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Tp-Te interval prolongs in hypertension independent of the left ventricular geometry

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Ethics Committee Approval
Kırşehir Ahi Evran University Medical Faculty Clinical Research Ethics Committee approved our study design in 2019.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Hypertension (HT) may modulate left ventricular (LV) geometry. Electrocardiographic Tp-Te, QT and QTc interval, and Tp-Te/QTc ratio are among the parameters of ventricular repolarization (VR) that may predict ventricular arrhytmogenic potential and possess prognostic significance. It is well known that left ventricular hypertrophy is associated with increase in the parameters of VR; however, little is known about the association of these parameters with other forms of LV geometry in HT. Our aim was to assess this association.

Methods: A total of 162 newly diagnosed essential HT patients were enrolled and divided into those with concentric LV remodeling (n=79) and those with normal LV geometry (n=83). Healthy normotensive subjects (n=76) comprised the control group. Data were gathered retrospectively from electrocardiographic, echocardiographic, and demographic records.

Results: QT interval, P-wave duration, and QRS duration were similar among the 3 groups ($P>0.05$). Tp-Te, QTc and Tp-Te/QTc were greater in the HT group compared with the controls ($P<0.001$). In a pair-wise comparison between 2 HT subgroups, these parameters were similar ($P>0.05$). There was no correlation between Tp-Te interval, LV mass and LV mass index among the study population.

Conclusion: Tp-Te may be useful in prognostic stratification of HT. Regardless of the LV geometry, HT patients have prolonged Tp-Te and QTc intervals, and increased Tp-Te/QTc ratio compared to the healthy subjects. Our findings may suggest possible utilization of Tp-Te as HT-related end-organ damage in the future.

Keywords: Tp-Te interval, Hypertension, Ventricular repolarization, Left ventricle geometry

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Introduction

Exposure to hypertension (HT) gives rise to an increase in the left ventricular mass in the long run, which in turn is linked to an increase in the incidence of cardiovascular diseases (CV), and CV-related and all-cause mortality [1]. HT patients with concentric left ventricular (LV) remodeling possess a poorer prognosis compared with those with normal LV geometry, and hence concentric remodeling is an independent predictor for future CV events [2, 3].

Electrocardiographic (ECG) time interval from T-wave peak to T-wave end, also referred to as Tp-Te interval, was proposed as a novel index of transmural dispersion of ventricular repolarization (VR) in some studies [4, 5], or an index of global VR in others [6]. Tp-Te/QT and Tp-Te/QTc ratios are also novel ECG parameters indicating ventricular arrhythmogenic potential.

Previous data has reached a consensus regarding prolongation in Tp-Te interval and Tp-e/QTc ratio in the presence of left ventricular hypertrophy (LVH) in various clinical settings including HT [7-10]. However, there is confounding data about the status of the parameters of VR in HT patients with concentric remodeling compared with HT patients with normal LV geometry. To the best of our knowledge, there is no study comparing the parameters of VR between HT patients with normal LV geometry and HT patients with concentric remodeling with healthy normotensive subjects with normal LV geometry. Therefore, we aimed to assess whether deterioration in some novel parameters of VR occurs in sub-clinic settings before the emergence of gross modification in LV morphology in newly diagnosed HT patients.

Materials and methods

Patient recruitment

Our study has a retrospective and cross-sectional nature, where hospital records of a total of 162 consecutive patients with newly diagnosed and never treated essential HT were assessed between June 2018 and February 2019. The patients were subdivided based on their echocardiographic LV geometry into two subgroups as the HT patients with normal LV geometry [n=83, mean age 46.9 (9.2) years] and HT patients with concentric LV remodeling [n=79 mean age 49.2 (7.6) years]. Furthermore, 76 healthy normotensive subjects [mean age 47.4 (8.8)] admitted with nonspecific symptoms to our cardiology outpatient polyclinics in which echocardiography revealed normal LV geometry composed the control group. We did not include the HT patients with LVH in our study, since we primarily sought to reveal the possible changes in ECG parameters of VR in subjects without dramatic modifications in LV morphology. Demographic, ECG and echocardiographic data were collected on the day of outpatient clinic admission. Exclusion criteria are defined as follows: Cardiovascular atherosclerotic diseases, diabetes mellitus, smoking, severe kidney failure attributable to secondary HT, physical and clinical features, endocrine disorders, arrhythmia, inflammatory diseases, LV systolic dysfunction, cerebrovascular diseases, pulmonary disease. The body-mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. All enrolled subjects gave a written informed consent. This study follows the ethical standards defined by the Helsinki Declaration and the Kırşehir Ahi Evran University Medical Faculty Clinical Research Ethics Committee approved our study protocol in 2019.

Echocardiography

All study participants were examined with a Vivid S3 Echocardiography device (General Electric, Vingmed Ultrasound AS, Horten, Norway) by an experienced cardiologist blinded to the study. Dimensions of left ventricle, wall thicknesses, and left atrial (LA) diameters were measured from parasternal long-axis images. LA area was measured through planimetry from the apical four-chamber view. Relative wall thickness (RWT) was calculated with the formula " 2 x posterior LV wall thickness / left ventricular end diastolic diameter " [11]. The modified Simpson's rule was used to determine the left ventricular ejection fraction (LVEF). Transmitral inflow velocities (E and A velocities), and E-deceleration time (EDT) were measured as the according to the relevant guideline [12]. LVMI was calculated using the Devereux's formula [11,13]. Normal LV geometry was defined as RWT ≤0.42 accompanied by LVMI ≤95 gr/m^2 for females and ≤115 gr/m^2 for males. Concentric LV remodeling was defined as the co-existence of RWT> 0.42, and LVMI ≤95 gr/m^2 for females and ≤115 gr/m^2 for males. LVH was defined as LVMI >95 gr/m^2 for females and >115 gr/m^2 for males according to the relevant literature [11]. Accordingly, HT patients compatible with the term "LVH" were not included in the study.

Ambulatory blood pressure monitoring

The participants with office blood pressure (BP) ≥ 140/90 mmHg underwent a 24-hour ABPM (Bravo HR ABP Sun Tech Medical Inc., Morrisville, NC, USA). After selection of the appropriate size, the cuff of the device was placed on the non-dominant arm and BP readings were recorded for 24 hours. On the other hand, 24-hour AMPM was implemented in all control subjects with office BP <140/90 mmHg to unearth any probable white-coat HT. During the daytime (6:00 am -10:00 pm), the measurement of the BP was performed every 15 minutes and during nighttime (10:00 pm -06:00 am), every 30 minutes. Each participant was asked to continue his/her daily routines and stand still and quiet during each measurement. Participants were excluded from the study if the device did not successfully record ≥80% of their BP readings. For each participant, 24-hour mean systolic BP, 24-hour mean diastolic BP, daytime mean systolic BP, daytime mean diastolic BP, nighttime mean systolic BP and nighttime mean diastolic BP were calculated. The diagnosis of hypertension based on ABPM was made in any patient if 24-hour mean systolic BP >130 mmHg and/or diastolic BP >80 mmHg, daytime mean systolic BP >135 mmHg and/or diastolic BP >85 mmHg or nighttime systolic BP >120 mmHg and/or diastolic BP >70 mmHg [14].

Electrocardiography

A 12-lead ECG strip (Nihon Kohden, Tokyo, Japan) recorded at 50 mm/s paper speed in every participant, which was then scanned and analyzed under x300% magnification in a personal computer. We preferred the longest measurement of Tp-Te interval in all precordial leads, as the precordial leads were much more specific for the measurement of Tp-Te in reflecting the best the transmural dispersion of repolarization [9,15,16]. QTc intervals were calculated by Bazett's equation:

QTc=QT/√(RR). Tp-Te/QTc ratios were calculated subsequently. Tangent and tail methods [17,18] are two common methods used to measure the Tp-Te interval. The tangent method was utilized in the current study that indicates the time interval between the peak of T and the point where the tangent of the steepest down-slope of the T wave intersects the isoelectric line [17]. RR interval, QT interval and P-wave duration were measured in Lead 2. Average of three consecutive complexes was calculated to obtain the ultimate value for every relevant parameter. All ECG parameters were assessed by two experienced cardiologists blinded to design of the study. Inter- and intra-observer coefficient of variation were 3.5% and 2.7%, respectively.

Statistical analysis

Statistical analyses were performed with PASW Statistics for Windows, Version 18.0 (Chicago: SPSS Inc). Using the Kolmogorov-Smirnov test, it was evaluated whether the parameters were normally distributed. The groups were compared with chi-square test for categorical variables and One-Way Variance Analysis (ANOVA) test for continuous variables. If the p value was statistically significant in one-way ANOVA test, post-hoc Tukey's tests were used to compare the differences between the groups. Pearson rank tests were used to analyze the relationship between the Tp-e interval and other variables. Multivariate and univariate logistic regression analysis was used to determine the parameters associated with the presence of HT. *P*-value <0.05 was considered statistically significant.

Results

Demographics and clinical features of the study population are provided in Table 1. There was no difference among the 3 groups with regards to age, gender, weight, height, and BMI ($P>0.05$). Results of the blood chemistry and lipid panel were also similar between the groups. As expected, office systolic and diastolic BPs were significantly higher in overall HT group compared with the controls ($P<0.001$). Office BP and ABPM recordings were normal in the control group, thus ruling out a probable masked HT in this group. All ABPM recordings were significantly greater in the HT group; however, pair-wise comparison of these recordings between HT patients with normal LV geometry and HT patients with concentric LV remodeling did not reveal any difference.

Echocardiographic findings were also presented in Table 1. As evident in the table, LV mass, LVMI and RWT were significantly greater in the HT group with concentric LV remodeling [169 (23.2) g, 87.4 (11.7) g/m2, and 0.45 (0.03), respectively] compared with the HT group with normal LV geometry [149.2 (26.7) g, 78.8 (13.6) g/m2, and 0.40 (0.05), respectively] and the controls [145.6 (33.3) g, 76.4 (13.1) g/m2, and 0.39 (0.03), respectively] ($P<0.001$ for all). In the pair-wise comparison, however, these parameters were similar between the HT group with normal LV geometry and the controls ($P>0.05$). LVEF, transmitral E/A velocity ratio, and LA area were similar between the three groups.

ECG findings of the study population were presented in Table 2. There was no significant difference among the groups with regards to QT interval, P-wave duration, and QRS duration ($P>0.05$). On the other hand, Tp-Te interval, QTc interval and Tp-Te/QTc ratio were significantly greater in the HT group, compared with the controls ($P<0.001$). In a pair-wise comparison between 2 HT subgroups, however, these parameters were similar ($P>0.05$) (Figure 1).

Table 1: General characteristics of the study population

	Hypertensive Patients			
	Normal LV Geometry (n= 76)	Normal LV Geometry (n=83)	Concentric LV Remodeling (n=79)	ANOVA *P*-value
Clinical characteristics				
Age, y	47.4 (8.8)	46.9 (9.2)	49.2 (7.6)	0.137
Gender, female, n (%)	37 (48.6%)	38 (45.7%)	34 (43%)	0.582
Height, cm	168.4 (9,8)	166.5 (8.5)	166.6 (8.7)	0.198
Weight, kg	76.8 (14.1)	78.6 (13.8)	82.5 (13.4)	0.310
BMI, kg/m²	27.1 (4.8)	28.2 (4.5)	28.7 (4.6)	0.094
TC, mg/dL	189.1 (39.7)	189.0 (34.6)	194.8 (27.3)	0.233
HDL-C, mg/dL	49.0 (12.3)	47.3 (13.5)	48.3 (11.8)	0.687
LDL-C, mg/dL	112.9 (36.5)	109.3 (29.4)	115.1 (26.5)	0.508
TG, mg/dL	159.2 (85.69	181.3 (59.5)	176.0 (119.49	0.136
Fasting glucose, mg/dL	93.1 (14.2)	96.7 (10.4)	95.1 (9.3)	0.212
BUN, mg/dL	32.7 (10.6)	31.4 (10.4)	32.9 (11.8)	0.696
Serum creatinine, mg/dL	0.88 (0.079)	0.86 (0.08)	0.85 (0.04)	0.385
BP profile				
Clinic systolic BP, mm Hg	124.3 (12.1)[a]	148.4 (15.3) [b]	151.4 (14.2) [b]	<0.001
Clinic diastolic BP, mm Hg	81.3 (9.8)[a]	95.4 (10.1) [b]	96.3 (13.4) [b]	<0.001
Heart rate, beats per min	75.5(9.4)	74.8 (8.4)	76.6 (7.6)	0.436
24-h systolic BP, mm Hg	118 (15.7)[a]	142 (9.7) [b]	145 (10.3) [b]	<0.001
24-h diastolic BP, mm Hg	72.7 (7.7)[a]	89.7 (6.6) [b]	90.4 (4.3) [b]	<0.001
Daytime systolic BP, mm Hg	122.2 (10.4)[a]	146.4 (7.8) [b]	148.6 (9.9) [b]	<0.001
Daytime diastolic BP, mm Hg	74.5 (6.4)[a]	93.3 (5.7) [b]	93.1 (7.1) [b]	<0.001
Nighttime systolic BP, mm Hg	116.7 (13.1) [a]	140.8 (12.48) [b]	142.4 (11.2) [b]	<0.001
Nighttime diastolic BP, mm Hg	69.8 (5.8) [a]	87.6 (7.2) [b]	89,4 (7.6) [b]	<0.001
Echocardiographic Parameters				
LV mass, g	145.6 (33.3) [b]	149.2 (26.7) [b]	169 (23.2) [a]	<0.001
LV mass/BSA, g/m²	76.4 (13.1) [b]	78.8 (13.6) [b]	87.4 (11.7) [a]	<0.001
LV mass/height, g/cm	86.2 (17.6) [b]	89.6 (15.9) [b]	101.3 (12.7) [a]	<0.001
RWT	0.39 (0.03) [b]	0.40 (0.05) [b]	0.45 (0.03) [a]	<0.001
LVEF, %	63.1 (2,8)	62.6 (3.1)	63.2 (2.9)	0.234
Transmitral E/A velocity ratio	1.2 (0.28)	1.1 (0.389	1.0 (0.31)	0.065
Left atrium area, cm ²	14.9 (1.8)	15.2 (2.39	15.7 (2.29	0.245

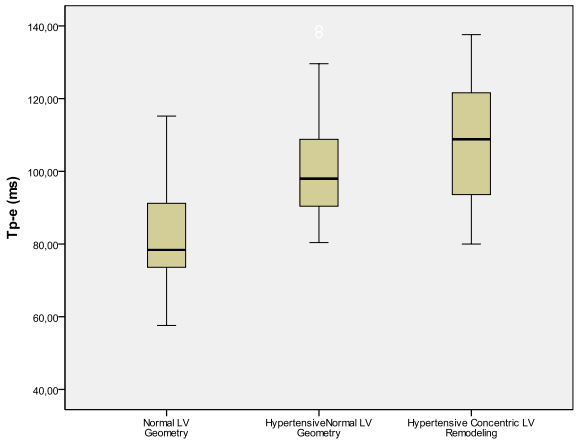
Data are given as number (percentage) for categorical variables and mean (standard deviation) for continuous variables. There is no statistically significant difference between the pairs marked with the same letter within the same line ($P>0.05$). ANOVA: analysis of variance, BMI: body mass index, BP: blood pressure, BSA: body surface area, BUN: blood urea nitrogen, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, LV: left ventricular, LVEF: left ventricular ejection fraction, RWT: Relative wall thickness, TC: total cholesterol, TG: triglycerides

Table 2: Electrocardiographic characteristics of study patients

	Hypertensive Patients			
	Normal LV Geometry (n=76)	Normal LV Geometry (n=83)	Concentric LV Remodeling (n=79)	ANOVA *P*-value
Tp-e	82.3 (12.79) [a]	102.0 (13.9) [b]	105.7 (17.0) [b]	<0.001
Tp-e/QTc ratios	0.23 (0.03) [a]	0.27 (0.049) [b]	0.28 (0.05) [b]	<0.001
Tp-e /QRS	1.03 (0.20) [a]	1.26 (0.19) [b]	1.28 (0.24) [b]	<0.001
QTc	346.1 (23.0) [a]	362.8 (26.5) [b]	361.8 (25.6) [b]	<0.001
QT	339.2 (23.7)	341.0 (25.7)	344.23 (15.6)	0.198
P wave	78.1 (13.1)	77.9 (14.0)	75.4 (16.5)	0.612
QRS	81.4 (11.7)	81.3 (12.4)	82.5 (9.5)	0.518
R wave peak	27.5 (11.0)	28.7 (7.3)	27.2 (7.1)	0.387

Data are given as mean (standard deviation) for continuous variables. There is no statistically significant difference between the pairs marked with the same letter within the same line ($P>0.05$). ANOVA: analysis of variance, LV: left ventricle

Figure 1: Comparison of Tp-Te interval among the three groups



There was no correlation between Tp-Te interval, LV mass and LVMI within the study population ($P>0.05$) (Table 3).

Table 3: Correlation of Tp-Te interval with LV mass and LVMI in study subjects

		LVMI	LVM
Hypertensive subjects	r	0.151	0.143
(n=162)	*P*-value	0.055	0.069
Normotensive subjects	r	0.110	0.115
(n=76)	*P*-value	0.338	0.312
All subjects	r	0.126	0.120
(n=238)	*P*-value	0.052	0.062

LVM: left ventricular mass, LVMI: left ventricular mass index

Discussion

The main findings of our study are that Tp-Te interval, QTc interval and Tp-Te/QTc ratio were significantly greater in overall HT patients compared with the normotensive controls. However, these ECG parameters were similar between HT patients with normal LV geometry and HT patients with concentric LV remodeling. Accordingly, our results indicate that deterioration in the ECG parameters of VR commences prior to the macroscopic changes take place in the LV geometry in patients with HT. In this respect, our findings are novel for demonstrating a worsening in the VR in HT patients with normal LV geometry compared with the healthy normotensive subjects with normal LV geometry.

A robust relationship is already known between prolonged QT and QTc intervals and ventricular arrhythmias [19-21]. Tp-Te interval has been a relatively new index of ventricular repolarization. Furthermore, prolonged Tp-Te interval is associated with ventricular arrhythmias and cardiac mortality [15, 22-24]. More recently, Tp-Te/QTc was suggested as a novel marker of VR and demonstrated to be a more accurate predictor of ventricular arrhythmias [25]. Furthermore, it is more accurate in terms of indicating the status of VR compared with Tp-Te or QT intervals [25]. Tp-Te interval is shown to be associated with increased all-cause and CV mortalities independent of HT in the general population [26]. Aside from its prognostic role, little is known about diagnostic role of Tp-Te interval in different clinical settings.

LVH is well known to associate with Tp-Te interval and Tp-e/QTc ratio in clinical setting including HT. However, the same does not hold true between these ECG parameters and concentric LV remodeling. Porthan et al. [7] reported a prolongation in Tp-Te interval, and a positive correlation between Tp-Te interval and LVMI in HT patients with LVH. In contrast, Saba et al. [8] subdivided a total of three hundred HT patients into three subgroups as those with normal LV geometry, those with concentric remodeling and those with LVH, and demonstrated a significantly prolonged Tp-Te interval in HT patients with LVH, but a significantly shorter Tp-Te interval in HT patients with concentric remodeling, compared with HT patients with normal LV geometry. In our study, however, we found no significant correlation between Tp-Te interval either with LV mass or LVMI, which propels us to consider that that it is the HT itself which incites prolongation in Tp-Te interval rather than a less dramatic LV remodeling other than LVH. In another small-sized study (n=50), Ferrucci et al. [27] detected a significant and positive correlation between Tp-Te interval and LV mass in newly diagnosed HT patients, compared with healthy subjects. Although HT patients in their study did not have LVH, they did not stratify the HT patients as those with normal geometry and the others with concentric remodeling to provide a pair-wise comparison among HT subgroups and the controls as in our study. Additionally, they demonstrated an association between Tp-Te and presence of HT. In this regard, our findings further extend their findings by stratifying the HT patients into two geometric subgroups and comparing Tp-Te between them.

Although exposure to increased BP for a sufficiently long time was reported to lead to an increase in LV mass [28], there is a weak association between the sole exposure to high BP and increase in LV mass [29]. Rather, increase in LV mass and progression of LVH are multifactorial, including a congeries of neurohormonal [30], genetic [31, 32] and renin-angiotensin system [33] contributors. Similarly, changes in the LV geometry observed in HT patients are also multifactorial and affected by chronic volume and pressure overload, race, gender, neurohormonal environment, genetics, extracellular matrix modifications [34]. Hence, to expect an absolute increase in LV mass and a change in LV geometry in all patients with HT is not reasonable due to this multifactorial nature. In a previous study, on the other hand, increase in the LV mass and wall thicknesses in normotensive subjects was proposed to associate with the development of a new HT [35]. These results, when combined, give rise to a chicken and egg situation as to which one, namely HT or change in LV geometry, comes first. For this reason, it is quite challenging to establish a robust relationship between the modification in LV geometry and BP. Lawler et al. [36] demonstrated that subclinical abnormalities at cellular level such as cardiomyocyte hypertrophy and fibrosis occurred long before the gross morphological changes in LV geometry in HT patients. Our finding that Tp-Te interval and Tp-Te/QTc ratio increased in overall HT patients regardless of the status of LV geometry compared with the controls propels us to consider that exposure to higher BP disrupts VR through subclinical modifications at cellular level.

Bombelli et al. [26] followed up both hypertensive and normotensive subjects for 16 years and demonstrated a significant association between prolonged Tp-Te interval and increased CV and all-cause mortality both in the general and hypertensive population. However, Tp-Te interval failed to predict the emergence of a future HT and LVH in normotensive patients at baseline. In this regard, prolongation of Tp-Te interval even in HT patients with normal LV geometry as compared with the healthy subjects with normal LV geometry in our study is quite likely to be associated with increased long-term mortality.

In the future, defining a probable cut-off value for such non-invasive and simple ECG parameters as Tp-Te interval and Tp-Te/QTc ratio to better predict mortality and major adverse CV events would prove especially useful in the risk stratification of newly diagnosed HT patients and even in the commence of appropriate therapy at an earlier time. More specifically, our study may prove useful in the differential diagnosis of a masked HT especially in patients without an elevated office BP, but with relevant symptomology to HT. Moreover, current guidelines offer electrocardiographic LVH as a surrogate for HT-related organ damage which necessitates prompt initiation, in addition to lifestyle modification or drug treatment even in the presence of grade-1 HT or high-normal BP [37]. Based on our findings, we conjecture that Tp-Te and Tp-Te/QTc could be used as another surrogate marker of HT-related organ damage to dictate early start of medical therapy in speculated settings such as grade 1

HT or high-normal BP when other conversional CV risks or end-organ damages are absent. However, future multicenter trials with large patient cohorts are warranted for this purpose to define likely cut-off values for these VR indices to stand conjointly for another surrogate marker of HT-related end-organ damage.

Limitations

Our study should be assessed together with a number of limitations. We conducted this study on a relatively small-scale population; and it is retrospective and cross-sectional in nature. Additionally, we did not follow patients for future adverse CV events and LV hypertrophy that may develop in both HT groups. Also, we did not include Tp-Te and P-wave dispersions in our study.

Conclusion

This study results show that regardless of the LV geometry, patients with HT are characterized with prolonged Tp-Te interval and increased Tp-Te/QTc ratio, as compared with the healthy normotensive subjects. In this regard, our findings may point out that increase in these parameters may reflect subclinical abnormalities at cellular and extracellular matrix levels long before the emergence of gross morphological changes in LV geometry, which may suggest that deterioration in VR parameters might be used as HT-related end-organ damage if can be warranted by future large-scale prospective studies.

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