase pulse wave velocity and the value of the systolic central aortic pressure (central SBP and PP), while decreasing the DBP value with extreme nocturnal dipping. In our group of patients, with a mean age of 58 years, mean PP values of 55 mmHg were recorded with a sphygmomanometer and 50 mmHg when ABPM measurements were used. Normal PP values for this age group are not precisely defined, however values ≤ 50 mmHg are considered to be normal when measured using sphygmomanometers and ≤ 45 mm with ABPM. Pierdomenico et al. studied a similar patient cohort and examined 742 treated hypertensive patients (without an RA diagnosis). 45% were male with an average age of 59 years and had a mean casual PP of 56 mmHg (139/85 mmHg) and awake PP using ABPM of 52 mmHg (131/79mmHg) [14]. In comparison, our RA patients appear to have only slightly increased PP values, which correspond to the age and PP in the general population of hypertensive patients.

One of the major risk factors for CV disease is an early morning surge of BP. Morning SBP and HR surge is one of the manifestations of changes in

activity of the autonomic nervous system, where increased sympathetic activity and up to a certain value of the SBP is physiological. At the time the sympathetic nervous system activity increases, the level of cortisol and procoagulant activity of blood increases along with renin-angiotensin-aldosterone system activates. Activation of all these factors and a significant SBP increase (of more than 34 mmHg compared to SBP during asleep) is the cause of increased incidence of stroke, myocardial infarction, arrhythmias, and sudden cardiac arrest during this period. In our cohort, 29 RA patients had a morning surge of SBP above 34 mmHg (48%).

BP variability (BPV) is nowadays considered a novel risk factor for CV disease. In recent years, a large number of preclinical and clinical studies have clearly identified the contribution of BPV to CV complications associated with hypertension [15,16]. Moreover, preliminary data from retrospective analysis of clinical trials suggest that BPV attenuation by antihypertensive agents is a factor in the prevention of major CV events. Short-term BPV is usually defined as the oscillation of BP within 24 hours. Fluctuation of BP in a time range from minutes to hours mainly reflects the influence of central and autonomic modulation and the elastic properties of arteries. Short-term BPV during ABPM can be detected by measuring the mean SBP SD, where a normal cut-off value is defined as 15 mmHg within 24 hours. A more accurate method is to determine the COV, with a normal value being below 10%. In our group of patients, SBP variability using COV was 9.95 ± 2.47%. In absolute terms, values were over 10% in 30 (50%) of the patients. In particular, the increased value of COV among 50% of RA patients substantiated an increased CV risk in our group Table 5.

We then focused on determining the number of dippers, nondippers, excessive dippers, and risers (see definition above) in our cohort without relying on the use of specific RA medications. Individuals with a decrease in BP during asleep by 10-20% compared to awake (dippers) had the lowest CV risk. In other cases including, nondippers (BP drop of less than 10% during asleep), excessive dippers (BP drop by more than 20% during asleep), and risers (increased BP during asleep compared to awake) the CV risk was significantly increased.

Nondippers suffer more often from hypertension than normotensive patients, patients with certain forms of secondary hypertension (possible effect of NSAIDs and corticosteroids in patients with RA), and individuals with kidney disease. In hypertensive patients, nondipping occurs in 20-30%, more often in SBP. Excessive dipping is less common (about 10% -15%, more in DBP) [17]. Excessive dippers are usually elderly individuals with impaired endothelial function, atherosclerosis, and reduced compliance of great arteries (the possible influence of RA immunological, inflammatory, and metabolic changes). They also have a higher risk of lacunar stroke and silent myocardial ischemia [18]. Risers have the highest risk of cardiovascular complications, since they are mostly patients with disorders of the autonomic nervous system (diabetes, neurological diseases). In a population of hypertensive patients comprising 6-10%, normotensives account for 3-5% [14].

Unfortunately reproducibility of diurnal BP values is relatively small with repeated measurements. 25%-32% of patients change the state of dipping (dippers in nondippers and vice versa) [18]. When we divided our cohort to only dippers (patients with ≥ 10% decrease in BP during asleep, the sum of the defined cohorts of dippers, and excessive dippers, who are usually studied together in the literature), and nondippers (including the above defined nondippers and risers), we found that according to the SBP, 65% were dippers and 35% nondippers. When these numbers are compared with published data, our proportion of nondippers was above the upper limit of what had been previously recorded for hypertensive patients without RA (up to 30%). In the DBP cohort, 85% were dippers and 15% nondippers. In comparison with the general hypertensive population, these values were identical Table 6.

In a more detailed analysis, the number of net dippers was 48% for SBP and 52% for DBP; excessive dippers were 18% for SBP and 37% for DBP. Compared to the published data, we reported a higher number of excessive dippers in both BP values. In particular, the number of excessive dippers in DBP was significantly higher (33% compared to the previously reported 10-15% in general hypertensive patients) [17]. Excessive dipping during sleep in these patients may be related to a stronger activation of the sympathetic nervous system when awake, however it may also be associated with endothelial and immunological changes leading to premature atherosclerosis as described above. Furthermore, hemodynamics may be responsible

for higher CV morbidity and mortality (coronary ischemia episodes during sleep, increased risk of arrhythmia, orthostatic hypotension with falls at night, cerebral ischemia with hypoactive delirium and greater risk of stroke, particularly lacunar) Table 6.

We also studied the effect of specific RA treatment on diurnal BP values. The majority of our patients used NSAIDs (n=50), corticosteroids (n=41) and methotrexate (37) as reported above. Among susceptible individuals, NSAIDs may increase BP values. The pathophysiological mechanism is probably the decrease in the levels of vasodilator prostaglandins in the kidneys, with associated increased vasoconstriction and sodium retention (and water) in the extracellular fluid. Hypertension has a character of volume hypertension with a lower antihypertensive effect of angiotensin convertase inhibitors (ACEI). Morrison et al. conducted an analysis of studies focusing on the effect of long-term use of NSAIDs on BP and hypertension. They found that ibuprofen increases SBP on average by 3.54 mmHg and DBP by 1.16 mmHg; and indomethacin increases SBP by 2.9 mmHg and DBP by 1.58 mmHg, both statistically significant. Diclofenac had no statistically significant effect on BP as well as naproxen, sulindac, and nabumetone, for which there was no relevant data available. Compared with a placebo, the relative risk of hypertension associated with ibuprofen treatment was 2.85 - statistically significantly increased [19].

Panoulas et al. in a second article assessed the effect of long-term treatment with corticosteroids in low (up to 7.5 mg prednisone daily) and moderate dose (above 7.5 mg of prednisone daily) on the prevalence and risk of hypertension in RA. They found that long-term administration of moderate doses of corticosteroids increases the prevalence of RA hypertension (84.7% *versus* 70.7% with a low dose and 67.3% without treatment with corticosteroids). With a long-term treatment of a moderate dose of corticosteroids, the risk of hypertension was 2.57 times higher than in patients who were not on corticosteroids [20].

It is therefore clear that the treatment with NSAIDs and corticosteroids increases the risk of hypertension and related CVD risk. Increased CVD risk may also be due to impaired diurnal BP rhythm. Therefore, we focused on the effect of various medicines on diurnal rhythm. With the use of NSAIDs and prednisone, we found a slightly higher percentage of nondippers (34% and 35%) in the SBP and a significantly higher percentage of excessive dippers (37% and 43%) in the DBP. During treatment with methotrexate, we noticed a higher number of physiological dippers during evaluations of the SBP and DBP. Excessive dippers comprised a significantly higher percentage, in particular during DBP evaluation (49%) Table 7. The results, on one hand, show less risk of nondipping and nocturnal BP increment in patients treated with methotrexate compared to prednisone and NSAIDs. However, there were a greater percentage of excessive dippers, which again increases the risk of CVD [21].

In our study, the average number of medications used in the treatment of hypertension was 2.1 with most being beta-blockers and ACE-I. Beta-blockers were indicated for increased sympathetic activity and a tendency to increase HR in RA patients. Despite the majority of our cohort taking beta-blockers (63%), the average HR was 74 beats.min^{-1}. Among the general hypertension population, treatment with beta-blockers often results in HR below 70 beats.min^{-1} [22]. RA patients therefore have slightly higher than average HR compared to other hypertensive patients, and this may be a factor contributing to higher cardiovascular risk [23].

44 (73%) of our patients were treated with monotherapy or a combination of two medications. They have mostly the 1st and 2nd grade hypertension Table 8.

Conclusion

Sixty percent of our RA patients achieved target BP with both casual measurements and ABPM.

RA patients had a slightly higher PP (5 mmHg compared to the general population) with both types of BP measurement.

Forty-eight percent of patients had sleep-trough morning surge of SBP risk values with ABPM (above 35 mmHg).

Fifty percent of individuals with RA and hypertension had an increased short-term 24-hour BP variability measured by COV (10% and more).

All of these factors, which may be caused by both neurohumoral changes and specific therapy, increase the CV risk in hypertensive patients with RA. Conversely, hypertension together with these circumstances can cause increased rigidity of the arteries, endothelial function impairment, and an elevated risk for atherosclerosis.

When evaluating the 24-hour diurnal BPV, we discovered among our entire cohort a higher incidence of nondippers (35%) for the SBP value in comparison with frequently cited published data. The percentage of nondippers for the SBP value was higher in patients treated with corticosteroids and NSAIDs (34% and 35%, respectively). We noticed a higher percentage of excessive dippers for the DBP value, both in the whole cohort (37 %) and especially in patients treated with methotrexate (49%), prednisone (37%) and NSAIDs (43%).

Nondipping and excessive dipping in addition to hypertension may also increase the risk of CV diseases.

Despite of treatment with beta-blockers (68%) our patient cohort had an increased mean HR (74 beats.min^{-1}), which can be an additional CV risk factor.

Limitations

The absence of clearly defined arbitrary values of certain risk parameters and its correlation to the CV risk (morning blood pressure surge, the value of PP, short-term BP variability). Missing second ABPM examination in assessing changes in diurnal BP patterns (due to the high variability of a control measurement values).

Missing comparison of diurnal BP levels in untreated and treated (prednisone and NSAIDs drugs) patients with RA. There is not clear the proportion of increased CV risk: it is mainly due to elevated BP, caused by inflammatory cytokines or specific treatment of RA?

There is not clear the proportion of patients with true essential hypertension and secondary hypertension caused by RA therapy.

Conflict of interest

The authors report no declarations for conflict of interest.

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