

## CLINICAL STUDY

# Adrenomedullin and non-dipping circadian pattern in newly diagnosed essential hypertension

Yucel O<sup>1</sup>, Gunes H<sup>2</sup>, Kerkutluoglu M<sup>2</sup>, Ozturk B<sup>2</sup>, Kirisci M<sup>3</sup>, Baylan Alkan F<sup>4</sup>

Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Cardiology, Kahramanmaras, Turkey. [drmuratkerk@gmail.com](mailto:drmuratkerk@gmail.com)

**ABSTRACT**

**OBJECTIVE:** There is frequently a relationship between nocturnal hypertension and non-dipping pattern and endothelial dysfunction. Studies conducted previously have indicated that adrenomedullin (AM) (a potent, long-lasting, vasodilatory peptide) is capable of regulating endothelial cell function. The aim of the current research is to investigate the association between absolute night-time blood pressure (BP) and circadian BP pattern with serum AM and high-sensitivity C-reactive protein (hsCRP) levels in cases in whom untreated arterial hypertension has been newly diagnosed.

**METHODS:** Ambulatory BP monitoring was performed in 100 individuals with hypertension (50 dippers, 50 non-dippers) and 50 healthy controls for 24 hours. Measurement and recording of AM and hsCRP serum levels were performed.

**RESULTS:** A strong correlation between night-time BP levels and AM and hsCRP levels was determined ( $p < 0.001$ ). On the contrary, higher AM levels were determined in the non-dipper group compared to the dipper and normotensive groups (non-dipper group,  $258 \pm 27$  pg/mL; dipper group,  $199 \pm 30$  pg/mL; normotensive group,  $150 \pm 11$  pg/mL;  $p < 0.001$ ). The non-dipper group exhibited significantly higher hsCRP levels in comparison with the remaining two groups ( $p = 0.017$ ). An independent association was determined between AM ( $p = 0.014$ ) and hsCRP ( $p = 0.032$ ) and a non-dipping pattern in a multivariate logistic regression analysis.

**CONCLUSIONS:** The nocturnal hypertensive and non-dipper groups exhibited increased AM levels. An independent association was identified between AM and hsCRP and a non-dipping pattern. It is implied that increased AM levels in individuals with non-dipper hypertension may be related to a longer exposure time to high BP. The mentioned findings indicate a potential future part of AM in identifying patients with hypertension that are at higher risk of target organ damage (Tab. 3, Fig. 4, Ref. 41). Text in PDF [www.elis.sk](http://www.elis.sk)

**KEY WORDS:** adrenomedullin, high-sensitivity C-reactive protein, dipper, non-dipper hypertension.

**Introduction**

Hypertension (HT) is among the most remarkable risk factors for unrecognized cardiovascular (CV) events (1). There is usually a relationship between high blood pressure (BP) and endothelial dysfunction and vascular complications (2). Ambulatory BP monitoring (ABPM) for 24 hours helps to diagnose HT and evaluate regulation and variability of BP. The averaged 24-h systolic BP (SBP) or diastolic BP (DBP)  $> 130$  mmHg and  $> 80$  mmHg is in the basis of the HT definition by means of ABPM. An increasing number of studies is conducted to determine the related impact of

all the factors produced by APBM (such as daytime BP, night-time BP, dipping status pattern) on the heart and intermediate CV and renal outcomes (3, 4). An increase in night-time BP (nocturnal HT) and non-dipping of BP in the course of sleep represent obvious entities frequently co-occurring and significant signs of left ventricular hypertrophy, arterial stiffness, microalbuminuria, and bad CV prognosis (5). The instructions for nocturnal BP in accordance with the American Heart Association Council on High Blood Pressure Research are presented below: nocturnal BP below the value of 115/65 mmHg is defined as optimal, below the value of 120/70 mmHg is defined as normal, and above the value of 125/75 mmHg is defined as abnormal. An association was determined between increased night-time BP and decreased endothelial function (6). A non-dipping BP profile is, in general, described as a nocturnal BP decrease below 10 % (7). A decrease in the release of endothelial nitric oxide is observed in hypertensive subjects, which causes reduced endothelium-dependent vasodilation, representing the first stage in the atherosclerosis development. Moreover, impairment in endothelium-dependent vasodilation is determined in individuals with non-dipper hypertension (7).

Vascular cells, in particular, endothelial cells, can secrete adrenomedullin (AM), which is a vasodilator peptide that was first

<sup>1</sup>Near East University, Department of Cardiology, Nicosia / TRNC, <sup>2</sup>Kahramanmaras Sutcu Imam University, Department of Cardiology, Kahramanmaras, Turkey, <sup>3</sup>Kahramanmaras Sutcu Imam University, Department of Cardiovascular Surgery, Kahramanmaras, Turkey, and <sup>4</sup>Kahramanmaras Sutcu Imam University, Department of Biochemistry, Kahramanmaras, Turkey

**Address for correspondence:** M. Kerkutluoglu, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Cardiology, Kahramanmaras, Turkey.  
Phone: +903443003376, Fax: +903443003409

identified from human pheochromocytoma (8-10). AM exhibits its activity in the cardiovascular system by means of receptor complexes consisting of the receptor activity modifying proteins and calcitonin receptor-like receptor. In vessels, the receptors for AM are expressed in endothelial as well as smooth muscle cells (11, 12). AM causes endothelium-dependent and -independent vasodilation, which depends on species and vascular beds (10).

In the present research, a relationship between absolute night-time BP and circadian BP pattern and serum levels of AM and high-sensitivity C-reactive protein (hsCRP) was examined in subjects in whom untreated arterial hypertension had been newly diagnosed.

## Methods

### Study population and design

Prospective screening of 117 cases from the cardiology polyclinic was performed. 100 patients with hypertension at the age between 18 and 75 years were enrolled in the study. 14 patients were excluded from the study (one patient with suspected adrenal adenoma, nine patients having accompanying diseases, four patients having obstructive sleep apnea, and three patients that were taking drugs having side effects). Following an ABPM evaluation for 24 hours, the cases were separated into two groups, including a dipper and a non-dipper group. Office BP  $\geq$  140 mmHg and/or  $\geq$  90 mmHg (the average of two appropriate readings or more measured on a minimum of two visits) was determined in all cases with hypertension included in the study. The diagnosis was made recently in all patients with hypertension that had not received antihypertensive therapy previously. Furthermore, 50 healthy controls with normotensive ABPM were included in the current research.

Criteria for exclusion from the study are presented below; patients refusing to participate in the research, and patients having secondary HT, systolic dysfunction of the left ventricle (ejection fraction less than 50%), diabetes, atrial fibrillation, history of coronary artery disease or angina, malignancy, moderate to severe valvular diseases, identified chronic obstructive pulmonary disease and obstructive sleep apnea (exclusion of obstructive sleep apnea was performed if obesity, daytime insomnia, and loud snoring were absent; in case of the presence of the mentioned conditions, the individual was directed to the chest diseases department for the purpose of excluding obstructive sleep apnea), moderate-severe renal (predicted glomerular filtration rate less than 60 mL/min) and hepatic dysfunction (in case of cirrhosis or alanine aminotransferase and/or aspartate aminotransferase  $> 3 \times$  ULN and total bilirubin  $> 2 \times$  ULN), active inflammatory diseases, chronic pharmacological treatment (such as lipid reducing and anti-inflammatory medications), and addiction to alcohol or substances.

Approval for the present research was obtained from the Institutional Ethics Committee of Maras Sutcu Imam University, and written informed consent was acquired from each participant. The research was conducted in accordance with the principles specified in the Declaration of Helsinki.

### Ambulatory blood pressure measurement

After measuring an office BP level, a 24-h ABPM (Bravo HR ABP Sun Tech Medical Inc., Morrisville, NC, USA) was performed in all patients included in the study. A suitable cuff size was selected for every patient. Measurement of BP was performed at 15-min intervals during the day (6:00 am to 10:00 pm) and at 30-min intervals at night (10:00 pm to 6:00 am). In case of less than 80 % valid measurements, the subjects were excluded from the study. HT was diagnosed in case of the presence of one of the issues indicated below: (1) averaged 24-h SBP  $> 130$  mmHg and/or DBP  $> 80$  mmHg, (2) averaged daytime SBP  $> 135$  mmHg and/or DBP  $> 85$  mmHg, or (3) averaged night-time SBP  $> 120$  mmHg and/or DBP  $> 70$  mmHg. A decrease smaller than 10 % in SBP between the daytime and night-time hours was described as a non-dipper pattern.

### Collection of blood samples and biochemical analysis

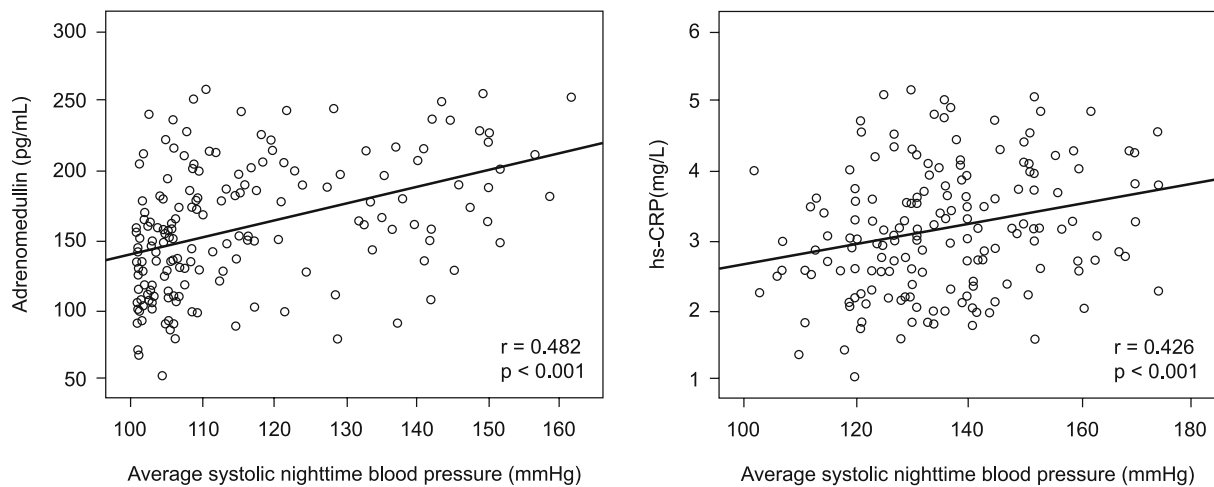
Collection of peripheral venous blood samples was performed from the antecubital vein at the time of admission. Measurement of baseline creatinine concentration, platelet count, white blood cell count, and hemoglobin level was performed. On the first morning following admission, measurement of hsCRP, lipid profile and other biochemical parameters was carried out by employing standard methods. Immediate centrifugation of the blood samples taken for AM was performed, and serum was kept at the temperature of  $-80^{\circ}\text{C}$  until analysis was conducted.

Serum levels of AM were measured using a human adrenomedullin enzyme-linked immunosorbent assay (Sunred Biological

**Tab. 1. Baseline characteristics of the study population.**

	Control (n=50)	Dipper (n=50)	Non-dipper (n=50)	p
Age, years	53 $\pm$ 7.2	49.2 $\pm$ 6.1	49.4 $\pm$ 5.1	0.195
Men, n (%)	15 (42%)	21 (60%)	16 (46%)	0.307
Body mass index, kg/m <sup>2</sup>	22.8 (20.3–24.4)	22.1 (19.9–25.8)	21.7 (19.3–25.7)	0.105
Smokers, n (%)	8 (22.9%)	4 (11.4%)	4 (11.4%)	0.307
Total cholesterol, mg/dL	184.9 $\pm$ 39.4	197.4 $\pm$ 48.6	192.3 $\pm$ 39.4	0.469
LDL cholesterol, mg/dL	130.2 $\pm$ 39.4	132.2 $\pm$ 40.8	135.8 $\pm$ 35.7	0.826
HDL cholesterol, mg/dL	46 (30–76)	44 (30–72)	44 (30–95)	0.863
Triglycerides, mg/dL	108 (48–294)	152 (46–253)	129 (55–300)	0.055
Creatinine, mg/dL	0.7 (0.5–1.4)	0.8 (0.5–1.3)	0.7 (0.4–1.1)	0.441
Fasting glucose, mg/dL	89 (77–116)	85 (69–109)	85 (51–112)	0.188
Haemoglobin, g/dL	14.2 $\pm$ 1.5	14.8 $\pm$ 1.1	14.2 $\pm$ 1.7	0.135
White blood cell count, 10 <sup>3</sup> /mm <sup>3</sup>	8.2 (4.8–11.4)	8.1 (4.8–10.6)	8.1 (5.0–14.4)	0.830
Adrenomedullin, pg/mL	150 $\pm$ 11.2	199 $\pm$ 30.1	258 $\pm$ 27.4	<b>&lt; 0.001</b>
HsCRP, mg/L	2.9 (0.1–15.0)	4.1 (0.1–11.0)	6.0 (1.0–13.84)	<b>0.017</b>
<b>Echocardiographic parameters:</b>				
Interventricular septum, mm	9.9 (7.3–11.8)	10.5 (8.1–13.2)	10.8 (7.9–13.5)	<b>0.019</b>
Posterior wall, mm	9.5 (7.1–11.1)	10.4 (8.3–12.4)	10.5 (7.8–12.9)	<b>0.022</b>
LV end diastolic diameter, mm	46 (39–56)	45 (39–51)	46 (39–60)	0.667
LV mass index, g/m <sup>2</sup>	83.3 (56.9–156.2)	91.6 (47.8–137.1)	97.5 (63.8–151)	<b>0.017</b>

All values are presented as mean and Standard deviation, median value (minimum–maximum) or number (percentage). HsCRP – high-sensitivity C-reactive protein; HDL – high-density lipoprotein; LDL – low-density lipoprotein; LV – left ventricular



**Fig. 1. A. Comparison of serum adrenomedullin levels with average systolic night-time blood pressure; B. Comparison of serum high-sensitivity C-reactive protein (hsCRP) levels with average systolic night-time blood pressure.**

Technology Co., Shanghai, PRC) in accordance with the manufacturer's instructions.

#### Statistical analysis

For conducting statistical analyses, the Statistical Package for the Social Sciences for Windows 21.0 (SPSS Inc., Chicago, IL, USA) was utilized. The Kolmogorov–Smirnov test was used to determine whether the continuous variables showed a normal distribution. Variables that showed a normal distribution were presented as mean and standard deviation, while variables that did not display a normal distribution were presented as median (minimum–maximum) values. Descriptive statistics are presented as a percentage and absolute values. An  $\chi^2$  test was utilized for comparing basal characteristics. Where suitable, a one-way analysis of variance (ANOVA) or Kruskal–Wallis test was carried out to compare the three groups in terms of continuous variables. Dunn's procedure was used to determine subgroup differences (for not normally distributed data). Data analysis was performed for the purpose of revealing whether there was an independent association between AM and the risk of non-dipper HT by means of univariate logistic and multivariate logistic regression models. Univariate analyses took such variables as body mass index, age, gender, hemoglobin,

hsCRP, LV mass index (LVMI), smoking, creatinine, and fasting blood glucose into account. Covariates with  $p < 0.1$  from univariate logistic regression were included for conducting the multivariate analysis. Receiver operating characteristic (ROC) analysis was conducted for the purpose of determining the most sensitive AM cutoff level to identify subjects having non-dipper HT.  $p < 0.05$  was accepted as statistically significant. Post hoc power analysis was carried out based on AM results (effect size: 0.60, alpha: 0.05), revealing an 86 % study power with the assumption of the parent distribution as a Laplace distribution.

#### Results

Table 1 presents information on the participants' demographic, laboratory, and echocardiographic properties. Higher serum triglyceride levels were detected in patients with hypertension compared to control subjects. However, the difference was found to be insignificant ( $p > 0.05$ ) (Tab. 1). The groups did not differ between each other in terms of the demographic characteristics, lipid profile, complete blood count, and creatinine ( $p > 0.05$ ). As a result of the echocardiographic evaluation, it was determined that the hypertensive group had a thicker LV wall than the control group. Moreover, higher LVMI was identified in hypertensive patients in comparison with healthy controls ( $p = 0.017$ ). The dipper and non-dipper groups did not differ significantly with regard to daytime and 24-h average SBP and DBP readings (Tab. 2). Normal daytime and night-time BP levels and normal nocturnal dip (average daytime BP  $125 \pm 9/82 \pm 5$  mmHg, average night-time BP  $108 \pm 4/72$  mmHg, average nocturnal dip 13%) were identified in the control group. A non-dipping pattern accompanied statistically significant high nocturnal BP ( $p < 0.001$ ).

There was a significant difference between the three groups in terms of AM levels ( $p < 0.001$ ). A significant positive association was found between average systolic night-time BP levels and AM ( $r = 0.482$ ,  $p < 0.001$ ) and hsCRP ( $r = 0.426$ ,  $p < 0.001$ ) (Fig.

**Tab. 2. 24-hour ambulatory blood pressure values of dipper and non-dipper groups.**

	Dipper (n=50)	Non-dipper (n=50)	p
Daytime SBP, mmHg	150±7	152±8	0.934
Daytime DBP, mmHg	91±7	93±4	0.599
Night-time SBP, mmHg	130±7	144±8	< 0.001
Night-time DBP, mmHg	81±7	88±4	< 0.001
24-h SBP, mmHg	147±8	150±9	0.120
24-h DBP, mmHg	92±5	93±9	0.703
Nocturnal dip	19%	6%	< 0.001

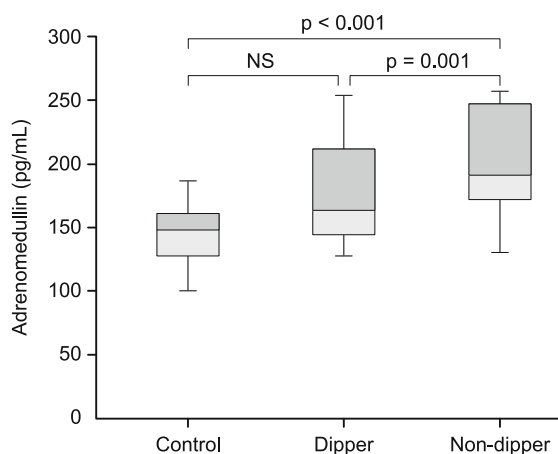
All values are presented as mean and Standard deviation or percentage; SBP – systolic blood pressure, DBP – diastolic blood pressure

**Tab. 3. Univariate and multivariate logistic regression analysis of associations between non-dipping status and variables in hypertensive patients.**

Variables	Univariate regression analysis		Multivariate regression analysis	
	$\beta$ (95% CI)	p	$\beta$ (95% CI)	p
Adrenomedullin	1.009 (1.002–1.015)	<b>0.004</b>	1.009 (1.003–1.015)	<b>0.014</b>
HsCRP	1.221 (1.045–1.426)	<b>0.017</b>	1.201 (1.005–1.435)	<b>0.032</b>
Age	1.034 (0.975–1.097)	0.260	–	–
Femalesex	0.561 (0.217–1.449)	0.233	–	–
Smoking	1.000 (0.229–4.361)	1.000	–	–
Haemoglobin	0.736 (0.522–1.038)	0.081	0.777 (0.532–1.137)	0.194
Fasting glucose	0.975 (0.940–1.011)	0.177	–	–
Creatinine	0.209 (0.016–2.718)	0.231	–	–
LVMI	1.015 (0.991–1.040)	0.225	–	–
BMI	0.787 (0.608–1.018)	0.068	0.789 (0.589–1.056)	0.111

BMI – body mass index; CI – confidence interval; LVMI – leftventricular mass index; HsCRP – high-sensitivity C-reactive protein

1A, B). As a result of a pairwise comparison, whereas higher AM levels were determined in the non-dipping group in comparison with the dipper HT and control groups, there was not a significant difference between the dipper HT and control groups in terms of AM levels ( $p > 0.05$ ) (Fig. 2). Significantly higher serum hsCRP levels were detected in the non-dipper group compared to the remaining groups (Fig. 3). As a result of a pairwise comparison, significantly higher hsCRP levels were identified in the non-dipper group compared to the dipper group. However, the dipper and control groups did not differ significantly ( $p > 0.05$ ). A positive



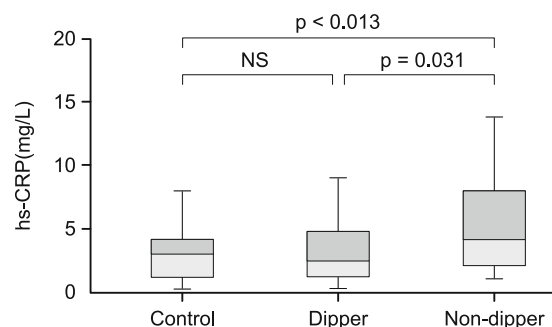
**Fig. 2. Comparison of serum adrenomedullin levels in non-dippers compared with dippers and controls; NS – non-significant.**

association was found between plasma AM levels and hsCRP in hypertensive patients ( $r = 0.247$ ,  $p = 0.039$ ). As a result of conducting multivariate analysis with adjustment for possible confounding variables, an independent association was found between higher AM and hsCRP levels and a non-dipping pattern (Tab. 3). ROC analysis demonstrated that AM levels above 229 pg/mL are capable of predicting a non-dipping status ( $p < 0.001$ ) as presented in Figure 4 (sensitivity: 85 %; specificity: 72 %; area under the curve: 0.804; 95 % confidence interval: (0.698–0.919).

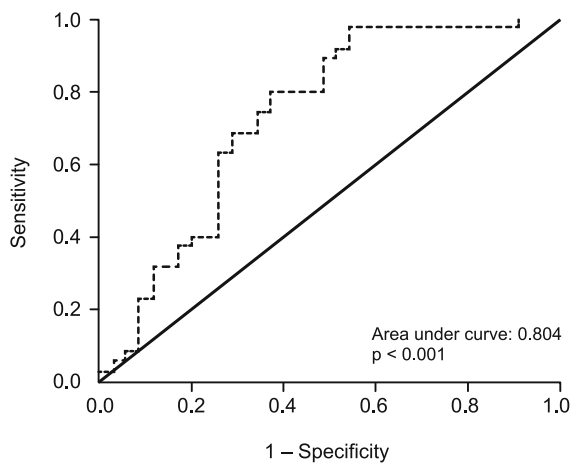
## Discussion

As a result of the present research, it was revealed that absolute night-time BP and AM levels were positively correlated. At the same time, subjects with non-dipper hypertension had higher serum AM levels compared to dipper hypertensive and normotensive subjects. Therefore, there was an independent association between serum AM levels and the non-dipping status. As far as we know, the current research is the first study that examines the association between blood AM levels and absolute night-time BP levels and daily circadian BP patterns.

The endothelium is essential for maintaining vascular homeostasis, and endothelial dysfunction takes part in the development and progression of CV diseases (13). AM causes endothelium-dependent and -independent vasodilation, that depends on species and vascular beds (10). The PI3K/Art/NO/cGMP pathway, the activation of cGMP-stimulated protein kinase G and/or the generation of a vasodilator prostanoid (possibly prostacyclin) (10, 14, 15) mediate endothelium-dependent vasodilation caused by AM, while endothelium-independent vasodilation caused by AM includes the opening of  $K^+$  channels ( $K^+$  channels activated



**Fig. 3. Comparison of serum high-sensitivity C-reactive protein (hsCRP) levels in non-dippers compared with dippers and controls; NS – non-significant.**



**Fig. 4. Receiver operating characteristic curve of adrenomedullin for predicting non-dipper hypertension.**

by calcium or K<sup>+</sup> channels sensitive to ATP, possibly depending on vascular beds) and the activation of cAMP-dependent protein kinase A (10, 16). Along with a vasodilator impact, AM was demonstrated to prevent angiotensin II-induced ROS production by NADPH (17), and mice with AM deficiency developed insulin resistance because of an increase in ROS (18). AM takes part in protecting the bone marrow-derived mononuclear cell and endothelial progenitor cells from apoptosis and has a vascular protective function (19,20). Moreover, AM has a protective impact on endothelial barrier function and causes a decrease in endothelial permeability as a reaction to inflammation and endotoxin (21–25).

There is a correlation between nocturnal HT and nocturnal non-dipping pattern with inflammation and endothelial dysfunction (6, 26–27). The clinical relevance of nocturnal HT and non-dipping status in subjects with hypertension is based on its confirmed correlation with more severe target organ damage and an increase in risk for CV events (28–29). Numerous studies have shown that LV hypertrophy, increased pulse wave velocity, carotid intima-media thickness, and microalbuminuria are more common in individuals having nocturnal HT and a non-dipping BP pattern (30–31). According to Kato et al (32), plasma levels of AM begin to increase with vascular inflammation, and subsequently, vascular inflammation occurs – accordingly, endothelial damage/dysfunction and atherosclerosis develop. In the phase in question, an increase in blood pressure is observed. Therefore, the increased AM level can be a harbinger of hypertension, and an increase in AM can be observed with developing atherosclerosis. Actually, considerably high AM levels are determined in cases having severe atherosclerotic diseases, e.g. peripheral arterial occlusive disease (33). Furthermore, the hypothesis in question is supported by the results indicating that there is a positive correlation between plasma AM levels and pulse wave velocity, which represents a marker of arterial stiffness (34). In the hypertension stage, the synthesis of AM is stimulated by high blood pressure itself, and AM levels are more increased by the accompanying

target organ damage. Elevation of plasma AM levels is observed in hypertensive subjects and patients having heart failure, atherosclerotic vascular diseases, and acute myocardial infarction, with a close association between the plasma level and the disease severity (35–37). There is also a correlation between elevated plasma AM levels and a worse prognosis in subjects having heart failure and acute myocardial infarction (38, 39). The mentioned results indicate a close association between the plasma level of AM and damage to the cardiovascular system. In the current research, an independent correlation was found between AM levels and a non-dipping pattern. Due to high inflammatory activity, the non-dipper group exhibited significantly higher hsCRP levels, and there was an independent association between them and the non-dipping pattern. On the contrary, a positive and graded association was determined between hsCRP and average night-time BP levels. Increased AM levels in nocturnal and non-dipper HT subjects are regarded as markers of inflammatory response and endothelial dysfunction. In the current research, the impact of higher night-time BP levels on AM might be considerable in the non-dipper group. In spite of the fact that the dipper and non-dipper groups did not differ in terms of average 24-h BP, increased hsCRP and AM levels could be associated with an increase in sympathetic tone. Endothelial dysfunction and autonomic nervous system imbalance frequently occur together in case of developing HT (40). Research conducted previously has demonstrated that the activated sympathetic system inhibits a reduction in nocturnal BP and is considered to take a significant part in endothelial activation (41). In the present research, subjects having nocturnal HT and/or a non-dipper pattern were subjected to more endothelial damage because of an overall hypertensive status during the day and night, which might explain a decrease in adropin levels. The mentioned and previous results indicate that adropin could be a dynamic biomarker of endothelial activation because of a hypertensive state.

Although higher AM levels were determined in subjects having dipper HT in comparison with the control group in the present research, they were not statistically significant. The result in question seems to contradict the research conducted previously. Nevertheless, it is thought that the present situation may originate from a comparatively low number of patients in the current research and the absence of the classification of patients with hypertension with regard to the circadian BP pattern in previous research.

#### Study limitation

The small sample size constitutes the major limitation of the current study. Prospective studies with a higher number of patients can distinctly indicate whether patients with hypertension at high risk can be predicted by AM. Furthermore, the findings of the present research would be much more robust in terms of the quantification of endothelial dysfunction. Another limitation of the study is not having measured pro-inflammatory markers. At the same time, day and night periods were defined constantly, and their modification was not performed in every patient on the basis of the diary.

## Conclusion

As a result, there was a significantly positive association between absolute night-time BP and AM levels. Moreover, the non-dipper group had higher circulatory AM levels in comparison with the dipper group and normotensive subjects. There was an independent association between AM and hsCRP and a non-dipping pattern. Based on the mentioned results, it is suggested that elevated AM levels in patients with non-dipper hypertension could be correlated with a longer exposure time to high BP during the day and night. Thus, AM could be a potential marker for the quantification of endothelial activation in individuals with hypertension and might take part in choosing patients with hypertension that are at higher risk or target organ damage.

## References

- Kannel W.** Blood pressure as a cardiovascular risk factor. *JAMA* 1996; 275: 1571–1576.
- Panza JA, Quyyumi AA, Brush JE, Epstein SE.** Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *N Engl J Med* 1990; 323: 22–27.
- Redon J, Plancha E, Swift PA, Pons S, Muñoz J, Martinez F.** Nocturnal blood pressure and progression to end-stage renal disease or death in nondiabetic chronic kidney disease stages 3 and 4. *J Hypertens* 2010; 28: 602–607.
- Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML et al.** Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008 Jan; 51 (1): 55–61.
- Friedman O, Logan AG.** Can nocturnal hypertension predict cardiovascular risk? *Integr Blood Press Control* 2009; 2: 25–37.
- Routledge FS, Hinderliter AL, McFetridge-Durdle J, Blumenthal JA, Paine NJ, Sherwood A.** Endothelial function in postmenopausal women with nighttime systolic hypertension. *Menopause* 2015; 22: 857–863.
- Yan B, Peng L, Han D, Sun L, Dong Q, Yang P et al.** Blood pressure reverse-dipping is associated with early formation of carotid plaque in senior hypertensive patients. *Medicine (Baltimore)* 2015; 94: 604.
- Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H et al.** Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. *Biochem Biophys Res Commun* 1993; 192: 553–560.
- Sugo S, Minamino N, Kangawa K, Miyamoto K, Kitamura K, Sakata J et al.** Endothelial cells actively synthesize and secrete adrenomedullin. *Biochem Biophys Res Commun* 1994; 201: 1160–1166.
- Passaglia P, Gonzaga NA, Tirapelli DP, Tirapelli LF, Tirapelli CR.** Pharmacological characterisation of the mechanisms underlying the relaxant effect of adrenomedullin in the rat carotid artery. *J Pharm Pharmacol* 2014; 66: 1734–1746.
- Kamitani S, Asakawa M, Shimekake Y, Kuwasako K, Nakahara K, Sakata T.** The RAMP2/CRLR complex is a functional adrenomedullin receptor in human endothelial and vascular smooth muscle cells. *FEBS Lett* 1999; 448: 111–114.
- Frayon S, Cueille C, Gnidéhou S, de Vernejoul MC, Garel JM.** Dexamethasone increases RAMP1 and CRLR mRNA expressions in human vascular smooth muscle cells. *Biochem Biophys Res Commun* 2000; 270: 1063–1067.
- Sumimoto T, Nishikimi T, Mukai M, Matsuzaki K, Murakami E, Takishita S et al.** Plasma adrenomedullin concentrations and cardiac and arterial hypertrophy in hypertension. *Hypertension* 1997; 30: 741–745.
- Terata K, Miura H, Liu Y, Loberiza F, Gutterman DD.** Human coronary arteriolar dilation to adrenomedullin: role of nitric oxide and K (+) channels. *Am J Physiol Heart Circ Physiol* 2000; 279: 2620–2626.
- Nishimatsu H, Suzuki E, Nagata D, Moriyama N, Satonaka H, Walsh K et al.** Adrenomedullin induces endothelium-dependent vasorelaxation via the phosphatidylinositol 3-kinase/Akt-dependent pathway in rat aorta. *Circ Res* 2001; 89: 63–70.
- Ross GR, Yallampalli C.** Endothelium-independent relaxation by adrenomedullin in pregnant rat mesenteric artery: role of cAMP-dependent protein kinase A and calcium-activated potassium channels. *J Pharmacol Exp Ther* 2006; 317: 1269–1275.
- Yoshimoto T, Gochou N, Fukai N, Sugiyama T, Shichiri M, Hirata Y.** Adrenomedullin inhibits angiotensin II-induced oxidative stress and gene expression in rat endothelial cells. *Hypertens Res* 2005; 28: 165–172.
- Shimosawa T, Ogihara T, Matsui H, Asano T, Ando K, Fujita T.** Deficiency of adrenomedullin induces insulin resistance by increasing oxidative stress. *Hypertension* 2003; 41: 1080–1085.
- Iwase T, Nagaya N, Fujii T, Itoh T, Ishibashi-Ueda H, Yamagishi M et al.** Adrenomedullin enhances angiogenic potency of bone marrow transplantation in a rat model of hindlimb ischemia. *Circulation* 2005; 111: 356–362.
- Kong XQ, Wang LX, Yang CS, Chen SF, Xue YZ, Liu YH.** Effects of adrenomedullin on the cell numbers and apoptosis of endothelial progenitor cells. *Clin Invest Med* 2008; 31: 117–122.
- Temmesfeld-Wollbrück B, Hocke AC, Suttorp N, Hippenstiel S.** Adrenomedullin and endothelial barrier function. *Thromb Haemost* 2007; 98: 944–951.
- Honda M, Nakagawa S, Hayashi K, Kitagawa N, Tsutsumi K, Nagata I et al.** Adrenomedullin improves the blood-brain barrier function through the expression of claudin-5. *Cell Mol Neurobiol* 2006; 26: 109–118.
- Dohgu S, Sumi N, Nishioku T, Takata F, Watanabe T, Naito M et al.** Cyclosporin A induces hyperpermeability of the blood-brain barrier by inhibiting autocrine adrenomedullin-mediated up-regulation of endothelial barrier function. *Eur J Pharmacol* 2010; 644: 5–9.
- Onur OE, Guneyssel O, Akoglu H, Denizbasi A, Onur E.** Adrenomedullin reduces the severity of cerulein-induced acute pancreatitis. *Peptides* 2007; 28: 2179–2183.
- Hippenstiel S, Witzernath M, Schmeck B, Hocke A, Krisp M, Krüll M et al.** Adrenomedullin reduces endothelial hyperpermeability. *Circ Res* 2002; 91: 618–625.
- Sarrazin S, Adam E, Lyon M, Depontieu F, Motte V, Landolfi C et al.** Endocan or endothelial cell specific molecule-1 (ESM-1): a potential novel endothelial cell marker and a new target for cancer therapy. *Biochim Biophys Acta*.2006; 1765: 25–37.

- 27. Tosu AR, Demir S, Selcuk M, Kaya Y, Akyol A, Ozdemir M et al.** Comparison of inflammatory markers in non-dipper hypertension vs. dipper hypertension and in normotensive individuals: uric acid, C-reactive protein and red blood cell distribution width readings. *Postepy Kardiol Interwencyjne* 2014; 10: 98–103.
- 28. Larochelle P.** Circadian variation in blood pressure: dipper or non-dipper. *J Clin Hypertens (Greenwich)* 2002; 4: 3–8
- 29. de la Sierra A, Redon J, Banegas JR, Segura J, Parati G, Gorostidi M et al.** Spanish Society of Hypertension Ambulatory Blood Pressure Monitoring Registry Investigators. Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. *Hypertension* 2009; 53: 466–472.
- 30. Lurbe E, Redon J, Kesani A, Pascual JM, Tacons J, Alvarez V et al.** Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *N Engl J Med* 2002; 347: 797–805.
- 31. Ozdemir E, Yildirimturk O, Cengiz B, Yurdakul S, Aytakin S.** Evaluation of carotid intima-media thickness and aortic elasticity in patients with nondipper hypertension. *Echocardiography* 2014; 31: 663–668.
- 32. Kato J, Kitamura K eto T.** Plasma adrenomedullin level and development of hypertension. *J Hum Hypertens* 2006; 20 (8): 566–570.
- 33. Suzuki Y, Horio T, Hayashi T, Nonogi H, Kitamura K eto T et al.** Plasma adrenomedullin concentration is increased in patients with peripheral arterial occlusive disease associated with vascular inflammation. *Regul Pept* 2004; 118: 99–104.
- 34. Kita T, Kitamura K, Hashida S, Morishita K eto T.** Plasma adrenomedullin is closely correlated with pulse wave velocity in middle-aged and elderly patients. *Hypertens Res* 2003; 26: 887–893.
- 35. Ishimitsu T, Nishikimi T, Saito Y, Kitamura K, Kangawa K et al.** Plasma levels of adrenomedullin, a newly identified hypotensive peptide, in patients with hypertension and renal failure. *J Clin Invest* 1994; 94: 2158–2161.
- 36. Kato J, Kobayashi K, Tanaka M, Kitamura K, Imamura T et al.** Plasma adrenomedullin concentration in patients with heart failure. *J Clin Endocrinol Metab* 1996; 81: 180–183.
- 37. Suzuki Y, Horio T, Hayashi T, Nonogi H, Kitamura K, et al.** Plasma adrenomedullin concentration is increased in patients with peripheral arterial occlusive disease associated with vascular inflammation. *Regul Pept* 2004; 118: 99–104.
- 38. Pousset F, Masson F, Chavirovskaia O, Isnard R, Carayon A, Gollmard JL et al.** Plasma adrenomedullin, a new independent predictor of prognosis in patients with chronic heart failure. *Eur Heart J* 2000; 21: 1009–1014.
- 39. Nagaya N, Nishikimi T, Uematsu M, Yoshitomi Y, Miyao Y, Miyazaki S et al.** Plasma adrenomedullin as an indicator of prognosis after acute myocardial infarction. *Heart* 1999; 81: 483–487.
- 40. Amiya E, Watanabe M, Komuro I.** The Relationship between Vascular Function and the Autonomic Nervous System. *Ann Vasc Dis* 2014; 7 (2): 109–119.
- 41. Millar-Craig MW, Bishop CN, Raftery EB.** Circadian variation of blood-pressure. *Lancet* 1978; 1 (8068): 795–797.

Received April 6, 2020.  
Accepted April 16, 2020.