QT interval and dispersion differences between normal and prehypertensive patients: effects of autonomic and left ventricular functional and structural changes

Normal ve prehipertansif hastalarda QT aralık ve dispersiyon farklılıkları: Otonomik ve sol ventriküler yapı ve fonksiyon değişikliklerin etkileri

Mehmet Tolga Doğru, Mahmut Güneri, Emine Tireli, Ömer Şahin, Turgay Çelik[1], Atila İyisoy[1]

Department of Cardiology, Faculty of Medicine, University of Kırıkkale, Kırıkkale
[1]Department of Cardiology, Faculty of Medicine, Gülhane Military Medical Academy, Ankara, Turkey

ABSTRACT

Objective: We aimed to investigate the effects of autonomic and left ventricular functional and structural changes on QT interval and dispersion differences between normal and prehypertensive patients.
Methods: A total of 291 normotensive patients (<140/90 mmHg) (135 males, age range: 16-75 years, mean age: 45±11 years; 156 females, age range: 17-71 years, mean age 38±10 years) were enrolled into this cross-sectional case-controlled study. Patients were categorized into two groups according to their blood pressure (BP) levels as Group 1 - patients with normal BP (<120/80 mmHg) or Group 2 - patients with prehypertensive BP (120-139/80-89 mmHg). We evaluated autonomic states by using heart rate variability measurements. Left ventricular structure and functions were evaluated by using Doppler echocardiography in both normal and prehypertensive BP groups regarding their effect on QT intervals and QT dispersion. Statistical analyses (Student's t and Mann-Whitney U tests) were used to evaluate the differences in QT intervals and QT dispersion between the BP groups.
Results: There were statistically significant differences between the two BP groups with respect to QT intervals and QT dispersion (for QT min, p<0.001, QTc min, p<0.001 and QT dispersion, p<0.001). We also detected that prehypertensive patients had increased sympathetic activity and slightly impaired left ventricular systolic and diastolic function (for low frequency power / high frequency power ratio -p=0.029, left ventricular ejection fraction - p=0.054, and transmitral peak A wave velocity - p<0.001).
Conclusion: QT interval and dispersion differences are present in prehypertension. Moreover, these differences are independent of left ventricular mass. Autonomic changes can be effective on these differences between the patient groups. *(Anadolu Kardiyol Derg 2009; 9: 15-22)*
Key words: Hypertension, electrocardiography, echocardiography, ventricular function, autonomic nervous system, repolarization

ÖZET

Amaç: Bu çalışmada normal ve prehipertansif (PHT) hastalar arasında QT interval ve dispersiyonu farklılıklarını, sol ventrikül (SV) yapı ve fonksiyonları ile otonomik fonksiyon farklılıklarının etkisini de göz önüne alarak incelemeyi amaçladık.
Yöntemler: Toplam 291 normotansif (<140/90 mmHg) hasta enine kesitli ve vaka kontrollü bu çalışmaya alındı (135 erkek, yaş aralığı: 16-75, ortalama yaş: 45±11; 156 kadın, yaş aralığı: 17-71, ortalama yaş: 38±10 yıl). Hastalar kan basıncı (KB) düzeylerine göre, normal KB (<120/80 mmHg) ve PHT KB (120-139/80-89 mmHg) olmak üzere 2 gruba ayrıldı. Normal ve prehipertansif KB'na sahip hastalarda QT interval ve dispersiyonu, otonomik fonksiyonlar, SV yapı ve fonksiyonları arasındaki farklılıkları incelemek amacıyla istatistiksel analizler (eşleştirilmemiş t ve Mann Whitney U testleri) yapıldı. Otonomik fonksiyonların değerlendirilmesinde kalp hızı değişkenliği ölçümleri kullanıldı. Sol ventrikül yapı ve fonksiyonları Doppler ekokardiyografi ile değerlendirildi. Çalışma sonuçları karşılaştırılarak, normal KB ve PHT KB'na sahip olan hastalarda QT intervali ve dispersiyonu ile SV yapısı, fonksiyonları ve otonomik fonksiyonların olası ilişkileri incelendi.
Bulgular: Normal KB ve PHT KB'na sahip hastalar arasında QT intervali ve dispersiyonu açısından önemli farklar saptandı (QT minimum için, p<0.001; QTc minimum için, p<0.001 ve QT dispersiyon için, p=0.002). Ayrıca PHT olan hastalarda SV sistolik ve diyastolik fonksiyonlarında hafifçe bozulma ve sempatik aktivitede artış izlendi (Düşük frekans değeri/Yüksek frekans değeri oranı için p=0.029; SV ejeksiyon fraksiyonu için p=0.054 ve transmitral pik A dalga hızı için, p<0.001).
Sonuç: Normal ve PHT KB sahip hastalar arasında QT intervali ve dispersiyonu açısından önemli farklılıklar mevcuttur. Her iki grup arasındaki sol ventrikül yapı ve fonksiyonları ile otonomik fonksiyon farklılıkları da bu sonuç ile bağıntılıdır. *(Anadolu Kardiyol Derg 2009; 9: 15-22)*
Anahtar kelimeler: Hipertansiyon, elektrokardiyografi, ekokardiyografi, ventriküler fonksiyon, otonomik sinir sistemi, repolarizasyon

Address for Correspondence/Yazışma Adresi: M. Tolga Doğru, MD, Asst. Prof. , Department of Cardiology, Kırıkkale University, Faculty of Medicine, Kırıkkale, Turkey
Phone: +90 318 225 24 85 Fax: +90 318 225 28 19 Gsm: +90 505 886 66 88 E-mail: mtolgadogru@gmail.com

Introduction

QT intervals are the electrocardiographic measurements of cardiac depolarization and repolarization periods. QT intervals and QT dispersion especially reflect the ventricular repolarization (VR) time and homogeneity. On the other hand, VR is a vulnerable period for the appearance of ventricular arrhythmias (1-4). Pathologic conditions that can cause a VR abnormality can also cause increased morbidity and mortality, especially due to increased incidence of ventricular arrhythmias (5-9, 10, 11). Several studies have shown that QT dispersion is valuable for predicting arrhythmias and morbidity and mortality in most pathologic conditions (5-9), among which hypertension is one of the most important due to its high prevalence and complications. Hypertension often leads to an increase in left ventricular mass (LVM) (12). Marked left ventricular hypertrophy (LVH) is associated with potentially arrhythmogenic VR abnormalities, which may contribute to the increased risk of sudden cardiac death in this disorder (12-15). Some recent studies have also shown that prehypertension (PHT) is not innocent because of the adverse effects and comorbidities. Several studies have shown that normotensive blood pressure (BP) levels have non-homogeneous characteristics (14-18). Moreover, patients with a high normal BP [According to European Society of Cardiology (ESC)](14) or PHT [According to Joint National Committee (JNC) 7] (15) have higher risk for hypertension than those with a normal BP. Prehypertension is considered a precursor of hypertension and a predictor of excessive cardiovascular risk (14-16). Additionally, some studies have shown impaired LV structure, systolic and diastolic functions and aortic elastic properties in subjects with prehypertensive BP levels (17, 18). Left ventricular structure, functions and inevitably QT interval have close relationship with autonomic activities (18, 21-30). Moreover, impaired autonomic functions were shown as an independent effective factor on QT intervals (29, 30).

Although the relationship between QT interval and high BP is well known for hypertensive BP levels, there are few data about the relationship among QT interval and QT dispersion alterations in normotensive BP levels from the point of the effects of autonomic and left ventricular functional and structural changes.

In this study, we aimed to investigate the effects of autonomic and left ventricular functional and structural changes on QT interval and dispersion differences between normal and prehypertensive patients.

Methods

Study Design. The study design was cross-sectional and case-controlled. The sample size for the study was defined with power of the study of 80% and significance level of 5% (2, 31, 32).

Patient Selection. Patients admitted to the hospitals for general health examination were diagnosed and classified according to the hypertension guideline of the Joint National Committee 7 (JNC 7) after detailed history and physical examination (15). Only those patients with BP <140/90 mmHg were selected for the study. During the study period, consecutively 985 patients were examined and finally a total of 291 patients were enrolled into the study after exclusion criteria.

It is well known that normotensive BP is categorized in two separate levels as normal BP (<120 mmHg systolic and <80 mmHg diastolic) and PHT BP (120-139 mmHg systolic and 80-89 mmHg diastolic) by JNC7 (16).

Concordantly, in our study, all patients were classified as either Group 1: Normal BP (<120/80 mmHg) (n=110) or Group 2: Prehypertensive BP (120-139/80-89 mmHg) (n=181).

Patients with acute or chronic renal dysfunction, diabetes mellitus, hypertension (≥140/90 mmHg), white coat hypertension (elevated office BP + normal BP out of the office), or masked hypertension (normal office BP + elevated BP out of the office) were excluded from the study. Moreover, patients with metabolic syndrome, impaired glucose tolerance, heart failure (ejection fraction [EF] <50%), valvular heart disease, cardiomyopathies, aortic disease (Marfan's syndrome, coarctation of aorta, aortic aneurysm or aortic surgery, etc.), history of coronary artery disease or proven coronary artery disease at coronary angiography or noninvasive tests, familial hyperlipidemia, asthma or chronic obstructive lung disease, morbid obesity [body mass index (BMI)>40kg/m^2], pregnancy or taking oral contraceptives, concurrent therapy with medications that might affect BP, connective tissue disorders, neurological problems, psychiatric diseases, endocrine diseases, alcohol or drug abuse, and use of medications for hormonal treatment within the last six months were excluded from the study. Patients with pathologic echocardiographic findings and electrocardiographic abnormalities including ischemia, previous infarction, bundle branch block, atrial fibrillation, sick sinus syndrome and ventricular pre-excitation were also not included in the current study.

Patients who fulfilled these criteria and who provided written informed consent were included in the study. The study was approved by the Local Ethical Committee.

Biochemical and Hormonal Analysis. We performed biochemical and hormonal analysis to investigate pathological results, which were pointing out any exclusion criteria. Laboratory work-up involved detailed biochemical analysis (glucose, lipid profile, thyroid, renal and liver function tests, electrolytes) and complete blood count. A fasting blood sample was drawn between $08.^{00}$ and $10.^{00}$ hours.

Anthropometric Measurements. Height (m): height was recorded with a wall mounted stadiometer to the nearest 0.1 cm without shoes.

Weight (kg): weight was measured with calibrated digital scale to the nearest 0.1 kg in the morning before eating or drinking anything.

Waist circumference (cm) and hip circumference (cm) were obtained by using a cloth tape. Waist circumference was measured during minimal respiration to the nearest 0.1 cm. The waist was defined as the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the midaxillary line, and the hips were measured at the level of the greater femoral trochanters (33).

Body mass index was calculated by dividing weight (in kilograms) by height (in square-meters) (kg/m^2).

Blood Pressure Measurements. Patients were informed to not smoke or consume caffeinated beverages or to perform excessive physical activity throughout the 3 hours prior to BP measurements. Blood pressure was measured three times for each patient with

a standard mercury sphygmomanometer on the right arm in sitting position following a 10-minute rest. Phase I and V Korotkoff sounds were used to determine systolic and diastolic BP measurements. In each patient, measurements were performed in the same room and at the same time of the day by a paramedic. The average of three measurements was used for the analyses.

Echocardiographic Examination. Transthoracic echocardiography was performed by using Ge-Vivid 7 Pro 2.5 MHz probe (General Electric, Florida, USA) in the left lateral decubitus position in a standard manner. Echocardiographic measurements were made on the screen by two cardiologists not aware of the patients' clinical data. M- mode tracings of the left ventricle were obtained in the parasternal long-axis views at a speed of 50 mm/sec. Five consecutive cardiac cycles were averaged for every echocardiographic measurement. Interventricular septum systolic and diastolic diameters [IVSDs, IVSDd], left ventricular internal systolic and diastolic diameters [LVIDs, LVIDd], left ventricular mass index [LVMI], aortic systolic diameter [AOd] (from sinotubular junction), and left atrial systolic diameter [LAd] were calculated from the parasternal long-axis view according to standard criteria. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), fractional shortening (FS) and EF were measured by software using the Teichholz formula (20). The LVM was calculated according to Devereux formula (19) and LVMI was obtained by LVM divided by body surface area.

The transmitral diastolic flow Doppler tracing was obtained from the apical four- chamber view by using pulsed Doppler echocardiography with the sample volume size of 1 to 2 mm between the tips of the mitral valve during diastole. To measure isovolumetric relaxation time (IVRT), a 3- to 4-mm size sample volume was placed in the area of the mitral leaflet tips. Next, the transducer beam was angulated toward the left ventricular outflow tract until aortic valve closure appeared above and below the baseline. The peak early transmitral filling during early diastole (E), peak transmitral atrial filling velocity during late diastole (A), deceleration time (DT) (time elapsed between peak E velocity and the point where the extrapolated deceleration slope of the E velocity crosses the zero baseline), and IVRT (time period between the end of mitral diastolic flow Doppler tracing and the starting point of aortic flow Doppler tracing) were used to assess left ventricular diastolic functions. TEI index was calculated as a myocardial performance index by using (IVRT + IVCT)/EJT formula (18) (IVCT: Isovolumetric contraction time; EJT: Ejection time).

Electrocardiography (ECG) and QT Interval Measurements: After the skin was rubbed, electrodes were applied, and 12-channel ECG was then obtained (Cardioline Delta1 plus, Remco, Italy). When the QT intervals were calculated,

- ECG paper speed was 50 mm/sec ,
- Three QT intervals were measured in every lead,
- We used the slope intercept technique to identify the end of the T wave (The slope intercept technique identifies the end of the T wave as the intercept of the line tangential to the point of maximum T wave down-slope with the isoelectric line) (1, 2, 34).

QTc minimum and QTc maximum values were then calculated by using Bazett's formula ($QTc = QT / \sqrt{}_{R-R}$) (1).

QT dispersion (QT max -QT min) was also calculated.

We also evaluated the T wave morphologies from 12-channel ECG recordings. We categorized the T wave morphologies into three subgroups: positive, flat or biphasic and negative.

All measurements were performed by two separate observers who were unaware of each other's results. In case of contradictory results, these measurements were performed by a third observer.

Heart Rate Variability (HRV) Measurements and Indirect Autonomic State Evaluations.

HRV measurements are related with R-R variations of a certain time period. It is well known that these measurements can reflect changes in autonomic states indirectly (35).

Measurement of 24-Hour HRV: Afterwards the clinical and laboratory tests ended, a Holter device was affixed and starting time was adjusted to second sensitivity and when the recording time ends (24 hours) measurement of 24-hour HRV was performed. Recordings were performed with 24-hour Holter monitoring and analyzed with Delmar-Impresario System (Delmar-Impresario Medical Systems, Irvine, California, USA). While evaluating the analyzed data, standard measurement criteria were utilized as stated by Task Force Report in 1996 (36).

The pNN50 and rMSSD was analyzed as the time domain HRV variables. The pNN50 was described as percentage of differences between successive RR intervals that are >50 milliseconds, computed over the 24- hour recording. The rMSSD was described as square root of the mean differences between successive RR intervals. The unit of the time domain measurement is milliseconds (msec) (36).

Power spectral (frequency) analysis of HRV was also performed using a fast Fourier transform to break down the time series to its underlying periodic function. Total power (TP) was defined as the energy in the heart period power spectrum from 0 to 0.40 Hz. frequencies. The very low frequency (VLF), low frequency (LF) and high frequency (HF) powers were defined as the energy in the heart period power spectrum between 0.003 - 0.04 Hz, 0.04 -0.15 Hz and 0.15 - 0.40 Hz, respectively. The unit of the frequency domain measurements is millisecond square $(msec)^2$ (36).

Then, the LF/HF ratio was calculated. Finally, LF and HF were also measured in normalized units, which represent the relative value of each power component in proportion to the total power minus the VLF component. Normalized LF (LFn) was calculated as LF power in normalized units LF/(total power-VLF)x100, and normalized HF (HFn) as HF power in normalized units HF/(total power-VLF)x100 (36).

The pNN50 and rMSSD reflect parasympathetic activity as the HF power and HFn in frequency domain data. The LF/HF and LFn reflect sympathovagal balance and increasing in these ratios are considered that reflect increased sympathetic activity (36).

Measurement of Day- and Night- time period of HRV: All frequency domain parameters that mentioned above were calculated separately for day- and night-time periods in semi-automated algorithm of Delmar Impresario system®. When the night period HRV parameters were calculated, only data during sleep period were taken into consideration. Because of this, we accepted the time between 23:00-05:59 as a night period time, and the time between 06:00-22:59 as day period. These periods were set according to HRV recording tool's characteristics.

Statistical Analyses

All statistical analyses were performed using SPSS version 15 (SPSS, Chicago, USA). Sample size estimation and power analysis was performed using MINITAB 15 (Minitab Inc., Pennsylvania, USA). Kolmogorov-Smirnov test was used for determination of the data distribution. Data with normal distribution were expressed as mean±standard deviation (SD), and Student's t test was used for analysis. Data with non-normal distribution were expressed as median value (25%-75% percentile), and Mann-Whitney U test was used for analysis. A p value of <0.05 was accepted as statistically significant.

Results

A total of 291 patients (135 males, age range: 16-75, mean age: 45±11 years; 156 females, age range: 17-71, mean age: 38±10 years) were enrolled into the study after exclusion criteria.

There were no differences in results of biochemical tests between the groups (p>0.05).

Furthermore, we did not detect any statistically significant difference between the groups regarding patient characteristics (Table 1).

Table 2 shows the differences in echocardiographic measurements according to BP levels. There were statistically significant differences between the groups with respect to left atrium diameter, IVSDs, LVIDs, transmitral atrial filling velocity during late diastole (transmitral A wave velocity) (p=0.001, p=0.001, p=0.023 and p<0.001, respectively). Although IVSDd, LVIDd, LVM and LVMI tended to increase in the prehypertensive group, no statistically significant differences were determined between the groups for these values (Table 2).

24-hour, day and night period HRV measurements are shown in Table 3.

There were increased LF/HF $_{24\ Hour}$, LFn $_{24\ Hour}$, LF/HF $_{Night}$ and diminished pNN50 and HFn $_{24\ Hour}$ values in prehypertensive patients group (p=0.029, p=0.016, p=0.039, and p=0.042, p=0.016, respectively).

Table 4 presents differences in QT interval and QT dispersion measurements according to the BP levels. No differences were determined between the groups with respect to maximum QT and QTc intervals (p>0.05 for both). However, statistically significant differences in minimum QT and QTc intervals between groups were determined (p<0.001 and p<0.001, respectively). We detected significant statistical differences in QT dispersion between the groups (p<0.001). On the other hand, there was no any difference between the BP groups regarding T wave morphologies (p>0.05)

Table 1. Patient characteristics according to blood pressure level

Parameters	Normal group (n=110)	Prehypertensive group (n=181)	p*
Age, years	39.66±11.01	42.70±12.05	NS
Height, cm	165.29±9.16	167.18±7.26	NS
Weight, cm	78.41±14.53	80.17±14.37	NS
Body Mass Index, kg/m^2	28.89±6.14	28.74±5.22	NS
Waist, cm	92.67±15.68	95.53±13.15	NS
Hip, cm	92.28±12.95	94.62±11.76	NS
Waist /Hip ratio	1.00±0.09	1.01±0.09	NS

Data are expressed as mean±SD
*- Student's t test.
NS - non-significant, p>0.05

Discussion

In the present study, we investigated autonomic functions, echocardiographic features and QT interval measurements at the same time. We detected that prehypertensive patients had increased sympathetic activity and slightly impaired left ventricular systolic and diastolic function. We also found that there were marked shortenings in minimum QT and QTc interval and marked prolongations in QT dispersion in the prehypertensive group compared to the normal group.

Altered electrocardiographic ventricular repolarization, indicating reduced repolarization reserve and possibly increased repolarization heterogeneity, is already present in hypertensive subjects with only mild LVM increase. At a population level, this may carry important risk implications for the large group of hypertensive patients (21). Prolonged QT dispersion-a marker of increased myocardial electrical instability, was associated with LVH and hypertension and was related mostly to concentric hypertrophy in hypertensives (22, 23). Systolic BP measured during exercise correlated with QTc maximum in hypertension (28). QT dispersion has been reported to increase in patients with essential hypertension, and abnormal QT dispersion is associated with arrhythmias and sudden cardiac death (25). Some studies have shown a positive association between QTc and BP in both men and women. In the same study, estimated increase in systolic and diastolic BP for each 100-millisecond increase in QTc was detected as 6.4 and 5.0 mmHg in men and 3.7 and 2.5 mmHg in women, respectively (26). Although there is a great amount of data in the literature about the associations among QT intervals, left ventricular structure, autonomic functions and hypertension, data regarding these parameters in normotensive BP levels is insufficient.

Zhu H et al. (27) have shown that there were no statistical differences in the parameters of left-ventricular structure between normotensive subjects and prehypertensive subjects. However, in that study, patients' body mass index and waist circumference were significantly greater in prehypertensive subjects than in normotensive subjects (27). On the other hand, Erdogan et al. (18) reported that left ventricular diastolic function was slightly impaired in subjects with PHT, and impairment of aortic elasticity was as severe as that in hypertension. Concordantly, according to our results, although there was not statistically significant difference in transmitral E/A ratio, there was a tendency to decrease for this ratio in PHT group. On the other hand, there were statistically significant differences between the BP groups in transmitral A wave velocity, with its greater values in PHT group. On the other hand, we detected some structural differences between the BP groups. According to our study results, LVIDs was greater in PHT group than that of normal BP group. The FS and EF in PHT group were less than in the normal BP group, but the differences were not statistically significant. We considered that, the results of increase in end-systolic volume and LVIDs in the prehypertensive BP group were due to the higher global arteriolar stiffness compensated with augmented left ventricular systolic performance.

Table 2. Differences in echocardiographic measurements between groups according to BP level

Variables	Normal group (n=110)	Prehypertensive group (n=181)	p
AOd, cm	2.60±0.48	2.68±0.45	NS
LAd, cm	3.16±0.45	3.38±0.48	0.001
IVSDd, cm	0.88(0.79-1.00)	0.91(0.79-1.06)	NS
LVIDd, cm	4.63±0.80	4.78±0.52	NS
LVPWDd, cm	0.91(0.84-1.02)	0.94(0.85-1.08)	NS
IVSDs, cm	1.08(0.96-1.26)	1.25(1.02-1.41)	0.001
LVIDs, cm	2.88±0.53	3.03±0.48	0.023
LVPWDs, cm	1.26±0.76	1.27±0.22	NS
EDV, ml	104.2±31.0	108.4±27.2	NS
ESV, ml	32.4(26.0-40.7)	35.8(26.2-45.7)	NS
SV, ml	70.7±18.7	70.7±16.4	NS
FS, %	37.6(35.1-40.4)	35.9(33.7-39.2)	0.011
EF, %	67.70±5.35	66.45±6.01	0.054
Relative wall thickness, cm	0.42±0.09	0.40±0.08	NS
Mitral deceleration time, msec	215.33±60.78	227.55±75.73	NS
Transmitral e wave velocity, cm/sec	0.83±0.21	0.87±0.19	NS
Transmitral a wave velocity, cm/sec	0.71±0.23	0.78±0.18	<0.001
Transmitral E/A ratio	1.22±0.29	1.16±0.33	NS
IVRT, msec	60.45±14.28	61.80±15.03	NS
IVCT, msec	41.97±11.49	40.96±11.43	NS
Ejection time, msec	280.53±33.03	289.23±39.66	NS
TEI index	0.37±0.07	0.36±0.08	NS
Left ventricular mass, g	156.71±43.96	167.52±46.88	NS
Left ventricular mass index, g/m^2	84.18±22.86	87.56±23.17	NS

Normally distributed data are expressed as Mean±SD and Student's t test is used for comparison
Non-normally distributed data are expressed as Median (minimum-maximum) and Mann-Whitney U test is used for comparison
A- filling due to atrial contraction, AOd- aortic systolic diameter, BP - blood pressure, E- early rapid filling wave, EF- left ventricular ejection fraction, FS- left ventricular fractional shortening, IVCT- isovolumetric contraction time, IVRT- isovolumetric relaxation time, IVSd- interventricular septum diameter (diastolic), IVSs- interventricular septum diameter (systolic), LAd-left atrial systolic diameter, LVIDd- left ventricular internal diameter (diastolic), LVIDs- left ventricular internal diameter (systolic), LVMI- left ventricular mass index, LVPWd- left ventricular posterior wall diameter (diastolic), LVPWs- left ventricular posterior wall diameter (systolic), NS- non-significant

At the same time, we detected that, QT min and QTc min intervals were shorter and QT dispersion was increased in the patients with PHT compared to those with normal BP level. Moreover, because there were no differences between the groups in LVM and relative wall thickness, these findings were independent of left ventricular structure. Although LVM was slightly greater in prehypertensive patients, we considered that LVM differences can not be sufficient to explain the statistically differences in QT interval and dispersion. Some studies have shown that QT interval and dispersion measurements are affected equally by the thickness of all left ventricular regions. There are also some studies which also showed interventricular septal thickness was more important for QT intervals (37). In our study, we also found that IVSDs were greater in PHT group. Several studies also revealed that IVS could predict future systolic hypertension (38). At this point of view, associations of BP, IVS and QT intervals gain more significance. It seems that, pathophysiologic mechanisms of the QT interval changes were not only attributable to changes in left ventricular structure or functions, but also coronary flow and autonomic activity changes can affect the QT interval changes in PHT.

It is well known that, coronary flow is impaired in prehypertensive patients (39) and this condition might cause QT interval prolongation and increased QT dispersion (9, 40).

On the other hand, autonomic activity changes can cause QT interval alterations (41). Several studies have shown that autonomic dysfunction, impaired nocturnal BP reduction, left ventricular hypertrophy (LVH), and oxidative stress can cause QT interval prolongation and increased QT dispersion in hypertension (24-24, 42, 43).

Prakash et al. (28) showed that patients with recent onset hypertension and high normal BP (14) had diminished vagal modulation and higher sympathetic activity during autonomic tests. On the other hand, Fazio et al. (44) reported that an exaggerated systolic BP response to exercise was frequent among prehypertensive subjects and was associated with cardiovascular remodeling and LVH.

Table 3. Differences in heart rate and heart rate variability (HRV) measurements between groups according to BP level

Variables	Normal group (n=110)	Prehypertensive group (n=181)	p
Maximal heart rate, beats/min	129±17	126±18	NS
Minimal heart rate, beats/min	54±7	53±7	NS
Mean heart rate, beats/min	77±8	75±10	NS
Frequency Domain Analysis			
LF/HF 24 Hour	2.05(1.09-2.98)	2.29(1.49-3.63)	0.029
LF/HF Day	3.41(2.03-4.65)	3.82(2.58-5.15)	NS
LF/HF Night	1.92(0.91-2.85)	2.22(1.42-3.26)	0.039
LFn 24 Hour	0.67(0.51-0.74)	0.70(0.60-0.79)	0.016
HFn 24 Hour	0.33(0.26-0.49)	0.30(0.21-0.40)	0.016
Time Domain Analysis			
pNN50, %	9.1(4.3-16.9)	6.8(2.2-13.6)	0.042
rMSSD, ms	36.9(27.7-49.7)	34.8(25.1-48.8)	NS

Normally distributed data are expressed as Mean±SD and Student's t test is used for comparison
Non-normally distributed data are expressed as Median (minimum-maximum) and Mann-Whitney U test is used for comparison
Heart rate values are the data detected per minutes.
LF/HF 24 Hour , LFn 24 Hour and HFn 24 Hour values are the data calculated for 24-hour period, LF/HF Day is the data calculated for day-time (06:00-22:59).
LF/HF Night is the data calculated for night-time (23:00-05:59)
BP - blood pressure, HF - high frequency power, HF - high frequency normalised power, LF- low frequency power, LF- low frequency normalised power, NS - non-significant, pNN50 - percentage of differences between successive RR intervals that are >50 msec, computed over the 24- hour recording, rMSSD - square root of the mean differences between successive RR intervals computed over the 24- hour recording

Table 4. Differences in QT interval measurements between the patient groups according to BP level

	Normal group (n=110)	Prehypertensive group (n=181)	p
Minimum QT, ms	260(240-280)	240(220-270)	<0.001
Maximum QT, ms	440(420-460)	450(420-470)	NS
Minimum QTc, ms	298±35	279±42	<0.001
Maximum QTc, ms	375±26	375±30	NS
QT Dispersion, ms	20(10-35)	30(18-42)	<0.001

Normally distributed data are expressed as Mean±SD and Student's t test is used for comparison
Non-normally distributed data are expressed as Median (minimum-maximum) and Mann-Whitney U test is used for comparison
NS - non-significant, p>0.05

According to our results, there were increased sympathetic and diminished parasympathetic activities in the prehypertensive BP group. In this study, we attributed QT interval changes primarily to increased sympathetic activity. Previous studies have shown that sympathetic activity could be reason for shorter QT, longer QTc intervals and increased dispersion of ventricular repolarization (42, 35, 46). Our results were also concordant to the results of previous studies about the changes in autonomic and left ventricular structure and function in PHT (17, 18, 28, 35, 44-47).

Limitations of the Study

Ambulatory blood pressure monitoring and serum catecholamine levels could not be performed in this study. Determination of simultaneous changes in HRV, ambulatory blood pressure monitoring measurements and serum catecholamine levels can be useful for evaluation of pathophysiologic mechanisms in PHT in further studies. Because of technical limitations, we could not perform tissue Doppler echocardiography for evaluation of left diastolic ventricular functions.

Conclusion

We concluded that patients with PHT have shorter QT min interval and increased QT dispersion when compared to patients with normal BP. Moreover, these differences are independent of left ventricular mass. Autonomic changes can be effective on these differences between the patient groups. Further and large-scale studies will show the importance of the changes in QT intervals and QT dispersion measurements in PHT.

References

1. Castellanos A., Interian Jr A., Myerburg R. The resting electrocardiogram. In: Fuster V, Alexander RW, O'Rourke R, Roberts R, King SB, Nash IS, Prytowsky EN. editors. The Heart, Hurst's. 11th edition. Philadelphia: McGraw-Hill; 2004. p. 299-321.
2. Batchvarov V, Malik M. Measurement and interpretation of QT dispersion. Prog Cardiovasc Dis 2000; 42: 325-44.
3. Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, et al. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report on a policy conference of the European Society of Cardiology. Eur Heart J. 2000; 21: 1216-31.
4. Malik M. QT dispersion: time for an obituary? Eur Heart J. 2000; 21: 955-7.
5. Giunti S, Bruno G, Lillaz E, Gruden G, Lolli V, Chaturvedi N, et al. Incidence and risk factors of prolonged QTc interval in type 1 diabetes: the EURODIAB Prospective Complications Study. Diabetes Care 2007; 30: 2057-63.

6. Bozbaş H, Atar I, Yıldırır A, Özgül A, Uyar M, Özdemir N, et al. Prevalence and predictors of arrhythmia in end stage renal disease patients on hemodialysis. Ren Fail 2007; 29: 331-9.
7. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol 2006; 47: 362-7.
8. Schillaci G, Pirro M, Ronti T, Gemelli F, Pucci G, Innocente S, et al. Prognostic impact of prolonged ventricular repolarization in hypertension. Arch Intern Med 2006; 166: 909-13.
9. Atak R, Turhan H, Sezgin AT, Yetkin O, Senen K, İleri M, et al. Effects of slow coronary artery flow on QT interval duration and dispersion. Ann Noninvasive Electrocardiol 2003; 8: 107-11.
10. Lauer MS, Martino D, Ishwaran H, Blackstone EH. Quantitative measures of electrocardiographic left ventricular mass, conduction, and repolarization, and long-term survival after coronary artery bypass grafting. Circulation 2007; 116: 888-93.
11. Piccirillo G, Magr` D, Matera S, Magnanti M, Torrini A, Pasquazzi E, et al. QT variability strongly predicts sudden cardiac death in asymptomatic subjects with mild or moderate left ventricular systolic dysfunction: a prospective study. Eur Heart J 2007; 28: 1344-50.
12. Kaplan NM. Sytemic hypertension: Mechanisms and Diagnosis. In: Zipes DP, Libby P, Bonow R, Braunwald E, editors. Braunwald' Heart Disease. Textbook of cardiovascular medicine. 7th. edition. Philadelphia: Elsevier Saunders; 2005. p. 959-87.
13. De Ambroggi L, Francia P, De Ambroggi G. Repolarization abnormalities and arrhythmogenesis in hypertrophic myocardium. Anadolu Kardiyol Derg. 2007; 7 Suppl 1: 71-2.
14. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. J Hypertens 2007; 25: 1751-62.
15. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42: 1206-52.
16. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet 2001; 358: 1682-6.
17. Drukteinis JS, Roman MJ, Fabsitz RR, Lee ET, Best LG, Russell M, et al. Cardiac and systemic hemodynamic characteristics of hypertension and prehypertension in adolescents and young adults: the Strong Heart Study. Circulation 2007; 115: 221-7.
18. Erdoğan D, Calışkan M, Yıldırım I, Güllü H, Baycan S, Çiftçi O, et al. Effects of normal blood pressure, prehypertension and hypertension on left ventricular diastolic function and aortic elastic properties. Blood Press 2007; 16: 114-21.
19. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986; 57: 450-8.
20. Otto CM. Echocardiographic evaluation of left and right ventricular systolic function. In: Otto CM editor. Textbook of Clinical Echocardiography. 2nd edition. Philadelphia: W.B. Saunders; 2000. p. 100-129.
21. Porthan K, Virolainen J, Hiltunen TP, Viitasalo M, Väänänen H, Dabek J, et al. Relationship of electrocardiographic repolarization measures to echocardiographic left ventricular mass in men with hypertension. J Hypertens 2007; 25: 1951-7.
22. Pshenichnikov I, Shipilova T, Kaik J, Volozh O, Abina J, Lass J, et al. QT dispersion in relation to left ventricular geometry and hypertension in a population study. Scand Cardiovasc J 2003; 37: 87-90.
23. Shipilova T, Pshenichnikov I, Kaik J, Volozh O, Abina J, Kalev M, et al. Arterial hypertension, left ventricular geometry and QT dispersion in a middle-aged Estonian female population. Blood Press 2003; 12: 12-8.
24. Lim PO, Rana BS, Struthers AD, MacDonald TM. Exercise blood pressure correlates with the maximum heart rate corrected QT interval in hypertension. J Hum Hypertens 2001; 15: 169-72.
25. Miyajima K, Minatoguchi S, Ito Y, Hukunishi M, Matsuno Y, Kakami M, et al. Reduction of QTc dispersion by the angiotensin II receptor blocker valsartan may be related to its anti-oxidative stress effect in patients with essential hypertension. Hypertens Res 2007; 30: 307-13.
26. Peng S, Yu Y, Hao K, Xing H, Li D, Chen C, et al. Heart rate-corrected QT interval duration is significantly associated with blood pressure in Chinese hypertensives. J Electrocardiol 2006; 39: 206-10.
27. Zhu H, Yan W, Ge D, Treiber FA, Harshfield GA, Kapuku G, et al. Cardiovascular characteristics in American youth with prehypertension. Am J Hypertens 2007; 20: 1051-7.
28. Prakash ES, Madanmohan, Sethuraman KR, Narayan SK.Cardiovascular autonomic regulation in subjects with normal blood pressure, high-normal blood pressure and recent-onset hypertension. Clin Exp Pharmacol Physiol 2005; 32: 488-94.
29. Mine T, Shimizu H, Hiromoto K, Furukawa Y, Kanemori T, Nakamura H, et al.Beat-to-beat QT interval variability is primarily affected by the autonomic nervous system. Ann Noninvasive Electrocardiol 2008; 13: 228-33.
30. Fossa AA. The impact of varying autonomic states on the dynamic beat-to-beat QT-RR and QT-TQ interval relationships. Br J Pharmacol 2008; 154: 1508-15.
31. Özer O, Özbala B, Sarı I, Davutoğlu V, Maden E, Baltacı Y, et al. Pacing Clin Electrophysiol. Acute sleep deprivation is associated with increased QT dispersion in healthy young adults 2008; 31: 979-84.
32. Tomiyama H, Doba N, Fu Y, Kushiro T, Hisaki R, Shinozaki Y, et al. Left ventricular geometric patterns and QT dispersion in borderline and mild hypertension: their evolution and regression. Am J Hypertens 1998; 11(3 Pt 1): 286-92.
33. Lohman TG. Anthropometric standardization. In: Lohman TG, Roche AF, Martorell R, editors. Anthropometric Standardization Reference Manual (abridged edition). Illinois, Champagne: Human Kinetics Books; 1988. p.1-71
34. Hunt AC. Accuracy of popular automatic QT interval algorithms assessed by a 'gold standard' and comparison with a Novel method: computer simulation study. BMC Cardiovasc Disord 2005; 5: 29.
35. Murakawa Y, Yamashita T, Ajiki K, Suzuki J, Hayami N, Fukui E, et al. Is the QT interval an indicator of autonomic state? Jpn Heart J 2000; 41: 713-21.
36. No authors listed. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) Circulation 1996; 93: 1043-65.
37. Sakata K, Shimizu M, Ino H, Yamaguchi M, Terai H, Hayashi K, et al. QT dispersion and left ventricular morphology in patients with hypertrophic cardiomyopathy. Heart 2003; 89: 882-6.
38. Grossman C, Grossman A, Koren-Morag N, Azaria B, Goldstein L, Grossman E. Interventricular septum thickness predicts future systolic hypertension in young healthy pilots. Hypertens Res 2008; 31: 15-20.
39. Erdoğan D, Yıldırım I, Çiftçi O, Özer I, Çalışkan M, Güllü H, et al. Effects of normal blood pressure, prehypertension, and hypertension on coronary microvascular function. Circulation 2007; 115: 593-9.
40. Sezgin AT, Barutçu I, Özdemir R, Güllü H, Topal E, Esen AM, et al. Effect of slow coronary flow on electrocardiographic parameters reflecting ventricular heterogeneity. Angiology 2007; 58: 289-94.

41. Neumann J, Ligtenberg G, Klein IH, Boer P, Oey PL, Koomans HA, et al. Sympathetic hyperactivity in hypertensive chronic kidney disease patients is reduced during standard treatment. Hypertension 2007; 49: 506-10.
42. Passino C, Magagna A, Conforti F, Buralli S, Kozáková M, Palombo C, et al. Ventricular repolarization is prolonged in nondipper hypertensive patients: role of left ventricular hypertrophy and autonomic dysfunction. J Hypertens 2003; 21: 445-51.
43. Karavanaki K, Kazianis G, Kakleas K, Konstantopoulos I, Karayianni C. QT interval prolongation in association with impaired circadian variation of blood pressure and heart rate in adolescents with type 1 diabetes. Diabet Med 2007; 24: 1247-53.
44. Fazio S, Palmieri EA, Izzo R, Affuso F, Romano M, Riccio G, et al. An exaggerated systolic blood pressure response to exercise is associated with cardiovascular remodeling in subjects with prehypertension. Ital Heart J 2005; 6: 886-92.
45. Veerasingham SJ, Raizada MK. Brain renin-angiotensin system dysfunction in hypertension: recent advances and perspectives. Br J Pharmacol 2003; 139: 191-202.
46. Anderson KP. Sympathetic nervous system activity and ventricular tachyarrhythmias: recent advances. Ann Noninvasive Electrocardiol 2003; 8: 75-89.
47. Thornton RM, Wyss JM, Oparil S. Impaired reflex response to volume expansion in NaCl-sensitive spontaneously hypertensive rats. Hypertension 1989; 14: 518-23.