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ORIGINAL ARTICLE

Comparison of atrial electromechanical coupling interval and P-wave dispersion in non-dipper versus dipper hypertensive subjects

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Abstract

Background. The lack of nocturnal BP fall less than 10% of the daytime, called non-dipper hypertension, is associated with increased cardiovascular morbidity and mortality. The aim of our study was to investigate atrial conduction time in patients with non-dipper hypertension using electromechanical coupling interval and P-wave dispersion (PWD), measured with the surface electrocardiogram and tissue Doppler echocardiographic imaging (TDI). *Methods.* Age- and sex-matched 43 dipper hypertensive patients (19 male, 24 female, mean age: 53.9 ± 10.5 years), 40 non-dipper patients (18 male, 22 female, mean age 54.3 ± 9.6 years) and 46 healthy subjects (22 male, 24 female, mean age: 52.8 ± 9.6 years) were included in the study. The difference between the maximum and minimum P-wave durations was calculated and defined as PWD. Atrial electromechanical coupling (PA), inter-atrial and intra-atrial electromechanical delays were measured with TDI. *Results.* PWD was significantly higher in patients with non-dippers compared with dippers ($p < 0.02$) and controls ($p < 0.001$). The inter-atrial conduction time was delayed in non-dippers compared with dippers ($p < 0.01$) and controls ($p < 0.001$). There was a positive correlation between left atrial (LA) diameter and inter-atrial conduction times ($r = 0.46$, $p < 0.001$). LA diameter was also correlated with PWD ($r = 0.44$, $p < 0.001$). *Conclusion.* The patients with non-dipper hypertension have higher P-wave duration, PWD and delayed inter-atrial electromechanical coupling intervals compared with those of dippers and controls. This indicates that these subjects may be more prone to atrial rhythm disturbances.

Key Words: *Inter-atrial electromechanical coupling intervals, non-dipper hypertension, P-wave dispersion*

Introduction

Hypertension is a common chronic disorder associated with left atrial (LA) dilatation and/or atrial hypertrophy and these morphological changes may induce various atrial arrhythmias (1–3). Indeed, atrial fibrillation (AF) is one of the most frequent supraventricular arrhythmias in hypertensive patients and the risk of AF increases by 1.5-fold in hypertension (4). Most of the hypertensive patients show BP fall between 10% and 20% during night-time hours, and are called dippers. Recent studies implied that the lack of a nocturnal BP fall of less than 10% of the daytime, called non-dipping, is associated not only with more left ventricular (LV) hypertrophy but also increased cardiovascular mortality, silent cerebrovascular disease and progressive nephropathy compared with patients with dipping BP (5–8). However, it is not clear that non-dippers are more prone to atrial rhythm disturbances than dippers.

The prolongation of intra-atrial and inter-atrial conduction times and the inhomogeneous propagation of sinus impulses are well-known electrophysiological characteristics of an atrium prone to fibrillation and it has been evaluated by tissue Doppler echocardiography and by two simple ECG markers: maximum P-wave duration (Pmax) and P-wave dispersion (PWD) (9–12). Therefore, we attempted to investigate atrial conduction abnormalities in non-dippers and to compare those of dippers and controls by using electromechanical coupling interval and PWD, measured with a surface electrocardiogram and tissue Doppler echocardiographic imaging (TDI).

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Methods

Patients

A total of 83 patients with hypertension and 46 healthy control subjects (22 male, 24 female, mean age: 52.8 ± 9.6 years) were included to study. Hypertensive patients were divided into two subgroups: 43 dipper (19 male, 24 female, mean age: 53.9 ± 10.5 years) and 40 non-dippers (18 male, 22 female, mean age 54.3 ± 9.6 years).

All patients were in sinus rhythm during the study period. Exclusion criteria were evidence of coronary artery disease, structural heart disease, left bundle or right bundle branch block, prior pacemaker implantation, renal or hepatic dysfunction, hematological disease, cancer, systemic inflammatory conditions, auto-immune disease, anemia, hyperthyroidism and obstructive sleep apnea. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic BP was ≥90 mmHg, or a history of taking antihypertensive medication. Non-dipper hypertension was defined as a less than 10% decrease in either systolic or diastolic BP during night-time recordings over 24-h ambulatory blood pressure monitoring (ABPM). Written informed consent was obtained from each subjects and an institutional review board approved the study protocol.

ABPM recordings

BP was measured using a mercury sphygmomanometer in an office setting. Following a 5-min resting period, systolic and diastolic BP was recorded at Korotkoff phases I and V, respectively. Three BP measurements were consecutively taken at 1-min intervals and averaged to define clinic systolic and diastolic values. The 24-h ABPM was performed using a portable compact digital recorder (Delmar Reynolds, Tracker NIBP2, Hertford, UK) and analyzer using customized analytical software. The device was set to obtain BP readings at 15-min intervals during the day (07.00–23.00 h) and at 30-min intervals during the night-time (23.00–07.00 h). The patients were instructed to attend their usual daily activities but to stay inactive during measurements. Recordings were accepted only if more than 85% of the raw data were valid. The absolute and the percentages of the decrease of night-time systolic BP vs daytime systolic BP were calculated in all subjects.

Echocardiographic analysis

Transthoracic echocardiographic examinations were performed on all participants by an ATL HDI-5000 equipped with a 3.5-MHz sector transducer (Philips Company, Bothel, WA, USA) from the left lateral decubitis position at rest. An average of three beats was analyzed. All the measurements were obtained by a single observer who was blinded to the clinical details. During echocardiographic examination, one-lead electrocardiogram was recorded continuously. LA dimension, LV diameters, LV ejection fraction, LV wall thickness including interventricular septum (IVST) and posterior wall (PWT) were obtained from parasternal long axis. LV mass was calculated as described and indexed to the body surface area index (13). All measurements were performed by M-mode imaging. Mitral inflow E and A waves, and E-wave deceleration time were also obtained from the apical four-chamber view by using Doppler.

TDI was performed by the same echocardiograph machine, adjusting the spectral pulsed Doppler signal filters with a Nyquist limit of 15–20 cm/s and using the minimal optimal gain. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. In an apical four-chamber view, the pulsed Doppler sample volume was obtained at the level of LV lateral mitral annulus, septal mitral annulus and right ventricular (RV) tricuspid annulus. The time interval from the onset of the P-wave on the surface ECG to the beginning of the late diastolic wave (A wave), which is named PA, was obtained from the lateral mitral annulus (lateral PA), septal mitral annulus (septal PA) and RV tricuspid annulus (tricuspid PA), respectively (Figure 1). The difference between lateral PA and tricuspid PA (lateral PA−tricuspid PA) was defined as inter-atrial electromechanical delay, and the difference between septal PA and tricuspid PA (septal PA−tricuspid PA) was defined as intra-atrial electromechanical delay (9).

The reproducibility of electromechanical parameters was assessed by coefficients of variation (standard deviation of differences between the repeated measurements divided by the mean value and expressed as a percentage) between measurements. Intra-observer variability was calculated from 40 subjects selected randomly from the study participants (25 patients with hypertension and 15 control subjects) by repeating the measurements under the same basal conditions. Intra-observer variability was 4.7% for lateral PA, 4.8% for septal PA and 4.1% for tricuspid PA; respectively. Inter-observer variability was 4.7% for lateral PA, 4.8% for septal PA and 4.7% for tricuspid PA, respectively.

Electrocardiographic analysis

All subjects underwent 12-lead surface ECG recording after a 20-min resting period in a supine position at a paper speed of 50 mm/s and 20 mm/mV. The P-wave duration was measured manually in all simultaneously recorded 12 leads of the surface ECG by two of the investigators unaware of the study hypothesis. In each lead, the mean values for the three complexes were calculated. The onset of the P-wave was defined as the point of first visible upward departure from baseline for positive waveforms, and as the point of first downward departure from the

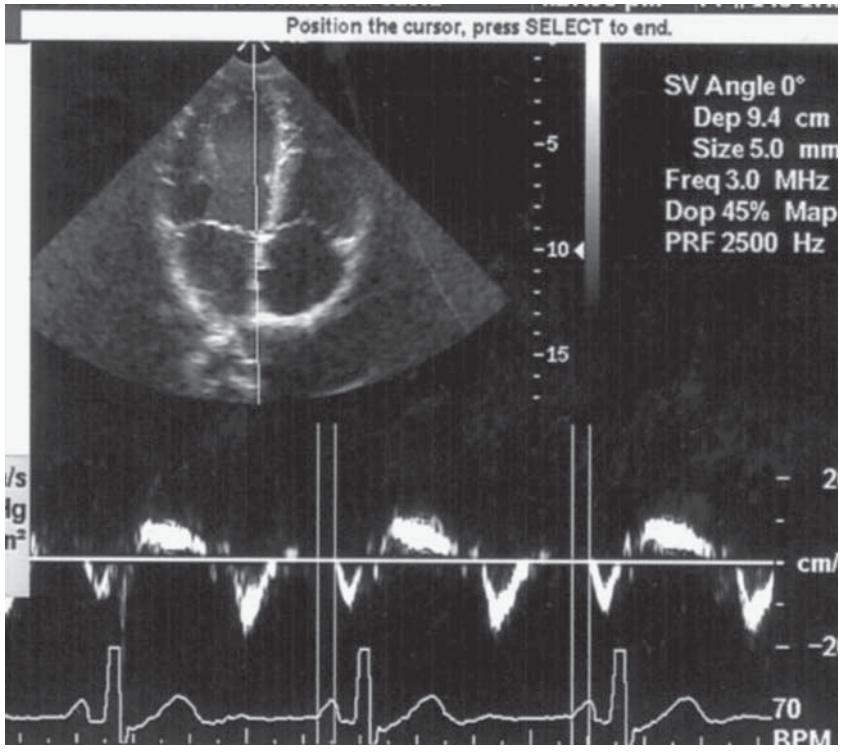

Figure 1. Measurement of the time interval from onset of the P-wave on surface ECG to beginning of the A wave (PA) with tissue Doppler echocardiography.

baseline for negative waveforms. The return to the baseline was considered the end of the P-wave. Pmax measured in any of the 12 leads was used as the longest atrial conduction time. The difference between Pmax and the minimum P-wave duration (Pmin) was calculated and defined as PWD. Analyses of ECG parameters were performed by two independent observers who were unaware of the clinical details. Intra- and inter-observer coefficients of variation [standard deviation (SD) of differences between two observations divided by the mean value and expressed in percent] were found as 4.2% and 4.3% for maximum P-wave duration and 4.2% and 4.4% for PWD, respectively.

Statistical analysis

Statistical analysis was performed using the SPSS for windows (version 11.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics of patients, including frequencies and percentages, were computed. Continuous variables are expressed as mean ± SD. Nominal parameters were expressed as percent. Significant differences between the three groups was assessed using one-way analysis of variance (ANOVA), followed by Sheffé *post hoc* test for ordinal parameters displaying normal distribution and Kruskal–Wallis test followed by Bonferroni corrected Mann–Whitney *U post hoc* test for ordinal parameters not displaying normal distribution. Significant differences between groups for nominal parameters was assessed by using the χ^2 test. Correlations between variables were evaluated by the Pearson and Spearman rank correlation test where appropriate. Statistical significance was accepted as p-value < 0.05.

Results

Comparison of baseline characteristics of the non-dipper, dipper and controls were shown in Table I. There was no significant difference between groups with respect to age, gender, resting heart rate, diabetes mellitus, serum creatinine levels and body mass index. Triglyceride, total cholesterol and low-density lipoprotein (LDL)-cholesterol levels were higher in dippers and non-dippers compared with controls ($p < 0.05$). HDL cholesterol levels were higher in dippers than non-dippers ($p < 0.05$). Clinic systolic and diastolic blood pressure in an office setting was similar in both hypertensive groups but higher than normotensives, as expected ($p < 0.001$). Distribution of the antihypertensive drugs was also illustrated in Table I. There was no difference between dippers and non-dippers with respect to use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers and diuretics.

The average daytime systolic, diastolic and mean BP levels were similar in non-dippers and dippers. In contrast, average night-time systolic, diastolic and mean BP values were significantly higher in non-dippers than dippers (Table II). Transthoracic

Table I. Laboratory parameters and clinical characteristics of study groups.

	Non-dippers (n = 40)	Dippers (n = 43)	Normotensives (n = 46)
Age	54.3 ± 9.6	53.9 ± 10.5	52.8 ± 9.6
Men, n (%)	18 (45)	19 (44.1)	22 (47.8%)
BMI (kg/m^2)	26.8 ± 4.4	27.3 ± 3.6	26.1 ± 3.9
Clinic SBP (mmHg)	149.8 ± 13.4*	148.3 ± 15.2*	110.8 ± 13.1*
Clinic DBP (mmHg)	94.2 ± 9.2*	93.6 ± 11.4*	71.7 ± 8.6*
Resting heart rate (beats/min)	73.5 ± 8.3	72.6 ± 9.2	71.1 ± 6.4
Diabetes, n (%)	5 (12.5)	6 (14)	7 (15.2)
Total cholesterol (mg/dl)	198.4 ± 32.7*	202.6 ± 41.2*	186.9 ± 26.9*
LDL-cholesterol (mg/dl)	130.2 ± 41.5*	132.1 ± 45.5*	119.2 ± 24.5*
HDL-cholesterol	38.5 ± 11.3**	42.4 ± 10.2**	41.6 ± 12.5
Triglyceride (mg/dl)	144.6 ± 52.6*	149.6 ± 58.2*	139.6 ± 39.8*
Creatinine (mg/dl)	0.9 ± 0.13	0.88 ± 0.16	0.86 ± 0.21
ACE inh. n (%)	14 (35)	16 (35.6)	–
ARB, n (%)	24 (60)	25 (58.1)	–
Ca–channel blockers, n (%)	9 (22.6)	10 (23.2)	–
Diuretics, n (%)	24 (60.0)	26 (60.1)	–

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACE inh, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. *$p < 0.05$ non-dippers and dippers vs normotensives. **$p < 0.05$ non-dippers vs dippers.

echocardiograpic and TDI measurements are showed in Table III. Inter-atrial conduction time was longer in non-dippers than dippers (Figure 2).

Pmax was significantly higher both in dipper and non-dipper hypertensive groups than controls (Table III). Pmin did not differ significantly among the groups. PWD was significantly higher both in dipper and non-dipper hypertensive groups than controls. PWD was significantly higher in non-dippers than dippers (Figure 3). There was a positive correlation between LA diameter and inter-atrial conduction times Pmax and PWD ($r = 0.46$, $p < 0.001$; $r = 0.4$, $p = 0.001$ and $r = 0.44$, $p < 0.001$, respectively). Inter-atrial electromechanical delay was also correlated with Pmax and PWD ($r = 0.39$, $p = 0.002$ and $r = 0.41$, $p < 0.001$, respectively; Figure 4).

Discussion

The principle findings of this study are: (i) both dipper and non-dipper hypertensive patients have delayed atrial electromecanical conduction intervals and inhomogeneous atrial conduction time compared with controls, as evidenced by PWD measurement and TDI; (ii) non-dipper hypertensive patients have increased PWD and prolonged atrial electromechanic conduction intervals compared with dipper subjects; (iii) LA diameter is correlated with atrial electromechanical conduction interval and PWD.

Impaired relaxation and reduced compliance of LV and LA dilatation and/or atrial hypertrophy are the basic manifestations of hypertension-induced cardiac changes (1). These morphological changes may induce various atrial arrhythmias (2,3). Accordingly, AF has been shown to be one of the most significant arrhythmia in hypertensive population (4). Previous studies reported that lack of nocturnal blood pressure decline was associated with more LV hypertrophy, reduced LV diastolic functions, changed LA mechanical functions, increased LA volume and increased carotid intima media thickness (5,14–17). Furthermore, it has been reported that organ damage and cardiovascular morbidity and mortality have significantly increased in non-dippers than dippers (5–8). However, it is not clear that the non-dippers are the more prone to rhythm disturbances compared with dippers.

Dilaveris et al. showed that PWD was prolonged in hypertensive patients with a history of paroxysmal AF compared with controls and concluded that PWD could be a predictor of paroxysmal AF (18). In the present study, we found that PWD was prolonged both in dipper and non-dipper hypertensive subjects compared with controls. We also found that PWD was significantly higher in non-dippers and correlated with LA diameter, suggesting increased risk of atrial rhythm disturbances.

Recent developments in tissue velocity imaging allow precise analysis of atrial motion from different regions of the RV and LV with high temporal

Table II. Comparison of ambulatory blood pressure monitoring results of dippers and non-dippers.

	Non-dippers	Dippers	p-value
24-h systolic BP	141.5 ± 9.3	134.5 ± 7.3	<0.001
24-h diastolic BP	90.0 ± 6.8	83.2 ± 5.9	<0.001
24-h mean BP	107.2 ± 7.3	100.2 ± 6.1	<0.001
Daytime systolic BP	145.2 ± 5.8	143.7 ± 6.4	NS
Daytime diastolic BP	90.3 ± 7.1	89.3 ± 7.7	NS
Daytime mean BP	108.5 ± 5.1	107.4 ± 5.7	NS
Night-time systolic BP	137.8 ± 7.9	126.2 ± 6.3	<0.001
Night-time diastolic BP	88.5 ± 6.2	78.1 ± 5.0	<0.001
Night-time mean BP	104.9 ± 5.4	94.1 ± 4.1	<0.001

BP, blood pressure; NS, non-significant.

Table III. Comparison of echocardiographic and electrocardiographic measurements.

	Non-dippers (n = 40)	Dippers (n = 43)	Normotensives (n = 46)	p-value
LA diameter (mm)	41.4 ± 4.7*	37.3 ± 3.9*	33.8 ± 2.9	<0.001
LVDD (mm)	46.5 ± 3.6	46.6 ± 3.3	45.5 ± 3.6	NS
LVSD (mm)	30.6 ± 3.4	29.9 ± 3.1	29.6 ± 2.8	NS
IVS (mm)	12.7 ± 0.8*	11.6 ± 0.7*	10.2 ± 0.7	<0.001
LVPW (mm)	12.1 ± 0.9*	11 ± 0.7*	9.3 ± 0.6	<0.001
LVMI (g/m^2)	118.6 ± 24.5*	105.9 ± 16.7*	96.8 ± 9.4	<0.001
Ejection fraction (%)	66.9 ± 3.1	67.7 ± 2.9	67.9 ± 2.9	NS
Mitral E max (cm/s)	70.8 ± 15.7	71.6 ± 13.6	80.6 ± 14.9	<0.001
Mitral A max(cm/s)	78.9 ± 14.4	77.5 ± 13.7	67.8 ± 11.9	<0.001
E/A	0.92 ± 0.14	0.94 ± 0.12	1.17 ± 0.11	<0.001
Mitral EDT	218.6 ± 38.9	209.6 ± 34.7	156.7 ± 27.8	<0.001
Lateral PA (ms)	79.5 ± 8.0*	71.0 ± 5.4*	62.4 ± 7.8	<0.001
Septal PA (ms)	58.9 ± 7.3*	53.5 ± 6.7*	52.3 ± 7.0	<0.01
Tricuspid PA (ms)	53.9 ± 7.3*	49.0 ± 6.9*	47.8 ± 7.7	<0.01
Lateral PA−tricuspid PA (ms)[a]	25.6 ± 4.3*	21.9 ± 5.3*	14.6 ± 4.2	<0.001
Septal PA−tricuspid PA (ms)[b]	4.9 ± 3.3	4.5 ± 3.2	4.5 ± 3.6	NS
Pmax (ms)	116.8 ± 12.0*	102.3 ± 10.6*	86 ± 10.9	<0.001
Pmin (ms)	54.5 ± 7.6	51.9 ± 9.3	53.4 ± 5.7	NS
PWD (ms)	57.9 ± 11.2*	51.3 ± 9.4*	32.6 ± 13.9	<0.001

NS, non-significant; LA, left atrium; LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; IVS, interventricular septum; LVPW, left ventricular posterior wall; LVMI, left ventricular mass index; EDT, E deceleration time; PA, time interval from the onset of the P-wave on the surface ECG to the beginning of the late diastolic wave (A wave); Pmax, maximum P-wave duration; Pmin, minimum P-wave duration; PWD, P-wave dispersion. [a]Inter-atrial electromechanical delay. [b]Intra-atrial electromechanical delay. *$p < 0.05$ non-dippers vs dippers.

resolution. Accordingly, inter-atrial electromechanical coupling intervals was found to be longer in patients with paroxysmal AF and mitral stenosis than in the control groups, and LA diameter was found to be correlated with inter-atrial electromechanical delay by using TDI (9,19). In agreement with these results, we found that inter-atrial electromechanical coupling intervals were correlated with LA diameter.

A possible explanation for prolonged atrial conduction time and increased PWD in non-dipper hypertensive patients may be long-standing diastolic dysfunction, leading to increased atrial stretch that occurs as a consequence of persistent pressure load during both day and night in non-dippers (17,20). Chronic atrial stretch leads to cellular hypertrophy, fibroblast proliferation, tissue fibrosis and dilatation, and thereby it may result in shortening of the refractory period with increased dispersion, loss of rate adaptation, and reduction of atrial conductivity (21). The other possible mechanism may be increased sympathetic activation. It has been shown that night-time fall in systolic or diastolic blood pressure is inversely correlated with sympathetic activity (22). The greater sympathetic activation leads to lower decrease in nocturnal blood pressure (23,24).

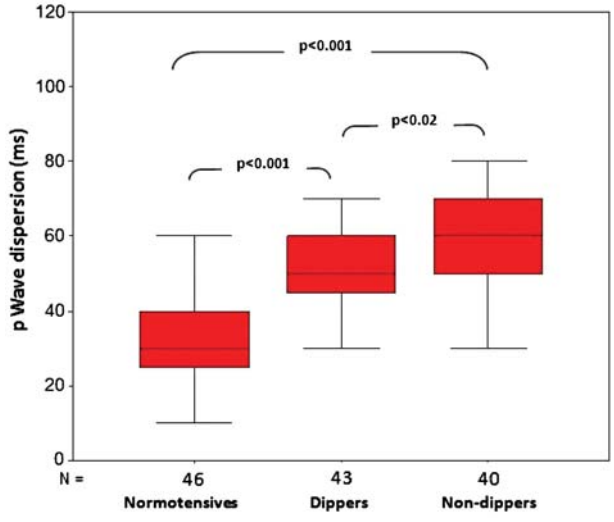

Figure 2. Comparison of P-wave dispersion among the three study groups.

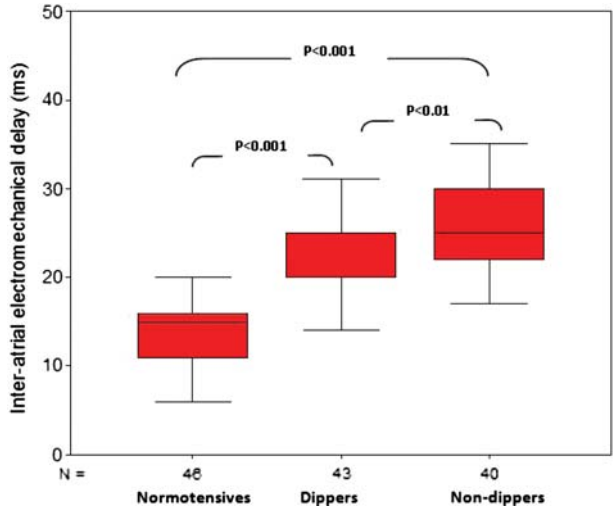

Figure 3. Comparison of inter-atrial electromechanical delay among the three study groups.

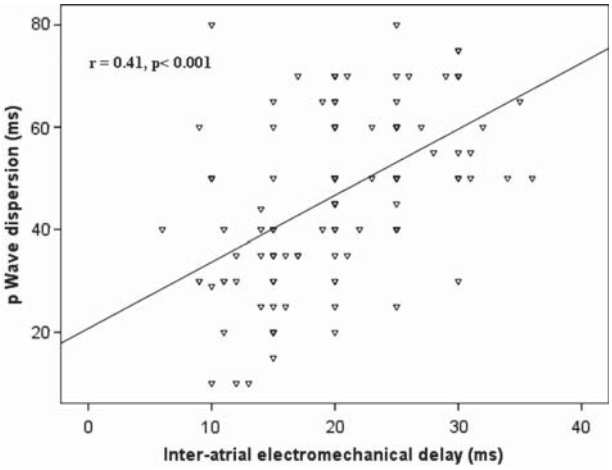

Figure 4. The figure shows positive correlation between inter-atrial electromechanical delay and P-wave dispersion.

Increased sympathetic activity may trigger atrial arrhythmias (23). Also, Tukek et al. observed that PWD and Pmax were increased in patients with paroxysmal AF compared with controls and that the Valsalva maneuver normalized these changes, and concluded that increased sympathetic activity may cause significant increase in PWD (25). Therefore, altered autonomic system regulation occurring in hypertension may be the other reason behind the higher P-wave duration and PWD, and delayed inter-atrial electromechanical coupling intervals in non-dippers.

Study limitations

The most important limitations of our study are the small sample size and cross-sectional design of the study, in which we could not follow up the patients prospectively for future arrhythmic events. Therefore, we do not know whether prolongation of PWD and atrial electromechanical delay predict atrial arrhythmias in non-dipper hypertensive patients. The study was conducted while the some patients were taking antihypertensive treatment. However, distribution of drug use was similar in both groups. Moreover, when these subjects were excluded from the study, statistical significance did not alter. In addition, to assess PWD, we used 12-lead ECG instead of signal-averaged electrocardiogram, which measures PWD more accurately (26). Therefore, measurement errors performed during manual evaluation are the main limitation of the study. However, manual measurement of PWD has been well accepted and has been used in several studies (13,27). Moreover, our inter- and intra-observer measures yielded minimal variability. Finally, the fact that the diagnosis of dipper vs non-dippers was based on single blood pressure measurements could be another limitation of the study.

Conclusion

The patients with non-dipper hypertension have higher P-wave duration, PWD and delayed inter-atrial electromechanical coupling intervals compared with those of dippers and controls. However, further large-scale studies are needed to determine whether non-dipper hypertensive subjects are further prone to atrial rhythm disturbances, and the more aggressive control of blood pressure may improve inter-atrial electromechanical coupling delay and PWD.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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