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Original Article

Novel ventricular repolarization indexes in prehypertensive and newly diagnosed hypertensive patients: Tp-e interval and Tp-e/QT ratio

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Abstract: Objectives: Tp-e interval and Tp-e/QT ratio are associated with malignant ventricular arrhythmias and cardiovascular mortality. We aimed to evaluate ventricular repolarization indexes in patients with prehypertension and new diagnosed hypertension. Materials: Our study population consisted of 95 subjects: 28 healthy volunteers with normotensive, 35 subjects with prehypertension, and 32 patients with newly diagnosed hypertension (HT). Tp-e interval and Tp-e/QT ratio were measured from a 12-lead electrocardiogram, and the Tp-e interval corrected for heart rate. These parameters were compared among groups. Results: Age, gender distribution, heart rate and lipit levels were similar, between of the study groups ($P > 0.05$). Corrected QT dispersion, corrected Tp-e interval and Tp-e/QT ratio were significantly increased in patients with HT when compared with normotensive and prehypertension subjects ($P < 0.001$, $P = 0.001$, $P = 0.001$ respectively). Conclusion: Tp-e interval and Tp-e/QT ratio were increased in HT patients with respect to normotensive subjects. These parameters were similar normotensive and prehypertensive subjects. Our results may contribute to pathophysiological mechanisms of increased prevalence of ventricular arrhythmias and cardiovascular mortality risk by indicating increased ventricular repolarization heterogeneity in hypertension patients.

Keywords: Hypertension, prehypertension, Tp-e interval, Tp-e/QT ratio

Introduction

Hypertension (HT) is one of the most common cardiovascular disorders encountered in daily practice. Prehypertension also causes unfavorable subclinical conditions in the cardiovascular system. If whith prehypertension persons do not completely therapeutic lifestyle changes, they are at increased risk to progress to hypertension [1].

Myocardial repolarization has been evaluated by various methods, including QT dispersion (QTd), corrected QT dispersion, and transmural dispersion of repolarization [2]. Recent studies indicated that the Tp-e interval, which is the interval between the peak and the end of the T wave on an electrocardiogram, can be used as an index of the total dispersion of repolarization [3-5]. Also, increased Tp-e interval might be a useful index to predict ventricular tachyarrhythmias and cardiovascular mortality [6-8]. However, the Tp-e interval is affected by variations of body weight and heart rate [9]. Recently a new index, the Tp-e/QT ratio, has been suggested to be a more accurate measure for the dispersion of ventricular repolarization compared to QTd, corrected QTd, and Tp-e intervals, and to be independent of alterations in heart rate [9, 10].

Our aimed to evaluate the ventricular repolarization indexes by using Tp-e interval and Tp-e/QT ratio in the prehypertensive and HT patients.

Materıal and methods

Study population

Normotensive, prehypertensive and HT patients who refer to our cardiology outpatient clinic

between September 2012 and April 2013 are enrolled in the study. Study group was consisted of 95 patients according to including and excluding criteria: NT healthy volunteers (n = 28, group I), prehypertensive patients (n = 35, group II) and newly diagnosed HT patients (n = 32, group III). Patients with coronary heart disease, heart failure, mild to moderate valvular heart disease, cardiomyopathy, congenital heart diseases, diabetes mellitus, tiroid diseases, chronic obstructive pulmonary disease, chronic systemic inflammatory disease, electrolyte disturbances, atrial fibrillation, known cardiac arrhythmias, bundle branch block on surface electrocardiography, prominent U wave and electrocardiography with poor quality and parazites are excluded in this study. None of the patients were under treatment for hypertension. All the cases in prehypertensive and HT groups were newly diagnosed and no history of taking antihypertensive drug before at any time. The age, gender, height, and weight of all patients were recorded. Detailed physical examination including 12-leads ECG, medical histories and smoking habits of all patients were recorded. All patients underwent transthoracic echocardiographic examination. Blood samples were taken to examine complete blood count, biochemical parameters and markers of inflammation. Approval of local ethics committee was obtained. All patients involved in this study provided written informed consent before the study.

Blood pressure measurement

Systolic blood pressure (SBP) and dyastolic blood pressure (DBP) were measured according to the Eighth Joint National Committee 8 (JNC 8) guideline [11] using a mercury column sphygmomanometer and a cuff suitable to the subject's arm circumference. Blood pressure was measured on three different days, by trained physicians after 15 minutes of rest in the sitting position, and the average of the measurements was recorded.

According to JNC-8, prehypertension was defined as SBP 120 to 139 mmHg and/or DBP 80 to 89 mmHg. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mm. Subjects were considered normotensive if SBP < 120 mmHg and DBP < 80 mmHg, and constituted the control group.

Electrocrdiography

The 12-lead ECG recording was performed after 10 minute of rest at supine position at 50 mm/s speed and 10 mm/mV amplitude (Nihon Kohden, Tokyo, Japan). ECG measurements of QT and Tp-e interval were performed by experienced two cardiologists by using calipers and magnifying glass. We measured the QT interval from the beginning of the QRS complex to the end of the T wave. The QT maximum (QTmax) and QT minimum (QTmin) were calculated in all leads of a 12-lead ECG. QTd was defined as the QTmax-QTmin interval and corrected QTd (cQTd) was calculated according to Bazett's Formula adjusted according to heart rate [12]. The measurements of Tp-e interval were performed from precordial V6 lead and were corrected according to heart rate. The Tp-e/QT ratios were subsequently calculated. The intra- and interobserver variability was 4.1% and 4.8% respectively.

Echocardiography

Transthoracic echocardiography (TTE) was performed in all patients at left lateral decubitus position. We used a Vivid 7 Dimension echocardiography device, with a 2.5-MHz probe (Vingmed Ultrasound, GE, Horten, Norway). Images at the parasternal longitudinal axis, short axis, apical four chambers and two chambers were obtained and evaluated by M-mode, 2-dimension (D), continuous wave Doppler, pulsed wave Doppler methods based on American Echocardiography Association criteria [13]. Left ventricle ejection fraction was assessed by Simpson's method using 2D images. Left ventricular mass was calculated using the Devereux equation and indexed to body surface area to obtain the LV mass index (LVMI). Values were measured on three separate beats and then the average was calculated for all parameters. We simultaneously recorded the peak velocity of early transmitral flow (E, cm/s), late transmitral flow (A, cm/s) and E/A ratio by using conventional Doppler images (CDI). Transmitral velocities (E, A) and mitral annular velocities (Em, Am) were measured, permitting calculation of the ratio of E to Em pulsed-wave tissue Doppler images (TDI) was performed by activating the TDI function on the same echocardiography machine. Sample volume placed at lateral mitral annulus, septal mitral annulus and

Table 1. Clinical characteristics, laboratory and echocardiographic findings of the groups

	Group I Normotension (n = 28)	Group II Prehypertension (n = 35)	Group III Hypertension (n = 32)	*P* value
Age (years)	49±11	44±12	48±10	0.41
Males, n (%)	7 (25)	13 (37)	13 (40)	0.46
Females, n %)	21 (75)	22 (63)	19 (60)	0.65
BMI (kg/m^2)	28.6±3.2	29.1±4.9	29.2±4.1	0.81
BSA (m^2)	1.89±0.16	1.93±0.18	1.92±0.17	0.50
Systolic BP (mmHg)	115.9±7.8	134.6±16.5	160.8±19.3	< 0.001
Diastolic BP (mmHg)	71.2±6.9	81.4±9.1	94.2±8.2	< 0.001
Heart rate (beats/min)	75.3±11.1	78.9±12.4	79.5±12.3	0.36
Aort dimension (mm)	27.8±2.6	27.8±3.0	29.0±2.8	0.20
LV EDD (mm)	46.3±3.4	47.1±3.7	48.2±3.0	0.12
LV EF (%)	66.2±2.8	66.5±2.8	65.9±2.6	0.57
LA dimension (mm)	33.9±3.5	33.8±3.4	36.5±3.1	0.002
LV mass index (g/m^2)	94.5±18.3	108.7±19.6	125.5±21.7	< 0.001
sPAP (mmHg)	24.9±2.7	25.7±1.2	24.7±2.9	0.37
Fasting glucose (mg/dl)	90.9±6.4	93.4±6.8	94.5±8.3	0.15
Total cholesterol (mg/dl)	187.7±.41.9	193.0±31.7	199.3±43.2	0.51
Triglyceride (mg/dl)	159.1±55.7	159.1±75.3	167.8±89.8	0.67
HDL-cholesterol (mg/dl)	49.4±9.1	46.9±10.4	48.5±14.3	0.69
LDL-cholesterol(mg/dl)	98.5±38.2	113.2±24.8	115.2±34.8	0.11
Hemoglobin (g/dl)	13.8±1.0	13.8±1.6	14.1±1.5	0.53
Creatinin (mg/dl)	0.76±0.12	0.77±0.19	0.79±0.19	0.75

BMI = body mass index; BSA = body surface area; BP = blood pressure; EF = ejection fraction; LV = Left ventricular; LVEDD = LV end-diastolic dimension; LVESD = Left ventricul end-systolic dimension. Data are presented as mean ± SD, median [interquartile range], or n (%). Statistically significant *P* values shown in bold.

lateral tricuspid annulus in the apical 4-chamber view, during end-expiratory apnea. Systolic myocardial velocity (Sm), early and late myocardial velocities (Em, Am) were measured at these three annular levels and mean Em/Ea and E/Em ratios calculated. Isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT) and ejection time (ET) were measured by TDI. Myocardial performance index (MPI) was calculated by the formula (ICT + IRT)/ET. The intra- and interobserver variability was 3.1% and 3.8% respectively.

Laboratory analyses

Venous blood samples were collected after 10 hours starvation for analysis of biochemical, complete blood count and inflammatory parameters. On biochemical analysis, fasting blood glucose, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and creatinine levels were measured (Siemens Advia 1800 Chemistry System).

Statistical analysis

All results were analyzed using SPSS® for Windows (Inc., version 15.0, Chicago, IL, USA). While the continuous data were expressed as "mean ± SD" (standard deviation), the categorical data were expressed as percentage values. The normal distribution of the data was tested using the Kolmogorov-Smirnov test. All variables were in normal distribution. Comparison of categorical variables was carried out by the chi-square test and of continuous variables with variation analysis (ANOVA). Post-Hoc Scheffe was used for the difference between groups. Pearson's correlation method was used to determine the correlations of different parameters among themselves. A p value of < 0.05 was accepted as statistically significant.

Results

The baseline clinical characteristics, laboratory, and echocardiographic findings of the three

Table 2. Comparison of conventional and tissue Doppler variables between patients and controls

	Group I Normotension (n = 28)	Group II Prehypertension (n = 35)	Group III Hypertension (n = 32)	*P* value
Conventional Doppler parameters				
Mitral E (cm/s)	85.8±21.6	76.4±19.9	72.6±17.3	0.03
Mitral A (cm/s)	68.4±18.1	78.4±18.9	85.9±15.4	0.001
Mitral E/A	1.31±0.41	1.02±0.32	0.86±0.19	< 0.001
Mitral DT (ms)	182.6±36.9	189.0±38.8	181.7±30.0	0.65
Trisuspid E (cm/s)	63.0±14.0	56.8±10.3	55.8±12.6	0.05
Tricuspid A (cm/s)	50.3±13.7	50.9±9.3	53.2±9.8	0.57
Tricuspid E/A	1.30±0.37	1.14±0.25	1.07±0.30	0.006
Tricuspid DT (cm/s)	186.1±41.5	190.1±34.6	201.6±37.5	0.25
Tissue Doppler parameters				
LV lateral annulus				
S_m (cm/s)	10.9±3.5	10.5±3.5	10.6±1.6	0.88
A_m (cm/s)	10.8±3.0	11.7±3.1	11.8±2.6	0.37
E_m (cm/s)	16.1±5.0	13.8±4.5	10.1±2.6	< 0.001
E_m/A_m	1.65±0.80	1.27±0.56	0.91±0.35	< 0.001
E/E_m	5.8±2.3	6.0±2.3	7.5±2.1	0.005
MPI	0.50±0.12	0.52±0.08	0.53±0.09	0.76
LV septal annulus				
S_m (cm/s)	7.9±1.2	8.1±2.2	7.5±1.4	0.30
A_m (cm/s)	9.0±2.4	10.5±2.3	10.2±2.1	0.03
E_m (cm/s)	10.8±3.0	9.7±2.5	7.7±2.6	< 0.001
E_m/A_m	1.30±0.51	0.98±0.38	0.79±0.35	< 0.001
E/E_m	8.4±2.6	8.2±2.2	10.0±2.7	0.007
MPI	0.50±0.09	0.53±0.08	0.54±0.08	0.08
RV lateral annulus				
S_m (cm/s)	14.4±3.6	14.7±3.3	14.9±4.0	0.89
A_m (cm/s)	15.2±4.9	18.3±5.7	17.6±4.1	0.05
E_m (cm/s)	13.6±3.3	12.1±3.0	12.1±2.7	0.09
E_m/A_m	0.98±0.39	0.72±0.27	0.72±0.25	0.001
E/E_m	4.9±1.7	5.0±1.6	4.8±1.4	0.90
MPI	0.55±0.13	0.57±0.10	0.56±0.09	0.78

A_m = late myocardial diastolic velocity; DT = mitral E-wave deceleration time; E_m = early myocardial diastolic velocity; IVRT = isovolumetric relaxation time; LV = left ventricular; MPI = myocardial performance index; NS = not significant; RV = right ventricul; S_m = systolic myocardial velocity.

groups were showed in **Table 1**. The mean age was 49±11 years in normotensive group, 44± 12 years in prehypertensive group, and 48±10 years in HT group with no significant difference between the groups. Males comprised 25%, 37%, and 40% in groups of normotensive, prehypertensive and HT respectively. Between three groups there was no significant difference in fasting blood glucose, creatinine, total cholesterol, TG, HDL and LDL cholesterol, hemoglobin, levels were similar in three groups (P > 0.05). Among echocardiographic parameters, the left atrium size of HT group was significantly higher than that of normotensive group and prehypertensive group. Also, LVMI of HT group was greater than those of both normotensive group and prehypertensive group, and LVMI of prehypertensive group was greater than that of normotensive group (P < 0.05).

Ecocardiographic parameters of diastolic functions of patients were listed in the **Table 2**. Em/Am ratio was significantly higher in normotensive group compared to prehypertensive group

Table 3. Electrocardiographic findings of the two groups

	Group I Normotension (n = 28)	Group II Prehypertension (n = 35)	Group III Hypertension (n = 32)	*P* value
QTmax (ms)	385.0±26.0	385.7±26.1	376.0±29.3	0.32
cQTmax (ms)	429.6±32.8	438.6±22.2	434.8±22.7	0.40
QTmin (ms)	354.3±27.6	355.3±25.1	334.7±31.8	0.006
cQTmin (ms)	395.3±33.0	405.2±24.7	387.0±27.7	0.04
QTd (ms)	30.7±9.3	29.4±9.0	41.3±14.0	< 0.001
cQTd (ms)	34.3±11.0	33.4±9.1	47.8±16.2	< 0.001
Tp-e (ms)	85.6±12.0	86.1±12.1	92.7±11.9	0.04
cTp-e (ms)	95.6±14.3	98.0±11.6	107.0±10.7	0.001
Tp-e/QT	0.22±0.03	0.22±0.03	0.25±0.03	0.001

QTmax = QT maximum; cQTmax = corrected QT maximum; QTmin = QT minimum; cQTmin = corrected QT minimum; QTd = QT dispersion; cQTd = corrected QT dispersion; Tp-e = transmural dispersion of repolarization; cTp-e = corrected transmural dispersion of repolarization.

Table 4. The parameters affecting the ventricular repolarization

	SBP		DBP		LVMI	
	r	p	r	p	r	p
cQTd	0.34	0.001	0.37	< 0.001	NS	NS
cTp-e	0.39	< 0.001	0.32	0.001	0.23	0.026
Tp-e/QT	0.37	0.001	0.29	0.009	0.20	0.050

cQTd = corrected QT dispersion; cTp-e = corrected transmural dispersion of repolarization; DBP = diastolic blood pressure; LVMI = left ventricul mass index; NS = non significant; SBP = systolic blood pressure.

and HT group (P < 0.05). Also, E/A ratio was higher in normotensive group than that of HT group (P < 0.05). Compared with the normotensive and prehypertensive group, Em/Am ratio at the lateral mitral annulus and the medial mitral annulus were significantly decreased in hypertensive patient group while in normotensive group Em/Am ratio at the lateral tricuspid annulus was significantly higher than the prehypertensive and HT group. E/Em ratio was significantly higher in HT patient group than normotensive and prehypertensive group (P < 0.05). MPI measurements from these three sites were similar between all groups.

Corrected QTd was significantly higher in HT patients compared to normotensive and prehypertensive groups. More recent ventricular repolarization markers corrected Tp-e (cTp-e) and Tp-e/QT ratios were also increased in HT patient group compared with the group of normotensive and prehypertensive (P < 0.05). All three ventricular repolarization index markers were similar in group of normotensive and prehypertensive (P > 0.05, **Table 3**).

Corrected QTd was coraleted SBP and DBP. Corrected Tp-e interval and Tp-e/QT ratio were coraleted whith SBP, DBP and LVMI (**Table 4**).

Discussion

Our study showed that the markers for dispersion of ventricular repolarization incluiding cQTd, cTp-e interval and Tp-e/QT ratio were similar in prehypertensive and normotensive while significantly higher in hypertensive patient group. Also, left ventricle diastolic function parameters were poor in hpertensive patient group.

Hypertensive patients have an increased risk of ventricular arrhythmias and related sudden cardiac death. Increased left ventricular wall stress activates tense receptors, resulting fibrosis of myofibroblasts [15]. Fibrosis disturbs mechanical and electrical activities of atrial and ventricular tissues [15, 16]. As a consequence of myocardial fibrosis and alterations in electrical interconnections between muscle bundles, low conduction velocities and conduction heterogeneties result in reentry and ectopic impulses [16, 17].

QT interval and QTd are the indexes of repolarization heterogeneity [2]. Increased QTd is related to increased frequency of sudden ventricular arrhythmias [18]. Recently, Tp-e interval and Tp-e/QT ratio were reported to indicate myocardial repolarization abnormalities and increased Tp-e interval and Tp-e/QT ratio have been associated with ventricular tachyarrhythmias and cardiovascular mortality [5-10]. The Tp-e/QT ratio is a relatively new index of ventricular repolarization that remains constant despite dynamic changes in heart rate within subject. It is considered to be a more sensitive index of arrhythmogenesis compared with the Tp-e or QT interval [9, 10].

Doğru et al and Clarkson et al showed that direct positive relationship between QTd and LVMI, SBP was reported in previous studies [19, 20]. Recently, Tp-e interval and Tp-e/QT ratio were studied as an index of repolarization

heterogeneity in hypertensive patients. Demir et al revealed that Tp-e and Tp-e/QT indexes were significantly higher in non dipper hypertensive patients compared to control group [21]. Likewise, Karaağaç et al reported longer Tp-e interval and Tp-e/QT ratio in non-dipper hypertensive patients with metabolic syndrome [22]. However, aforementioned studies covered only hypertensive patients, prehypertensive patients were not included. In a study with 47 prehypertensive and 37 normotensive adult patients conducted by Tanindi et al [23], Tp-e, Tp-e/QT, and cQTd were increased in prehypertensives compared with normotensives; but in this study, hypertensive patients were not included.

In our results, cTp-e interval, Tp-e/QT ratio and cQTd were higher in hypertensive patient group compared to prehypertensive and normotensive groups. There was no statistically significant difference between prehypertensive and normotensive patient groups. Compatible with findings of Doğru MT et al in our study indixes of ventricular repolarization were significantly correlated with SBP and DBP, LVMI and LV diastolic function parameters. Mitral E/A ratio was significantly lower in HT and prehypertensive groups compared to normotensive group. Tricuspid E/A ratio was significantly lower only in HT group compared to others, while similar in normotensive and prehypertensive groups. TDI is more sensitive than CDI in detecting diastolic function [24]. We evaluated both right ventricular and left ventricular diastolic functions with TDI. Consistent with the literature, left ventricular diastolic function parameters were significantly worse in HT patients compared to prehypertensive and normotensive. Even in prehypertensive patients, diastolic function parameters were significantly worse than normotensive patients. MPI is echocardiographic variable used for assessment of systolic and diastolic performances together [25]. According to our results, MPI, which was calculated with a multisegmental approach, via TDI were similar in all groups. This was probably due to HT group in our study was consisted of newly diagnosed, instead of long term known hypertensive patients.

Limitations

In this study, there are several limitations. Main limitations of this study include its location at a single center, small sample size and its cross-sectional nature. The cross-sectional, correlational nature of the design limits causal interpretations. Other limitation was end–organ damages examined in hypertensive patients, therefore, any relation ventricular repolarization indexes and end-organ damages were not seeked. Another limitation is QT and Tp-e measured manually, not digital. Last, relation between ventricular repolarization indexes and ventricular arrythmia incidence was not searched. Meanwhile, larger populaltion-based studies with long term patient follow-ups, endorsed with 24 hours rhythm holter monitors are needed to assert importance of Tp-e interval and Tp-e/QT ratio in hypertensive patients.

Conclusion

Our results demonstrate that ventricular repolarization indixes, cQTd, cTp-e interval and Tp-e/QT ratios were higher in the HT patient group while similar in the prehypertensive and normotensive groups. Also, these indixes were significantly correlated with blood pressure values and LVMI. Finally, increased heterogeneity of ventricular repolarization in hypertensive patients, may contribute to understand pathophysiology of increased ventricular arrhythmias and cardiovascular mortality in hypertensive patients.

Disclosure of conflict of interest

None.

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