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Relationships of Different Blood Pressure Categories to Indices of Inflammation and Platelet Activity in Sustained Hypertensive Patients with Uncontrolled Office Blood Pressure

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Failure to decrease blood pressure (BP) normally during nighttime (non-dipping) in hypertension is associated with higher cardiovascular morbidity and mortality. In addition, non-dipping BP is associated with increased platelet activity and inflammatory response; however, there has been no study to evaluate the relationship of non-dipping BP to indices of platelet activity and inflammation in uncontrolled hypertensive patients. In the present study, hypertensive subjects with uncontrolled office BP were firstly divided into three groups: 84 subjects with white coat effect and 365 subjects with true uncontrolled hypertension. Then, true uncontrolled hypertensive patients were divided into two groups: 158 patients with dipping and 207 patients with non-dipping. Mean platelet volume (MPV), uric acid (UA), γ-glutamyltransferase (GGT), C-reactive protein (CRP), and high-sensitivity CRP (hs-CRP) levels were studied. The general characteristics and risk factors for coronary artery disease (CAD) of the study population were similar among the groups. MPV, UA, GGT, CRP, and hs-CRP levels were significantly higher in non-dipper group than both dipper and white coat effect groups, and were significantly higher in dipper group than in white coat effect group (MPV: 9.1 ± 1.3, 8.7 ± 1.1, and 8.0 ± 0.9 fL; UA: 6.9 ± 1.2, 5.9 ± 1.4, and 4.1 ± 0.8 mg/dL; GGT: 38.9 ± 11.1, 33.6 ± 14.9, and 25.2 ± 9.2 U/L; CRP: 7.1 ± 2.4, 6.2 ± 1.9, and 3.9 ± 0.8 mg/dL; hs-CRP: 3.8 ± 1.5, 3.3 ± 1.2, and 2.0 ± 0.6, non-dipper, dipper, and white coat effect groups, respectively, all p values <0.01). All study parameters strongly correlated with each other. In conclusion, in hypertensive patients with uncontrolled office BP, presence of non-dipping BP is associated with increased platelet activity and inflammation, which can be one of the underlying plausible mechanisms of non-dipping BP status.

Keywords: Ambulatory blood pressure, atherosclerosis, inflammation, non-dipper, platelet function

INTRODUCTION

Previous cross-sectional and longitudinal studies have shown that blood pressure (BP) measurements obtained by ambulatory BP monitoring (ABPM) are more prominently correlated with hypertension (HT)-related target organ damage, and have a stronger relationship to cardiovascular (CV) event than office BP measurements in both untreated and treated hypertensives (Mancia et al., 2001, 2007). It has also been suggested that lower achieved ambulatory BPs are associated with a lower rate of CV outcomes (Clement et al., 2003). Furthermore, BP measurements obtained by ABPM is more accurate than office BP in estimating the extent of BP reduction induced by treatment due to higher reproducibility over time (Coats et al., 1992), and ABPM allows for eliminating ''white coat effect'' in hypertensive patients who were taking antihypertensive therapy.

Hypertensive individuals are divided into two groups, dippers and non-dippers, according to nighttime reduction in BP $\geq$10% or <10%, respectively. Indeed, antihypertensive treatment similarly changes both daytime and nighttime BPs. However, the prognostic value of nighttime BP is superior to that of daytime BP (Björklund et al., 2004; Kikuya et al., 2005; Sega et al., 2005). Therefore, 24-h ABPM can be more useful at the time of diagnosis and at varying intervals during treatment in hypertensive patients. Accordingly, current guidelines have recommended that effort should be made to extend ABPM to 24 h in order to obtain information on both daytime and nighttime BP profiles, day-night blood pressure difference, morning blood

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pressure rise, and blood pressure variability (Daskalopoulou et al., 2012; Mansia et al., 2007). Normally, it is anticipated that both systolic and diastolic BPs decrease as low as 10% during nighttime. Failure to decrease in systolic BP normally during nighttime is called non-dipping.

Although substantial evidence supports the contention that nighttime BP is more important than daytime BP in predicting outcome and development of target organ damage, particularly in individuals who have nighttime BP fall <10% (non-dipping), to date, there is no study investigating relationship of non-dipping BP to platelet activity and atherosclerosis-related inflammatory markers in uncontrolled hypertensive patients treated by antihypertensive agents regularly. In the present study, we aimed to investigate relationships of BP categories to platelet activity and atherosclerosis-related inflammatory markers in uncontrolled essential hypertensive subjects who were regularly taking antihypertensive drugs.

METHODS

Study Population

Between February 2011 and August 2012, a total of 1196 sustained essential hypertensive subjects, who were regularly taking antihypertensive therapy at least 6 mos, were evaluated in the office setting, and 502 (42%) sustained hypertensive subjects with uncontrolled office BP were screened. However, 52 subjects were excluded due to exclusion criteria. Accordingly, the overall study population consisted of 450 subjects. Inclusion criteria were to be 30–75 yrs of age, absence of secondary causes, and regularly taking antihypertensive therapy at least 6 mos. All subjects were asymptomatic and free from a history of CV disease. Exclusion criteria were to have any concomitant systemic disease except diabetes mellitus (DM), such as hemolytic, rheumatic, hepatic, and renal diseases, that could affect studied parameters. The subjects with excessive alcohol consumption (>120 g/d) were also excluded. All patients were on regular antihypertensive treatment for at least 6 mos. Subjects who had not previously taken any antihypertensive therapy were excluded. Written informed consent was obtained from each subject, and the institutional ethics committee approved the study protocol and adhered to the ethical standards outlined in the Helsinki Declaration (Portaluppi et al., 2010).

Blood Pressure Measurement at the Office Setting

According to current guidelines (Daskalopoulou et al., 2012; Mansia et al., 2007), BP was measured using a mercury sphygmomanometer in office setting; first and fifth phases of Korotkoff sounds were used for systolic and diastolic BPs, respectively. Appropriate cuff sizes were chosen for each subject's arm circumference. BP was measured three times by skilled, trained physicians after 15 min of rest in the sitting position. The measurements were repeated after 48 h and the average of all measurements was recorded. Physical examination included measurement of height (centimeters) and weight (kilograms), and a resting 12-lead electrocardiogram (ECG) was recorded. The subjects who had a BP above 140/90 mm Hg were considered as uncontrolled hypertensives.

Ambulatory Blood Pressure Monitoring

Noninvasive 24-h ABPM were performed with a portable compact digital recorder (Tracker NIBP2; Del Mar. Reynolds Medical, Hertford, UK), and analyzed using a customized analytical software (CardioNavigator, Spacelabs Healthcare, Issaquah, WA, USA). Appropriate cuff sizes were chosen for each subject. All subjects wore an ABPM device for a single 24-h period. The device was programmed to inflate and record BP at prespecified intervals (every 15 min during daytime hours and every 30 min during nighttime hours), which provided approximately 80 BP recordings during the 24-h period. The display of ABPM was inactivated so that viewing each BP reading did not distract subjects.

Reports generated from a session of ABPM contained BP recordings for the entire 24 h, heart rate, mean arterial pressure, and BP load as well as summary statistics for the overall 24-h, daytime, and nighttime periods. If at least 80% of the total BP readings were valid, the ABPM record was considered satisfactory and used for further analyses. The daytime and nighttime periods were set according to patients' sleeping time.

Patient Classification

All of the patients used their prescribed antihypertensive medications during ABPM. Based on the definition of current guidelines (Daskalopoulou et al., 2012; Mansia et al., 2007) and according to 24-h ABPM results, the sustained hypertensive subjects with uncontrolled office BP were firstly divided into two groups: false uncontrolled (white coat effect) and true uncontrolled hypertensives. Patients who had a systolic BP ≥140 mm Hg and/or a diastolic BP ≥90 mm Hg in office setting, an average 24-h systolic BP <130 mm Hg and diastolic BP <80 mm Hg, an average daytime systolic BP <135 mm Hg and diastolic BP <85 mm Hg, and an average nighttime systolic BP <120 mm Hg and diastolic BP <70 mm Hg in ABPM were considered as false uncontrolled (white coat effect: group I); patients who had a systolic BP ≥140 mm Hg and/or a diastolic BP ≥90 mm Hg in office setting, an average 24-h systolic BP ≥130 mm Hg and/or diastolic BP ≥80 mm Hg, and an average daytime systolic BP >135 mm Hg and/or diastolic BP ≥85 mm Hg or an average nighttime systolic BP ≥120 mm Hg and/or diastolic BP ≥70 mm Hg in ABPM were diagnosed as true uncontrolled hypertensives. Then, true uncontrolled hypertensive patients were divided into two groups: dipper (group II) and

non-dipper (group III), according to nighttime reduction in systolic BP ≥10% or <10%, respectively.

Blood Collection and Laboratory Analysis

Blood samples were drawn from the antecubital vein by careful veinpuncture in a 21-G sterile syringe without stasis at 08:00–10:00 h after a fasting period of 12 h. Hematologic and biochemical measurements including liver enzymes were studied. An automatic blood counter (LH 780 Hematology Analyzer, Beckman Coulter Inc., Miami, FL) was used for whole blood counts. Mean platelet volume (MPV) was measured in a blood sample collected in dipotassium ethylenediaminetetraacetic acid (EDTA) tubes within 30 min after sampling to prevent EDTA-induced platelet swelling. Serum uric acid (UA) levels were measured using Olympus AU2700 autoanalyzer using its own kits (Olympus AU640; Olympus, Tokyo, Japan). Its normal range is 3.5–7.2 mg/dL. Serum γ-glutamyltransferase (GGT) levels were measured by the enzymatic calorimetric method using available kits test with autoanalyzer (Olympus AU 640; Olympus). Its normal ranges is 5–50 U/L. Serum C-reactive protein (CRP) levels were measured using BN2 Nephelometry Analyzer II (Dade Behring, Kalletal, Germany), and serum high-sensitivity CRP (hs-CRP) levels were measured using Siemens Immulite 2000 Immunoassay System Analyzer (Siemens, Los Angeles, CA, USA). The normal values for CRP and hs-CRP are 0–6 and 0–1.1 mg/L, respectively.

Power Calculation and Statistical Analysis

Based on previous data (Ermis et al., 2012; Kaya et al., 2010), we hypothesized that non-dipper hypertensive patients had plasma MPV, hs-CRP, and GGT levels approximately 0.20–30 of a standard deviation higher as compared with dipper hypertensives. To reach these numbers at $p<0.05$ and $1-\beta=0.85$, about 180–200 subjects were required for non-dipper group. We recruited in excess of this number to minimize the risk of type II error.

The analyses were performed using SPSS for windows 9.0 (SPSS, Chicago, IL, USA). Categorical variables were defined as percentage and numeric data are expressed as mean ± SD. The groups were compared using chi-square test regarding categorical variables. One-way analysis of variance (ANOVA) followed by Tukey's test or Kruskal-Wallis test (comparison of a characteristic across the three study groups if that characteristic did not have a normal distribution, such as GGT, hs-CRP, and triglyceride) was used to compare continuous variables. Univariate correlations were analyzed using Pearson or Spearman (if data were not normally distributed) correlation test, and to provide more statistical power the results were corrected by multiple testing using Bonferroni procedures when the common correlation among the multiple variables exceeded 0.50. Multivariate analysis was used to assess associations of studied markers with potential confounders via multivariate linear regression model. A p value less than 0.05 was considered significant.

RESULTS

Clinical Characteristics of the Study Population

According to ambulatory BP measurements, 450 sustained essential hypertensive patients with uncontrolled office BP were divided into three group: 84 (19%) subjects with white coat effect (group I), 158 (35%) patients with dipper HT (group II), and 207 (46%) patients with non-dipper HT (group III). Their demographic and clinical data are shown in Table 1. The general characteristics and risk factors for CV disease of

TABLE 1. Demographic characteristics and medications of the each study groups.

Characteristic	Group I: White coat effect ($n=85$)	Group II: Dipper HT ($n=158$)	Group III: Non-dipper HT ($n=207$)
Age (years)	50.4 ± 8.3	51.8 ± 5.5	51.9 ± 10.2
Male/female (*n*/*n*)	47/38	28/32	119/88
Body mass index (kg/m^2)	29.1 ± 2.8	29.4 ± 3.1	29.1 ± 3.6
Body mass index ≥30 kg/m^2 (%)	42	44	39
Diabetes mellitus (%)	15	16	15
Dyslipidemia (%)	24	27	32
Current smoker (%)	6	5	12
Duration of HT (months)	62.6 ± 45.2	65.8 ± 41.7	66.9 ± 44.9
Office systolic BP (mm Hg)	159.5 ± 5.2	159.8 ± 9.7	161.6 ± 9.9
Office diastolic BP (mm Hg)	90.2 ± 4.9	89.9 ± 7.5	93.8 ± 8.7
Heart rate (bpm)	77.5 ± 10.4	76.6 ± 9.5	79.6 ± 9.7
ACEI/ARB usage (%)	88	87	92
Beta-blocker usage (%)	28	24	28
Calcium channel blocker usage (%)	14	16	12
Diuretic usage (%)	65	58	59
Oral antidiabetic usage (%)	15	16	15
Statin usage (%)	21	23	24
Aspirin usage (%)	18	24	21

HT = hypertension; BP = blood pressure; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

the study population are presented in Table 1. Age, gender, body mass index, duration of HT, office BPs, heart rate, percentage of diabetes mellitus and dyslipidemia, smoking status, and medication status were not significantly different among the groups.

Ambulatory Blood Pressure Monitoring Analysis

The results of ambulatory blood pressure monitoring analysis are presented in Table 2. Average heart rates in all periods were significantly higher in non-dipper group than both dipper and white coat effect groups. Average heart rate was different between dipper and white coat effect groups at only nighttime period.

Analyses of the Laboratory Findings

The study groups were comparable with respect to hemoglobin, hematocrit, blood urea nitrogen, glucose, lipids, calcium, and liver enzymes (alkaline phosphatase, aspartate transaminase, alanine transaminase). White blood cell count was significantly higher in non-dipper group than both dipper and white coat effect groups. Platelet count was significantly lower in non-dipper group than both dipper and white coat effect groups, and was significantly lower in dipper group than in white coat effect group. Creatinine levels were significantly different between non-dipper and white coat effect groups. MPV, UA, GGT CRP, and hs-CRP levels were significantly higher in non-dipper group than both dipper and white coat effect groups, and were significantly higher in dipper group than in white coat effect group (Table 3, Figure 1). In the white coat effect group, subjects with non-dipping BP ($n=44$) had had significantly increased GGT and UA levels as compared with those with non-dipping BP (GGT: 27.8 ± 10.7 versus 22.1 ± 6.1 U/L, $p=0.004$; UA: 4.32 ± 0.87 versus 3.94 ± 0.81 mg/dL, $p=0.02$). However, the groups were comparable with respect to MPV, CRP, and hs-CRP levels. When the dipper hypertensives were divided into two groups based on dipping ratio, extreme dipper hypertensives had lower MPV, GGT, UA, and hs-CRP levels than dipper hypertensives (MPV: 8.3 ± 1.0 versus. 8.8 ± 1.1 fL, $p=0.007$; GGT: 27.1 ± 13.1 versus 34.4 ± 11.2 U/L, $p<0.001$; UA: 5.5 ± 1.3 versus 6.3 ± 1.2 mg/dL, $p<0.001$; hs-CRP: 3.0 ± 1.1 versus 3.6 ± 1.3 mg/dL, $p=0.003$). The hypertensive patients with diabetes had significantly increased MPV, GGT, CRP, and hs-CRP levels as compared with those without diabetes (MPV: 9.3 ± 1.3 versus 8.7 ± 1.1 fL, $p<0.01$; GGT: 41.2 ± 13.6 versus 33.9 ± 12.4 U/L, $p<0.0001$; CRP: 7.0 ± 3.0 versus 6.1 ± 2.2 mg/dL, $p<0.01$; hs-CRP: 4.1 ± 1.8 versus 3.2 ± 1.4 mg/dL, $p<0.0001$).

Correlation Analyses

Correlations of the study variables with demographic characteristics and risk factors are presented in Table 4. MPV was significantly and positively correlated with glucose levels, presence of DM and non-dipping, and smoking. GGT was significantly and positively correlated with BMI, presence of DM and non-dipping, and smoking. UA was significantly and positively correlated with smoking and presence of non-dipping. Hs-CRP was significantly and positively correlated with creatinine and glucose levels, presence of DM and non-dipping, and smoking. On the other hand, all study variables were strongly correlated with each other (Table 5). Furthermore, in multivariable analysis, GGT, UA, hs-CRP, and MPV were separately taken as dependent, the BP classification status of the subjects (white coat effect, dipper, and non-dipper), age, BMI, lipids, presence of diabetes, smoking, and other confounders including the other hematologic and biochemical parameters were taken as independent, and we found that the presence of non-dipping was a significant predictor of higher GGT, UA, hs-CRP, and MPV ($\beta=0.36$, $p<0.001$; $\beta=0.57$, $p<0.001$; $\beta=0.37$, $p<0.001$; $\beta=0.30$, $p<0.001$, respectively).

In multivariate analysis, GGT and MPV were also independently associated with presence of diabetes ($\beta=0.36$, $p<0.001$; $\beta=0.20$, $p<0.001$, respectively) and BMI ($\beta=0.13$, $p<0.01$ for each). In addition, hs-

TABLE 2. Data from ambulatory blood pressure monitoring of the study groups.

Parameter	Group I: White coat effect ($n=85$)	Group II: Dipper ($n=158$)	Group III: Non-dipper ($n=207$)
Average 24-h systolic BP	121.3 ± 6.9	131.8 ± 5.8†	135.6 ± 9.8†¶
Average 24-h diastolic BP	75.7 ± 6.0	78.0 ± 6.0†	83.0 ± 8.4†‡
Average 24-h mean BP	88.8 ± 8.7	94.6 ± 6.5†	99.2 ± 9.7†‡
24-h mean heart rate (bpm)	71.7 ± 8.2	72.6 ± 5.2	77.3 ± 8.9†‡
Average daytime systolic BP	126.0 ± 8.8	141.2 ± 6.2†	138.6 ± 11.2†
Average daytime diastolic BP	76.7 ± 6.7	82.8 ± 6.2†	84.9 ± 9.0†
Average daytime mean BP	96.9 ± 7.1	101.1 ± 6.5†	101.5 ± 10.3†
Daytime mean heart rate (bpm)	79.0 ± 8.4	78.6 ± 5.6	81.7 ± 9.7*¶
Average nighttime systolic BP	103.5 ± 7.9	112.0 ± 5.6†	129.5 ± 8.5†‡
Average nighttime diastolic BP	65.9 ± 5.4	70.0 ± 5.6†	78.3 ± 8.9†‡
Average nighttime mean BP	80.3 ± 7.3	83.9 ± 5.0†	93.9 ± 9.5†‡
Nighttime mean heart rate (bpm)	61.6 ± 9.7	65.3 ± 5.7*	69.9 ± 9.1†‡

BP = blood pressure.
¶$p<0.01$ versus dipper; †$p<0.0001$ versus white coat effect; ‡$p<0.0001$ versus dipper; *$p<0.05$ versus white coat effect.

TABLE 3. Hematologic and biochemical data of the each study groups.

Parameter	Group I: White coat effect ($n=85$)	Group II: Dipper HT ($n=158$)	Group III: Non-dipper HT ($n=207$)
Hemoglobin (g/dL)	14.4 ± 1.6	14.8 ± 1.3	14.5 ± 1.3
Hematocrit (%)	42.1 ± 4.1	42.8 ± 4.8	42.7 ± 3.9
White blood cell count ($\times 10^3/mm^3$)	7.62 ± 1.57	7.84 ± 1.96	9.07 ± 2.24†‡
Platelet count ($\times 10^3/mm^3$)	361.1 ± 89.1	266.2 ± 84.0†	242.8 ± 64.0†¶
PDW (%)	15.8 ± 1.4	15.0 ± 1.1†	14.9 ± 1.4†¶
BUN (mg/dL)	14.9 ± 4.5	15.3 ± 4.4	15.6 ± 4.2
Creatinine (mg/dL)	0.85 ± 0.19	0.89 ± 0.17	0.91 ± 0.18*
Glucose (mg/dL)	98.7 ± 16.1	100.8 ± 10.1	101.4 ± 12.9
Total cholesterol (mg/dL)	189.4 ± 38.7	188.4 ± 32.0	189.7 ± 32.0
HDL cholesterol (mg/dL)	47.8 ± 12.6	48.0 ± 13.1	46.4 ± 10.1
LDL cholesterol (mg/dL)	107.4 ± 30.9	110.0 ± 29.4	112.8 ± 29.3
Triglyceride (mg/dL)	165.4 ± 119.4	153.5 ± 64.6	149.8 ± 76.8
Calcium (mg/dL)	9.3 ± 0.6	9.4 ± 0.5	9.3 ± 0.6
ALP (IU/L)	69.4 ± 18.2	72.6 ± 16.7	70.4 ± 17.3
AST (U/L)	24.0 ± 10.2	23.5 ± 6.9	23.5 ± 10.3
ALT (U/L)	28.9 ± 18.1	28.4 ± 8.3	28.0 ± 13.3
CRP (mg/L)	3.9 ± 0.8	6.2 ± 1.9†	7.1 ± 2.4†¶
Hs-CRP (mg/dL)	2.0 ± 0.6	3.3 ± 1.2†	3.8 ± 1.5†¶
MPV (fL)	8.0 ± 0.9	8.7 ± 1.1**	9.1 ± 1.3†¶
Uric acid (mg/dL)	4.1 ± 0.8	5.9 ± 1.4†	6.9 ± 1.2†‡
GGT (U/L)	25.2 ± 9.2	33.6 ± 14.9†	38.9 ± 11.1†¶

PDW = platelet distribution width; BUN = blood urea nitrogen; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ALP = alkaline phosphatase; AST = aspartate transaminase; ALT = alanine transaminase; CRP = C-reactive protein.

*$p<0.05$ versus white coat effect; **$p<0.01$ versus white coat effect; †$p<0.0001$ versus white coat effect; ¶$p<0.01$ versus dipper; ‡$p<0.0001$ versus dipper.

CRP was also independently associated with presence of diabetes ($\beta=0.22$, $p<0.001$).

DISCUSSION

It is well known that there is a strong association between high BP and CV diseases such as coronary artery disease (CAD) and stroke. In addition, CAD and stroke are the most common forms of target organ damage and most common causes of mortality associated with HT (Sega et al., 2005; Staessen et al., 2001). Although BP measurements in the office setting still remains the cornerstone for decision-making in HT, and most therapeutic trials of HT have used lowering office BP measurements, it has been well documented that BP measurement with ABPM provides a more accurate diagnosis of HT and a better prediction of CV events (Hermida et al., 2013b; Staessen et al., 2001). In addition, BP measurements with ABPM are more closely related to indices of preclinical target organ damage and a better predictor of CV events than BP measurements in the office setting (Staessen et al., 2001; Turnbull, 2003). Furthermore, ABPM can allow white coat effect to be excluded and for detecting masked HT. Indeed, home BP measurements shares similar advantages with ABPM. However, 24-h ABPM gives complete data, especially in the nighttime period, which is considered to be a better marker of CV risk and mortality than daytime period (Fagard et al., 2008; Sega et al., 2005). Normally, both systolic and diastolic BPs decrease about 15–25% in nighttime. A nocturnal systolic BP fall of <10% is called non-dipping, and failure to decrease in systolic BP is associated with a 2.5 times higher risk of CV events (Verdecchia et al., 1997). Non-dipping BP status is associated with known CV risk factors and is frequent in diabetes. The prevalence of blunted nighttime BP is more than twice in uncontrolled hypertensive patients with type 2 diabetes as compared with those without diabetes (Ayala et al., 2013). There is a significant increase of a blunted nighttime BP decline in treated hypertensive subjects with metabolic syndrome (Hermida et al., 2011b). In the present study, the number of diabetics was relatively small and the percentage of patients with diabetes did not differ among the groups. Although the percentage of diabetics was similar among the groups, there were statistically significant differences between diabetic and nondiabetic hypertensives with respect to GGT, CRP, hs-CRP, and MPV. The prevalence of blunted nighttime BP also elevates with increasing age, and blunted nighttime BP pattern is 4 times more prevalent in patients ≥60 yrs of age than those <60 yrs of age (Hermida et al., 2013a). However, administration of one or more antihypertensive medications at bedtime results in an attenuation of the prevalence of blunted nighttime BP decline at all ages as compared with ingestion of all antihypertensive medications at awakening, (Hermida et al., 2013a). Similarly, previous studies have shown that bedtime administration of long-acting antihypertensive agents provides a greater reduction of nighttime BP than morning administration (Hermida et al., 2009, 2010, 2011a). Furthermore, results from the Heart Outcomes

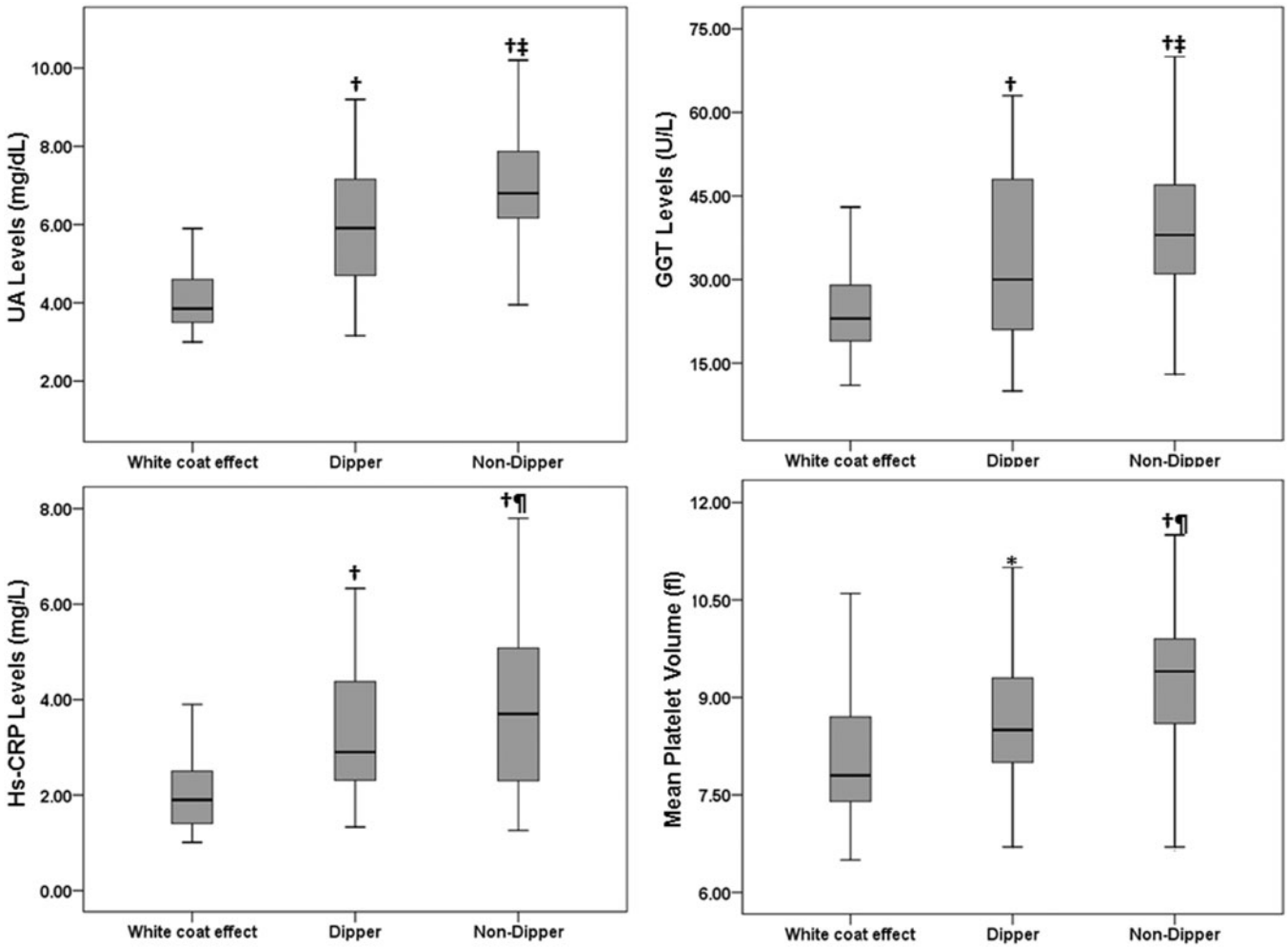

FIGURE 1. Indices of inflammation and platelet activity of the each study groups. hs-CRP = high-sensitivity C-reactive protein. †$p < 0.0001$ versus white coat effect; ‡$p < 0.0001$ versus dipper; ¶$p < 0.01$ versus dipper; *$p < 0.01$ versus white coat effect.

TABLE 4. Relationships of the study variables to demographic characteristics and risk factors.

	Correlations with			
Characteristic	GGT	UA	hs-CRP	MPV
Age	0.02	−0.03	0.04	−0.06
Gender (male)	−0.04	−0.01	−0.04	−0.03
Presence of DM	0.20‡	0.04	0.18‡	0.18‡
Smoking	0.21‡	0.17†	0.22‡	0.20‡
Presence of non-dipping	0.38‡	0.60‡	0.37‡	0.35‡
Presence of dipping	0.06	−0.07	0.03	−0.04
Body mass index	0.11*	0.05	0.04	0.08
Creatinine (mg/dL)	0.06	0.09	0.11*	0.03
Glucose (mg/dL)	0.10	0.01	0.14†	0.10*
Total cholesterol (mg/dL)	0.03	0.03	0.03	0.00
HDL cholesterol (mg/dL)	0.04	0.04	0.02	0.01
LDL cholesterol (mg/dL)	0.09	0.11*	0.09	0.06
Triglyceride (mg/dL)	0.08	0.04	−0.08	−0.07

DM = diabetes mellitus.
*Correlation is significant at the 0.05 level (two-tailed).
†Correlation is significant at the 0.01 level (two-tailed).
‡Correlation is significant at the 0.0001 level (two-tailed).

TABLE 5. Correlations of the study variables.

Variable	GGT	UA	hs-CRP	MPV
GGT	–	0.38‡	0.55‡	0.48‡
UA		–	0.39‡	0.35‡
hs-CRP			–	0.18‡
MPV				–

GGT = γ-glutamyl transpherase; UA = uric acid; hs-CRP = high-sensitivity C-reactive protein; MPV = mean platelet volume.
‡Correlation is significant at the 0.0001 level (two-tailed).

Prevention Evaluation Study (HOPE) substudy where patients were evaluated by ABPM indicated a significant BP reduction mainly during nighttime period if ramipril was administered at bedtime (Svensson et al., 2001). The authors reported that an 8% increase in the diurnal/nocturnal BP ratio was associated with beneficial effects in CV mortality and morbidity. In addition, it has recently been shown that increasing the diurnal/nocturnal ratio of BP was markedly correlated with a

significant decrease in urinary albumin excretion (Hermida et al., 2005).

Although there has been strong evidence that hypertensive patients with non-dipping BP have an increased risk for CV disease and target organ damage, and achievement of nocturnal BP decrease with antihypertensive treatment is associated with beneficial effects in CV morbidity and mortality, there have been limited data evaluating the possible underlying pathophysiologic mechanisms of increased CV risk in non-dipper hypertensive patients. In the present study, we showed that sustained hypertensive patients with uncontrolled office BP and non-dipping BP in ABPM had increased serum MPV, GGT, UA, and hs-CRP levels as compared with false uncontrolled (white coat effect) and dipper hypertensives.

Several laboratory techniques have been developed to detect platelet activation. Platelet number and size and the concentration of released substances after platelet activation are surrogate markers of increased platelet activity. Larger MPV is an indicator of increased in vivo platelet activation, and MPV correlates well with platelet activity whether measured as aggregation, thromboxane A2 or 3-thromboglobulin release, or adhesion molecule expression (Bath & Butterworth, 1996). Elevated MPV can predict the outcome in vascular thrombotic events such as myocardial and cerebral infarction (D'Erasmo et al., 1990). Previous studies have reported that as compared with normotensive controls, hypertensive patients had increased platelet activity, and there is a relationship between indices of platelet activity and target organ damage in high-risk hypertensive patients (Nadar et al., 2004).

There has been strong evidence that increased serum hs-CRP is a heritable marker of chronic inflammation that is strongly associated with CV disease. Furthermore, as described in the current guidelines, the inflammatory biomarker hs-CRP is now recognized as a major cardiovascular risk factor and as a secondary target for statin therapy (Genest et al., 2009). Previous studies have shown that hypertensive patients with non-dipping BP have increased serum CRP levels compared with those with non-dipping (Kaya et al., 2010; Tsioufis et al., 2008). Serum GGT level is an independent risk factor for CV disease, and there is a strong association between serum GGT levels and most CV risk factors including HT (Lee et al., 2003; Ruttmann et al., 2005). In addition, it has recently been shown that there is a relationship between serum GGT levels and microalbuminuria as well as coronary microvascular function, which are surrogate markers of hypertensive target organ damage (Caliskan et al., 2007; Lee et al., 2005). Patients with elevated serum UA levels had a mean 10-fold increased risk of developing CAD or HT, and that gout incidence was 3-fold higher in hypertensive individuals compared with normotensive subjects (Campion et al., 1987; Fessel, 1980). However, evidence is contradictory regarding whether serum UA level is an independent risk factor for the development of CAD and hypertension because in two epidemiological studies, hyperuricemia could not be recognized as an independent CV risk factor. An analysis from the National Health and Nutrition Examination Survey (NHANES) III study ensured relevant knowledge to clarify whether serum UA level is an independent risk factor for the development of CAD and HT. This analysis revealed that hypertensive individuals with elevated serum UA levels had a significantly higher relative risk for both heart attack and stroke (Ward, 1998). These results strongly support the hypothesis that elevated serum UA level is an independent risk factor for HT-associated mortality and morbidity. In the present study, we found that MPV, UA, GGT, CRP, and hs-CRP levels were significantly higher in non-dipper hypertensives than both dipper hypertensive and individuals with white coat effect. Furthermore, we also found that there was an independent association between the presence of non-dipping and higher GGT, UA, CRP, hs-CRP, and MPV levels as individually. In addition to the data mentioned above, previous studies have shown that there is a clear relationship among GGT, UA, hs-CRP, and MPV (Bo et al., 2005; Kaya et al., 2010). In line with these findings, we found that GGT, UA, hs-CRP, and MPV were strongly correlated with each other.

In conclusion, the present study showed that non-dipper hypertensives had increased MPV, uric acid, GGT, CRP, and hs-CRP levels as compared with dipper hypertensive patients and individuals with white coat effect. Our results are consistent with the idea that the presence of non-dipping BP is associated with increased platelet activity and inflammation. Accordingly, increased platelet activity and inflammation can be one of the underlying plausible mechanisms of non-dipping BP status, and increased platelet activity and inflammation could contribute to increase the risk of atherosclerotic CV disease and target organ damage in non-dipper hypertensive patients.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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