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Association between non-dipping status and carotid intima-media thickness in patients with elevated blood pressure category

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ABSTRACT

Objectives: This study aims to evaluate the relationship between non-dipping pattern and carotid intima-media thickness (CIMT) in patients with elevated blood pressure (BP).

Patients and methods: Between November 2019 and April 2019, a total of 150 consecutive patients (84 males, 66 females; mean age 52.3±10.1 years; range, 40 to 65 years) with elevated BP (systolic BP between 120 and 129 mmHg and diastolic BP less than 80 mmHg) were included. The patients were divided into two groups as the dipper (n=92) and non-dipper (n=58) groups according to the ambulatory BP measurements. The CIMT was measured using ultrasonography and compared between the groups.

Results: The CIMT was significantly higher in the non-dipper group (0.7±0.2 mm vs. 1.0±0.2 mm, respectively; p<0.001). The CIMT was an independent predictor of non-dipping pattern in the multivariate logistic regression analysis (odds ratio: 1.098, 95% confidence interval: 1.062-1.135; p<0.001).

Conclusion: Our study results show that the non-dipping status is closely associated with the known indicator for atherosclerosis such as CIMT in elevated blood pressure category.

Keywords: Carotid intima-media thickness, levated blood pressure, non-dipping status.

A meta-analysis of observational studies has shown that elevated blood pressure (BP) is closely related to cardiovascular diseases, subclinical atherosclerosis, and all-cause death.[1] Recent studies have shown that 24-h ambulatory BP monitoring (ABPM) is more accurate compared to office BP measurements in predicting adverse cardiovascular events, particularly due to the opportunity of nocturnal BP measurements.[2-6] During the sleep period, the BP should decrease by more than 10% compared to daytime (dipping status). If the mean systolic BP (SBP) and diastolic BP (DBP) levels decrease by less than 10% or do not fall, it is considered a non-dipping status.[7] There is an insufficient cardiac index, pulse index, and sympathetic activity reduction at night compared to daytime in non-dipping status.[8] The association of the non-dipping pattern with target organ damage and worsening cardiovascular outcomes is due to the relatively high BP exposure of the cardiovascular system during the night, and the compensatory structural and functional changes in the vascular structures lead to irreversible damage in the entire vascular system.[9]

Elevated BP term, newly included in the classification of 2017 American College of Cardiology (ACC)/American Heart Association (AHA) High Blood Pressure in Adults Clinical Practice Guideline, refers to an SBP of 120 to 129 mmHg and a DBP of <80 mmHg.[10] This definition covers lower levels of BP and should not to be confused with the prehypertension term which was previously defined in the JNC 7 report, as SBP 120 and 139 mmHg and DBP of 80 to 89 mmHg in more than two or more separate readings in two or more separate occasions.[11]

Increased carotid intima-media thickness (CIMT) is a thickening of intima, media, or both layers. While intimal thickening is more likely a result of

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similar pathogenetic mechanisms of atherosclerotic plaques, thickening of media is primarily related to hypertension. That is why CIMT is one of the most reliable markers of preclinical atherosclerosis. Also, CIMT is an important surrogate marker of target organ damage in the hypertensive patient.[12] High BP, as one of the most important cardiovascular risk factors, has been shown to be associated with the progression of CIMT.[13]

The association between non-dipper pattern and increased CIMT is shown in essential hypertension and some normotensive cohorts such as overweight men or polycystic ovary syndrome patients in different studies.[14] However, as a result of the literature search, we found no study investigating the relationship between CIMT and elevated BP patients' non-dipping status, as a novel issue.

In the present study, we aimed to evaluate the relationship between the CIMT and non-dipping pattern in patients with elevated BP.

PATIENTS AND METHODS

In this cross-sectional study, a total of 150 consecutive patients (84 males, 66 females; mean age 52.3±10.1 years; range, 40 to 65 years) who were admitted to our clinic with elevated BP (systolic BP between 120 and 129 mmHg and diastolic BP less than 80 mmHg) between November 2019 and April 2019 were included. Patients with hypertensive history were not included in this study. In the initial phase, 172 patients were enrolled in our study. However, five with coronary artery disease, three with severe heart valve diseases (one severe aortic stenosis and two moderate mitral insufficiencies), three with diabetes, and two with chronic renal insufficiency with an abnormal approximate glomerular filtration rate were excluded from the study. A 24-h ABPM was done. Six with normal BP and two with masked hypertension (based on ABMP) and one extreme dipper subject were excluded. Finally, 150 patients were eligible to include in our study. The patients were divided into two groups as the dipper (nocturnal decline in mean BP ≥10%; n=92) and non-dipper (nocturnal decline in mean BP <10%; n=58) groups according to the ambulatory BP measurements. The body weight and height measurements were recorded according to standard protocols with ultimate calibrated instruments. Echocardiographic examination and CIMT measurements were performed once at the time of admission. A written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of Sanko University (Date: 27.05.2018, No: 2018/6). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Definitions

All patients were comprehensively assessed for clinical risk factors such as age, sex, and smoking status, and office DBP and SBP, and heart rate (HR) measurements were recorded. The patients were considered to have elevated BP if they had a SBP between 120 and 129 mmHg and DBP less than 80 mmHg on average of at least two measurements obtained on two occasions, according to 2017 High Blood Pressure Clinical Practice Guideline.[15] Smoking was defined as at least one pack/year of smoking history.

Office and ambulatory BP measurements

The HR and BP were measured using a non-invasive automated system (Mobil-O-Graph NG, I.E.M., Stolberg, Germany) at 30-min intervals for 24 h. The British Hypertension Association and the European Hypertension Association have approved the use of this device following BP measurement.[16] All patients underwent ABPM for 24 h with the same usual working day.[17] The patients were kept on a regular schedule throughout the study, at 08:00 A.M. (wake up), and the room lights were closed at 10:00 P.M. The records were not accepted without at least 50 measurements in 24 h and at least one measurement was performed every 2 h. The mean day and night SBP and DBP of each patient were calculated.

Carotid artery ultrasonographic measurements

The common carotid artery (CCA) was visualized using a Vivid E9 (Bioject Medical Technologies Inc., OR, USA) with an MLA-15 transducer. The CIMT measurement was performed on the supine position at an angle of 45°. One-cm segment was identified within the first 2 cm distal region from the main carotid artery bulb and the images were recorded on the computer. From these images, the mean CIMT (CIMTmean) values of the segment studied were determined based on the remote edge measurement method with a special intima-media thickness measurement program (M'Ath ver 2.0; Metris, Argenteuil, France). The measurement was performed for both main carotid

arteries. Later, these values were evaluated separately and averaged. All measurements were performed by an experienced radiologist who was blinded to the study data.[18]

Echocardiographic measurements

Echocardiographic recordings were obtained by two qualified cardiologists who were blinded to the study data. Standard two-dimensional and M-mode echocardiographic parameters were obtained using the Vivid 7 GE echocardiography device (GE Healthcare, Little Chalfont, UK). Parasternal long and short axis, apical four-space, and apical two-chamber images were used for the evaluation of the left ventricular (LV) and valve functions. Pulsed Doppler ultrasonic examination was performed with a 2.5 MHz transducer. Parasternal and apical images were acquired, while the patient lied in the left lateral decubitus position. M-Mode measurements were applied according to the guidelines from the American Society of Echocardiography.[19] Posterior wall thickness (PWT), interventricular septum (IVS) thickness, end-diastolic, and end-systolic diameters, and LV ejection fraction were measured with M-mode echocardiography in the parasternal long-axis position (at the level of the mitral valve, perpendicular to the ventricular long axis). All measurements were calculated over three successive heartbeats.

Using pulsed-wave Doppler sample-volumes (before and during Valsalva maneuver), LV inflow velocities were recorded 0.5 cm above the mitral valve annulus in the apical four-chamber view. From the obtained data, mitral E and A velocities, isovolumetric relaxation, and contraction times (IVRT and IVCT), deceleration time (DT) were measured. The three left atrial dimensions (LAD) were obtained: D1 was measured from the middle of the mitral annular plane to the

Table 1
Baseline characteristics of the study population

	Dipper group (n=92)			Non-dipper group (n=58)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			51.8±9.9			52.8±10.6	0.560*
Sex Male	49	53.3		35	60.3		0.395**
Smoking	24	26		33	56		0.498**
Body mass index (kg/m^2)			28.2±2.7			28.7±2.5	0.222*
Glucose (mg/dL)			92.6±8.5			95.9±3.3	0.134*
Creatinine (mg/dL)			0.83±0.12			0.86±0.12	0.155*
Creatinine clearance (mL/min)			67.0±19.8			75.4±31.8	0.076*
Total cholesterol (mg/dL)			185.5±47.9			191.5±36.7	0.415*
Triglyceride (mg/dL)			175.8±30.1			201.0±34.2	0.266*
High density lipoprotein (mg/dL)			36.3±8.1			36.4±8.7	0.954*
Low density lipoprotein (mg/dL)			116.9±26.9			121.1±27.2	0.361*
Heart rate (beats/pm)			79.8±10.9			78.9±10.0	0.674*
Office SBP (mmHg)			122.2±8.6			123.2±7.8	0.672*
Office DBP (mmHg)			72.6±6.4			72.9±6.2	0.822*
Ambulatory 24-h SBP (mmHg)			115.7±10.8			116.2±9.3	0.492*
Ambulatory 24-h DBP (mmHg)			70.1±5.6			70.9±6.3	0.724*
Ambulatory day-time SBP (mmHg)			120.8±9.6			117.9±10.1	0.117*
Ambulatory day-time DBP (mmHg			72.8±7.1			72.3±7.4	0.251*
Ambulatory night-time SBP (mmHg)			106.1±5.8			117.6±6.9	**0.024***
Ambulatory night-time DBP (mmHg)			64.8±6.2			70.1±6.9	**0.046***

SD: Standard deviation; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; * Student t test and Mann-Whitney U test; ** Chi-square test.

superior aspect of the left atrium (LA); D2 was the orthogonal short-dimension to D1 in a four-chamber view; and D3 was the anterior-posterior diameter measured in a parasternal long-axis. The LA volume calculated with an ellipsoid formula: LA volume (mL)= π/6 (D1)(D2)(D3).[20] The left atrial volume index (LAVI) formula is LA volume/body surface area (BSA).[21] The LV mass index (LVMI) was calculated using the Devereux formula.[22] with diastolic measurements of LV internal diameter (LVID), interventricular septal thickness (IVST), and PWT.

Laboratory parameters

All biomarkers were examined in the serum samples obtained from the patients' blood. Blood samples were drawn after 20 min of rest, following 12-h starvation and centrifuged at 2,000 rpm for 10 min within 20 min. The samples were flash-frozen in the liquid nitrogen and immediately stored at -80°C until analysis. Standard biochemical parameters including blood glucose, creatine, and lipid panels were measured.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 24.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normality of data distribution. Categorical variables were expressed in number and frequency, while continuous variables were expressed in mean ± standard deviation (SD) or median (min-max). Continuous parametric variables were compared using the Student t-test. The chi-square (χ^2) test was used to compare groups with categorical variables. The Mann-Whitney U test was used to compare groups with continuous non-parametric variables. In the univariate logistic regression, variables with a significance level of $p<0.25$ were identified as the potential risk-takers and were included in the multivariate model as covariates. The last model was formed by determining the discriminant factors between the groups based on logistic regression analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Table 1 summarizes the baseline characteristics of the study population. The baseline characteristics were similar between the groups ($p>0.05$ for all) (Table 1). The LAD, LA volume, and LAVI were significantly higher in the non-dipping group than the dipping

Table 2
Carotid intima-media thickness and echocardiographic parameters

	Dipper group (n=92)	Non-dipper group (n=58)	
	Mean±SD	Mean±SD	p
Left ventricular ejection fraction (%)	58.3±6.2	59.2±2.8	0.334
Intraventricular septum (cm)	13.8±1.5	14.3±2.2	0.254
Posterior wall thickness (cm)	11.8±1.7	12.5±1.9	0.352
End diastolic diameter (cm)	35.6±4.5	36.3±4.7	0.428
End systolic diameter (cm)	27.4±4.0	27.4±3.4	0.949
Left ventricle mass index (g)	101.1±22.4	112.5±22.7	0.022
Left atrial diameter (mm)	31.8±3.6	34.3±2.6	<0.001
Left atrium volume (mm^3)	28.2±2.2	38.6±2.8	<0.001
Left atrial volume index (mL/m^2)	21.3±5.5	28.5±6.7	<0.001
E/A	0.83±0.14	0.76±0.13	0.009
Deceleration time (msec)	243.1±35.2	246.4±36.6	0.703
Isovolumetric relaxation time (msec)	74.1±5.3	74.9±5.5	0.380
Isovolumetric contraction time (msec)	75.3±2.6	75.2±2.4	0.758
Carotid intima-media thickness (mm)	0.74±0.17	0.97±0.15	<0.001

SD: Standard deviation; E: Mitral early diastolic velocity; A: Mitral late diastolic velocity; All tests were made by Student t test and Mann-Whitney U test.

Table 3
Independent determinants of non-dipping status

	Linear regression analysis			Logistic regression analysis		
	Coefficients	95% CI	*p*	OR	95% CI	*p*
Body mass index	0.016	-0.007-0.039	0.162			
Smoking	0.072	-0.058-0.202	0.273			
Age	0.004	-0.002-0.011	0.155			
Heart rate	-0.001	-0.007- 0.004	0.660			
Low density lipoprotein	0.002	-0.004-0.004	0.096			
Left ventricular ejection fraction	0.003	-0.009-0.015	0.653			
Left ventricle mass index	0.001	-0.001-0.004	0.212			
Left atrial volume index	0.008	0.002-0.014	<0.001	1.055	1.007-1.106	0.025
E/A	0.475	0.031-0.920	0.036			
Carotid intima-media thickness	1.211	0.911-1.511	<0.001	1.098	1.062-1.135	<0.001

E: Mitral early diastolic velocity; A: Mitral late diastolic velocity; Variables with p<0.25 in univariate regression were included into multivariate regression.

group (p<0.001 for all). The E/A ratio was lower and LVMI was moderately higher in the non-dipping group than the dipping group (p=0.009 and p=0.022, respectively). The CIMT was significantly higher in the non-dipping group than the dipping group (p<0.001) (Table 2).

The LAVI and CIMT were found to be associated with the non-dipping status. Both were independent predictors of non-dipping status in the multivariate analysis (odds ratio [OR]: 1.055, 95% confidence interval [CI]: 1.007-1.106; p=0.025 and OR: 1.098, 95% CI: 1.062–1.135; p<0.001, respectively) (Table 3).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the possible relationship between elevated BP category and CIMT. In this study, we found the following findings: *(i)* CIMT was significantly higher in the non-dipping group than the dipping group; *(ii)* CIMT was strongly correlated with the non-dipping status; and *(iii)* CIMT was independent predictors of the non-dipping status.

The European Society of Hypertension (ESH)/ European Society of Cardiology (ESC) guidelines for the management of hypertension suggest a cut-off value for CIMT greater than 0.9 mm as being a conservative estimate of asymptomatic organ damage.[23] The main results of the study showed that patients with elevated BP had increased CIMT values and those with non-dipping status had statistically significant higher CIMT values, independent from other risk factors.

The relationship between the time of the BP variation and the increased CIMT has been proven by a previous study.[17] The relationship between high BP and carotid artery hypertrophy was also reported.[24] The presence of intima-media thickening and carotid plaques of CCA may be a sign of subclinical atherosclerosis and a predictor of future adverse cardiovascular events.[25] Pierdomanico et al.[26] showed a significant increase in the prevalence of CIMT in non-dippers. Pellegrino[27] also reported that CIMT was higher in individuals with high BP than in normal subjects and higher in non-dippers versus dippers. Similarly, in our study, the mean CIMT was higher in the non-dippers compared to the dippers.

The pathophysiological mechanisms of the link between non-dipping pattern and carotid intima-media thickening have not been fully elucidated, yet. However, higher BP effects on endothelial cells during day and night, high molecular levels associated with endothelial dysfunction and atherosclerosis, procoagulant processes and increased platelet activation have been thought to be possible mechanisms of this relationship.[28] In a study, Ren et al.[29] showed a relationship between BP and CIMT in the Chinese population living in the rural Tianjin region, where the incidence of stroke and prevalence of hypertension were high. A study showed SBP elevation and hypertension history as the main risk

factors for CIMT development.[30] Slightly elevated SBP in middle-aged men had a great influence on the progression of CIMT, and there was a strong and direct effect of SBP on CIMT.[13] It has was also shown that SBP had a linear and continuous correlation with high CIMT across the BP levels.[31]

To date, several studies have reported that DBP does not affect the CIMT increase.[13,31] Only one study reported a weak, direct association between the DBP and maximal CIMT increase after adjusting for other risk factors, but not after further adjusting for SBP.[13] Su et al.[33] found that the mean time-weighted 24-h ambulatory DBP was a negative predictor of CIMT. It was also shown that high pulse pressure levels caused the progression of CIMT, and increased CIMT was associated with pulse pressure widening.[32]

Many studies have claimed that males have increased CIMT values than females and age and sex strongly affect the CIMT measurement, while older age is a significant predictor of increased CIMT.[33] Vicenzini et al.[34] reported that the mean CIMT had a linear relationship with age. In our study, dipper and non-dipper groups were similar in terms of age. The increased CIMT in smokers was previously reported,[35] but in our study, there was no significant difference in terms of smoking between the non-dipper group and the dipper group which can be attributable to a small sample size. Richey et al.[36] also observed that individuals with ambulatory hypertension had increased LVMI after controlling for BMI and race. Previous studies demonstrated an increase in the LV mass index in non-dipper patients.[37,38] Similarly, our study suggested that non-dippers had significantly increased LVMI, compared to dippers. Seo et al.[39] showed that non-dippers had impaired LV systolic and diastolic dysfunction without significantly altered levels of LVMI and LAVI parameter. Nevertheless, in our study, the LAVI was higher and E/A ratio was lower in the non-dippers, as expected.

Elevated BP is the category following normal BP, in which no pharmacological treatment is recommended, whereas it is associated with an increased risk of cardiovascular diseases, end-stage renal disease, subclinical atherosclerosis, and all-cause death compared to normotensives.[40] Measurement of CIMT can be considered a determinant of early target organ damage and is valuable in the identification of elevated BP subjects with higher cardiovascular risk. Moreover, considering worse cardiovascular prognosis in patients with an increased CIMT and increased CIMT values in non-dipper group, the ABPM should be recommended in elevated BP group not only for screening for masked hypertension but to distinguish dipper and non-dipper status.

The main limitation of this study is its relatively small sample size in both groups. The lack of observation of coronary anatomy by angiography is another limitation, although we attempted to overcome this problem by excluding the suspicion of coronary artery disease according to its clinical features, medical history, and electrocardiographic findings. Positive lifestyle habits such as weight loss, regular exercise, and salt restriction were unable to be evaluated, as this study is not a follow-up study in nature. Therefore, further larger scale, prospective, randomized studies are needed to confirm these results.

In conclusion, our study results indicate that higher levels of CIMT are seen in elevated BP patients with non-dipping status. In our study, we found a correlation between the non-dipping status and the known indicator for atherosclerosis such as CIMT. Besides, the increased CIMT level was an independent predictor of non-dipping pattern. This result suggests that it is important to control nocturnal BP to prevent cardiovascular disease and target organ damage in elevated BP individuals. Of note, it has been suggested that non-dipping BP pattern in our study may be a useful risk indicator for cardiovascular events and may need close follow-up for this pattern.

Declaration of conflicting interests

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