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Are maximum P wave duration and P wave dispersion a marker of target organ damage in the hypertensive population?

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Abstract *Background* High blood pressure, left ventricular hypertrophy and diastolic dysfunction may cause hemodynamic and morphological changes in the left atrium, consequently instability and heterogeneity in atrial conduction. This is seen as an increase in maximum P wave duration (P_{max}) and P wave dispersion (PD) on the electrocardiogram (ECG). P wave dispersion on ECG has been encountered as a risk factor for atrial fibrillation (AF). The aim of this study is to examine whether PD and P_{max} can be used as a non-invasive marker of target organ damage (LVH and diastolic dysfunction) in a hypertensive population. *Material and methods* The study registered a total of 120 cases (mean age 46.9 ± 10.6 years; 58 [48.3%] males and 62 [51.7%] females), of whom 60 were patients diagnosed as essential hypertension (group 1), and 60 were healthy individuals, who constituted the control group (group 2). Systolic and diastolic functions of all cases were evaluated by echocardiography, and maximum P wave duration (P_{max}), and PD was calculated. *Results* Maximum P wave duration was 91.6 ± 10.2 ms in group 1, and 64 ± 10.2 ms in group 2 ($p < 0.01$), while PD was 56.1 ± 5.8 ms in group 1, and 30.3 ± 6.6 ms in group 2 ($p < 0.01$). Blood pressure, left atrium diameter, DT, IVRT, and E/A ratio, as well as left ventricular mass index increased markedly in group 1. *Conclusion* High blood pressure, LVH, diastolic dysfunction and increased left atrium diameter and volume shows parallelism in hypertensive cases. These physiopathological changes may cause different and heterogeneous atrial electrical conduction. This led to a marked increase in P_{max} and PD in our cases. Thus, the results support the hypothesis that PD can be used as a non-invasive marker of target organ damage (LVH and LV diastolic dysfunction) in the hypertension population.

Key words hypertension – P wave duration – target organ damage

Introduction

Target organ damage secondary to hypertension is a significant health problem in society. In the course of hypertension, target organ damage of cardiac origin can develop at a rate of 50%, of cerebrovascular origin at a rate of 30%, of renal origin 5–10%, and of ocular origin 12–18% [1, 2]. Cardiovascular complications like left ventricle hypertrophy and diastolic dysfunction are accepted as target organ damage

in hypertension [3, 4]. Left ventricle hypertrophy and diastolic dysfunction in hypertension are associated with high mortality and morbidity [5–7].

It is known that hypertensive patients have left atrium dilatation. Tsang TS et al. found in a study that left atrial volume was related to left ventricle mass, diastolic function grade and cardiovascular risk score [8]. Tukek et al., in addition, found that left atrial diastolic volume was related to PWD in paroxysmal atrial fibrillation [9]. Left ventricular hypertrophy and diastolic dysfunction secondary to hypertension can cause an increase in atrial strain, atrial fibrosis, and dilation [5]. The increase in atrial strain, as well as dilation and fibrosis bring about a heterogeneous and different conduction in the atrial myocardium [5, 10–12]. Such pathophysiological changes trigger atrial re-entry, thus, playing an important role in the development of atrial fibrillation (AF) [5]. It has been reported that P wave dispersion (PD) and maximum P wave duration (P_{max}) can be used as a non-invasive marker of heterogeneous and different atrial conduction [10, 11].

The aim of this study was to investigate whether P wave dispersion could be used to determine diastolic dysfunction and left ventricle hypertrophy, which are accepted as target organ damage, in the hypertensive population.

Materials and methods

Patient population

The study registered 120 cases, of whom 60 (group 1) were diagnosed as essential hypertension in the hypertension polyclinic of Fırat University Medical School and met the inclusion criteria, and 60 were healthy volunteers (group 2) (mean age 46.9 ± 10.6; 58 [48.3%] males and 62 [51.7%] females). The study was conducted after approval of local Ethics Committee was taken in accordance with the Helsinki Declaration.

Inclusion criteria

The study included cases who were diagnosed as having hypertension for the first time between 18 and 50 years of age or were followed due to hypertension diagnosis (who suspended treatment for at least 15 days for any reason), who had stage I (those whose systolic blood pressure was between 140 and 159 mmHg, and diastolic blood pressure was between 90 and 99 mmHg) or stage II (those with systolic blood pressure above 160 mmHg or diastolic blood pressure above 100 mmHg) hypertension, and who consented to take part in the study.

Exclusion criteria

The patients who were diagnosed as having secondary, malignant or accelerated HT had coronary artery disease, diabetes mellitus, arrhythmia, pace maker rhythm, bundle branch blocks, chronic obstructive lung disease, pulmonary hypertension, neurological or renal disease, who were pregnant or morbidly obese (with body mass index above 35), whose echocardiography did not produce technically adequate images, whose left ventricular systolic function was impaired (with ejection fraction below 45%), who had rheumatoid valve disease, received anti-arrhythmic treatment (beta-blockers, calcium channel blockers, digitalis, etc.), whose QRS duration was longer than 120 ms, P amplitude was low, the end of P wave could not be discerned, P-P measurement could not be conducted in at least 9 derivations on the electrocardiography (ECG) were excluded from the study.

Electrocardiography

A 12-lead surface ECG was obtained from all subjects in the supine position by using the Nihon Kohden Electrocardiograph (Japan) machine. All patients were breathing freely but not allowed to speak during the ECG recordings. The ECG was recorded at a paper speed of 50 mm/s. Three leads were recorded simultaneously. P wave durations were measured manually by ×10 magnifying lens in all derivations. The beginning of the P wave was accepted as the point where isoelectric line and P wave intersected. P_{max} duration was accepted as the longest P wave (the longest atrial conduction time). The difference between the longest and the shortest P waves was regarded as PD [10–12]. The measurements were evaluated separately and single-blindly by two cardiologists, who did not know the clinical characteristics of the patients. The mean of these two measurements were accepted as P_{max} and PD. Inter-observer variability was 3 ± 4% and intra-observer variability was 1 ± 3%.

Echocardiography

Echocardiography examination was performed in all study subjects by using a commercially available system (Acuson Sequa 512 machine with a 3-MHz transducer). M-Mode echocardiograph measurements were

obtained on the basis of the standards of the American Society of Echocardiography. Left atrial diameter (LA), Left ventricle (LV) end-systolic and end-diastolic diameters, end-diastolic interventricular septal thickness (IVST), and end-diastolic LV posterior wall thickness (PWT), Left ventricular ejection fraction (EF) were measured. Diastolic transmitral doppler parameters such as peak of early diastolic (E) and late diastolic (A) mitral flow velocity, E/A ratio, deceleration time (DT) and isovolumetric relaxation time (IVRT) of flow velocity in early diastole were measured by pulsed Doppler [11].

Evaluation of diastolic functions

The definition of diastolic heart failure was based on two criteria: (1) the echocardiographically measured left ventricular ejection fraction was more than 55%; and (2) echocardiographic evidences of abnormalities of left ventricular relaxation were an E/A ratio <1.0 (<55 years old) or <0.8 (>55 years old); E peak deceleration time of more than 240 ms or isovolumic relaxation time of less than 100 ms [14].

Evaluation of left ventricle hypertrophy

Echocardiography, which is regarded as the gold standard, was used in this evaluation. Posterior wall thickness, IVST, left ventricle systole-end diameter (LVESD) and left ventricle diastole-end diameter (LVEDD) were measured in millimeters from the parasternal long axis. Left ventricle mass index (LVMI) was calculated using the Devereux method [15].

According to the Devereux method:

$$LVMI = 1.04\ ([IVST + LVEDD + PWT]^3 - LVEDD^3) - 13.6\ (g)/\text{body surface area}\ (g/m^2).$$

The upper limit of left ventricle mass index was accepted to be 134 g/m^2 in men and 110 g/m^2 in women [16]. The values above these were regarded as "left ventricle hypertrophy".

Statistical evaluation

The statistical data were evaluated using SPSS 11.00 package software. General descriptive properties were assessed as mean ± standard deviation (SD). Chi-square test was employed in the comparison of sex and risk factors. Significance between basal values of the groups was evaluated by the student T test. The correlations between P_{max} and P wave dispersion, and left atrium size, minimal, maximal and ejaculation volumes, left ventricular mass and mass index, $E_{velocity}/A_{velocity}$ ratio, DT and IVRT were evaluated with Person's Correlation test. The lowest level of significance was accepted as $p<0.05$.

Results

Demographic characteristics of the groups are presented in Table 1. Maximum P wave duration was 91.6 ± 10.2 ms in group 1 and 64 ± 9.4 ms in group 2 ($p<0.001$), while PD was 56.1 ± 5.8 ms in group 1 and 30.3 ± 6.6 ms in group 2 ($p<0.001$) (Table 2, Fig. 1). Left atrium diameter was found 46.5 ± 3.9 mm in group 1, and 34.5 ± 2.8 mm in group 2 ($p=0.002$). Left atrium maximal volume was $40.2 \pm 13.3\ cm^3$ in group 1, and $37.8 \pm 8.8\ cm^3$ in group 2 ($p=0.24$), whereas left atrium minimal volume was $17.5 \pm 8.8\ cm^3$ in group 1, and $17.0 \pm 6.5\ cm^3$ in group 2 ($p=0.74$) (Table 2, Fig. 2). Atrial ejaculation volume was $22.3 \pm 7.2\ cm^3$ in group 1, and $20.5 \pm 5.7\ cm^3$ in group 2 ($p=0.13$).

There was a significant correlation between P_{max}, and atrial maximum volume ($r=0.23$ $p=0.044$), and ejaculation volume ($r=0.25$ $p=0.048$) and also between P_{max} and atrial minimal volume ($r=0.65$ $p>0.05$) in group 1 (Fig. 3). No correlation was found between P wave dispersion, and atrial maximal or minimal volume ($r=0.56$, $p>0.05$).

When the groups were examined in terms of diastolic functions, it was seen that DT was 277.6 ± 48.8 ms in group 1 and 243.7 ± 21.1 ms in group 2 ($p<0.001$),

Table 1 General demographical data about the groups

	Group 1 (n = 60)	Group 2 (n = 60)	p value
Age (year)	48.1 ± 10.3	45.7 ± 10.8	> 0.05
Gender (male/female)	27 (45%) 33 (55%)	31(51.7%) 29 (48.3%)	> 0.05
BMI (kg/m^2)	26.9 ± 4.4	27.2 ± 5.1	> 0.05
Cigarette smoking (present/absent)	17/43	14/46	> 0.05
Familial history of cardiovascular disease (present/absent)	5/55	2/58	> 0.05
Dyslipidemia (present/absent)	8/52	2/58	> 0.05
Systolic blood pressure (mmHg)	161.7 ± 26.8	123.4 ± 19.8	< 0.001 [a]
Diastolic blood pressure (mmHg)	98.3 ± 18.7	83.6 ± 15.3	< 0.001 [a]
Heart rate (beat/min)	78.1 ± 7.3	76.7 ± 6.3	> 0.05

[a] Statistically meaningful

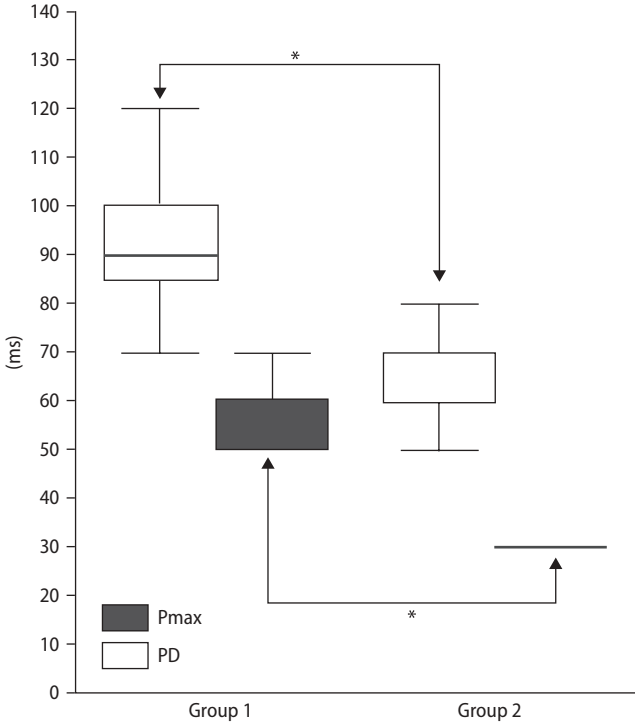

Fig. 1 Comparison of P_{max} and P wave dispersion between groups (* $p < 0.001$) (P_{max} Maximum P wave duration, *PD* P wave dispersion)

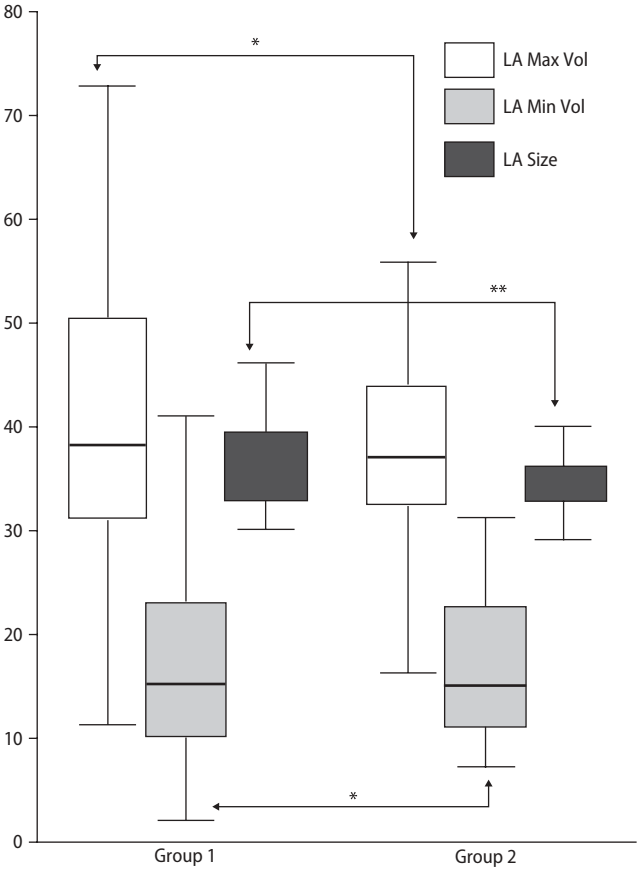

Fig. 2 Comparison of LA diastolic volume, systolic volume and size between groups (* $p > 0.05$, ** $p = 0.002$) (*LA Max Vol* Left atrial diastolic volume [cm^3], *LA Min Vol* Left atrial systolic volume [cm^3])

Table 2 Comparison of data between groups

	Group 1 (n = 60)	Group 2 (n = 60)	p value
Maximum P wave duration (ms)	91.6 ± 10.2	64 ± 9.4	< 0.001 [a]
P wave dispersion (ms)	56.1 ± 5.8	30.3 ± 6.6	< 0.001 [a]
Left atrial maximal volume (cm^3)	40.2 ± 13.3	37.8 ± 8.8	0.24
Left atrial minimal volume (cm^3)	17.5 ± 8.8	17 ± 6.5	0.74
Atrial ejaculation volume (cm^3)	22.3 ± 7.2	20.5 ± 5.7	0.13
Left atrial size (mm)	46.5 ± 3.9	34.5 ± 2.8	0.002 [a]
Ejection fraction (%)	60.7 ± 5	61.9 ± 3.7	0.15
DT (ms)	277.6 ± 48.8	243.7 ± 21.1	< 0.001 [a]
IVRT (ms)	122 ± 15.2	112 ± 11.5	< 0.001 [a]
E/A			
Normal (n)	13 (21.7%)	46 (76.7%)	< 0.001 [a]
Diastolic dysfunction (n)	8 (13.3%)	8 (13.3%)	< 0.001 [a]
Equal (n)	39 (65%)	6 (10%)	< 0.001 [a]
Left ventricular mass index (g/m^2)	108.1 ± 17.1	82.7 ± 12.6	< 0.05 [a]

[a] Statistically meaningful, *DT* deceleration time, *IVRT* isovolumetric relaxation time

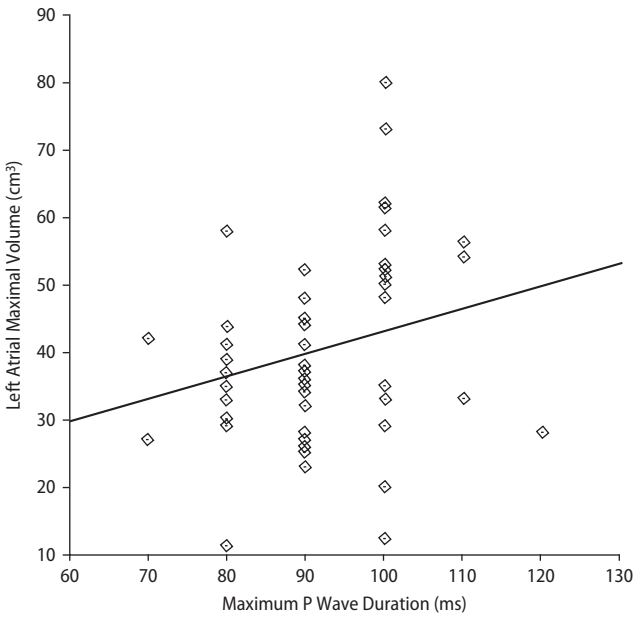

Fig. 3 Correlation between P_{max} and left atrial maximal volume ($r = 0.23$, $p < 0.04$)

while IVRT was 122 ± 15.2 ms in group 1 and 112 ± 11.5 ms in group 2 ($p < 0.001$) (Table 2). Comparison of the E/A ratio is shown in Table 2. The left ventricle mass index was 108.1 ± 17.1 g/m^2 in group 1 and 82.7 ± 12.6 g/m^2 in group 2 ($p < 0.05$).

Discussion

Hypertension is a significant cause of mortality and morbidity due to the target organ damage it leads to. One of the major target organ damages is cardiovascular damage. When dealing with cardiovascular events in hypertension [7], the importance of atrial pump function is generally neglected. The increase in left atrial volume and strain caused by diastolic dysfunction and left ventricular hypertrophy (left ventricular mass increase) in hypertension can impair the function of the atrial pump. Furthermore, it can bring about important changes in the structural and molecular structure of the atrium. Consequently, it may have an unfavorable effect on left ventricular systolic and diastolic function [17–19].

Maximum P wave duration and PD are non-invasive markers that show the heterogeneous and instable distribution of stimulations originating from the sinus node on the atrium wall [10–12, 20]. P wave dispersion and P_{max} can be used as non-invasive markers to determine the risk of AF development in such diseases as paroxysmal AF, mitral stenosis, dilated cardiomyopathy, atherosclerotic heart disease, and acute myocardial infarction [9–12, 20–24]. The elevation of heterogeneous and different electrical activity in the atrial myocardium plays an important role in the onset of atrial re-entry by causing a different conduction rate and the heterogeneity of the refractory period. Atrial re-entry developing in hypertension can be one of the mechanisms explaining the developmental pathophysiology of AF in our study; Group 1 P_{max} and PD were higher than those of group 2.

Maximum P wave duration and P wave dispersion have been reported to be correlated with age [23], left atrium size and volume [9], atrial pump function [21], and left ventricle systolic and diastolic functions [5, 21, 22]. The elevation of the maximal volume of the left atrium results in an increase in intracavitary pressure and strain. This increase in intracavitary pressure and strain triggers disorganization of myocardial fibers and fibrosis [11, 19], and plays an important role in the onset of discontinue atrial conduction and re-entry. Heterogeneous and different atrial conduction presents itself as an increase in P_{max} and P wave dispersion on the ECG [11, 22, 23]. Our study has demonstrated that P_{max} and P wave dispersion could be correlated with left atrium diameter, atrial maximal and ejaculation volume, left ventricular index and diastolic functions in hypertensive cases. It supports that left atrium diameter, left atrium maximal volume, diastolic functions and left ventricular mass can have an important part in the development of atrial fibrillation in hypertensive cases. Therefore, our study provides support to the hypothesis that P_{max} and P wave dispersion can be used to show the risk of AF development due to the above-mentioned mechanisms in the hypertensive population.

There may be changes in the diameter, volume and strain of the left atrium secondary to LVH and diastolic dysfunction during the course of hypertension. This may result in an increase in atrial volume, strain and pressure, which partially tampers with the feeding of the atrial myocardium, leading to ischemia [9, 17]. Lammers et. al. reported that the deceleration of conduction in ischemic atrial tissue could lead to secondary heterogeneous and different electrical atrial conduction [25]. This may explain the mechanism of the increase in P_{max} and P wave dispersion observed in our hypertensive cases.

Elevation of catecholamines and angiotensin II in essential hypertension can activate the sympathetic nervous system, and thereby impair the autonomous balance of the heart. Besides, angiotensin II and catecholamines were reported to increase atrial fibrosis [17, 18, 26]. Both the activation of the sympathetic nervous system and the increase in myocardial fibrosis increase atrial conduction time (P_{max}) and P wave dispersion [11, 27] through heterogeneous and different atrial conduction [28]. Dagli et al. showed that decreasing blood pressure with nebivolol in hypertensive patients resulted in a marked decline in P wave dispersion and P_{max}. This finding supports that high blood pressure leads to an increase of P_{max} and P wave dispersion [29]. Activation of the sympathetic nervous system, increase in angiotensin II, and high blood pressure can explain the increase in P_{max} and P wave dispersion in our hypertensive cases.

High blood pressure in the hypertensive population can elevate the left atrial pressure and strain either through diastolic dysfunction or by its direct effect. Furthermore, change in the left ventricular end-diastolic pressure can lead to an increase in atrial strain [5, 19, 30]. The change in atrial strain and pressure can trigger supra-ventricular arrhythmias via atrial re-entry. The mechanism by which the increase in P_{max} and P wave dispersion in the hypertensive group is explained may be the increase in atrial pressure and strain that develops secondary to high blood pressure.

The Framingham heart study reported a correlation between left atrium size and high blood pres-

sure [30]. Left atrium dilation developing in hypertension was reported to be able to cause an increase in P_{max} and P wave dispersion [19, 25]. The fact that left atrium diameter in the hypertensive cases was statistically significantly larger than that in the control group was interpreted as one of the mechanisms explaining the increase in P_{max} and P wave dispersion. Our findings were consistent with literature results.

Left ventricle hypertrophy is one of the compensatory mechanisms, which initially develops in order to protect the systolic functions of the heart, but turns out to increase its workload [31]. High blood pressure causes thickening of myocytes and concentric hypertrophy. High blood pressure and LVH are associated with premature impairment of diastolic function [4, 6]. Consequently, left ventricle hypertrophy and diastolic dysfunction can elevate the atrial volume and pressure. In our study left ventricle mass index was found to be markedly higher in hypertensive patients.

Diastolic dysfunction and left ventricle hypertrophy tend to co-exist in hypertension [17]. Consequently both can bring about an increase in P_{max} and P wave dispersion. The presence of a statistically significant difference in E/A ratio, DT, IVRT, left ventricle mass index and atrium size in our study provides support to our hypothesis that these parameters can be employed as a non-invasive marker to determine P wave dispersion and target organ damage in the hypertensive population.

Limitations of the study

Electrophysiological evaluations were not carried out in our study. Electrocardiographic measurements were conducted manually with the help of a magnifying lens without using computer software. In order to discard any medication effects, the measurements in group 1 were made in hypertensive cases who did not use any medication or who stopped taking medications for any reason and completed the washout period.

Conclusion

P_{max} and P wave dispersion in hypertensive cases can show LVH and diastolic dysfunction which play an important role in atrial dilatation and atrial volume increase in a non-invasive manner. Furthermore, LVH and diastolic dysfunction, held responsible for mortality and morbidity in hypertension, can be used as a non-invasive marker to determine the risk of atrial fibrillation development. This is an original study in that it has shown that P_{max} and P wave dispersion can be utilized as a non-invasive marker to determine the risk of atrial fibrillation.

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