ORIGINAL ARTICLE

Relation of red cell distribution width with dipper and non-dipper hypertension

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ABSTRACT

Aim Red cell distribution width (RDW), an index of erythrocyte size, is associated with high risk for cardiovascular disease. Non-dipping hypertension (HT) is lack of nocturnal fall in blood pressure (BP). The association between RDW and non-dipping BP in normotensive and hypertensive patients was investigated.

Methods A total of 170 patients were categorized into 4 groups: Normotensive-Dipper (NT-D), Normotensive-Non-dipper (NT-ND), Hypertensive-Dipper (HT-D) and Hypertensive-Non-dipper (HT-ND). RDW and hs-CRP levels were measured.

Results Hypertensive patients had higher RDW and hs-CRP levels (14.5 ± 0.87 vs.12.7 ± 0.66, $p<0.001$ for RDW; 0.99 ± 0.52 vs.0.63 ± 0.43, $p<0.001$ for hs-CRP). Besides, the RDW levels were higher in non-dippers (13.0 ± 0.63 vs.12.4 ± 0.55, $p<0.001$ for NT-ND and NT-D; 14.9 ± 0.78 vs.14.2 ± 0.82, $p<0.001$ for HT-ND and HT-D)

Conclusion RDW is elevated in non-dipping BP both in normotensive and hypertensive subjects, which may be related with increased inflammatory state.

Key words: blood pressure, circadian rhythm, erythrocyte size, inflammation

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INTRODUCTION

Red cell distribution width (RDW), an index for size variability of circulating erythrocytes, is a routine component of complete blood count (CBC) analysis and traditionally used in the differential diagnosis of anemia (1). An elevated RDW value is seen in hematological disorders such as hemolysis, impaired red cell production due to iron, vitamin B12 or folate deficiency as well as some certain clinical settings, namely hypertension, prehypertension, pregnancy, thrombotic thrombocytopenic purpura (TTP), and inflammatory bowel diseases (IBDs) (2-5). Moreover, RDW was found to be associated with adverse outcomes in patients with heart failure, coronary artery disease and acute myocardial infarction (6-9).

Hypertension (HT) is well established and modifiable risk factor for cardiovascular disease (10). Blood pressure (BP) levels show a circadian pattern in which both the systolic and diastolic BP decrease more than 10% in the night. Non-dipping HT is defined as lack of nocturnal fall in the circadian BP pattern which was shown to be associated with higher risk of cardiovascular, renal and cerebrovascular diseases (11-13). There are few reports about the association between RDW and the dipping and non-dipping patterns of BP in normotensive and hypertensive patients, however none of these studies involved newly diagnosed hypertensive patients (14-15). Therefore, in this study we aimed to investigate the association between RDW, a routinely reported parameter of CBC analysis, with the dipping and non-dipping patterns of BP in normotensive subjects and in patients with newly diagnosed HT.

PATIENTS AND METHODS

A total of 170 patients were recruited in this prospective randomized controlled study. In one hundred and ten newly diagnosed hypertensive patients according to the Joint National Committee (JNC) 7 criteria (16) were evaluated by ambulatory blood pressure monitoring (ABPM) (Suntech Medical Inc., Morrisville, NC, USA) for the dipping and non-dipping pattern. Sixty age- and sex- matched outpatient subjects without HT were taken as a control group. The patients were categorized into 4 groups as "Normotensive-Dipper" (NT-D), "Normotensive-Non-dipper" (NT-ND), "Hypertensive-Dipper" (HT-D) and "Hypertensive-Non-dipper" (HT-ND) group. A monitor recorded heart rate, systolic BP, and diastolic BP readings every 15 minutes during the daytime (7 AM to 11 PM) and every 30 minutes overnight (11 PM to 7 AM) for the 24-hour period. A greater than 10% fall both in the nocturnal systolic and diastolic BP than those of the day time values was defined as dipping pattern in concordance with the definition reported by Verdecchia (17). Detection of less than 10% decrease in either systolic BP or diastolic BP was regarded as non-dipper HT.

Patients with known coronary artery disease, secondary HT, renal failure, hepatic failure, chronic obstructive lung disease and/or manifest heart disease, such as cardiac failure (left ventricular ejection fraction<50%), atrial fibrillation and moderate to severe cardiac valve disease, diabetes mellitus, anemia, any prior blood transfusion, pregnancy, hyperthyroidism, TTP, IBDs were excluded from the study. All the participants included in the study were informed about the study and their oral and written consents on voluntary participation were obtained.

After questioning clinical history of risk factors such as age, sex, hypercholesterolemia, smoking and family history, prior medication for each participant, height and weight were measured. By dividing weight in kilograms by height in meters squared (kg/m^2), the body mass index (BMI) was calculated. All, hemoglobin (Hb), RDW, and white blood cell (WBC) counts were measured as part of the automated complete blood count analyzed by Beckman-Coulter Gen-S system device (Beckman-Coulter Inc., USA). Anemia was defined as a baseline Hb < 13 g/dL in males and Hb < 12 g/dL in females in accordance with the criteria of the World Health Organization (18).

Serum glucose, urea, creatinine, plasma total cholesterol, triglycerides (TG), high-density lipoprotein-cholesterol (HDL), low-density lipoprotein cholesterol (LDL) levels and high-sensitivity C-reactive protein (hs-CRP) were measured in venous blood samples obtained in the morning after eight-hour fasting. Blood urea nitrogen, serum creatinine, thyroid stimulating hormone (TSH), serum levels of high-density lipoprotein, low-density lipoprotein and triglycerides were recorded. hs-CRP was measured in serum by EIA

(Immage hs-CRP EIA kit, Beckman Coulter Inc., USA). Transthoracic echocardiography was performed and biplane Simpson's ejection fraction (%) was calculated before coronary angiography.

The study was approved by the Dicle University Medical Faculty Ethics Committee.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as percentages. The differences in numeric variables were evaluated by Mann-Whitney U test or Kruskal-Wallis variance analysis as appropriate. Chi–square ($\chi 2$) test was employed for the comparison of categorical variables. In order to determine the independent predictors of "non-dipping pattern" in patients with HT, uni- and multivariate analysis were performed. The parameters that were found to have a significance ($p<0.10$) in the univariate analysis were evaluated by stepwise logistic regression analysis. Ninety-five percent confidence interval and odds ratios (OR) were presented together. An explanatory evaluation of additional cut points was performed using the receiver operating characteristics (ROC) curve analysis. A $p < 0.05$ was considered as statistically significant.

RESULTS

In total 170 patients (42.4 ± 3.0 years, 64.1% comprised of males) were included in the study. Baseline clinical and laboratory characteristics of the patients relative to dipping and non-dipping status were shown in Table 1. Age, sex, BMI and medication were not different between the groups. In the normotensive group, dippers and non-dippers had similar daytime systolic and diastolic BP (114.5±6.2 vs. 111.9±9.1, p=0.24; 73.2±5.5 vs. 71.6±9.0, p=0.46), and 24-hour mean systolic and diastolic BP (108.9±6.4 vs. 110.8±8.4, p=0.40; 68.16±5.9 vs.70.7±8.4, p=0.26); however non-dippers had significantly higher nighttime systolic and diastolic BP (108.7±7.6 vs. 97.8±7.8, p<0.001; 68.7±7.6 vs. 57.8±7.8, p<0.001). In the hypertensive patients, however, while daytime systolic and diastolic BP (157.3±11.1 vs. 159.2±11.9, p=0.47; 95.8±6.2 vs. 96.9±6.0, p=0.39) was similar in the dippers and non-dippers, the hypertensive non-dippers had higher 24-hour mean systolic and diastolic BP (157.0±11.8 vs. 149.8±10.9, p=0.001; 95.0±5.4 vs. 90.0±5.9, p<0.001) and nighttime systolic and diastolic BP (152.5±12.0 vs. 134.8±10.9, p<0.001; 91.0±5.4 vs. 78.3±7.1, p<0.001) (Table 2). Daytime and nighttime heart rate values were similar in all groups.

Table 1. Baseline clinical and laboratory characteristics of patient groups

Variables	Normotensive - Dipper (n=31)	Normotensive-Non-dipper (n=29)	Hypertensive-Dipper (n=59)	Hypertensive-Non-dipper (n=51)	p
Age (years)	41.4±3.2	41.8±2.6	42.6±2.9	42.9±2.9	0.08
Sex, males (%)	21(67%)	18 (62%)	37 (62.7%)	33(64.7%)	0.81
BMI (kg/m2)	25.6±2.5	25.6±4.3	27.3±5.0	26.0 ±5.1	0.1
Smoking (%)	14 (45.2%)	14 (48.3%)	27 (45.8%)	22 (43.1%)	0.68
Ejection Fraction (%)	60.2±4.1	61±2.7	59.3±3.1	61±2.8	0.46
Medications (%)					
Aspirin	5 (16)	5 (17)	10 (16.9)	9 (17.6)	0.62
Statin	10 (25.8)	8 (27.5)	16 (27.1)	13 (25.5)	0.22
Glucose (mg/dL)	86.4±12.5	87.3±18.1	84.7±15.1	86.9±17.4	0.68
HDL-C (mg/dL)	33.0±9.2	34.4±9.9	34.5±8.7	35.4±9.6	0.72
LDL-C (mg/dL)	106.7±30.5	116.6±32.7	122.5±33.9	123.1±30.6	0.17
TG (mg/dL)	162.5±94.5	177.4±122.7	178.8±85	158.1±92.1	0.17
Creatinine	0.90±0.3	0.93±0.2	0.9±0.19	0.93±0.2	0.73
TSH	1.6±0.1	1.36±1.08	1.34±0.82	1.52±1.4	0.45
hsCRP	0.47±0.29	0.78±0.5	0.86±0.42	1.12±0.06	<0.001
Hemoglobin (g/dL)	13.1±1.4	13.1±0.99	13.5±1.1	13.4±1.4	0.33
RDW (%)	12.3±0.5	12.9±0.6	14.2±0.82	14.9±0.78	<0.001

BMI, body mass index; HDL-C, high density lipoprotein cholesterol; hsCRP, high sensitivity C reactive protein; LDL-C, low density lipoprotein cholesterol; RDW, red cell distribution width; TSH, thyroid stimulating hormone.

The patients with HT had higher RDW and serum hs-CRP levels than the normotensive patients (14.5 ± 0.87 vs.12.7 ± 0.66, p<0.001 for RDW; 0.99 ± 0.52 vs.0.63 ± 0.43, p<0.001 for hs-CRP). Moreover, the RDW levels were higher in non-dippers than the dippers in the groups (13.0 ± 0.63 vs.12.4 ± 0.55, p<0.001 for NT-ND and NT-D; 14.9 ± 0.78 vs.14.2 ± 0.82, p<0.001 for HT-ND and HT-D) (Figure 1). Similarly, serum hs-CRP levels were higher in non-dippers than the dippers in the groups as well (0.78 ± 0.5 vs.0.48 ± 0.3, p=0.017 for NT-ND and NT-D; 1.13 ± 0.6 vs.0.86 ± 0.42, p=0.016 for HT-ND and HT-D) (Figure 1). When subgroups were analyzed it was

Table 2. Ambulatory blood pressure monitoring results of dippers and non-dippers among individuals with normal and high 24-h blood pressure

Variables	Normotensive subjects			Hypertensive subjects		
	Dipper	Non-dipper	p	Dipper	Non-dipper	p
24-h systolic	108.9±6.4	110.8±8.4	p:0.40	149.8±10.9	157.0±11.8	p:0.001
24-h diastolic	68.16±5.9	70.7±8.4	p:0.26	89.9±5.9	95.0±5.4	p<0.001
Day-time systolic	114.5±6.2	111.9±9.1	p:0.24	157.3±11.2	159.2±11.9	p:0.47
Day-time diastolic	73.2.6±5.5	71.6±9.0	p:0.46	95.8±6.2	96.9±6.0	p:0.39
Night-time systolic	97.8±7.7	108.7±7.5	p<0.001	134.8±10.9	152.5±12.0	p<0.001
Night-time diastolic	57.8±7.8	68.7±7.6	p<0.001	78.3±7.1	91.0±5.4	p<0.001
24-hour heart rate	68.4±5.8	70.2±6.5	p:0.45	67.3±6.5	69.6±5.8	p:0.66

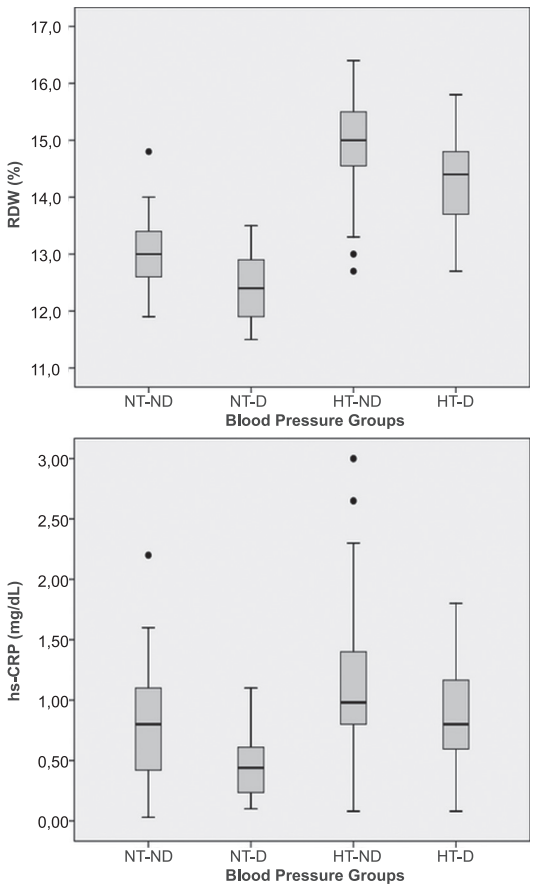

Figure 1. Correlation plot for RDW and hs-CRP

found that the serum hs-CRP levels were higher in the HT-ND group, and similar in HT-D and NT-ND groups (for HT-ND vs. HT-D groups 1.13 ± 0.6 vs.0.86 ± 0.42, p=0.016; for HT-ND vs. NT-ND groups 1.13 ± 0.6 vs. 0.78 ± 0.5, p=0.010; for HT-D vs. NT-ND groups 0.86 ± 0.42 vs. 0.78 ± 0.5, p=0.36). The serum hs-CRP levels were significantly lower than all groups in the NT-D group. Univariate correlation analysis revealed a positive correlation between RDW levels and hs-CRP levels (Rho=0.40, p<0.001) (Figure 2).

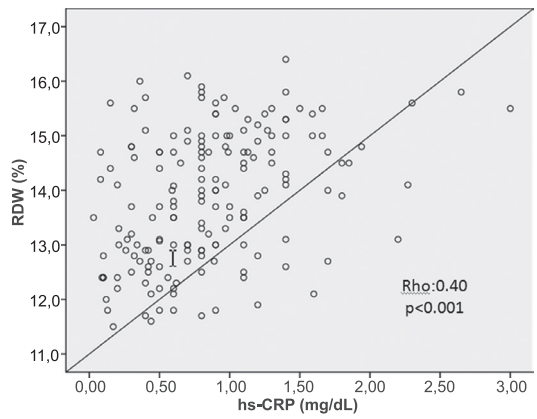

Figure 2. RDW and hs-CRP levels according to the blood pressure groups

The ROC curve analysis further revealed that RDW was a strong indicator of the "non-dipping status" in patients with HT with an AUC of 0.74 (95% CI: 0.64 to 0.83) (Figure 3). The optimal threshold of RDW level that maximized the combined specificity and sensitivity to predict the "non-dipping status" was 14.5%. Sensitivity, specificity, positive predictive value and negative predictive value to identify "non-dipper hypertensive" patients was 75%, 60%, 78, and 54%, respectively.

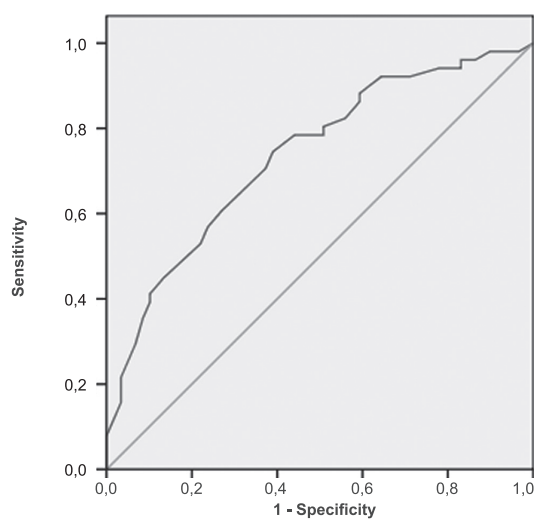

Figure 3. ROC curve showing the sensitivity and specificity of RDW with regard to "non-dipping status" in patients with hypertension. (RDW≥14.5)

For determining predictors of the "non-dipping pattern" in patients with hypertension, uni- and multivariate analyses were performed. For predicting the "non-dipping pattern" in patients with hypertension, the RDW score was dichotomized into high (RDW≥14.5) and low (<14.5) groups. In the multivariate analysis, the parameters showing significance in the univariate analysis (mean systolic BP, mean diastolic BP, hs-CRP) were evaluated by multivariate analysis in order to determine independent predictors of "non-dipping pattern". Thus, mean diastolic BP and hs-CRP were found as independent predictors of the "non-dipping pattern" (Table 3).

Table 3. Significant predictors of "non-dipping pattern" in patients with hypertension in invariable and stepwise multivariable logistic regression analyses for the red cell distribution width (RDW) cutoff of 14.5%

Variable	Univariate		Stepwise multivariate	
	OR (95 % CI)	p	OR (95 % CI)	p
"Non-dipping pattern" in HT patients				
Age	1.01 (0.88-1.15)	0.88		
Sex	1.00 (0.45-2.20)	0.99		
BMI	0.98 (0.91-1.06)	0.69		
Smoking	0.89 (0.42-1.9)	0.78		
Mean systolic BP	1.04 (1.04-1.08)	0.03	0.96 (0.92-1.00)	0.067
Mean diastolic BP	1.06 (0.99-1.13)	0.05	0.85 (0.78-0.93)	<0.001
Glucose	0.99 (0.97-1.01)	0.41		
LDL-C	1.0 (0.98-1.01)	0.38		
HDL-C	1.02 (0.89-1.06)	0.37		
Triglyceride	0.99 (0.99-1.00)	0.54		
hs-CRP	2.5 (1.09-5.8)	0.03	0.39 (0.16-0.96)	0.04
TSH	1.06 (0.75-1.5)	0.72		

BP, blood pressure; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low density lipoprotein cholesterol; OR, odds ratio; TSH, thyroid stimulating hormone

DISCUSSION

In this study the relationship between RDW and dipping and non-dipping patterns of BP both in normotensive and hypertensive subjects was investigated. This study revealed that non-dipping pattern in the circadian BP course was associated with elevated RDW levels in both normotensive and hypertensive subjects, which may be related with increased inflammatory state.

The RDW is an index for the size variability of the circulating erythrocytes routinely reported with complete blood count analysis and commonly used in the differential diagnosis of anemia (19-20). Recent studies revealed that in many clinical settings including hemolysis, impaired red cell production due to iron, vitamin B12 or folate deficiency, hypertension, prehypertension, pregnancy, thrombotic thrombocytopenic purpura (TTP), stroke, colon cancer and inflammatory bowel diseases (IBDs), the RDW values were found to be elevated (2-5, 21-22). Additionally, in patients with heart failure, coronary artery disease and acute myocardial infarction (6-9, 23) RDW was found to be associated with adverse outcomes (24).

Hypertension is a well known risk factor for left ventricular dysfunction and atherosclerotic cardiovascular disease with inflammatory background (25-27). Blood pressure level shows a circadian pattern in which both the systolic and diastolic BP decrease more than 10% in the night. Non-dipping HT is defined as a lack of nocturnal fall in the BP (11,28). Daily nocturnal BP fall is a pattern which is seen not only in hypertensive patients but also in normotensive people (28). There are many studies showing that the non-dipping of blood pressure means higher risk for cardiovascular diseases for both hypertensive and normotensive subjects (28-30).

Results of the present study have shown that hypertensive patients had higher RDW level when compared to normotensive subjects, which is in accordance with the previous studies (31). It is well established that HT has inflammatory background (25) and the association of RDW with inflammatory markers is well known, which both may be related with the increased inflammatory status in patients with HT (24). In addition, this study has found that RDW and hs-CRP levels were correlated, which in turn reflected the increase of inflammatory status. However, according to subgroup analysis, hs-CRP levels of HT-D and NT-ND groups were not different. Based on this finding, it could be concluded that HT-D patients have similar inflammatory status as NT-ND patients, and accordingly, non-dipping BP may be concurrently present with an undiagnosed inflammatory condition, which may be the reason for the non-dipping pattern as well. The exact pathophysiological mechanism for non-dipping BP is not clearly established for the time being, however it is known that non-dippers have higher cardiovascular risk (28-30). On the other hand, higher RDW levels are found to be a consequence of oxidative stress causing cytoskeletal structural changes and endothelial dysfunction (32-33).

Non-dippers had higher RDW levels than the dippers for both normotensive and hypertensive subjects in this study. Thus, the link between high RDW and hs-CRP levels may be oxidative stress causing endothelial dysfunction, which in turn impairs the autonomic nervous system and circadian BP pattern. According to the multivariate analysis, independent predictors of non-dipper HT were found to be mean diastolic pressure and hs-CRP, which may imply that an inflammatory condition is the reason for the change of the circadian BP pattern; however the exact mechanism seems to be obscure for the time being.

A major limitation of the current study is the lack of other anemia parameters such as iron, vitamin B12, folate and other inflammatory markers such as IL-6, TNF-alpha. Besides, it would be better to include more patients in order to increase the statistical power. Another point is that we did not include patients with prehypertension. In one study, the RDW levels were found to be elevated in prehypertensive subjects (7) but there is no data about the circadian BP patterns in prehypertensive subjects. So it may be regarded as a limitation that we did not include subjects with prehypertension. Because there is a lack of data for long-term follow-up, this study did not provide any prognostic data in terms of future cardiovascular events and effects of antihypertensive medication, which is another limitation of the study.

In conclusion, RDW, a routinely reported hematological parameter, is elevated in non-dipping BP both in normotensive and hypertensive patients, which may be related to increased inflammatory state.

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Conflict of interest: None to declare.

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