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The pattern of systemic inflammation index in normotensive non-dipper and dipper hypertensive patients

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Abstract

Objective: Continuous inflammation at the level of the vascular endothelium plays an important role in the formation of hypertension. Diurnal blood pressure (BP) variation also is a risk factor for hypertensive target organ damage. This study planned to evaluate these inflammation processes in normotensive and hypertensive patients.

Methods: This study is observational cross-sectional cohort in-design. 151 patients with a prediagnosis of hypertension included. The patients were divided into three groups (group 1: dipper normotensive, group 2: non-dipper normotensive, group 3: dipper-hypertensive) based on the results of ambulatory blood pressure monitoring. The groups were compared in terms of systemic inflammation index (SII; platelet count×neutrophil count/lymphocyte count), neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and other inflammation processes.

Results: There was a significant difference between the three groups in terms of mean platelet volume (MPV) and red blood cell distribution width (RDW) levels ($p=0.001$ and $p<0.001$, respectively). A statistically significant difference was found between the groups in terms of NLR, PLR, systemic inflammation index, lymphocyte-monocyte ratio (LMR). In subgroup analysis, NLR and systemic inflammation index were similar in group 2 and group 3, but higher than in group 1 in both groups. LMR was similar in group 2 and group 3 but lower than in group 1. In subgroup analysis PLR levels were similar in group 2 and group 3 but higher than in group 1 in both groups.

Conclusion: This study showed that normotensive non-dipper patients had inflammation as much as dipper hypertensive patients according to measurement of MPV, RDW systemic inflammation index, PLR, NLR levels.

Keywords: Hypertension, blood pressure, ambulatory blood pressure monitoring, mean platelet volume, red blood cell distribution width, circadian variation, non-dipper

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Introduction

All hypertension patterns are risk factor for adverse cardiovascular events. Lack of nocturnal blood pressure (BP) fall (non-dipping) was also found to be associated with target organ damage and worsened cardiovascular outcomes. In meta-analyses of many studies, increased BP was found to be associated with mortality in individuals who had an ischemic event (1).

Causes such as vasoconstriction, remodeling of the vascular wall, and in situ thrombosis contribute to the development of high BP (2). In a remarkable way, there is an increased platelet activation and aggregation in hypertension. Possible underlying mechanism is that platelets with large volume and mass are more active enzymatically. They can secrete more prothrombotic material (3, 4). Elevated mean platelet volume (MPV) and red blood cell distribution width (RDW) levels are independent predictors for increased myocardial infarction and also predict death or recurrent vascular events after myocardial infarction (5).

High nocturnal BP induces further endothelial damage. And, MPV was found higher in non-dipper hypertensive patients, than in dipper hypertensive patients (6).

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There is not enough information in the literature about the inflammatory profile of different types of hypertension.

There is the scarcity of knowledge on the inflammatory profile of different types of hypertension including white coat and secondary hypertension types.

This study was conducted to reveal this condition in question by assessing inflammation indexes such as systemic inflammation index (SII; platelet × neutrophil /lymphocyte), neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) which are easily obtained from peripheral blood cells in patients with hypertension and normotensive individuals and to evaluate their association with BP circadian patterns.

Methods

Study population and design

The research was performed in accordance with the principles set by the Declaration of Helsinki, the International Good Clinical Practice guidelines and all applicable legal requirements. The study protocol was approved by Tekirdag Namık Kemal University Ethics Committee.

This study, observational cross-sectional cohort in-design, included 151 patients over the age of 18 with a prediagnosis of hypertension. All patients were informed about the study and their written consent was obtained.

Patients with secondary hypertension, congestive heart failure, cardiac valve diseases, active infection, inflammatory disease, malignancy, renal or hepatic dysfunction that might affect the inflammation indexes were excluded from the study. Also, patients on treatment with statins or other drugs with potential antiinflammatory potential which may interfere with the results were excluded from the study.

The patients were divided into three groups: Group 1 - dipper normotensive, Group 2 - non-dipper normotensive, Group 3 - dipper-hypertensive, based on the results of ambulatory blood pressure monitoring (ABPM).

Assuming an alpha of 0.05, a power of 0.80, and 20% at least difference in terms of baseline selected inflammation indexes value consistent with previous reports, the estimated sample size was at least 50 patients in each group.

Ambulatory blood pressure monitoring

BP and heart rate were measured and recorded automatically by ABPM system (Darwin Professional Medilog; Schiller BR-102, Switzerland). Hypertension was defined as systolic BP>140mm Hg or diastolic BP>90mm Hg in the sitting position as the average of three different measurements at home or office. On ABPM, average systolic BP over > 135/85 mmHg at daytime (awake), average systolic BP over >120/70 mmHg at nighttime (asleep) or in average 24-hour measurements systolic BP over >130/80 mmHg, was defined as hypertension. The device was set to obtain BP readings at 15 min intervals during the day (07:00 am–10:00 pm) and at 30 min intervals during the night (10:00 pm–07:00 am). Patients with a mean of three measurements below 140/90 in office blood pressure measurements and those with BP measurements below the above-mentioned values in ABPM were considered normotensive.

The group whose average nighttime systolic and diastolic BP decreased by 10-20% compared to daytime BP was defined as dipper. The group whose systolic BP or diastolic BP at night decreased by 10% or less compared to daytime was named as non-dipper.

Pre-hypertension (high-normal) is defined as office SBP values 130-139 mmHg and/or diastolic BP (DBP) values 85-89 mmHg at daytime based on 2018 ESC/ESH Guidelines for the management of arterial hypertension (7).

Systemic inflammation indexes

Peripheral venous blood samples were drawn from antecubital vein between 08:00 - 10:00 am after overnight fasting within the first 24 hours of index hospitalization. Complete blood count (CBC) was performed using the Mindray Auto Hematology Analyzer-BC-6800 device (A. Menarini Diagnostics Ltd, Wokingham, UK). CBC consisted of white blood cells count, hematocrit and hemoglobin, MPV and platelet count, and rates of each leukocyte parameter. C-reactive protein (CRP) was analyzed by an immunoturbidimetric method (Roche Modular P, Hitachi, Mannheim, Germany). SII index was calculated with the formula platelet×neutrophil /lymphocyte. NLR and PLR were defined as the total number of neutrophils or platelets divided by the total number of lymphocytes.

Statistical analysis

SPSS for Windows Version 22 (SPSS Inc., IL, USA) was used for all statistical analysis. Continuous variables, were expressed as mean (standard deviation), and categorical variables were expressed as percentage. Whether the parameters conformed to the normal distribution was evaluated with the Kolmogorov Smirnov test. One-way ANOVA test was used for comparison of three groups continuous data with normal distribution. In post hoc analysis, parameters with equality of variance according to the Levene test were evaluated with the Tukey test, and parameters without equality of variance were evaluated with the Tamhane test. Abnormally distributed data in the three groups were compared using the Kruskal Wallis test and Mann-Whitney U test was used for comparison of parameters between 2 groups. The Chi-square test was used for comparing categorical variables. .P value less than 0.05 was accepted statistically significant.

Results

The clinical and demographic data of the study population is summarized in Table 1. According to ABPM results, 50 subjects were classified as dipper normotensive, 50 subjects were classified as non-dipper normotensive, and the last 51 subjects were in the dipper-hypertensive group. Age was found to be significantly higher in dipper hypertensive group ($p<0.05$). The group with the lowest mean age was the dipper normotensive group. There were no significant differences in gender, smoking

habit, peripheral artery disease, presence of atrial fibrillation, coronary artery disease, and height between the three groups. Diabetes mellitus and hyperlipidemia rates were higher in the dipper hypertensive group (Group 3) and weight was higher in the non-dipper normotensive group (Group 2) (p<0.05 for both). While beta-blocker, Ca–channel blocker,angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker, diuretic use was highest in group 3 and acetylsalicylic acid use was highest in group 2 (p<0.05 for all).

Table 1. Baseline characteristics of the groups

Variables	Group 1 (n=50)	Group 2 (n=50)	Group 3 (n=51)	p
Age, years	42.7(12.4)	50.8(11.5)	54.6 (12.3)	<0.001*a/c
Male, n(%)	23 (46)	18 (36)	28 (54.9)	0.162†
Female, n(%)	27 (54)	32 (64)	23 (45.1)	0.162†
Height, cm	167.1 (5.8)	163.8 (8.5)	165.8 (12.8)	0.405*
Hyperlipidemia, %	0 (0)	9 (18.4)	10 (19.6)	0.004†
BMI, kg/m^2	24.7 (3.3)	25.0 (4.1)	24.0 (3.9)	0.03*a/c
Smokers, n(%)	2 (4)	2 (4)	0 (0)	0.351†
Diabetes mellitus, n(%)	1 (2)	7 (14)	16 (31.4)	<0.001†
Peripheral artery disease, n(%)	1 (2)	0 (0)	0 (0)	0.362†
Coronary artery disease, n(%)	0 (0)	2 (4)	0 (0)	0.129†
Presence of atrial fibrillation, n(%)	0 (0)	0 (0)	1 (1.91)	0.085†
Beta blocker, n(%)	1(2)	11 (22)	20 (39.2)	<0.001†
Ca–channel blocker %	1 (2)	16 (32)	17 (33.3)	<0.001†
ACE-I/ARBs, n(%)	0 (0)	5 (10)	15 (29.4)	<0.001†
Diuretic, n(%)	0 (0)	8 (16)	23 (45.1)	<0.001†
Acetyl salicylic acid, n(%)	0 (0)	7 (14)	4 (7.8)	0.026†

Group 1: Dipper normotensive, Group 2: Non-dipper normotensive, Group 3: Dipper-hypertensive
*One-Way ANOVA test a: p<0.05: Group 1 vs. Group 2; b: p<0.05: Group 2 vs. Group 3; c: p<0.05: Group 1 vs. Group 3
† Chi square test (percentage)
BMI-body mass index, ACE-I - angiotensin-converting enzyme inhibitors, ARBs - angiotensin receptor blockers

There was a statistically significant difference between the groups in terms of monocyte count, MPV, RDW, NLR, SII, PLR, lymphocyte- to-monocyte ratio (LMR), Glomerular filtration rate (GFR) levels (Table 2) (p<0.05). There was no difference between the groups in terms of other laboratory parameters. In terms of ABPM results, all BP levels were significantly higher in group 3 (p<0.05).

Table 2. Laboratory parameters of the groups

Variables	Group 1 (n=50)	Group 2 (n=50)	Group 3 (n=51)	p
Glucose, mg/dl	97 (74-215)	100 (72-164)	103 (76-438)	0.083‡
Hemoglobin, g/dl	14.0 (1.4)	13.8 (1.4)	13.9 (1.5)	0.767
Hematocrit %	41.7 (5.7)	41.4 (3.9)	41.8 (4.5)	0.698
Platelet count, ×103/µL	260.0 (61.6)	265.0 (64.4)	254 (53)	0.618
Serum creatinine, mg/dl	0.75(0.36-1.41)	0.79(0.54-9.67)	1 (0.55-5.96)	0.796‡
Total cholesterol	215.7 (43.5)	218.8 (41.9)	207.4 (45.5)	0.400
High density lipoprotein-cholesterol, mg/dl	54 (32-84.5)	46 (25-82)	49.6 (30-79)	0.150‡
Low-density lipoprotein cholesterol, mg/dl	121 (50-257)	125 (41-225)	128 (31-204)	0.718‡
Triglyceride, mg/dl	148 (32-366)	164.5 (41-707)	140 (68-526)	0.460‡
High sensitivity C-reactive protein, mg/dl	6.1 (25.5)	5.0 (20.8)	11.5 (32.8)	0.862*
White blood cell count, ×103/µL	7.4 (3.53-17.30)	7.6 (4.74-13.09)	7.2 (4.5-12.78)	0.579‡
Neutrophil count, ×103/µL	4.1(1.54-12.9)	4.6(2.25-8.33)	4.1(2.15-9.6)	0.309‡
Lymphocyte count2, ×103/µL	2.3 (0.62)	2.3 (0.78)	2.2 (0.75)	0.602*
Monocyte count, ×103/µL	0.53 (0.1)	0.54 (0.4)	0.52 (0.1)	0.036*b
Eosinophil, ×103/µL	0.14 (0.03-0.49)	0.15 (0.04-1.28)	0.16 (0.02-0.47)	0.696‡
Basophil, 103/µL	0.0310 (0.13)	0.051 (0.75)	0.034 (0.24)	0.061*
Mean platelet volume, fl	8.9 (0.7)	9.6 (1.0)	9.5 (0.9)	0.001*a/c
Red cell distribution width, %	13 (10-15.2)	14.3 (11-16)	14.4 (12.8-16)	<0.001‡
Neutrophil- to- Lymphocyte ratio	1.8 (0.61-7.15)	3.3 (1.55-8.4)	2.8 (1.34-13.87)	<0.001‡
Systemic immune inflammation index	286.9 (91.322-929.651)	821.2 (300.00-2160.00)	719.9 (258.-3134.83)	<0.001‡
Platelet- to- Lymphocyte ratio	71.4 (24.3)	195.6 (55.9)	204.5 (50.5)	<0.001*a/
Lymphocyte - to-Monocyte ratio	15.8 (4.67-86.67)	9.7 (1.35-38.4)	8.9 (2.89-61.5)	<0.001‡
Glomerular filtration rate	101 (51-129)	96.5 (47-130)	89 (63-140)	0.000‡
Monocyte/ High density lipoprotein-cholesterol	10.5 (4.6)	11.6 (10.7)	10.7 (4.1)	0.712*
Daytime mean SBP, mmHg	112(98-125)	110(100-155)	155(138-172)	<0.001‡
Daytime mean DBP, mmHg	75 (64-82)	72 (62-123)	96 (85-112)	<0.001‡
Night-time mean SBP, mmHg	100 (85-110)	105 (74-120)	138 (120-150)	<0.001‡
Night-time mean DBP, mmHg	65 (55-75)	68 (58-115)	85 (70-101)	<0.001‡

‡ Kruskal Wallis (median, minimum-maximum), *One-Way ANOVA (mean (standard deviation)) a: p<0.05: Group 1 vs. Group 2; b: p<0.05: Group 2 vs. Group 3; c: p<0.05: Group 1 vs. Group 3
Group 1: Dipper normotensive, Group 2: Non-dipper normotensive, Group 3: Dipper-hypertensive
SBP - systolic blood pressure, DBP - diastolic blood pressure

There was no difference in inflammation indexes and MPV, RDW values between group 2 and group 3, except for LMR (Table 3). Inflammation indexes, MPV, RDW levels in both groups were higher than in group 1 (p<0.001). LMR levels were higher in group 2 than in both groups (p<0.001) (Table 3).

Table 3. Subgroup analysis of the indexes

Variables	Group 1-2 p	Group 1-3 p	Group 2-3 p
NLR (Neutrophil-to Lymphocyte ratio)	<0.001	<0.001	0.146†
PLR (Platelet- to-Lymphocyte ratio)	<0.001	<0.001	0.655*
LMR (Lymphocyte-to-Monocyte ratio)	<0.001	<0.001	<0.001†
SII (Systemic immune inflammation index)	<0.001	<0.001	0.128†
MPV(Mean platelet volume)	0.001	0.003	0.914*
RDW(Red cell distribution width)	<0.001	<0.001	0.789†

* Tamhane Test was used in ANOVA post hoc analysis, Mann Whitney U test was used in Kruskal-Wallis post hoc analysis

Discussion

In this study, we found MPV and RDW levels similar in both non-dipper normotensives and dipper-hypertensives, but in both groups, MPV and RDW levels were higher than dipper normotensives.

Awareness among clinicians on subtypes of hypertension has recently increased. Many articles mainly focus the etiopathogenesis of dipper and non-dipper HT and causative factors. However, a non-dipper BP pattern is also thought to be a risk factor for target organ damage and cardiovascular diseases. Therefore, this study primarily aimed to evaluate the importance of diurnal blood pressure variation in normotensive patients by taking dipper hypertensive as the control group.

Previous studies have shown that hypertensive patients (especially the non-dipper group) may have higher MPV and RDW values compared to patients with normal blood pressure (8). Also, in previous studies, it is found a significant increase in MPV among pre-hypertensive patients, which is similar to our study (9). MPV is also a marker of platelet activation and platelet size, which is an independent risk factor for hypertension, myocardial infarction, and stroke (10,11).

In hypertensive patients with increased platelet volume, and RDW levels the risk of mortality and stent thrombosis after acute myocardial infarction is increased (12). RDW increases as a result of increased erythrocyte destruction or ineffective erythropoiesis. Changes in the RDW interval can predict other results of cardiovascular disease, including coronary artery disease, pulmonary hypertension, and heart failure.

RDW is a measurement of the range in the volume and size of erythrocytes. RDW, which is a marker of inflammation, is increased in non-dipper and dipper hypertensive individuals compared to normotensive individuals (13). In non-dipper individuals, increased oxidative stress suppresses the bone marrow and causes immature erythrocytes and platelets entrance into the blood circulation, which causes an increase in RDW and MPV (14). In another study, increased C-reactive protein and RDW levels were observed in hypertensive individuals compared to normotensives (15). Overactivity of the sympathetic nervous system in non-dipper individuals may also increase erythropoiesis and affect the stimulation of erythropoiesis (16). Increased angiotensin II levels in hypertensive patients can stimulate the proliferation of erythrocyte progenitors and increase the RDW range (17). In our study, we found PLR, SII, NLR levels, which are inflammation markers, were higher in dipper hypertensive and non-dipper normotensive groups compared to the normotensive group. In addition, LMR levels were lower in these two groups.

Leukocytes, monocytes, eosinophils, and platelets in the peripheral circulation take part in the initiation and maintenance of atherosclerosis and hypertension (18, 19). It was found that high NLR and PLR, SII levels, as well as low LMR levels, could be beneficial to demonstrate the severity of coronary artery disease (20).

Both innate and adaptive immunity, vascular endothelial cells, platelets and, coagulation factors take part in the formation, progression, and complication of atherosclerosis and hypertension. And this study argued that MPV and RDW may indirectly indicate platelet aggregation and activation in hypertensive patients. The difference in condition can be observed in both dipper hypertensive and non-dipper normotensive patients.

Considering that the prevalence of hypertension is increasing today, Holter monitoring is a time-consuming and expensive procedure. Inexpensive, easy to work with biomarkers such as MPV, RDW, or inflammation markers such as NLR, PLR, SII can help us in early diagnosis and treatment. New scoring systems that will be created from these inflammation indexes and biomarkers may be useful in diagnosis and treatment in the future. These results suggest the role of the inflammation indexes and biomarkers in the failure of the expected nighttime drop in BP values because systemic inflammation index may be a noninvasive marker and an indicator of autonomic nervous system functions in these populations.

Study limitations

There are limitations that must be considered when interpreting these results. The patients with advanced heart failure, secondary hypertension, new heart attack, or valvular

heart disease were not included in the study. Therefore, the results of our study cannot be attributed to all hypertensive or pre-hypertensive patients. Another limitation of our study is that non-dipper HT patients were not included in the study. The small sample size was also a limitation of the study. So, the hypothesis should be tested in a larger trial. And, the conducted analysis does not allow answering the question: whether the obtained data are independent of age, diabetes mellitus, and hyperlipidemia. Furthermore, this study is a pioneer call for further research.

Conclusion

This study showed that normotensive non-dipper patients had inflammation as much as dipper hypertensive patients according to measurement of MPV, RDW systemic inflammation index, PLR, NLR levels. Non-dipper normotensive patients may be in the early stage of hypertension, blood pressure pattern changes and inflammatory parameters increase before clinical blood pressure increases.

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Avramenko Hanna - "Healing Colors", BSMU Students Art Club, Chernivtsi, Ukraine.

You must agree that often each of us experiences moments of sadness, despair, hopelessness. Domestic problems, the disorder in your relationships...This is such nonsense compared to when it comes to health. Of course, there can be many factors in the development of diseases (heredity, professional, bad habits, etc.), but the older I become, the more I understand: the instability of psychological well-being plays almost the main role in the triggering mechanism of all diseases, including oncology, which is gaining speed more and more every day! You should think about it: what is your inner world like when you are worried or sad? The world is filled with gray colors. Take a deeper look inside yourself. Imagine what makes you happy and brings you a state of serenity and joy. Delicious food, sea, communication with beloved ones, travel, hobbies. Do you feel how the soul is filled with light and bright colors? We are able to help ourselves, help others, adding emotions and hobbies every day to a new color. The doctor does everything possible so that the patient gets out of the fetters of the disease, helping with all his might. Keep your inner rainbow alive!