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PLASMA N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE LEVELS IDENTIFYING NON-DIPPING PATTERN IN PATIENTS WITH HYPERTENSION

Original Article

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ABSTRACT

Objectives: The N-amino-terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP) serves as a sensitive marker of left ventricular hypertrophy and volume expansion. It has been demonstrated that hypervolemia, an increase in sympathetic function, may contribute to the occurrence of the non-dipping pattern. In addition, both higher NT-proBNP levels and non-dipper hypertension have been shown to predict cardiovascular events and mortality in the general population. Thus, we investigated whether NT-proBNP could be used to detect non-dipping pattern in hypertensive patients.

Methods: We enrolled 309 hypertensive patients with no cardiovascular disease or renal failure (mean age 49.9 ± 10.8 years, 50.6% men). The ambulatory blood pressure (ABP) of all the patients was measured, and the patients were divided into two groups according to ABP: non-dipper hypertensive group (n=174) and dipper hypertensive group (n=135).

Results: NT-proBNP values were higher in the non-dipper hypertensive group (81.5± 94 pg/ml) than in the dipper hypertensive group (48.7±66 pg/ml) ($p<0.001$). In a logistic multivariate analysis, the NT-proBNP value was found to be an independent predictor of non-dipping pattern development (odds ratio: 1.022; 95% confidence interval (CI): 1.007–1.038; $p<0.05$). In a receiver operating characteristic (ROC) curve analysis, a BNP value of 38.5 pg/ml was identified as an effective cutoff point for non-dipper hypertension (area under curve=0.663; 95% CI: 0.64–0.721; $p<0.001$). An NT-proBNP value >38.5 pg/mL yielded a sensitivity of 61.6% and a specificity of 60% for non-dipper hypertension. There was a correlation between NT-proBNP and systolic blood pressure (especially at night) and age ($r=0.233$, $p<0.001$ and $r=0.339$, $p<0.001$). There was no correlation between NT-proBNP and diastolic blood pressure, except night diastolic blood pressure ($r=0.130$, $p<0.019$).

Conclusion: We were able to identify non-dipper patterns using NT-proBNP levels in hypertensive patients without clinical cardiovascular disease or renal failure in clinical practice.

Key Words: NT-proBNP, non-dipping pattern, hypertension

INTRODUCTION

Arterial blood pressure (BP) exhibits a diurnal rhythm and is higher during the day than at night (1,2); a nocturnal decline in BP of less than 10% of the daytime value has been termed non-dipper (3). Continuous 24-h ambulatory blood pressure (ABP) monitoring has been used to show the diurnal rhythm of arterial BP (4). The mechanisms underlying the pathogenesis of lack of nocturnal BP decline are unclear; however, it has been demonstrated that hypervolemia, a decrease in parasympathetic function, and an increase in sympathetic function might contribute to the occurrence of the non-dipping pattern (5, 6). A lack of nocturnal BP decline is a predictor of target organ damage, adverse cardiovascular event, stroke, and renal failure (7-10).

The N-amino-terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP) is secreted from ventricular myocytes in response to ventricular wall stretching and tension (11, 12), and plasma NT-proBNP level serves as a sensitive marker of left ventricular hypertrophy and hypervolemia (13). Increased levels of NT-proBNP predict cardiovascular events and mortality in patients with heart failure (HF), acute coronary syndromes, and in the general population (14, 15, 16).

Both NT-proBNP and non-dipper hypertension are associated with adverse cardiovascular events and hypervolemia. Accordingly, we investigated whether NT-proBNP could be used to detect a non-dipping pattern in patients with essential hypertension.

METHODS

In this cross sectional study a total of 309 outpatients between the ages of 18 and 80 years were evaluated with ABP monitoring in the Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital. Physical examination

was performed from patients by cardiologists. HT was defined as an office blood pressure (OBP) of ≥140/90 mm Hg, daytime ABP of ≥135/85 mm Hg or the active use of antihypertensive drugs (17). Non-dippers were defined as those with nocturnal decrease in systolic blood pressure (SBP) or diastolic blood pressure (DBP) of less than 10% in daytime (3). Patients were divided into two groups according to ABP values, namely, non-dipper hypertensive (n=174) and dipper hypertensive (n=135).

Diabetes was defined based on the American Diabetes Association guidelines as fasting serum glucose of ≥126 mg/dL (7 mmol/L) or nonfasting glucose of ≥200 mg/dL (11.1 mmol/L), or active use antidiabetic treatment (18). Smoking habit was defined as a history of tobacco use at admission. Body mass index was calculated as (weight in kilograms)/(height in meters)^2.
The urinary albumin-to-creatinine ratio (UACR) was determined as milligrams per gram. Albuminuria was defined as an albumin-to-creatinine ratio of 30 mg/g or higher, with microalbuminuria defined as an albumin-to-creatinine ratio of 30–299 mg/g and macroalbuminuria defined as an albumin-to-creatinine ratio of 300 mg/g or higher.

Echocardiograhic examination of patients were performed by a cardiologist using Vivid 7 system (General Electric Vivid 7 GE Vingmend Ultrasound AS, Horten, Norway). The left – ventricular mass in grams was calculated from M-mode echocardiograms according to the formula described by Devereux et al. (19). LV mass was indexed to body surface area as LV mass index (LVMI) in g/m^{2}body surface area. The peak early (E) transmitral flow velocities were measured. The mitral flow velocity was obtained from apical 4-chamber view by placing a pulsed-wave (PW) Doppler sample volume between mitral leaflet tips during diastole. Tissue Doppler imaging (TDI) was performed by means of mitral annulus in four-chamber

view. The early peak diastolic annular (E') was determined from the TDI recordings. The ratio of peak early (E) to tissue Doppler early diastolic (E') was calculated.(E/E')

The exclusion criteria of this study were secondary hypertension, cardiac failure, coronary artery disease, moderate to severe valvular diseases, chronic renal failure (serum creatinine >1.5 mg/dl, blood urea nitrogen>30 mg/dl) and patients with chronic obstructive pulmonary disease.

Informed consent was obtained from the patients and the study protocol was approved by the local ethics committee.

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) was performed for 24 h using an ambulatory BP monitor (Tonoport V, GE Healthcare). The monitor was programmed to measure BP every 15 min from 08:00 to 20:00 and every 30 min from 20:00 to 08:00. Daytime and nighttime BP was defined from 07:00 to 23:00 for daytime and from 23:00 to 07:00 for nighttime.

Blood Sampling

Blood samples were drawn from the antecubital vein between 08.00 and 10.00 AM after an overnight fasting and were taken into standardized tubes containing dipotassium ethylenedinitrotetraacetic acid (EDTA) to be stored at room temperature. An automatic blood counter (Beckman Coulter, Miami, FL) was used for whole blood counts. Other biochemical analyses were determined by standard methods.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 17. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov) to determine whether the variables were normally distributed. Descriptive analyses were presented as the mean±standard deviation (SD) and categorical variables were expressed as percentages. The univariate analyses to identify variables associated with non-dipper hypertension was investigated using chi-square, Student's t (age, total-cholesterol, low-density lipoprotein, high-density lipoprotein) and Mann-Whitney U tests, where appropriate. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of non-dipper hypertension. A Spearman correlation analysis was performed to describe the association of NT-pro BNP with age, 24-h SBP, 24-h diastolic blood pressure (DBP), day and night systolic and diastolic BP, hematocrit, E/E', UACR, LVMI, BMI, creatinine. The capacity of serum NT-pro BNP value in predicting the presence of non-dipper hypertension was analyzed using ROC (Receiver Operating Characteristics)curve analysis. When a significant cut–off value was observed, the sensitivity, specificity values were presented. An overall 5% type-I error level was used to infer statistical significance.

RESULTS

A total of 309 patients were included in the study. The patients were divided into two groups, non-dipper (n=174) and dipper (n=135) hypertension, according to ABP levels. The mean age of the patients was 49.9±10.8 years, and 50.6% were male. The main characteristics of the patients included in the study are shown in Table 1.

Table 1. Characteristics of the study population.

	Non-dippers (n=174)	**Dippers (n=135)**	**p-value**
Gender (male) n,(%)	90 (50.8)	77 (50.3)	0.925
Age,years	50±10	49±11	0.219
BMI,kg/m²	30±4	30±5	0.729
Smoking,n(%)	52(29.9)	34(25.2)	0.361
Diabetes ,n(%)	38(21.8)	24(17.8)	0.377
Glucose,mg/dl	109±32	102±20	0.800
Creatinine,mg/dl	0.8±0.2	0.7±0.2	0.672
Total-cholesterol,mg/dl	207±45	197±43	0.512
Hematocrit,(%)	42±4	41±5	**0.008**
LVMI,g/m²	95±21	89±24	**0.045**
UACR,mg/mmol	47.3± 88.3	35±57.2	0.051
E/E’	9.1±2.9	7.9±2.9	**0.007**
NT-proBNP,pg/ml	81.5±94	48.7±66	**<0.001**
ACE-I/ARB use, n (%)	65 (37.4)	52(38.5)	0.835
Beta-blocker use, n (%)	27 (15.7)	28(20.7)	0.234
CCB use, n(%)	25 (14.4)	28(20.7)	0.140
Diuretic use, n(%)	47(32.7)	34(25.2)	0.717

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CCB: Ca-channel blocker; DBP: diastolic blood pressure; LDL: low-densty lipoprotein; HDL: high-density lipoprotein; LVMI: left ventricular mass index; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP: systolic blood pressure; UACR: urinary albumin-creatinine ratio

The mean NT-pro BNP was found to be 66±84 pg/ml in all patients, and NT-pro BNP values were found to be significantly higher in the non-dipper hypertension group (81.5±94 and 48.7 ± 66, respectively; p<0.001). In addition, left ventricular mass index (LVMI) (p=0.045) and LVMI (p=0.045) and the ratio of peak early transmitral flow velocity to tissue Doppler early peak diastolic annular (E/E') (p=0.007) levels were found to be higher in the non-dipper hypertension group. The two groups were similar in terms of use of antihypertensive treatment. Although urinary albumin/creatinine ratio (UACR) was higher in the non-dipper hypertension group, the difference was not statistically significant (47.3±88.3 and 35±57.2, respectively; p=0.051). The ABP values of both groups are shown in Table 2.

Table 2. Comparison of the ambulatory blood pressure monitoring variables.

	Non-dippers	**Dippers**	**p-value**
Daytime-SBP, mmHg	150±13	146±17	0.473
Daytime-DBP, mmHg	95±9	92±12	0.552
Nighttime-SBP, mmHg	144±15	127±14	**<0.001**
Nighttime-DBP, mmHg	88±10	76±10	**<0.001**
24-h-SBP, mmHg	149±13	142±16	**0.001**
24-h-DBP, mmHg	94±9	88±13	**<0.001**

SBP: systolic blood pressure; DBP: diastolic blood pressure

Nocturnal and 24-hour systolic and diastolic blood pressure values were statistically significantly higher in the non-dipper hypertension group. Daytime systolic and diastolic blood pressure values were similar in both groups.

Nocturnal SBP, 24-h SBP, age, LVMI, E/E, nocturnal DBP, and UACR were positively correlated with NT-pro BNP, while hematocrit was inversely correlated with NT-pro BNP (Table 3). Creatinine, all DBP except nocturnal DBP, and glucose were not correlated with NT-pro BNP (Table 3).

Table 3. Correlations between selected variables and NT-proBNP.

	R	**p**
Age	0.339	**<0.001**
Body mass index	-0.03	0.962
24-h diastolic blood pressure	-0.09	0.871
24-h systolic blood pressure	0.157	**0.004**
Day systolic blood pressure	0.112	**0.041**
Day diastolic blood pressure	-0.43	0.438
Night systolic blood pressure	0.233	**<0.001**
Night diastolic blood pressure	0.130	**0.019**
E/E’	0.258	**0.007**
LVMI	0.167	**0.009**

UACR	0.259	**0.010**
Total cholesterol	-0.031	0.600
Creatinine	-0.066	0.234
Hematocrit	-0.175	**0.001**
Glucose	0.066	0.234

A univariate logistic regression analysis showed a relationship between non-dipper hypertension and NT-proBNP, total cholesterol, E/E', and LVMI (Table4). In a multivariate logistic regression analysis, a significant relationship was found only between NT-pro BNP and non-dipper hypertension (OR 1.022; CI:1.007–1.038; p<0.05) (Table 4).

Table 4. Univariate and multiple stepwise logistic regression model of non-dipper hypertension.

	Univariate			**Multivariate**		
	OR	**(%95 CI)**	**p**	**OR**	**(%95 CI)**	**p**
NT-proBNP	1.006	1.002-1.01	**<0.001**	1.022	1.007-1.038	**<0.05**
T.cholesterol	1.005	1-1.011	0.050			
LVMI	1.011	1-1.023	**0.046**			
E/E'	1.152	1.004-1.321	**0.043**			

NT-proBNP: N-terminal pro-brain natriuretic peptide; LVMl: left ventricular mass index

In a receiver operating characteristic (ROC) curve analysis, a BNP value of 38.5 pg/ml was identified as an effective cutoff point for non-dipper hypertension (area under curve=0.663; 95% confidence interval (CI) 0.64–0.721; p<0.001). NT-pro BNP levels >38.5 pg/ mL yielded a sensitivity of 61.6% and a specificity of 60% for non-dipper hypertension (Figure 1).

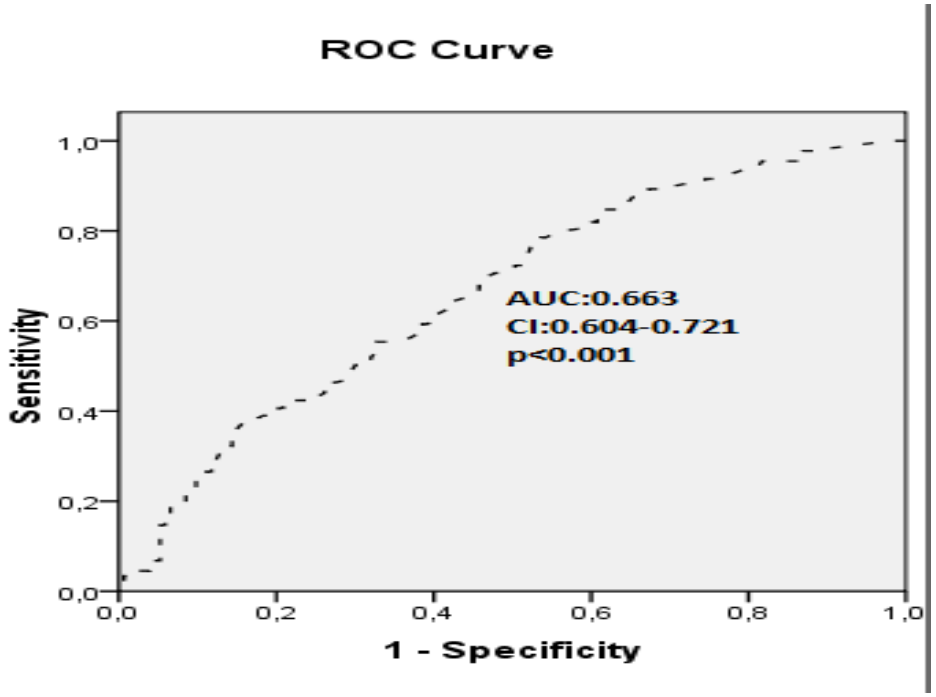

Figure 1: The receiver-operating characteristic (ROC) curve with regard to non-dipper hypertension for high NT- pro BNP with area under curve of 0.63.

DISCUSSION

The main findings of the present single-center study are as follows: 1) NT-pro BNP levels were higher in the non-dipper hypertension group than in the dipper hypertension group. 2) NT-pro BNP levels were correlated positively with all systolic blood pressures, nocturnal diastolic blood pressure, age, E/E', LVMI, and UACR, while hematocrit was inversely correlated with NT-pro BNP. 3) After an adjustment for potential confounders, it was found

that a just level of NT-pro BNP was an independent predictor of development of non-dipper hypertension.

Non-dipper hypertension occurs in approximately 25% of the hypertension population. It is observed most commonly in patients with diabetes mellitus and chronic renal diseases, in African-Americans, and in patients with hypertensive organ damage. Nocturnal decrease in blood pressure has been reported to have many causes; one of the most important causes is decreased sympathetic system activity. This theory was supported by a demonstration of decreases in nocturnal plasma catecholamine level (20) and muscle sympathetic nerve activity (21). Another factor that affects nocturnal decrease in blood pressure is volume and electrolyte status. In one study, normotensive patients with chronic renal failure who received hemodialysis exhibited diurnal variation in blood pressure the first day after hemodialysis, but it disappeared on the second day (22). Takakuva et al. found that the reason for insufficient decrease in blood pressure in patients with essential hypertension was insufficient decrease in nocturnal cardiac index and stroke volume. Stroke volume depends on myocardial contractility, which is under the control of the sympathetic nervous system and venous return to the heart, which, in turn, is determined by renal sodium handling and blood distribution. Therefore, relative volume expansion and insufficient inhibition of sympathetic activity have been proposed as causes of non-dipper hypertension (23).

In the Ohasama study, a population-based prognostic study of Japanese people, it was found that non-dippers were at increased risk of cardiovascular morbidity than dippers (7). Timio et

al. (24) showed that the loss of nocturnal decrease of diastolic BP in patients with chronic renal insufficiency might accelerate the rate of progression of renal insufficiency.

NT-pro-BNP is a cardiac neurohormone that is released from the ventricular myocytes, depending on increased ventricular wall stress (25). Arterial vasodilatation, natriuresis, and diuresis have significant roles in cardiac remodeling and volume homeostasis by inhibiting the sympathetic nervous system and fibrosis (26, 27). Increased NT-pro BNP levels have also been found to be related to cardiovascular events and increased mortality in the general population, chronic renal failure patients, and diabetic patients (14, 17, 28, 29). Increased NT-pro BNP levels might also predict renal disease progression (30).

In our study, we found that NT-pro BNP levels were significantly higher in non-dipper hypertension than in dipper hypertension patients. This finding may have many causes. Hypervolemia and increased activity of the sympathetic nervous system, which cause non-dipper hypertension, might have caused an increase in NT-pro BNP levels by increasing ventricular wall stress. In addition hypertension and ECG-LVH have been reported to affect NT-pro BNP levels (31, 32), and in the non-dipper hypertension group, hypertension (especially nocturnal systolic hypertension) and LVMI were higher. These factors could lead to an increase in NT-pro BNP by increasing vascular resistance and ventricular filling pressure.

Natriuretic peptides have been used in the diagnosis and prediction of many cardiac conditions; a NT-pro BNP level of 125 pg/ml is used as a standard threshold value to

discriminate between patients with and without heart failure (33). Lubien et al. found that elevated levels of the peptide were an accurate indicator of diastolic abnormalities detected by echocardiography, regardless of the patient's history or signs and symptoms of congestive heart failure (34). Sonodo et al. showed that a NT-proBNP value <56.5 pg/ml predicted normal EF and LV relaxation in patients at a cardiac catheterization laboratory who were evaluated for coronary artery disease (35).

In a previous study, we established that a BNP admission cutoff point of 42.4 pg/ mL yielded a sensitivity of 60.0% and a specificity of 61.1% in patients with ST-elevation MI who underwent percutaneous intervention (36). Plasma NT-proBNP levels reflected LV hemodynamic conditions similar to those observed for plasma BNP levels (37). In the present study, an NT-proBNP value >38.5 pg/ mL yielded a sensitivity of 61.6% and a specificity of 60% for non-dipper hypertension in patients with hypertension.

In the present study, a correlation was found between NT-proBNP and all systolic hypertension values, especially nocturnal systolic hypertension values, whereas a weak correlation was found between NT-proBNP and nocturnal diastolic hypertension values. No correlation was found between the other diastolic blood pressure values and NT-proBNP (Table 4). These results suggest that nocturnal systolic hypertension, in particular, is a more significant risk factor for the development of adverse cardiovascular events in hypertensive patients. In an analysis of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, it was found that the nocturnal/daytime systolic blood pressure ratio was an independent risk factor for the development of adverse cardiovascular events (38).

We found no correlation with between serum creatinine and NT-proBNP levels in hypertensive patients. BNP and NT-proBNP levels are usually both elevated in patients with renal dysfunction and end-stage renal disease (39, 40). Although the relationship between increased creatinine and proBNP cannot be elucidated fully, increased left ventricular muscle mass, volume overload, and decreased NT-proBNP clearance (eliminated by the kidneys) in the group of patients might have caused increased NT-proBNP levels (12,40). In our study, patients with a creatinine level above 1.5 mg/dl were excluded from the study; the mean creatinine value in this study was 0.79±19 mg/dl. Some have reported that renal impact is minor if the degree of dysfunction is small (39), which might be the reason we could not find a correlation between NT-proBNP and creatinine. Similarly, Lee et al. could not find an independent correlation between creatinine and NT-proBNP in the general Korean population (41).

LIMITATIONS

The present study has some limitations. First, this study was a single-center, non-randomized, retrospective study, and thus, was subject to selection bias. Second, we excluded patients with clinically overt cardiovascular disease (such as coronary artery disease, cerebrovascular disease, and renal failure), and therefore, our results cannot be extrapolated to all hypertensive subjects. Third, we did not measure blood volume, sympathetic activity, or 24-hour urine sodium in the patients. Therefore, we could not state if the increase in NT-proBNP in non-dipper hypertension was caused by hypervolemia or increased sympathetic system activity.

CONCLUSION

NT-proBNP levels were higher in the non-dipper hypertension group compared to the dipper hypertension group; in particular, NT–proBNP correlated with nocturnal systolic hypertension and age. It is important to recognize that non-dipper hypertension and NT-proBNP values >38.5 pg/ml can be used to identify non-dipping patterns in hypertensive patients without cardiovascular disease and chronic renal failure in clinical practice.

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