European Review for Medical and Pharmacological Sciences 2021; 25: 6678-6683

The association of C-reactive protein to albumin ratio with non-dipping status in hypertensive patients

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Abstract. – OBJECTIVE: A reduction of less than 10% in nocturnal blood pressure (BP) compared to daytime BP is defined as non-dipper hypertension (HT). The C-reactive protein/albumin ratio (CAR) emerged as a popular and useful biomarker for cardiovascular disease. The main purpose of this study was to examine the relationship between CAR and non-dipper status.

PATIENTS AND METHODS: This was a cross-sectional study conducted between October 1, 2020 and December 1, 2020 and included 200 consecutive patients with elevated BP (102 women and 98 men). The numbers of dipper HT [mean BP drop at night >10%], and non-dipper HT [mean BP drop at night <10%] patients were equal in the entire study population. All data of the patients eligible for the study were retrieved from the hospital's electronic medical records. Student's *t*-test, Mann-Whitney U and chi-square tests, and linear and logistic regression analyses were used for statistical analyses as appropriate). A *p*-value <0.05 was considered statistically significant.

RESULTS: The CAR was higher in non-dipper group than dippers (38 and 19; *p*<0.001). Moreover, CAR independently predicted non-dipper status [odds ratio (OR) 1.825 95% confidence interval (CI) 0.887-2.206; *p* = 0.012].

CONCLUSIONS: In our study, patients with non-dipper HT showed higher CAR values and CAR was independently associated with non-dipper status. Larger studies are needed to establish the relationship between CAR and non-dipper status and to generalize our conclusions for clinical practice.

Key Words:
Blood pressure, C-reactive protein/albumin ratio, Non-dipper hypertension.

Introduction

In healthy individuals, blood pressure (BP) peaks in the morning hours, decreases gradually during the day and reaches its lowest levels at night. The difference between daytime and nighttime systolic BP (SBP) and diastolic BP (DBP) values is normally greater than 10%. Individuals with a less than 10% reduction in nocturnal BP compared to daytime BPare considered to have non-dipper hypertension[1]. Ambulatory blood pressure monitoring (ABPM) are better correlated with a poor prognosis than clinical BP measurements. Hypertensive patients can be classified as dipper and non-dipper using ABPM values[2]. Hypertension (HT) accelerates the development of cardiovascular disease (CVD)[3].

C-reactive protein (CRP) and albumin provide important clues about cardiovascular (CV) complications[4,5]. In particular, CRP affects the progression of CVD by causing endothelial dysfunction[6]. Serum albumin contributes to the maintenance of vital functions in the human body, and in case of infection, its level decreases as the production-catabolism balance is disrupted[7]. CRP/albumin ratio (CAR) better reflects the prognosis in acute conditions and malignancy compared to CRP or albumin alone[8]. Pfützner et al[9] showed the association of elevated high-sensitivity CRP with CVD such as HT. We aimed to investigate the association of CAR with non-dipper HT.

Patients and Methods

This was a cross-sectional study conducted between October 1, 2020 to December 1, 2020 and included 200 consecutive patients (114 females and 86 males) presenting to the outpatient clinic of our hospital. The numbers of patients with dipper HT [mean BP drop at night >10%], and non-dipper HT [mean BP drop at night <10%] were equal in the entire study population. Height and weight measurements of each patient were

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obtained using standard methodology and calibrated devices. Of note, CAR values were measured only once on admission. Antihypertensive medications used by the patients included calcium channel blockers (70.0%), angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) (66.0%), B blockers (38.0%), and thiazide diuretics (26.0%).

Initially, 214 patients were enrolled in the study, but subsequently, patients with coronary artery disease (CAD) (6), severe valvular heart disease (2), diabetes (3), chronic renal failure (2), and severe dipper HT (1) were excluded. Ultimately, the study was conducted with 200 patients.

DBP, SBP, and heart rate (HR) measurements were recorded and clinical risk factors (e.g., age, sex, HT, and smoking status) questioned for all patients. Sequential BP measurements were performed at optimal conditions (quiet room, after 5 minutes of rest, from the same arm, at sitting position, using validated devices). HT was defined as office SBP values ≥140 mmHg and/or DBP values ≥90 mmHg on at least three measurements[10].

We successfully measured posterior wall thickness (PWT), interventricular septum thickness (IVS), end-diastolic diameter, and LV ejection fraction using the M-mode echocardiography method. Left ventricular mass (LVM) was calculated from transthoracic echocardiography measurements using the ASE formula. Left ventricular mass index (LVMI) was calculated by dividing LVM by body surface area[11].

ABPM

A non-invasive ABPM device (MOBIL-O-GRAPH NG Version 12. I.E.M. GmbH. Stolberg, Germany) was used to measure HR and BP at 30-minute intervals for 24 hours. The British Hypertension Society and the European Society of Hypertension protocols have approved the use of ABPM device for BP monitoring[12,13]. We analyzed the 24-hour daytime and nighttime mean SBP, DBP, and HR by looking at each patient's Holter records. The daytime was defined as the time period from 08.00 to 22.00 hours and the nighttime was defined as the time period between 22.00 and 08.00 hours. During the study, patients were instructed to get up at 08:00 in the morning and turn off the room light at 22:00. This schedule was clearly explained to each patient. Less than 50 measurements and/or at least one measurement every 2 hours in the entire 24-hour period were not considered as acceptable ABPM records.

Laboratory Measurements

Blood samples were taken from the antecubital vein and collected in standard dipotassium EDTA tubes. Blood samples were tested within 30 minutes to prevent EDTA-induced platelet swelling. Sera were extracted from patients' blood samples. The bromocresol green method was used determine serum total protein and albumin levels on the C8000 analyzer (Abbott Laboratories, Abbott Park, IL, USA). CRP values were obtained using the nephelometry method (BN ProSpec System, Siemens, Germany). The Cockcroft-Gault equation was used to calculate estimated glomerular filtration rate.

Statistical Analysis

The SPSS for Windows software package, version 25 (SPSS Inc., Armonk, NY, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to check the normality of data distribution. Mean, standard deviation or median values were provided for the data that were normally distributed. The Student's *t*-test and Mann-Whitney U test were used to compare the means and medians between the study groups. Chi-square test was used for statistical analysis of categorical variables. Data with a $p<0.25$ in the linear regression analysis were included in the logistic regression analysis. Logistic regression analysis was applied for the prediction of non-dipper status. A *p*-value less than 0.05 was considered significant.

Results

Baseline characteristics are shown in Table I. The mean age was 55.2 ± 2.6 years in the dipper group and 56.8 ± 1.8 years in the non-dipper group. Mean ages were similar between groups. Baseline demographic characteristics were not different between groups, except for smoking (all $p> 0.05$). SBP, DBP, heart rate, glucose, creatinine, eGFR and WBC values were similar between groups (all $p>0.05$). BMI, triglyceride, and LDL were significantly higher and HDL and albumin were significantly lower in the non-dipper group. On the other hand, C-reactive protein and CAR values were significantly higher in the non-dipper group. There was no significant difference between the groups in terms of echocardiographic parameters and treatment regimens (all $p > 0.05$).

Table I. Characteristics of the study population.

	Dipper HT (n = 106)	Non-dipper HT (n = 94)	*p*-value
Age, years	55.2 ± 2.6	56.8 ± 1.8	0.340
Sex, male, n, (%)	48 (45)	50 (53)	0.064
Diabetes mellitus, n (%)	16 (15)	13 (13)	0.356
Smoking, n, (%)	32(30)	45 (47)	< **0.001**
Hyperlipidemia, n (%)	32 (30)	34 (36)	0.712
Family history, n, (%)	18 (16)	21 (22)	0.212
BMI, kg/m^2	25.2 ± 2.6	28.6 ± 4.1	**0.006**
SBP, mmHg	154.1 ± 6.3	158.8 ± 8.8	0.122
DBP, mmHg	92.3± 5.8	94.0 ± 6.4	0.102
Heart rate, beats/min	78.1 ± 1.2	80.2 ± 2.0	0.662
Glucose, mg/dL	97.5 ± 8.7	103.8 ± 9.4	0.256
Creatinine, mg/dL	0.71 ± 0.08	0.79 ± 0.06	0.652
eGFR, mL/min	95.6(67.2-108.8)	94.2 (64.5-102.1)	0.774
Triglyceride, mg/dL	148.0 ± 8.5	172.1 ± 9.8	**0.042**
HDL-C, mg/dl	48.5 ± 8.4	42.1 ± 4.7	**0.026**
LDL-C, mg/dl	105.8 ± 11.7	122.8 ± 10.4	**0.036**
WBC, $10^3 \times \mu L$	8.1 ± 0,9	8.9 ± 1.2	0.282
C-reactive protein, mg/dL	0.81 (0.3-2.1)	1.56 (0.6-2.8)	**< 0.001**
Albumin, g/dL	4.24 ± 0.3	3.42 ± 0.5	**< 0.001**
CAR, *100	19 (8-32)	38 (20-56)	**< 0.001**
Echocardiographic parameters			
LVEF, (%)	56.8±2.9	55.2 ± 1.7	0.540
IVS, mm	10.1 (8.4-14.2)	10.7 (8.1-14.5)	0.475
Posterior wall (mm)	9.4 (6.3-12.4)	9.8 (5.8-13.1)	0.522
LVEDD (mm)	42 (32-56)	43 (34-61)	0.667
LVMI, g/m^2	92.2 (46.8-147.1)	98.5 (73.8-152)	0.437
Baseline antihypertensive therapy, n, (%)			
ACE inhibitor or ARB	36 (36)	30 (30)	0.244
Calcium antagonist	32 (38)	38 (38)	0.102
Beta-adrenergic blocker	18 (18)	20 (20)	0.677
Thiazide diuretic	14 (14)	12 (12)	0.702

WBC: white blood cell count, DBP: diastolic blood pressure, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, BMI: body mass index.

24-hour ABPM values of the study groups are presented in Table II. Except for the mean nighttime SBP and DBP, all ABPM measurements were similar between the two groups (all $p > 0.05$). Mean nighttime SBP and DBP were significantly greater in the non-dipper group than in the dipper group (all $p < 0.001$).

In the linear regression analysis, BMI and CAR were correlated with non-dipping status. In the regression analysis, only CAR was found to be a significant independent predictor of non-dipping status [odds ratio (OR) 1.825 95% confidence interval (CI) 0.887-2.206; $p = 0.012$] (Table III).

Table II. 24-hour ambulatory blood pressure values of groups.

	Dipper (n = 106)	Non-dipper (n = 94)	*p*-value
Daytime mean SBP, (mmHg)	142 ± 8	141 ± 7	0.356
Daytime mean DBP, (mmHg)	92 ± 8	91 ± 9	0.482
Nighttime mean SBP, (mmHg)	130 ± 2	145 ± 6	< 0.001
Nighttime mean DBP, (mmHg)	82 ± 3	93 ± 7	< 0.001
24-h SBP, (mmHg)	142 ± 2	142 ± 6	0.882
24-h DBP, (mmHg)	91 ± 3	92 ± 2	0.803

SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table III. Independent determinants of non-dipping status.

	Linear regression analysis			Logistic regression analysis		
	Coefficients	95% CI	*p*-value	OR	95% CI	*p*-value
BMI	0.012	0.003-0.019	**0.042**	1.177	0.711-1.313	0.116
Smoking	0.006	0.001-0.015	0.273			
Age	0.004	-0.002-0.011	0.155			
LDL-C	0.002	-0.004-0.004	0.096			
LVEF	0.003	-0.009-0.015	0.653			
CAR	0.025	0.011-0.054	**0.010**	1.825	0.887-2.206	**0.012**
LVMI	0.002	-0.002-0.014	0.212			

Variables with $p < 0.25$ in univariate regression were included into multivariate regression.BMI: body mass index, HR: heart rate, LDL-C: low density lipoprotein cholesterol, LVEF: left ventricular ejection fraction, LVMI: left ventricular mass index, CAR: C-reactive protein to albumin ratio.

Discussion

To the best of our knowledge, this is the first study to show higher CAR values in patients with non-dipping nocturnal blood pressure. CAR values were associated with a non-dipping pattern in this study.

Blood pressure, heart rate and coronary tone show circadian changes over 24 hours[14]. On ABPM measurements, BP gradually decreases during the day and reaches its lowest values during the night[15]. Circadian BP patterns are categorized as dipper and non-dipper based on whether there is a ≥10% drop in nocturnal BP[16]. In non-dipper individuals over the age of 55, increased peripheral vascular resistance was observed due to increased circulating norepinephrine levels[14].

Insufficient reduction in BP in such patients during the night is associated with a marked increase in the risk of cerebrovascular disease, CVD, and left ventricular mass[17-19]. In our study, no difference was observed between the groups. Since the patients could not be followed further, it is not possible for us comment about the future cerebrovascular events and CVD.

In non-dipper patients, there is a vicious cycle of high nocturnal BP and endothelial damage, representing a bidirectional relationship[20]. There is considerable evidence on the effect of inflammation on endothelial dysfunction. Elevated BP induces proinflammatory state by triggering endothelial injury. In turn, endothelial damage precipitates proinflammation. CRP values increase as a result of increased inflammation. In a study of 15,215 women, patients with high BP showed significantly higher CRP levels[21]. Similarly, non-dipping pattern resulted in an elevation of CRP levels in the current study.

Elevated CRP levels cause an increase in angiotensin-II and endothelin-I levels and a reduction in nitric oxide (NO) levels[21]. Bautista et al[22] have demonstrated that CRP is a potential independent risk factor for HT. In line with our findings, Tosu et al[16] observed higher CRP values in non-dipper patients.

Defects in the balance between albumin synthesis and catabolism have been associated with increased inflammation[23]. Hypoalbuminemia leads to impairment of platelet functions, decreased platelet aggregation, and CAD. It is also one of the important causes of endothelial dysfunction[24]. Some studies[25,26] reported that hypoalbuminemia contributes to the development of CVD. Consistently, albumin levels were also lower in the non-dipper group in our study. It has also been shown that as a component of CAR, albumin may independently predict non-dipper status.

Compared to CRP or albumin, CAR has been reported to predict the prognosis of acute medical conditions and malignancy much better[27]. As a marker of inflammation, CAR may be a critical indicator of inflammatory conditions, such as atherogenesis and endothelial dysfunction[6]. Some authors recently argued that CAR is a useful biomarker in predicting adverse CV events[28].

Cagdas et al[29] showed a close relationship between the SYNTAX scores indicating the severity of CAD and CAR. In malignancies with poor prognosis, CAR has been successful in predicting the prognosis and progression of the disease[30,31]. These results suggests that CAR may be a practical and accessible biomarker in determining the severity and prognosis of various diseases, especially CVD. In our study, elevated CAR levels were observed in non-dipper group, and CAR strongly predicted non-dipper status.

Study Limitations

Larger studies are needed to establish the predictive role of serum CAR. The prognostic role of CAR was not determined in the present study and future research is warranted. Mortality data were not available due to the study design. The specificity and sensitivity of CAR in predicting non-dipper status should be investigated further because CAR may be altered in many medical conditions and infections. Although all participants were considered as new hypertensive patients, the duration of HT is not known. It is not easy to standardize the lifestyle of every patient and to maintain equal sleep quality among all patients. Further evidence is needed for this study to contribute to clinical practice. Larger studies are needed to establish the relationship between CAR and non-dipper status and to generalize our conclusions for clinical practice.

Conclusions

In recent years, CAR level, a marker of inflammation, has been shown to be independently associated with CV disease. Current results showed that non-dippers had higher CAR values than dippers. CAR was independently associated with non-dipper status.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee for Clinical Research of Adiyaman University (Adiyaman, Turkey) (2021-01/40).

Informed Consent

Informed consent was obtained from all individuals prior to their participation in the study.

Authors' Contribution

All authors contributed equally to the study, from data collection/analysis, writing and revising the manuscript until the final approval of the version to be published. We all agree to be accountable for all the technical and moral aspects of the work.

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