Cardiac Autonomic Neuropathy and Complications of Primary Hypertension: Is Autonomic Neuropathy a Cause or a Result?

Kardiyak Otonomik Nöropati ve Primer Hipertansiyonun Komplikasyonları: Otonomik Nöropati Bir Sebep mi ya da Bir Sonuç mu?

ABSTRACT

OBJECTIVE: Cardiac autonomic dysfunction (COD) is one of the important factors implicated in the pathogenesis of primary hypertension (HT). Heart rate variability (HRV) measurement has been used widely to determine the COD. We aimed to examine the HRV in primary hypertension and its relationships with end organ damage.

MATERIAL and METHODS: Ninety adult patients and 28 healthy controls were included into the study. Heart rates (HRs) and HRV parameters were measured by monitoring with 24-hour Holter electrocardiographic records. Patients were assessed in terms of retinopathy, microalbuminuria and left ventricle hypertrophy.

RESULTS: Primary hypertensive patients had significantly higher blood pressure (BP) values than those of the controls. Minimum HRs of all patients were significantly higher than controls, while HRV parameters showed significantly lower values in the patients compared to controls. The HRV parameters showed no significant correlations with retinopathy, left ventricle hypertrophy, microalbuminuria and cardiovascular risk factors.

CONCLUSION: Lower HRV parameters in hypertensive patients probably suggests the presence of a COD. However, such a difference was not observed between the newly and previously diagnosed patients indicating that the HRV seems not to be influenced by antihypertensive treatment.

KEY WORDS: Primary hypertension, Cardiac autonomic dysfunction, Heart rate variability

ÖZ

AMAÇ: Kardiyak otonomik disfonksiyon (KOD) primer hipertansiyonun patogenezinden sorumlu önemli bir faktördür. Kalp hızı değişkenliği (KHD) ise KOD belirlenmesinde yaygın kullanılan bir ölçümdür. Biz burada, primer hipertansiyonda KHD'ni ve bunun son organ hasarı ile ilişkisini incelemeyi amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya 90 erişkin hasta ve 28 sağlıklı kontrol dahil edildi. Kalp hızları(KH) ve KHD parametreleri 24 saat holter elektrokardiyografi ile kayıt altına alındı. Hastalar retinopati, mikroalbuminüri ve sol ventrikül hipertrofisi yönünden değerlendirildi.

BULGULAR: Primer hipertansif hastaların kan basınçları kontrol grubundan anlamlı şekilde yüksekti. Hastaların KHD parametreleri kontrollere göre anlamlı şekilde düşükken, minimum KH'ları ise anlamlı şekilde yüksek saptandı. KHD parametreleri ile retinopati, sol ventrikül hipertrofisi, mikroalbuminüri ve kardiyovasküler risk faktörleri arasında anlamlı ilişki yoktu.

SONUÇ: Hipertansif hastalardaki düşük KHD parametreleri olası KOD varlığını göstermekteydi. Bununla beraber, yeni tanı alan ve eskiden beri hipertansif olan hastalar arasında KHD yönünden farklılık olmaması, KHD'nin antihipertansif tedaviden etkilenmediğini düşündürtmekteydi.

ANAHTAR SÖZCÜKLER: Primer hipertansiyon, Kardiyak otonomik disfonksiyon, Kalp hızı değişkenliği

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INTRODUCTION

Hypertension constitutes a major public health problem with an incidence and prevalence that increases with age (1). It is a heterogeneous disease with a complex pathophysiology where genetic, environmental and endogenous factors may play a role. Endothelial dysfunction, autonomic nervous system (ANS) changes, and the activation of the renin-angiotensin system (RAS) are responsible for the pathogenetic mechanisms.

Cardiac output was found to be elevated in young, borderline hypertensive patients with hyperkinetic circulation. Increased cardiac output responsible for hypertension may occur in two ways: either as a result of the increased liquid volume (preload), or an increase of the neural stimulation of the heart contractility (2). Neural stimulation of the heart is under the control of the ANS. The sympathetic and parasympathetic nervous systems maintain the heart's nerve conduction, heart rate (HR) and HR changes in a balanced manner. Increased sympathetic activation contributes to the development of hypertension. Increased activation of the sympathetic nervous system, in people with normal blood pressure as well as in patients with hypertension, raises blood pressure by causing an increase in vascular resistance, cardiac output and fluid uptake via the stimulation of the peripheral vascular bed, heart, and kidney (3). A decrease in vagal activity also contributes to increased blood pressure. A relationship between autonomic disorders and the severity of the disease is considered. In a large number of epidemiological studies, increased HR has been shown to be an independent factor in predicting the development of hypertension (4). In addition, increased HR and decreased heart rate variability (HRV) may predict the cardiovascular mortality rate as they are, at least partly, associated with other cardiovascular risk factors (5,6).

HRV is one of the most common and useful tests used to determine cardiac autonomic function. HRV can be defined as cyclic changes in the sinus rate over time. In other words, it means the fluctuations of HR around an average. HRV measurement can be performed with a 5-minute short or long-term ECG recordings, over a 24-hour period, with time-dependent, frequency-dependent, geometric or non-linear methods (7).

Measurements of HRV may provide important data about the autonomic tone and the stimulation of the heart, such as in diabetes, coronary heart disease (CHD), myocardial infarction (MI) and about the prognosis of disease states, such as sudden death, cardiac death, and general mortality risks (8). Although lowering blood pressure in individuals with hypertension has been shown to be associated with improvement in HRV parameters (9), its role in lowering bad outcomes is not fully understood.

The purpose of this study was to determine cardiovascular autonomic neuropathy, examine the relationship between HRV and cardiac risk factors and signs of end organ damage in hypertensive individuals, and investigate the role of HRV in estimating the complications of hypertension.

MATERIAL and METHODS

Patients

The study was carried out between November 2010 - April 2012 in the outpatient clinics of the Department of Internal Medicine. Patients diagnosed with primary hypertension according to the European Society of Hypertension – European Society of Cardiology 2013 guidelines (10) and healthy individuals visiting the outpatient clinic for control purposes were included in the study. Patients between the ages of 18-65, with a diagnosis of primary hypertension, a body mass index 30 kg/m^2 or under, and providing informed consent were included in the study. Patients with a secondary cause of hypertension, a cardiovascular disease other than hypertension, diabetes, thyroid dysfunction, kidney or liver failure and other systemic diseases such as malignancy and those lacking informed consent were excluded. After a detailed clinical history of the patients included in the study, systemic examination was performed.

Cases were evaluated as proposed in the ESH - ESC manual in terms of routine laboratory studies (Table III), ocular fundus assessment, microalbuminuria and left ventricular hypertrophy. Fundus staging was performed according to the Keith-Wagener classification. For evaluation of renal function damage, urea and creatinine levels were measured as well as the 24-hour urine microalbumin. Measured microalbumin level below 30 mg/day was considered as microalbuminuria negative; 30-300 mg/day as microalbuminuria positive, and higher than 300 mg/day was considered as overt proteinuria. Assessment of left ventricular hypertrophy was performed using a GE Vivid7 3 MHz probe echocardiography device. Standard 2-dimensional, M-mode and color Doppler techniques were used to evaluate the dimensions of the cardiac chambers, left ventricular wall thickness, ejection fraction, fractional shortening, cover structure and function, pulse wave doppler at the level of the mitral valve and diastolic functions. Left ventricular mass, left ventricular mass index and relative wall thickness were calculated according to the current formula (11). Patients with left ventricular systolic dysfunction, cardiomyopathy, and moderate-to-severe valvular heart disease were not included in the study.

Blood Pressure Measurement

Blood pressure was measured by the same investigator, unaware of the experimental design of the study, three times on the right arm in the sitting position, following 20 min of rest and using a mercury sphygmomanometer. The average of the three measurements was used for the analysis. Phase I and V Korotkoff sounds were employed to assess systolic and diastolic blood pressure, respectively. Hypertension was diagnosed when the systolic BP was ≥ 140 mmHg and the diastolic BP was ≥ 90 mmHg.

Holter ECG Recordings

In order to determine the status of cardiac autonomic function, HRV analysis from ECG recordings were obtained with a 24-hour Holter ECG machine (Lifecard CF digital recorder, Reynolds Medical Ltd, Hertford, England). Records were transferred to a computer program where they were analyzed (Pathfinder Holter System, V8.602 Del Mar Reynolds Medical Ltd., England). Records were examined visually and noisy regions were excluded from analysis. Then the time domain HRV measurements over a 24-hour Holter ECG recordings (**NN50**: percentage of differences between successive RR intervals that are greater than 50 msec; **PNN 50**: percent division of NN 50 by the total number of NN; **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; **RMSSD**: square root of the mean squared differences between successive normal-to-normal (NN) intervals) were automatically calculated. In addition, the maximum, minimum and average HRs of the cases were noted.

Statistical Analysis

For statistical analysis, the SPSS (Statistical Package for the Social Sciences ver. 15.0, SPSS Inc, Chicago, Illinois, USA) computer program was used. Quantitative variables were expressed as mean ± standard deviation. Kruskal-Wallis H and Mann-Whitney U tests were used for the comparison of the groups as the variables did not show a normal distribution. Categorical variables were compared by the Chi-square test. Pearson correlation analysis was used to evaluate the relationship between variables. $p<0.05$ was considered statistically significant.

RESULTS

Demographic Characteristics

One hundred and eighteen patients (mean age=43.98±11.5 years) were included in the current study. Twenty eight of them were healthy controls (male=21) and 90 were hypertensive (male=53). Hypertensive patients were divided into two groups: 45 patients (male=20) already on treatment with a former HT diagnosis and 45 newly diagnosed hypertensives (male=17). When the hypertensive group was compared with the control group in terms of demographic characteristics, laboratory and blood pressure measurements, there were differences between the two groups (Table I). In the evaluation of hypertensive sub-groups, old and new diagnosed cases of HT had similar characteristics except for blood pressure values (Table II).

Comparison of the HR and HRV Values

When the control group and all hypertensive patients were compared in terms of HR and HRV parameters; the SDNN, SDNN index, PNN 50, and NN50 measurements were significantly lower, but HR was significantly higher in the hypertensive group (Table III). In patients with hypertension, HR and HRV parameters were compared in subgroups, but there was no statistically significant difference (Table IV). In the hypertensive group, there were significant negative correlations between HRV measurements and minimum and average HR but there was no significant correlation between HRV and maximum HR. In hypertensive subgroups, there were significant positive correlations between systolic blood pressure and maximum HR ($r = 0.272$, $p = 0.009$) and mean HR ($r = 0.303$ $p = 0.004$) but there was no significant association with HRV measurements. There was no association between diastolic blood pressure and HR and HRV.

Assessment of HR, HRV, and End Organ Damage

In the hypertensive group, the relationship between end-organ damage due to hypertension with HR and HRV parameters was examined. There was no significant relationship between retinopathy and HR and measurements of HRV. In correlation analysis between microalbuminuria and HR and HRV parameters in all hypertensive patients, only SDNN ($r = 0.243$ and $p = 0.027$) had a mild to moderate positive correlation with microalbuminuria. In formerly diagnosed hypertensive patients, microalbuminuria had a mild to moderate positive correlation with SDNN ($r = 0.344$ and $p = 0.03$) and NN50 ($r = 0.345$ and $p = 0.029$). In newly diagnosed hypertensives, microalbuminuria had no significant correlation with HR and HRV measurements. In the hypertensive patients, the hypertensive group and subgroups as former and newly diagnosed hypertension, HR and HRV measurements lacked any association with left ventricular hypertrophy.

Assessment of HR, HRV, and Risk Factors

In the control group, the relationship between HR and HRV measurements were analyzed in terms of gender and the maximum HR was significantly higher in females (male-max HR: 137 ± 20 m/min, female-max HR: 155 ± 17 m/min; $p = 0.027$). In the hypertensive group, the relationship between HR and HRV measurements were analyzed in terms of gender. The maximum HR (male-max HR: 142 ± 25 m/min, female-max HR: 151 ± 23 m/min, $p = 0.016$) and minimum HRs (male-min HR: 43 ± 10 m/min, woman-min HR: 48 ± 9 m/min, $p = 0.032$) were significantly higher in women. In the control group, those with a family history of cardiovascular and cerebrovascular events in first-degree relatives had significantly lower maximum HR (positive family history-max HR: 141 m/min, and negative family history-max heart speed: 158 m/min, $p = 0.026$) and average HR (positive family history-average HR: 76 m/min, and negative family history-average HR: 80 m/min, $p = 0.044$) measurements compared to non-event relative control subjects. In hypertensives, no statistically significant correlation was observed between parameters of HRV and HR with a family history of risk factors.

Table I: Comparison of blood pressure measurements, demographic and laboratory data of control and hypertensive groups.

	Control (n=28)	Hypertension (n=90)	p
Age (yrs)	39±10	46±12	0.004
Sex (n, F/M)	21/7	53/37	0.124
BMI (kg/m²)	23.54±2.59	27.30±2.65	<0.001
Systolic BP (mmHg)	106±10	144±14	<0.001
Diastolic BP (mmHg)	65±8	89±10	<0.001
Fasting Plasma Glucose (mg/dl)	90±8	93±9	0.135
Urea (mg/dl)	25±6	28±8	0.042
Creatinine (mg/dl)	0.83±0.13	0.88±0.12	0.061
Uric acid (mg/dl)	4.2±1.3	5.0±1.2	0.007
Total cholesterol (mg/dl)	102±57	138±52	0.052
HDL (mg/dl)	55±11	49±12	0.015
LDL (mg/dl)	113±25	126±22	0.017
Triglyceride (mg/dl)	102±57	138±52	<0.001
Hemoglobin (g/dl)	13.8±1.3	14.4±1.4	0.093
Hematocrit (%)	41.7±3.5	41.6±3.9	0.885
Thrombocyte (10^3/mm³)	257±48	255±60	0.902
WBC (/mm³)	6018±1468	6853±1568	0.030
Microalbumin (mg/day)	6.1±2.7	22.4±26.4	<0.001
LVM (gr)	158.7±48.1	198.6±52.0	0.001
LVMI (gr/m²)	92.0±24.4	107.7±30.5	0.013
RWT	0.44±0.06	0.45±0.06	0.808

Values are given as mean ± standard deviation. **NS:** Not significant, **BMI:** Body mass index, **HDL:** High-density lipoprotein cholesterol, **LDL:** Low-density lipoprotein cholesterol, **LVM:** Left ventricular mass, **LVMI:** Left ventricular mass index, **RWT:** Relative wall thickness.

In hypertensive patients, only RMSSD of HRV parameters was found to be significantly higher in patients with regular alcohol consumption (alcohol-user-RMSSD: 54 ms, alcohol-non user-RMSSD: 44 ms p = 0.04).

Among hypertensives; smokers and non-smokers, and those who exercise regularly and those who do not were compared in terms of HR and HRV measures, and there was no significant association between HRV parameters.

DISCUSSION

Similar to patients with diabetes or those in the post-MI period, hypertensive individuals suffer from cardiovascular events as a leading cause of death. Morbidity and mortality rates in post-MI patients or those with diabetes have been demonstrated to be in strong relationship with the presence of autonomic neuropathy in the heart in many previous studies (12-14). HRV measurement methods that best show autonomic neuropathy in the heart of these patients are therefore frequently and widely used. It comes to the pathogenesis of hypertension so that whether there is a similar situation, although the place of HRV measurement methods to assess the morbidity and mortality in hypertensive patients is not clearly known and they are not used so often.

In a study by Huikuri et al, patients with hypertension were compared with normotensive subjects. In measurements of HRV parameters, hypertensive patients were shown to have lower values, particularly SDNN (15). Yet in another study by Guzzetti et al. in hypertensive subjects, high blood pressure was shown to be closely related to HRV parameters, particularly SDNN (16). In our study, measurements of HRV in hypertensive patients,

Table II: Comparison of blood pressure measurements, demographic and laboratory data of formerly and newly diagnosed hypertensive groups.

	Newly Diagnosed (n=45)	Formerly Diagnosed (n=45)	p
Age (yrs)	45±11	47±12	0.375
Sex (n, F/M)	28/17	25/20	0.247
BMI (kg/m^2)	27.37±2.78	27.23±2.56	0.811
Smoker/non smoker	20/25	22/23	0.85
Systolic BP (mmHg)	149±14	138±13	<0.001
Diastolic BP (mmHg)	93±9	86±10	0.001
Fasting Plasma Glucose (mg/dl)	93±9	93±9	0.735
Urea (mg/dl)	28±8	27±7	0.580
Creatinine (mg/dl)	0.88±0.11	0.89±0.13	0.831
Uric acid (mg/dl)	4.9±1.1	5.1±1.4	0.435
Total cholesterol (mg/dl)	208±29	198±29	0.116
HDL (mg/dl)	51±12	48±12	0.223
LDL (mg/dl)	129±21	122±24	0.157
Triglyceride (mg/dl)	136±55	139±50	0.779
Hemoglobin (g/dl)	14.4±1.3	14.3±1.5	0.734
Hematocrit (%)	41.7±3.5	41.6±4.3	0.940
Thrombocyte (10^3/mm^3)	247±62	264±58	0.188
WBC (/mm^3)	6962±1422	7262±1600	0.350
Microalbumin (mg/day)	22.7±19.2	22.0±32.6	0.907
LVM (gr)	198.0±49.8	199.2±54.6	0.910
LVMI (gr/m^2)	107.3±26.7	108.1±34.1	0.903
RWT	0.44±0.06	0.45±0.05	0.689

Values are given as mean ± standard deviation. **NS:** Not significant, **BMI:** Body mass index, **HDL:** High-density lipoprotein cholesterol, **LDL:** Low-density lipoprotein cholesterol, **LVM:** Left ventricular mass, **LVMI:** Left ventricular mass index, **RWT:** Relative wall thickness.

including the SDNN parameter, were found to be lower than that of the control group, and minimum HR was significantly higher in hypertensive subjects suggesting cardiac autonomic neuropathy.

According to an epidemiological study which included 1436 hypertensive, prehypertensive and normotensive patients and subjects, hypertensive and prehypertensive patients had decreased HRV measurements compared to normotensive individuals, and similarly hypertensives had lower measurements compared to prehypertensives (17). In our study, no significant difference was observed between patients previously treated for hypertension and those newly diagnosed hypertensives in terms of demographic, clinical and laboratory data in the subgroup analysis of the hypertensive individuals, but blood pressure measurements were significantly lower in previously treated patients. Additionally, the comparison of measurements of HR and HRV in hypertensive subgroups did not differ significantly. When we consider previous studies in hypertensive, prehypertensive and normotensive patients lacking the measurements of HRV in new and former hypertensives, as we could not reach any, our study is probably the first in this respect. Several studies indicate that lowering blood pressure in patients with hypertension is associated with improvement in HRV parameters (9). In particular, angiotensin-converting enzyme inhibitors and beta-blockers have shown positive effects on HRV in some studies (18,19).

Table III: Comparison of heart rate and HRV parameters in the control and hypertensive groups.

	Control (n=28)	Hypertension (n=90)	p
pNN 50 (%)	14.6±9.4	9.0±7.3	0.002
SDNN (msn)	157±30	143±31	0.046
SDNN index (msec)	69±18	60±19	0.003
SDANN (msec)	30±10	29±13	0.574
RMSSD (msec)	50±23	46±28	0457
NN50 number	14760±9563	8514±6728	0.001
Maximum heart rate (beats/min)	150±19	147±24	0.504
Minimum heart rate (beats/min)	40±13	46±10	0.017
Average heart rate (beats/min)	79±7	79±10	0.954

Values are given as mean ± standard deviation, **NS:** Not significant.

Table IV: Comparison of heart rate and HRV parameters in the hypertensive sub-groups.

	Newly Diagnosed (n=45)	Formerly Diagnosed (n=45)	p
pNN 50 (%)	8.5±7.7	9.5±6.9	0.553
SDNN (msn)	143±34	143±28	0.949
SDNN index (msec)	58±19	62±19	0.244
SDANN (msec)	28±12	30±13	0.495
RMSSD (msec)	41±22	51±33	0.095
NN50 number	8234±7562	8795±5852	0.694
Maximum heart rate (beats/min)	150±23	145±24	0.334
Minimum heart rate (beats/min)	47±10	45±9	0.386
Average heart rate (beats/min)	80±8	78±9	0.211

Values are given as mean ± standard deviation, **NS:** Not significant.

In the current study, no significant difference between HR and HRV parameters was found despite blood pressure differences between the two groups. In our study, these results represent that control of blood pressure with treatment has no significant positive effects on HRV parameters, and our study differs from previous studies in this respect. This points to an hypothesis that cardiac autonomic dysfunction predates the increase of blood pressure in the pathogenesis of essential hypertension, and that this may not be prevented with treatment after the disease occurs. Therefore, in contrast to diabetes mellitus or post-MI patients, autonomic neuropathy in the heart could be a cause or trigger resulting in hypertension. In this regard, a very homogeneous distribution except for the blood pressure of our hypertensive groups shows a benefit in terms of comparison, while the inability to obtain a sufficient number of patients and a lack of grouping by treatment drug seems to be important limitations of the current study.

Non-dipper hypertensives had lower HRV measurements than dipper hypertensive patients and a poor prognosis of end-organ damage also supports the findings of previous studies on non-dipper hypertensives (20). The authors explained the diminished decrease in nocturnal blood pressure with lower HRV measurements, and thought that the worse end-organ damage findings may notably be associated with disruption of the HRV indices in non-dipper cases. In another study, there was no relationship between end-organ damage and HRV in hypertension (21). Our study lacked any significant relationship

between HRV and the findings of end-organ damage in hypertensive patients such as left ventricular hypertrophy and retinopathy, but hypertensive patients with microalbuminuria had a positive significant correlation with only the SDNN parameter. As microalbuminuria was by itself and differed from the previous studies in this respect, this was accepted as a random finding. However, these findings, as mentioned earlier, should point to our aforementioned hypothesis that cardiac autonomic neuropathy should be a cause or trigger rather than being a consequence of high blood pressure in hypertension, and that the treatment may not improve this situation.

The minimum and maximum HRs for women in the hypertensive group were found to be significantly higher than men. Our work also supports previous studies on the issue that women had higher average HRs (22). However, a significant negative correlation between HRs and HRV parameters was observed in our study. The presence of a significant difference in terms of HRV parameters between males and females may point to a fact that a risk factor, sex, may influence the heart's autonomic function due to HRV differences.

In a study by Wu et al., patients evaluated in terms of HRV were divided into groups of normotensive subjects, prehypertensives and hypertensives with and without family risk factors. A significant reduction in HRV measurements was seen in all groups, from no risk factor normotensives to hypertensives (17). In the hypertensive patients in our study, no statistically significant effect of family risk factors were seen on the parameters of HRV. This difference from previous studies may partly be due to the inadequate number of patients.

If we look at the relationship between alcohol use and HRV, alcohol consumption significantly increased the RMSSD parameter. This seems to be the reverse of the negative effects of alcohol use in hypertensive patients but such a single parameter of HRV could be considered random or meaningless in this situation, and this matter should be considered and evaluated in a large number of patients.

Regular exercise and ceasing smoking have been clearly demonstrated to decrease blood pressure and have cardioprotective effects in hypertensive patients in large-scale studies such as the Framingham Heart Study. In our study, neither condition affected HRV parameters.

Study Limitations: This study has limitations. The major limitation is the fact that it had a nonrandomized design. As previously mentioned, some antihypertensive drugs such as angiotensin-converting enzyme inhibitors and beta-blockers, have shown positive effects on HRV in some studies. However, the inability to obtain a sufficient number of patients and a lack of grouping by treatment drug seem to be the important limitations of our study.

CONCLUSION

In this study, we observed impaired HRVs in hypertensive individuals similar to after MI in patients and those with diabetes, indicating the presence of cardiac autonomic neuropathy. Autonomic dysfunction of the heart seemed not to be different among patients with newly diagnosed hypertension and the former hypertensives under follow-up with treatment. This led to the idea that antihypertensive treatment does not affect autonomic dysfunction in a beneficial way. Unlike the findings of HRV in post-MI patients and those with diabetes, no relationship between end-organ damage due to hypertension and HRV parameters was observed. This result led to the conclusion that HRV is not a useful method for predicting complications of hypertension. In addition, HRV was not influenced by cardiovascular risk factors.

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