Incremental effects of serum uric acid levels, autonomic dysfunction, and low-grade inflammation on nocturnal blood pressure in untreated hypertensive patients and normotensive individuals

Tedavi edilmemiş hipertansif hastalarda ve normotansif bireylerde serum ürik asit düzeyi, otonom disfonksiyon ve düşük dereceli enflamasyonun gece kan basıncı üzerine artırıcı etkileri

Murat Erden, M.D., Sinan Altan Kocaman, M.D., Fatih Poyraz, M.D., Salih Topal, M.D., Asife Şahinarslan, M.D., Bülent Boyacı, M.D., Atiye Çengel, M.D., Mehmet Rıdvan Yalçın, M.D.

Department of Cardiology, Medicine Faculty of Gazi University, Ankara

ABSTRACT

Objectives: We aimed to evaluate the associations between nocturnal blood pressure (BP) and serum uric acid (SUA) level, low-grade inflammation, and cardiac autonomic function in untreated dipper and nondipper hypertensive patients and normotensive individuals.

Study design: The study included 92 consecutive patients (44 men, 48 women; mean age 51.6±9.7 years) who presented for initial evaluation of hypertension. All patients underwent 24-hour Holter monitoring to assess heart rate variability (HRV) and ambulatory BP. Serum high-sensitivity C-reactive protein (hs-CRP) and SUA levels were measured. Due to the non-normal distribution of hs-CRP and microalbuminuria (MAU), they were normalized by logarithmic transformation.

Results: Of the study group, 60 patients (65.2%) were diagnosed as hypertensive (50% nondippers). In univariate correlation analysis, log(MAU) showed a significant correlation with nocturnal BP (r=0.560, p<0.001). Among HRV parameters, SDNN, SDANN, and triangular index were inversely correlated with log(hs-CRP) (r=-0.356, p=0.001; r=-0.350, p=0.001; r=-0.314, p=0.002, respectively) and nighttime BP (r=-0.286, p=0.006; r=-0.251, p=0.02; r=-0.294, p=0.004, respectively). Log(hs-CRP) was positively correlated with nighttime BP (r=0.302, p=0.003). Serum UA levels were correlated with only nocturnal BP; i.e., nocturnal mean (r=0.260, p=0.01), systolic (r=0.249, p=0.016), and diastolic BP (r=0.249, p=0.017). In multiple linear regression analysis, log(hs-CRP) and age were independent predictors of cardiac autonomic dysfunction, and log(hs-CRP), SUA, and HRV parameters were independent predictors of nocturnal BP measurements.

Conclusion: Our findings suggest the role of low-grade inflammation, uric acid levels, and autonomic dysfunction even in the early stages of hypertension.

ÖZET

Amaç: Bu çalışmada tedavi edilmemiş dipper ve nondipper hipertansif hastalarda ve normotansif bireylerde gece kan basıncı (KB) ile serum ürik asit (UA) düzeyi, düşük dereceli enflamasyon ve kardiyak otonomik disfonksiyon arasındaki ilişkinin değerlendirilmesi amaçlandı.

Çalışma planı: Çalışmada, hipertansiyon için ilk kez değerlendirilecek olan ardışık 92 hasta (44 erkek, 48 kadın; ort. yaş 51.6±9.7) incelendi. Tüm hastalarda kalp hızı değişkenliği (KHD) parametrelerinin değerlendirilmesi ve kan basıncı ölçümleri için 24 saatlik Holter izlemi yapıldı ve serumda yüksek duyarlıklı C-reaktif protein (hs-CRP) ve UA düzeyleri ölçüldü. Normal dağılım göstermeyen hs-CRP ve mikroalbüminüri (MAU) logaritmik dönüştürüm ile normalleştirildi.

Bulgular: Çalışmada 60 hasta (%65.2) hipertansif (%50'si nondipper) bulundu. Tekdeğişkenli korelasyon analizinde log(MAU) gece KB ölçümleri ile anlamlı ilişki gösterdi (r=0.560, p<0.001). Kalp hızı değişkenliği parametrelerinden SDNN, SDANN ve triangüler indeks log(hs-CRP) (sırasıyla, r=-0.356, p=0.001; r=-0.350, p=0.001; r=-0.314, p=0.002) ve gece ortalama KB (sırasıyla, r=-0.286, p=0.006; r=-0.251, p=0.02; r=-0.294, p=0.004) ile ters ilişkiliydi. Log(hs-CRP) gece ortalama KB ile doğrusal ilişki gösterdi (r=0.302, p=0.003). Serum UA düzeyi sadece gece KB ölçümleri ile ilişkiliydi (gece KB için, r=0.260, p=0.01; gece sistolik KB için, r=0.249, p=0.016; gece diyastolik KB için, r=0.249, p=0.017). Çokdeğişkenli lineer regresyon analizinde, log(hs-CRP) ve yaş kardiyak otonom disfonksiyonun, log(hs-CRP), serum UA ve KHD parametreleri gece KB ölçümlerinin bağımsız öngördürücüleri olarak bulundu.

Sonuç: Bulgularımız düşük dereceli enflamasyon, ürik asit düzeyi ve otonom disfonksiyonun hipertansiyonun erken aşamalarında bile rol oynadığını düşündürmektedir.

Received: February 2, 2011 *Accepted:* July 22, 2011

Correspondence: Dr. Sinan Altan Kocaman. Gazi Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 06500 Beşevler, Ankara, Turkey. Tel: +90 312 - 202 56 29 e-mail: sinanaltan@gmail.com

Hypertension is a multifactorial and heterogeneous disease that presents as high blood pressure. It is the leading cause of cardiovascular morbidity and mortality. Despite the advances in diagnosis, pathophysiological mechanisms, and treatment of hypertension, its cardiovascular mortality is still high and frequently presents as sudden cardiac death.[1] In most cases, this results from lack of understanding its exact etiology and curable treatments.

Pathological increases in BP may begin at different ages with diverse clinical entities and dominant mechanisms. However, hypertension cannot be diagnosed at normotensive stage because there is no differential diagnostic criteria to establish its diagnosis. Some patients with end-organ damage but no evident causative factor at normotensive stage may present the early stages in hypertensive process.

Despite the advances in diagnosis, pathophysiological mechanisms and treatment, the exact causative mechanisms of essential hypertension are still unclear. Therefore, we do not have definite curable treatment options for these patients.

In this study, we aimed to evaluate the association of nocturnal blood pressure with serum uric acid, low-grade inflammation, and cardiac autonomic functions in untreated dipper and nondipper hypertensive patients and normotensive individuals.

PATIENTS AND METHODS

This cross-sectional study included 92 consecutive patients (44 men, 48 women; mean age 51.6±9.7 years) who presented to our institution for initial evaluation of hypertension between June 2008 and July 2008. The local ethics committee of Gazi University Faculty of Medicine approved the study.

The participants were divided into two groups based on BP levels of <130/80 mmHg (normotensive) and ≥130/80 mmHg (hypertensive). Each group was further analyzed based on day and night time fluctuations derived from ambulatory BP measurements, i.e., nocturnal decline in BP by ≥10% (dipper) and <10% (nondipper).

Exclusion criteria were the presence of the following: diabetes mellitus, atrial fibrillation, coronary artery disease, typical angina pectoris, hyper- or hypothyroidism, left ventricular systolic dysfunction, cardiomyopathies, moderate-to-severe valvular diseases, symptomatic peripheral vascular diseases (transient ischemic attack, stroke, intermittent claudication, peripheral revascularization, or amputation), evidence for ongoing infection or inflammation, hematological disorders, known malignancy, drug history including anti-gout agents, and any other continual drug use.

Abbreviations:

ANS	*Autonomic nervous system*
BP	*Blood pressure*
HRV	*Heart rate variability*
MAU	*Microalbuminuria*
NBP	*Nocturnal blood pressure*
NN	*Normal-to-normal*
SUA	*Serum uric acid*

Blood samples were drawn by venipuncture for routine blood chemistry after fasting for at least eight hours. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were recorded. Serum uric acid levels were determined with enzymatic colorimetric method (uricase-peroxidase method) on a clinical chemistry auto-analyzer (Aeroset, Abbott Laboratories, Abbott Park, IL, USA). Microalbuminuria was measured in 24-hour urine collection. Serum high-sensitivity C-reactive protein (hs-CRP) level was determined using the nephelometric method.

All patients underwent 24-hour Holter monitoring to assess heart rate variability parameters according to the previously published guidelines.[2] Holter monitoring was performed on a 3-channel digitized recorder (Tracker NIBP, Del Mar Reynolds Medical, Hertford, UK) and the recordings were evaluated by an experienced physician who was totally blind to the study population. Data were manually pre-processed before analysis. Recordings lasting for at least 18 hours and of sufficient quality for evaluation were included in the analysis; otherwise, the recording was repeated. The following time-domain HRV parameters were analyzed using statistical methods: rMSSD: square root of the mean squared differences between successive normal-to-normal (NN) intervals; SDNN: standard deviation of all NN intervals; SDNN index: mean of the standard deviations of all 5-min NN intervals of the entire recording; SDANN: standard deviation of the averages of NN intervals in all 5-min periods of the entire recording. By using geometrical methods, HRV triangular index (TI) was measured as the total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7.8125 msec (1/128 sec).

To determine day and night variations in BP, night/day ratio was calculated with the following formula: [1 - (mean night systolic BP / mean day systolic BP)] x 100.

All patients underwent complete transthoracic examination including two-dimensional, color flow and pulsed Doppler and tissue Doppler imaging using a GE-Vingmed Vivid 7 ultrasound system (GE Ving-

med, Horten, Norway) and a 2.5-3.5 MHz transducer. Left ventricular mass was calculated and left ventricular mass index was derived from division of left ventricular mass by body surface area.[3]

Statistical analysis

Continuous variables were expressed as mean± standard deviation, and categorical variables were expressed as counts and percentages. Data were tested for normal distribution using the Kolmogorov-Smirnov test. As high-sensitivity CRP and MAU showed non-normal distributions, they were normalized by logarithmic transformation as log(hs-CRP) and log(MAU). The chi-square test was used for categorical variables and the Pearson correlation coefficient was used for correlation analysis. The means of different groups were compared by the two-way ANOVA test. Linear regression analysis with a stepwise method was used for multivariate analysis after exclusion of irrelevant variables from the model. All tests of significance were two-tailed. Statistical significance was defined as $p<0.05$. The SPSS statistical software (SPSS 15.0 for Windows) was used for all statistical calculations.

RESULTS

Of the study group, 60 patients (65.2%) were assigned as hypertensives, and 32 (34.8%) were assigned as normotensives. Demographic characteristics and labo-

Table 1. Clinical characteristics of untreated dipper and nondipper hypertensive patients and controls

	Hypertensive (n=60)		Normotensive (n=32)			
	Nondipper (n=30) Mean±SD or n (%)	Dipper (n=30) Mean±SD or n (%)	Nondipper (n=19) Mean±SD or n (%)	Dipper (n=13) Mean±SD or n (%)	p^1	p^2
Age (years)	52±9	52±9	55±10	45±11	N S	**0.029**
Gender					N S	N S
Male	16 (53.3%)	13 (43.3%)	10 (52.6%)	5 (38.59%)		
Female	14 (46.7%)	17 (56.7%)	9 (47.4%)	8 (61.5%)		
Height (cm)	168±9	165±9	164±9	164±7	N S	N S
Weight (kg)	80±15	74±11	79±16	72±10	N S	**0.050**
Body mass index (kg/m^2)	28±4	27±3	29±5	27±4	N S	N S
Body surface area (m^2)	1.9±0.2	1.8±0.2	1.9±0.2	1.8±0.1	N S	N S
Smoking	16 (53.3%)	14 (46.7%)	7 (36.8%)	5 (38.5%)	N S	N S
Total cholesterol (mg/dl)	191±39	210±27	217±40	191±31	N S	N S
LDL cholesterol (mg/dl)	118±32	134±21	134±30	117±25	N S	N S
HDL cholesterol (mg/dl)	47±14	51±15	49±10	49±11	N S	N S
Triglycerides (mg/dl)	131±57	127±38	172±77	132±75	N S	N S
Fasting plasma glucose (mg/dl)	91±11	94±13	100±9	91±9	N S	N S
Serum creatinine (mg/dl)	0.9±0.2	0.8±0.1	0.8±0.1	0.8±0.1	N S	N S
Estimated glomerular filtration rate (ml/min)	105±25	101±21	103±22	108±28	N S	N S
Hemoglobin (mg/dl)	13.9±1.1	14.1±1.4	13.5±1.1	13.3±1.2	**0.032**	N S
Uric acid (mg/dl)	4.5±1.1	4.0±1.1	3.9±1.2	3.8±1.1	N S	N S
Microalbuminuria (mg/day) Median (25th-75th percentiles)	29 (13-44)	15 (7-27)	7 (6-11)	8 (6-10)	**0.015**	N S
Log(Microalbuminuria) (mg/day)	1.4±0.4	1.2±0.4	0.9±0.2	1.0±0.4	**<0.001**	N S
High-sensitivity CRP (mg/dl) Median (25th-75th percentiles)	0.5 (0.3-0.6)	0.3 (0.2-0.5)	0.3 (0.2-0.8)	0.2 (0.1-0.3)	**0.041**	**0.004**
Log(high-sensitivity CRP) (mg/dl)	-0.4±0.4	-0.5±0.3	-0.6±0.5	-0.8±0.3	**0.007**	**0.019**

p^1: Hypertensive *vs.* normotensive groups; p^2: Nondipper *vs.* dipper groups; NS: Not significant.

ratory data of the patients are shown in Table 1. Blood pressure measurements, HRV parameters, and echocardiographic data are shown in Table 2.

In univariate correlation analysis, log(MAU) showed a significant correlation primarily with night BP measurement (r=0.560, p<0.001, Fig. 1a). Among HRV parameters, SDNN, SDANN, and triangular index were inversely correlated with age (r=-0.291, p=0.005; r=-0.307, p=0.003; r=-0.189, p=0.072, respectively), log(hs-CRP) (r=-0.356, p=0.001, Fig. 1b; r=-0.350, p=0.001; r=-0.314, p=0.002, respectively) and nighttime mean BP (r=-0.286, p=0.006, Fig. 1c; r=-0.251, p=0.02; r=-0.294, p=0.004, respectively).

Log(hs-CRP) was positively correlated with overall mean BP (r=0.245, p=0.02), daytime mean BP (r=0.210, p=0.04), and nighttime mean BP (r=0.302, p=0.003).

Table 2. Blood pressure measurements, heart rate variability, and echocardiographic parameters in untreated dipper and nondipper hypertensive patients and controls

	Hypertensive (n=60)		Normotensive (n=32)			
	Nondipper (n=30) Mean±SD	Dipper (n=30) Mean±SD	Nondipper (n=19) Mean±SD	Dipper (n=13) Mean±SD	p^1	p^2
Blood pressure (mmHg)						
Overall mean	101±6	100±6	85±7	84±5	**<0.001**	N S
Overall systolic	138±7	136±7	117±7	117±5	**<0.001**	N S
Overall diastolic	83±7	82±6	69±7	68±6	**<0.001**	N S
Daytime mean	103±7	104±6	86±7	88±6	**<0.001**	N S
Daytime systolic	140±7	141±7	118±7	121±6	**<0.001**	N S
Daytime diastolic	84±8	85±7	70±8	72±6	**<0.001**	N S
Nighttime mean	98±7	89±6	81±6	74±6	**<0.001**	**<0.001**
Nighttime systolic	134±9	121±7	113±7	105±5	**<0.001**	**<0.001**
Nighttime diastolic	80±8	73±6	65±7	58±7	**<0.001**	**<0.001**
Day-night ratio (%)	4±4	14±3	5±4	13±3	N S	**<0.001**
Heart rate variability						
Heart rate (beats/min)	81±8	77±10	74±11	80±8	N S	N S
SDNN (msec)	110±31	119±27	125±35	136±24	**0.019**	N S
SDANN (msec)	101±30	110±25	109±29	128±24	**0.041**	**0.026**
SDNN index (msec)	41±14	47±14	49±18	47±16	N S	N S
rMSSD (msec)	23±11	26±12	24±13	23±12	N S	N S
Triangular index	29±10	34±9	35±11	37±9	0.057	N S
Echocardiographic parameters						
Left ventricle						
Ejection fraction (%)	67±4	67±3	66±3	69±3	N S	N S
End-diastolic diameter (mm)	46.0±3.7	45.4±4.1	45.7±4.3	44.9±3.8	N S	N S
End-systolic diameter (mm)	28.6±2.8	28.4±2.8	29.1±3.0	27.6±2.0	N S	N S
Interventricular septum diameter (mm)	11.0±1.5	10.9±1.5	10.5±1.5	10.2±1.7	0.069	N S
Posterior wall diameter (mm)	10.4±1.1	10.4±1.2	10.0±1.1	10.0±1.6	**0.017**	N S
Mass (g)	177±41	172±38	163±40	151±33	0.051	N S
Lass index (g/m^2)	92±21	93±20	87±18	83±16	0.069	N S
Left atrium diameter (mm)	35.6±3.4	35.8±3.0	34.7±4.0	33.6±2.8	**0.043**	N S

p^1: Hypertensive *vs.* normotensive groups; p^2: Nondipper *vs.* dipper groups;NS: Not significant. *Heart rate variability parameters:* SDNN: Standard deviation of all normal-to-normal intervals; SDNN index: Mean of the standard deviations of all 5-min normal-to-normal intervals of the entire recording; SDANN: Standard deviation of the averages of normal-to-normal intervals in all 5-min periods of the entire recording; rMSDD: Square root of the mean squared differences between successive normal-to-normal intervals.

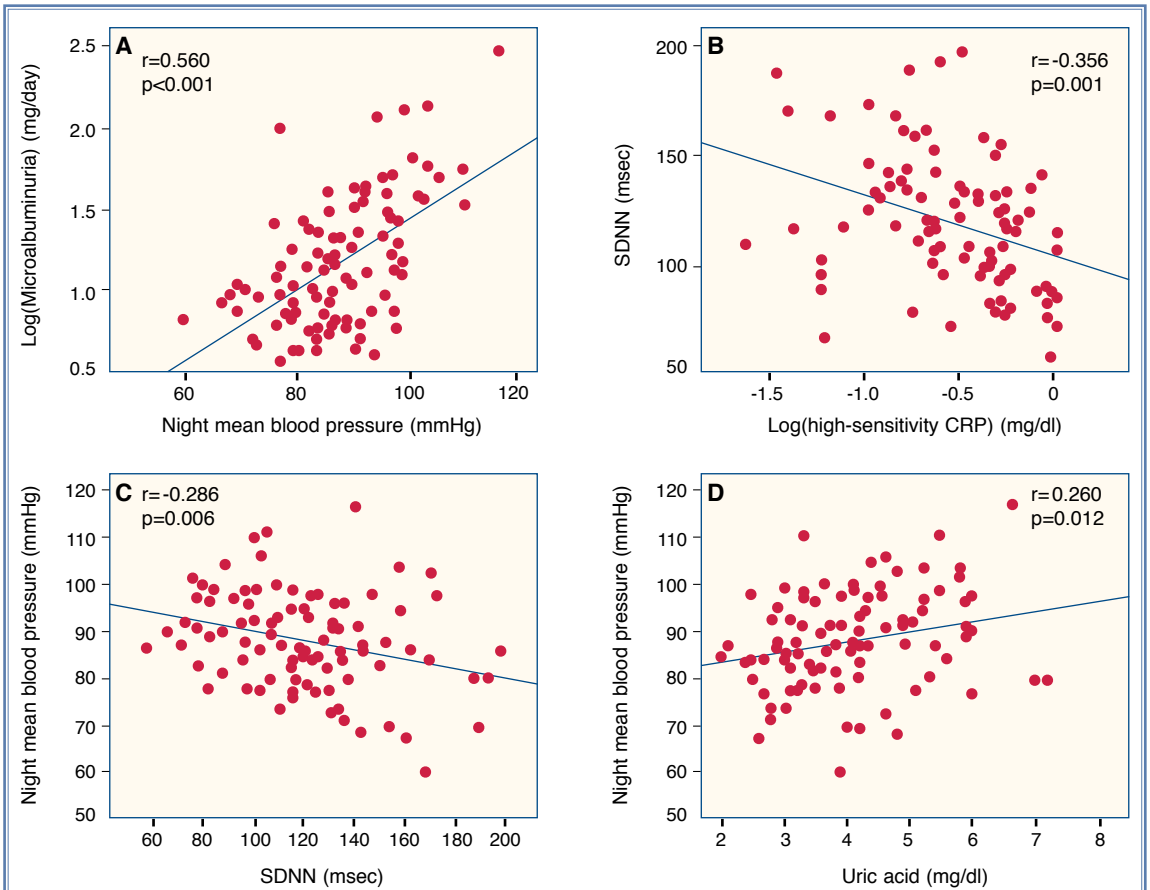

Figure 1. Correlations between **(A)** normalized microalbuminuria and nighttime mean blood pressure, **(B)** SDNN and normalized high-sensitivity CRP level, **(C)** nighttime mean blood pressure and SDNN, and **(D)** nighttime mean blood pressure and serum uric acid level.

Serum UA levels were correlated with only NBP measurements; hence, nocturnal mean BP (r=0.260, p=0.01, Fig. 1d), nocturnal systolic BP (r=0.249, p=0.016), and nocturnal diastolic BP (r=0.249, p=0.017).

In linear regression analysis, log(hs-CRP) and age were independent predictors of cardiac autonomic dysfunction, and log(hs-CRP), SUA and HRV parameters were independent predictors of NBP measurements (Table 3).

DISCUSSION

In this study, we evaluated the relationship between night BP, uric acid, low-grade inflammation, and cardiac autonomic functions in untreated dipper and nondipper hypertensive patients and normotensive individuals. We found that a relatively high NBP level was independently related with low-grade inflammation, SUA, and autonomic dysfunction. Additionally, MAU was mainly determined by night BP levels, and autonomic dysfunction was independently affected by age and low-grade inflammation.

In recent years, frequent use of ambulatory BP measurements in clinical practice has given rise to new diagnostic and prognostic concepts in hypertension, most important being the nondipper condition. Patients with this impaired physiology suffer from cardiovascular events more frequently than dippers. However, the underlying causative mechanisms have not been clearly elucidated.[4] In general, NBP shows an average decrease of 15% in normotensive and hypertensive patients.[5] Patients having a decrease of less than 10% and greater than 10% in NBP are classified as nondipper and dipper hypertensives, respectively. Impaired autonomic functions are thought to underlie the mechanism of lack of nocturnal decline in NBP. In nondipper patients, renal impairment (i.e., MAU, proteinuria, and decreased creatinine clearance) associated with cardiovascular mortality, nonfatal vascular events, and hypertension is significantly higher than dipper hypertensive patients.[6,7]

Table 3. The results of multiple linear regression analysis: independent factors predicting cardiac autonomic functions and nocturnal blood pressure levels

	Dependent variable	Independent predictors	Unstandardized coefficient (B±SE)	Standardized coefficient (β)	*p*
Cardiac autonomic functions	SDNN	Age	-0.8±0.3	-0.261	**0.008**
		Log (hs-CRP)	-26±7.5	-0.332	**0.001**
		Constant	148±17		**<0.001**
		R^2		0.194	
	SDNN index	Age	-0.4±0.2	-0.241	**0.01**
		Log (hs-CRP)	-13±3.9	-0.325	**0.001**
		Constant	58±9		**<0.001**
		R^2		0.178	
	SDANN	Age	-0.8±0.3	-0.278	**0.004**
		Log (hs-CRP)	-24±7.1	-0.325	**0.001**
		Constant	138±15		**<0.001**
		R^2		0.199	
	Triangular index	Age	-0.2±0.1	-0.162	0.1
		Log (hs-CRP)	-7.8±2.6	-0.299	**0.003**
		Constant	37±6		**<0.001**
		R^2		0.124	
Nocturnal blood pressure (BP)	Nighttime mean BP	Log (hs-CRP)	5.6±2.8	0.205	**0.048**
		SDNN	-0.08±0.04	-0.242	**0.021**
		Serum uric acid	2.5±0.9	0.276	**0.005**
		Constant	91±5		**<0.001**
		R^2		0.202	
	Nighttime systolic BP	Log (hs-CRP)	7.4±3.4	0.221	**0.031**
		SDNN	-0.1±0.04	-0.259	**0.012**
		Serum uric acid	3.0±1.1	0.267	**0.006**
		Constant	126±6		**<0.001**
		R^2		0.219	
	Nighttime diastolic BP	Log (hs-CRP)	4.8±2.8	0.180	0.087
		SDNN	-0.07±0.04	-0.215	**0.044**
		Serum uric acid	2.3±0.9	0.264	**0.009**
		Constant	73±5		**<0.001**
		R^2		0.168	

Heart rate variability parameters reflect the autonomic balance and autonomic nervous system functionality.[2] This analysis is frequently used in cardiovascular research and clinical practice to quantify the alterations in intervals between sinus heart beats as the heart rate oscillates around a mean value. These oscillations are modulated by the ANS and can be analyzed by different methods. The association between functional status of the ANS and autonomic imbalance in congestive heart failure has been shown by HRV analysis.[8] Heart rate variability is a standardized tool for examining ANS activity in various disease states such as hypertension, diabetes mellitus, coronary artery disease, and myocardial dysfunction. Sudden cardiac death is frequent in the course of cardiovascular diseases. Autonomic imbalance is an important causative mechanism of malignant arrhythmias which are the most important etiology of sudden cardiac death. In particular, it is a powerful and simple indicator of diabetic autonomic neuropathy.[9] It is also impaired

during the course of acute coronary syndromes and postdischarge term,[10] congestive heart failure,[11] and hypertension.[12] In addition, impaired HRV has been determined as an important predictor of future cardiovascular events in the above-mentioned diseases and even in healthy individuals.[13,14] However, the underlying pathophysiological mechanisms have not been clearly established.

Heart rate variability is regulated by central nervous signals sent to the heart via the sympathetic and parasympathetic nerves. A recent study has demonstrated that the central nervous system can decrease cytokine production via activity of parasympathetic fibers in the vagus nerve.[15]

Stimulation of the vagus nerve significantly inhibits the release of tumor necrosis factor-alpha in animals.[16] Furthermore, experimental models studying sepsis, myocardial ischemia, and pancreatitis have documented the inhibition of cytokine activity through vagus nerve stimulation.[17,18] Only a small fraction of the vagus nerve innervates the heart. The other ANS innervations may play a more important role in the development of nondipping pattern. Although impaired HRV has been linked to poor prognosis in hypertensive patients, the underlying pathophysiological mechanisms are not clear.

C-reactive protein is an acute phase protein (reactant) with a pentameric configuration and is mainly produced by the liver.[19] It significantly increases in acute infective diseases, autoimmune disorders, and during the course of malignancies. In recent years, since the relationship between CRP and cardiovascular diseases was shown,[20] the potential role of CRP in the diagnosis and prognosis of cardiovascular diseases has become a popular area of research. In particular, increased CRP levels in patients who are under moderate risk for coronary artery disease have been found to be a predictor of future cardiovascular events as satisfactory as classical risk factors.[21,22] Aggressive risk factor modification has provided a significant reduction in cardiovascular morbidity and mortality in studies using CRP as an indicator of cardiovascular risk.[23] The reverse association of HRV with elevated serum CRP levels shown in a general Japanese population, also shown by our findings, may provide more insight into the possible pathophysiological mechanisms.[24]

In humans and higher primates, uric acid is the main end-product of purine metabolism due to the mutations that render the uricase gene nonfunctional.[25,26] There has been strong evidence that higher SUA levels are associated with end-point and target organ damage in hypertensive individuals. Recent experimental and clinical studies have shown that elevated SUA levels correlate with age, male gender, hyperlipidemia, obesity, hyperinsulinemia, diabetes mellitus, glucose intolerance,[27] systemic inflammation,[28] increased CRP levels,[29] endothelial dysfunction,[30] hypertension,[31] and impaired small artery elasticity.[32] In many clinical and epidemiological studies, SUA has been found to be related with the development of hypertension, inflammation, impaired arterial elasticity, and coronary atherosclerosis.[33-35] Elevated SUA levels have also been found to be related with an accelerated progression of hypertension and development of end-organ injury.[36] Although asymptomatic hyperuricemia is currently considered to be benign and do not require treatment, impaired endothelial-dependent vasodilatation is commonly present in hyperuricemic patients even in the absence of underlying cardiovascular disease.[37]

Study limitations

Our study has some limitations. The main limitation may be its small sample size. On the other hand, we focused more specifically on the relationships in untreated dipper and nondipper hypertensive patients and normotensive individuals in early stages of hypertension rather than in patients with old diagnosis of hypertension and receiving treatment. These two factors might have resulted in low correlation coefficients for the study parameters. Many patients in this study had slightly high BP measurements and nearly 35% of the study population were normotensive. Therefore, the presence of white-coat hypertension could not be eliminated.

To our best knowledge, this is the first study which shows that low-grade inflammation, SUA, and autonomic dysfunction have profound relationships with relatively high NBP levels, which may be important for the development of hypertension and vascular end-organ damage. These significant correlations were found even though our study population consisted of individuals who had relatively low risk, low BP values, and no significant end-organ damage. Therefore, these findings support that parameters of low-grade inflammation, uric acid, and autonomic dysfunction may be valid even in the early stages of hypertension. Further clinical studies focusing on SUA, autonomic functions, and inflammation are needed to clarify our findings on hypertension.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Kannel WB, Cupples LA, D'Agostino RB, Stokes J 3rd. Hypertension, antihypertensive treatment, and sudden coronary death. The Framingham Study. Hypertension 1988; 11:II45-50.
2. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354-81.
3. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977;55:613-8.
4. Kobrin I, Oigman W, Kumar A, Ventura HO, Messerli FH, Frohlich ED, et al. Diurnal variation of blood pressure in elderly patients with essential hypertension. J Am Geriatr Soc 1984;32:896-9.
5. Cifkova R, Erdine S, Fagard R, Farsang C, Heagerty AM, Kiowski W, et al. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. J Hypertens 2003;21:1779-86.
6. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. Hypertension 1994;24:793-801.
7. Timio M, Venanzi S, Lolli S, Lippi C, Verdura E, Guerrini E, Monarca C. Night time blood pressure and progression of renal insufficiency. High Blood Press Cardiovasc Prev 1994;3:39-44.
8. Eisenhofer G, Friberg P, Rundqvist B, Quyyumi AA, Lambert G, Kaye DM, et al. Cardiac sympathetic nerve function in congestive heart failure. Circulation 1996;93:1667-76.
9. Pagani M, Malfatto G, Pierini S, Casati R, Masu AM, Poli M, et al. Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. J Auton Nerv Syst 1988;23:143-53.
10. Farrell TG, Bashir Y, Cripps T, Malik M, Poloniecki J, Bennett ED, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. J Am Coll Cardiol 1991;18:687-97.
11. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, Haaksma J, Dijk WA, Visser KR, et al. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. The Dutch Ibopamine Multicenter Trial Study Group. J Am Coll Cardiol 1996;28:1183-9.
12. Guzzetti S, Dassi S, Pecis M, Casati R, Masu AM, Longoni P, et al. Altered pattern of circadian neural control of heart period in mild hypertension. J Hypertens 1991;9:831-8.
13. Tsuji H, Venditti FJ Jr, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation 1994;90:878-83.
14. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996;94:2850-5.
15. Tracey KJ. The inflammatory reflex. Nature 2002;420:853-9.
16. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). Circulation 1998;98:1510-6.
17. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000;405:458-62.
18. Saeed RW, Varma S, Peng-Nemeroff T, Sherry B, Balakhaneh D, Huston J, et al. Cholinergic stimulation blocks endothelial cell activation and leukocyte recruitment during inflammation. J Exp Med 2005;201:1113-23.
19. Black S, Kushner I, Samols D. C-reactive Protein. J Biol Chem 2004;279:48487-90.
20. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-43.
21. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.
22. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. Circulation 2002;105:2595-9.
23. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 2009;373:1175-82.
24. Kon H, Nagano M, Tanaka F, Satoh K, Segawa T, Nakamura M. Association of decreased variation of R-R interval and elevated serum C-reactive protein level in a general population in Japan. Int Heart J 2006;47:867-76.
25. Wu XW, Muzny DM, Lee CC, Caskey CT. Two independent mutational events in the loss of urate oxidase during hominoid evolution. J Mol Evol 1992;34:78-84.
26. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. Hypertension 2002;40:355-60.
27. Lee J, Sparrow D, Vokonas PS, Landsberg L, Weiss ST. Uric acid and coronary heart disease risk: evidence for a role of uric acid in the obesity-insulin resistance syndrome. The Normative Aging Study. Am J Epidemiol 1995;142: 288-94.
28. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107:1991-7.

29. Saito M, Ishimitsu T, Minami J, Ono H, Ohrui M, Matsuoka H. Relations of plasma high-sensitivity C-reactive protein to traditional cardiovascular risk factors. Atherosclerosis 2003;167:73-9.
30. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. Kidney Int 2005;67:1739-42.
31. Johnson RJ, Feig DI, Herrera-Acosta J, Kang DH. Resurrection of uric acid as a causal risk factor in essential hypertension. Hypertension 2005;45:18-20.
32. Fazlıoğlu M, Sentürk T, Kumbay E, Kaderli AA, Yılmaz Y, Özdemir B, et al. Small arterial elasticity predicts the extent of coronary artery disease: Relationship with serum uric acid. Atherosclerosis 2009;202:200-4.
33. Meisinger C, Koenig W, Baumert J, Döring A. Uric acid levels are associated with all-cause and cardiovascular disease mortality independent of systemic inflammation in men from the general population: the MONICA/KORA cohort study. Arterioscler Thromb Vasc Biol 2008; 28:1186-92.
34. Gagliardi AC, Miname MH, Santos RD. Uric acid: a marker of increased cardiovascular risk. Atherosclerosis 2009; 202:11-7.
35. Kocaman SA, Şahinarslan A, Cemri M, Timurkaynak T, Boyacı B, Çengel A. Independent relationship of serum uric acid levels with leukocytes and coronary atherosclerotic burden. Nutr Metab Cardiovasc Dis 2009;19:729-35.
36. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002;282:F991-7.
37. Kato M, Hisatome I, Tomikura Y, Kotani K, Kinugawa T, Ogino K, et al. Status of endothelial dependent vasodilation in patients with hyperuricemia. Am J Cardiol 2005; 96:1576-8.

Key words: Blood pressure monitoring, ambulatory; C-reactive protein; electrocardiography; heart rate/physiology; hypertension; uric acid.

Anahtar sözcükler: Kan basıncını izleme, ambulatuvar; C-reaktif protein; elektrokardiyografi; kalp hızı/fizyoloji; hipertansiyon; ürik asit.