

Association of P wave dispersion and left ventricular diastolic dysfunction in non-dipper and dipper hypertensive patients

Non-dipper ve dipper hipertansif hastalarda P dalga dispersiyonu ile diyastolik disfonksiyon arasındaki ilişkisi

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ABSTRACT

Objective: Objective of this study was to investigate the correlation between P wave dispersion and left ventricular diastolic function, which are associated with the increased cardiovascular events in patients with dipper and non-dipper HT.

Methods: Eighty sex and age matched patients with dipper and non-dipper HT, and 40 control subject were included in this observational cross-sectional study. P wave dispersion was measured through electrocardiography obtained during the admission. The left ventricle (LV) ejection fraction was measured using the modified Simpson's rule by echocardiography. In addition, diastolic parameters including E/A rate, deceleration time (DT) and isovolumetric relaxation time (IVRT) were recorded. Independent samples Bonferroni, Scheffe and Tamhane tests and correlation test (Spearman and Pearson) were used for statistical analysis.

Results: P wave dispersion was found to be significantly increased in the non-dipper than in the dipper group (56.0 ± 5.6 vs. 49.1 ± 5.3 , $p < 0.001$). P_{max} duration was found significantly higher (115.1 ± 5.6 vs. 111.1 ± 5.8 , $p = 0.003$) and P_{min} duration significantly lower (59.0 ± 5.6 vs. 62.3 ± 5.3 , $p = 0.009$) in the non-dippers. Correlation analysis demonstrated presence of moderate but significant correlation between P-wave dispersion and left ventricular mass index (LVMI) ($r = 0.412$, $p = 0.011$), IVRT ($r = 0.290$, $p = 0.009$), DT ($r = 0.210$, $p = 0.052$) and interventricular septum (IVS) thickness ($r = 0.230$, $p = 0.04$).

Conclusion: P wave dispersion and P Max were found to be significantly increased and P min significantly decreased in the non-dipper HT patients compared to the dipper HT patients. P-wave dispersion is associated with left ventricular dysfunction in non-dipper and dipper HT. (*Anadolu Kardiyol Derg 2014; 14(0): 000-000*)

Key words: hypertension, non-dipper hypertension, p wave dispersion, diastolic function

ÖZET

Amaç: Bu çalışmanın amacı, dipper ve non-dipper hipertansiyon (HT) bulunan hastalarda kardiyovasküler olaylardaki artışla ilişkili olan P dalga dispersiyonu ile sol ventriküler diyastolik fonksiyon arasındaki ilişkiyi incelemektir.

Yöntemler: Dipper ve non-dipper HT olmak üzere 80 yaş ve cinsiyet uyumlu hasta ile 40 sağlıklı kontrol bu gözlemsel enine kesit çalışmasına dahil edilmiştir. P dalga dispersiyonları hastaneye kabul sırasında elektrokardiyografi aracılığıyla ölçülmüştür. Ekokardiyografi ile sol ventriküler ejeksiyon fraksiyonu modifiye Simpson yöntemi yardımıyla ölçülmüştür. Ayrıca E/A hızı, deselerasyon zamanı (DT) ve izovolümetrik relaksasyon zamanı (IVRT) gibi diyastolik parametreler de kaydedilmiştir. İstatistiksel analizlerde Bonferroni, Scheffe ve Tamhane testleri ve korelasyon testi (Spearman and Pearson) kullanılmıştır.

Bulgular: P dalga dispersiyonu non-dipper grupta dipper gruptan anlamlı olarak yüksek bulunmuştur ($56,0 \pm 5,6$ 'ya karşı $49,1 \pm 5,3$, $p < 0,001$). Maksimum P dalga süresi non-dipper grupta anlamlı olarak yüksek ($115,1 \pm 5,6$ 'ya karşı $111,1 \pm 5,8$, $p = 0,003$), minimum P dalga süresi ise anlamlı olarak düşük bulunmuştur ($59,0 \pm 5,6$ 'ya karşı $62,3 \pm 5,3$, $p = 0,009$). Korelasyon analizi P dalga dispersiyonu ile sol ventrikül kitle indeksi (LVMI) ($r = 0,412$, $p = 0,011$), IVRT ($r = 0,290$, $p = 0,009$), DT ($r = 0,210$, $p = 0,052$) ve interventriküler septum (IVS) kalınlığı ($r = 0,230$, $p = 0,04$) arasında orta derecede, ancak anlamlı bir korelasyon bulunduğunu göstermiştir.

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Sonuç: P dalga dispersiyonu ile maksimum P dalga süresinin non-dipper HT hastalarında dipper HT hastalarına kıyasla anlamlı olarak arttığı, minimum P dalga süresinin ise anlamlı olarak azaldığı bulunmuştur. Non-dipper ve dipper HT hastalarında P dalga dispersiyonu sol ventriküler disfonksiyonla ilişkilidir. (*Anadolu Kardiyol Derg 2014; 14(0): 000-000*)

Anahtar kelimeler: hipertansiyon, non-dipper hipertansiyon, p dalga dispersiyonu, diyastolik disfonksiyon

Introduction

The circadian rhythm in the neurohumoral system results in a circadian rhythm in blood pressure. Depending on the circadian rhythm, blood pressure reaches its highest value in the morning, shows a gradual decrease during the day and courses at the lowest levels at night (1). The condition in which blood pressure the nocturnal blood pressure falls 10% or more compared to the diurnal blood pressure is defined as dipper hypertension (DHT) and the condition with a fall of the nocturnal blood pressure falling less than 10% compared to the diurnal blood pressure is defined as non-dipper hypertension (NDHT) (2). NDHT is associated with high rates of end organ damages (3, 4) and cardiovascular morbidity (such as AF) and mortality (5, 6).

Maximal P wave duration and P wave dispersion (Pd) are non-invasive markers showing the heterogeneous and instable distribution of the impulses arising from the sinus node on a standard ECG. Maximal P wave duration is an indicator of the disrupted inter-atrial conduction, while Pd shows the heterogeneous electrical conduction. Maximal P wave duration and P wave dispersion are used as non-invasive indicators in prediction of the risk for AF in the patients with paroxysmal AF, mitral stenosis, aortic stenosis, dilated cardiomyopathy, acute myocardial infarction, atherosclerotic heart disease and angina (7-13). In the previous studies, hypertension was demonstrated to be an independent risk factor for atrial fibrillation (AF) (14).

Several studies demonstrated that P-wave dispersion is increased in dipper and non-dipper hypertension (15, 16) but the mechanisms have not been well clarified. Diastolic dysfunction will be suggested between these mechanisms (17, 18). In this study, we aimed to compare P wave dispersion in dipper and non-dipper HT patients and evaluate its association with left ventricular dysfunction.

Methods

Study population

This is an observational cross-sectional study. The approval of the local Ethics Committee was obtained for this study and informed consent were taken from the patients who were participated to the study. For the purposes of our study, 40 healthy subjects and 80 patients with hypertension were included to study. Hypertensive patients were selected from patients who had presented to the cardiology clinic of our hospital within the last year and were previously diagnosed with primary (essential) hypertension and followed up under treatment with the same group of anti-hypertensives (combination therapy with ACE inhibitors+thiazide). Hypertensive patients were divided into two subgroups: 40 dipper (group I: 18 male, 22 female, mean age:

54.2±7.0 years) and 40 non-dippers (group II: 17 male, 23 female, mean age 54.4±7.1 years). The classification of the dippers and non dippers were based on the ambulatory blood pressure monitoring (19). Those with atrial fibrillation, history of ischemic heart disease, left ventricular systolic dysfunction, left ventricular hypertrophy, renal and hepatic failure (serum creatinine >1.5 mg/dL and AST-ALT >2 times the normal values), hypothyroidism, hepatic dysfunction, haemolytic disease, concomitant inflammatory diseases such as autoimmune disorders, neoplastic disease, recent major surgery or any systemic disorders, diseases of the respiratory tract (chronic obstructive pulmonary disease, chronic bronchitis, pulmonary embolism), primary pulmonary hypertension, isolated right heart failure, congenital heart disease and valvular disease were excluded from the study. Physical examination findings, risk factors, medical history data, and resting 12-lead electrocardiograms were obtained from all groups. In addition, whole blood count, fasting blood glucose, blood urea nitrogen, creatinine, serum sodium, potassium levels, HDL, LDL, total cholesterol, triglyceride levels, liver and thyroid function test measurements were performed.

The patients body mass indices (BMI) and smoking status were specified

The body mass index (BMI) was calculated by dividing the weight in kilograms by the height in square meters (kg/m²). In line with the World Health Organization criteria, anemia at the presentation was defined and as a baseline Hgb concentration below 13 mg/dL in males and below 12 mg/dL in females (20). The diagnosis of DM was based on previous history of diabetes treated with or without medical therapy (21). Stable angina was defined as discomfort in the chest, jaw, shoulder, back, or arms; typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin. Current smokers were defined as those who had smoked for some period during the past year. Those patients dependent on chronic dialysis were considered as having end-stage renal disease (ESRD).

Blood pressure measurements

Ambulatory blood pressure monitoring was performed using the non invasive recording system (DiaSys Diagnostic Systems GmbH, Holzheim, Germany). The device was programmed to repeat the measurements every 15 minutes throughout the daytime (06.00-20.00) and every 30 minutes during the night (20.00-06.00) for 24 hours. Those patients in which the mean systolic and diastolic BP values measured during the night showed a 10% or greater decrease compared to the mean daytime values were classified into the DHT group, while those with decreases below 10% were classified into the non-DHT group.

Electrocardiographic recording and P wave dispersion measurement

Following a resting period of 20 minutes, 12-lead ECG was recorded at supine position at a paper speed of 50-mm/s and an amplitude of 20 mm/mV. The onset of P wave was defined as the point of first downward departure from the top of baseline for negative waves. The return to the baseline of the bottom of trace was considered to be the end of the P wave. The difference between the maximum and minimum P wave duration calculated from any derivation of the 12-lead ECG and was defined as the Pd (Pd=Pmax-Pmin).

Transthoracic echocardiography

The transthoracic echocardiography was carried out before the discharge by a system V (Vingmed; GE, Horten, Norway) device and using a 2.5 MHz phased-array transducer. Recordings were performed while the patients were in the left lateral decubitus position. The left ventricle (LV) ejection fraction was measured using the modified Simpson's rule. In addition, diastolic parameters including E/A rate, deceleration time (DT) and isovolumetric relaxation time (IVRT) were recorded. Furthermore, left atrial diameter and interventricular septal thickness (IVS) were measured from the parasternal long-axis with M-mode method (22).

Table 1. Baseline characteristics of study patients

	Group 1 (n=40) Mean±SD	Group 2 (n=40) Mean±SD	Control (n=40) Mean±SD	*p
Age	54.2±7.0	54.4±7.1	53.8±8.9	0.864
Male, n,	18 (45)	17 (42.5)	18 (45)	0.417
Smokers, n, %	11 (27.5)	14 (35)	12 (30)	0.372
HDL, mg/dL	41.5±17.1	40.2±3.5	43.2±4.1	0.148
LDL, mg/dL	129.2±30.7	119.5±29.6	127.5±27.3	0.187
Triglyceride, mg/dL	178.9±24	188.5±22.8	192.5±32.1	0.219
BMI, kg/m ²	28.1±4.1	27.1±5.1	28.0±5.1	0.201

BMI - body mass index, HDL - high density lipoprotein, LDL - low density lipoprotein, Group 1 - dipper hypertension, Group 2 - non-dipper hypertension. Data are presented as mean±SD and number (percentage), *ANOVA test

Table 2. Echocardiographic parameters of study patients

	Control (n=40) Mean±SD	Group 1 (n=40) Mean±SD	Group 2 (n=40) Mean±SD	P1	P2	P3
LV Mi, g/m ²	74.6±17.6	89.3±18.5	97.6±16.1	>0.01	>0.01	0.02
LA Diameter, cm	3.4±0.4	3.8±0.4	4.0±0.2	>0.01	>0.01	0.044
DT, msn	172.7±20.8	199.4±37.4	218.6±35.0	>0.01	>0.01	0.013
IVRT, msn	82.6±21.2	85.3±11.5	94.1±12.7	>0.01	>0.01	0.021
E/A ratio	1.4±0.24	1.2±0.4	1.1±0.3	>0.01	>0.01	0.562
IVS thickness, cm	0.9±0.1	1.0±0.1	1.0±0.2	>0.01	>0.01	0.986

DT - deceleration time, IVRT - isovolumetric relaxation time, IVS - interventricular septum, LA - left atrial, LVMi - left ventricular mass index. P1: Control group versus Group I, P2 - Control group versus Group II, P3- C=Group I versus Group II
Data are presented as mean±SD (percentage).

Statistical analyses

Statistical analyses were performed using the IBM SPSS version 20 .0 for Windows (IBM Corp. SPSS, Chicago IL. USA). Continuous variables in the group data are indicated as mean±standard deviation (AVG±SD). Categorical variables are given in numbers and percentages. Single direction variance analysis was used in general comparison between the groups, while Kruskal Wallis test was used to compare quantitative measurements between the groups. Bonferroni, Scheffe and Tamhane tests were used in inter-group subgroup comparisons in cases of the quantitative measurements according to the homogeneity of the variances. Mann-Whitney U test with Bonferroni correction was used in case of the binary sub-group comparisons. Parametric or nonparametric (Pearson and Spearman) correlation analysis was performed to identify the relationship between continuous variables. Statistical significance was accepted as p<0.05.

Results

Baseline characteristics

In total, 80 patients were enrolled in the study (54.1±7.2, male: 29%). Group I had 40 patients (54.2±7.0, Male: 25%) and Group II had 40 patients (54.4±7.1, Male: 33%). The groups were similar in terms of the smoking history, BMI and lipid parameters (Table 1). Considering the atrial conduction to be affected, non-diabetic patients were included in the study.

LV diastolic function in dipper and non-dipper hypertension

Group 2 showed a higher left ventricular mass index (LVMi) (89.3±18.5 vs. 97.6±16.1, p=0.02) left atrial diameter (3.8±0.4 vs. 4.0±0.2 p=0.044), DT (218.6±35.0 vs. 199.4±37.4, p=0.01) and IVRT (94.1±12.7 vs. 85.3±11.5, p=0.02). There was no difference between the groups in regard to left E/A ratio (1.1±0.3 vs. 1.2±0.4, p=0.56 and IVS diameter (1.0±0.2 vs. 1.0±0.1, p=0.98) (Table 2).

P wave dispersion in dipper and non-dipper hypertension

There was no difference between the groups in regard to heart rate (70.7±3.8 vs. 70.2±3.6, p=0.57). Group 2 showed higher P max (115.1±5.6 vs. 111.1±5.8, p=0.003) and P dispersion values

Table 3. Electrocardiographic parameters of study patients

	Control (n=40) Mean±SD	Group 1 (n=40) Mean±SD	Group 2 (n=40) Mean±SD	P1	P2	P3
Heart rate, bpm	7.2±3.1	70.2±3.6	70.7±3.8	0.362	0.435	0.570
P maximum, msn	102.1±6.6	111.1±5.8	115.1±5.6	>0.01	>0.01	0.03
P minimum, msn	68.3±6.1	62.3±5.3	59.2±5.6	>0.01	>0.01	0.009
P dispersion, msn	36.4±6.9	49.1±5.3	56.1±5.6	>0.01	>0.01	>0.01

P1- Control group versus Group I, P2- control group versus Group II, P3- C-group I versus Group II
Data are presented as mean±SD (percentage)

Table 4. Relationship of P wave dispersion with echocardiographic parameters

		LVMi	LAd	DT	IVRT	E/A	IVS
P dispersion	r	0.412	0.769	0.210	0.290	0.477	0.230
	p	0.011	0.033	0.052	0.009	-0.081	0.04

DT - deceleration time, IVRT - isovolumetric relaxation time, IVS - interventricular septum, LAD-left atrium diameter, LVMi - left ventricular mass index
Pearson correlation analysis

(56.0±5.6 vs. 49.1±5.3, p<0.001) when compared with group 1. But Group 2 showed lower P min values (59.0±5.6 vs. 62.3±5.3, p=0.009) when compared with Group 1 (Table 3).

Correlation analysis

When clinical and echocardiographic qualifications that affect P wave period were examined, it was obtained that P dispersion did not have any relation with clinical parameters such as age, gender, heart rate etc., echocardiographic parameters such as left atrium diameter and E/A proportion and there is a significant correlation with LVMi (r=0.412, p=0.011), IVRT (r=0.290 p=0.009), DT (r=0.210, p=0.052) and IVS thickness (r=0.230 p=0.04) (Table 4).

Discussion

Main findings of our study were P wave dispersion to be found significantly increased in the patients having non-dipper hypertension and related to left ventricular diastolic dysfunction. The need for making a classification as nocturnal decreasing and non-decreasing blood pressure, resulted from cardiovascular morbidity to be different between two groups. Case control studies conducted with hypertensive patients showed that target organ damage was significantly greater in the patient having not nocturnal decrease (23). Whereas in prospective studies, non-decreasing nocturnal blood pressure or nocturnal blood pressure higher than daytime were found to be independent risk factors for cardiovascular disease (24-26). Arterial hypertension is an important risk factor in development of AF (14). Increased atrial tension may lead to structural alterations such as disorganization in the myocardial fibers and fibrosis in hypertension (11, 12). Furthermore, levels of plasma renin, nor-epinephrine and angiotensin II increase in pre-hypertension and hypertension (27, 28). Angiotensin and catecholamines cause

development of fibrosis in atrium and a heterogeneous and different conduction. Previous studies reported that atrial ischemia may develop in hypertension (29). Deceleration in the ischemic area lead to electrical instability in atrial myocardium (13, 30). This situation was reported may increase inter-atrial and intra-atrial conduction time (maximum P wave time) and P dispersion may increase. P wave dispersion is an important non-invasive ECG marker indicating heterogeneity of intra-atrial conduction. Dilaveris et al. (31) investigated for the first time the correlation between Pd and development of AF in hypertensive patients and found that development of AF was higher in the group with higher Pd. In a study by Aytemir et al. (9), P wave dispersion was reported to be a predictor of atrial fibrillation in hypertensive patients. In another study, P wave dispersion was reported to show prolongation in 19 hypertensive patients who developed atrial fibrillation compared to 78 hypertensive patient who did not develop AF at the end of 2-year follow-up period (32). Unlike these studies, in our study hypertensive patients were compared as dipper and non-dipper. P wave dispersion and P_{max} time were found to increase and P_{min} time to decrease in non-dipper hypertensive group. Compensatory wall hypertrophy resulted from the increased pressure load in systemic hypertension causes prolongation of ventricular relaxation and flexibility and diastolic dysfunction (33). Increased end-diastolic pressure may develop direct atrial pump dysfunction in diastolic dysfunction. This physiopathologic condition causes an increase in the atrial volume and tension. Increased atrial tension stimulates collagen synthesis in the atrial myocytes, causing fibrosis and hypertrophy. Resultant hypertrophy and fibrosis exacerbate symptoms of arrhythmia and diastolic heart failure. This vicious circle may explain the mechanism of AF development in hypertension (34, 35). In a study by Tsai et al. (36) P wave dispersion was demonstrated to be correlated with increased volume index and development of diastolic dysfunction in hypertensive patients. Numerous studies reported that frequency of SVH and SVDFB was higher in NDHT patients than in DHT patients (17, 18). Ferrara et al. (37) found that E wave velocity and E/A ratio decreased in both DHT and NDHT patient groups, while A wave velocity significantly increased only in NDHT group. In this study, we found that DT, IVRT and left atrial diameter significantly increased in the non-dipper hypertensive group compared to the dipper hypertensive group. Again we found a significant correlation between P wave dispersion and interventricular septum thick-

ness, IVRT and DT that are among echocardiographic parameters. Therefore, persistence of distolic dysfunction was found to be an important clinical variable determining P wave dispersion.

Study limitations

Possible limitations of the present study are: First, the study was conducted in a single center and included only a small number of patients. Second, cytokines related to inflammation were not investigated. Several previous studies demonstrated increased inflammation in the non-dipper hypertension compared to the dipper hypertension. Third, we did not perform an analysis to prognostic value of Pd. However, the correlation between Pd and AF has been shown in the previous studies.

Conclusion

In conclusion, in the present study, we found that the levels of Pd and P_{max} were increased in the non-dipper compared with dipper group and these changes were related to LV dysfunction. With this study, we demonstrated that hypertensive patients having prolonged Pd and Pmax values might be the patients without a sufficient nocturnal fall. We believe that administration of more aggressive anti-HT therapies to provide a circadian rhythm could decrease the risk for AF. Of course further prospective multicenter randomized controlled studies are needed to confirm this and to verify this hypothesis.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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