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Original Article

Effect of non-dipper and dipper blood pressure patterns on Tp-Te interval and Tp-Te/QT ratio in patients with metabolic syndrome

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Abstract: The purpose of this study was to evaluate the effect of blood pressure (BP) rhythm on the values of Tp-Te interval and Tp-Te/QT ratio in patients with metabolic syndrome. Seventy patients with newly diagnosed hypertension who fulfilled the metabolic syndrome criteria according to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP/ATP-III) were evaluated with 24-hour blood pressure holter monitoring. According to blood pressure rhythm, 35 patients with dipper blood pressure pattern and 35 patients with non-dipper blood pressure pattern were enrolled as two groups in our study. QT, corrected QT (QTc), Tp-Te interval and Tp-Te/QT ratio were measured from the 12-lead electrocardiogram. These parameters were compared between the groups. The nocturnal systolic and diastolic blood pressures were significantly higher in non-dipper patients than the dipper group. Baseline characteristics and QT, QTc intervals were similar in both groups. Tp-Te (91±12.24 vs 74±9.96; $p < 0.001$), Tp-Te/QT (0.24±0.027 vs 0.20±0.025; $p < 0.001$) and Tp-Te/QTc (0.22±0.023 vs 0.18±0.023; $p < 0.001$) were significantly increased in non-dipper group. These findings suggest that Tp-Te interval, Tp-Te/QT ratio end Tp-Te/QTc ratio were prominently increased in non-dipper hypertensive patients than dippers with metabolic syndrome.

Keywords: Nondipper, Tp-Te interval, Tp-Te/QT

Introduction

The metabolic syndrome represents a cluster of cardiovascular risk factors which are closely linked to insulin resistance, an entity which prevalence is high and rapidly rising in the Western population [1-3]. The working definition of the metabolic syndrome proposed in the NCEP/ATP-III [4] is based on the presence of three or more of the following five characteristics: 1- abdominal obesity (waist circumference: men > 102 cm, women > 88 cm), 2- high blood pressure (BP) (≥ 130/85 mmHg) or patient receiving antihypertensive treatment 3- high fasting glucose (≥ 110 mg/dl), 4- high triglycerides (≥ 150 mg/dl) and 5- reduced levels of high-density lipoprotein cholesterol (HDL) (men < 40 mg/dl, women < 50 mg/dl).

Systolic and diastolic blood pressure decrease more than 10% during sleep compared to daytime. This diurnal pattern is considered to be normal. The term non-dipper refers to patients whose blood pressure does not demonstrate this diurnal pattern. Non-dipper patients have a higher cardiovascular risk and target organ damage than dippers [5, 6]. Myocardial repolarization has been evaluated by various methods. Recent studies indicated that Tp-Te interval, which is the interval between the peak and the end of T wave on electrocardiogram (ECG), can be used as an index of total (transmural, apicobasal and global) dispersion of repolarization [7]. Also, increased Tp-Te interval might be a useful index to predict ventricular tachyarrhythmias and cardiovascular mortality [8]. Recently, a new index, the Tp-Te/QT ratio has been suggested to be a more accurate measure for the dispersion of ventricular repolarization compared to QTd, cQTd and Tp-Te intervals which is independent of alterations in heart rate [9]. Although ventricular repolarization was evalu-

ated by using T wave and QT interval measurements in patients with non-dipper hypertension in previously [10], the novel repolarization indexes Tp-Te interval and Tp-Te/QT ratio, is not studied in these patients before.

The aim of this study was to evaluate the effect of non-dipping blood pressure pattern on repolarization (including Tp-Te interval and Tp-Te/QT ratio) in patients with non-dipper hypertension of metabolic syndrome.

Material and method

Patient records of Bursa Yuksek Ihtisas Hospital were retrospectively analyzed. A total of 125 consecutive newly diagnosed hypertensive patients, who fulfilled the criteria for metabolic syndrome according to NCEP/ATP-III and visited the cardiology department were enrolled. Patients' 24-hour blood pressure holter data were examined. According to blood pressure pattern, all consecutive patients enrolled until dipper group reached to 35 patients. We continued to examine the hypertensive patients with ABPM until the non-dipper patient number reached to 35. We finalized the study enrollment with 35 dipper and 35 non-dipper patients. Patients with diabetes mellitus, secondary hypertension, chronic renal failure, chronic liver disorders, chronic lung disease, moderate or severe valvular disease, atrial fibrillation, bundle branch block or evidence of any other intraventricular conduction defect, prior pacemaker implantation, congenital heart disease, left ventricular systolic dysfunction on echocardiography (EF < 50%), obstructive sleep apnea, thyroid dysfunction are excluded from the study. All patients' fasted weight, height, waist circumference and hip circumference were gained from patient files. Body mass index (BMI) was calculated using the formula "weight (kg)/height (m^2)". Clinical blood pressure measurements were performed using a mercury sphygmomanometer following 10 minutes rest in the sitting position. Three consecutive readings were obtained using 2-minutes interval settings and the mean of these readings were considered as clinical BP. A 24-hour ABPM was performed using a portable digital recorder (Bravo HR ABP Sun Tech Medical Inc., Morrisville, USA). The recorder was programmed to function between 07 AM-11 PM (daytime BP values) for every 20 minutes and between 11 PM-07 AM for every 30 minutes (nocturnal BP values). Patients with mean circadian systolic BP of > 130 mmHg and/or diastolic BP of > 80 mmHg were considered to be hypertensive [11]. The percentage of nocturnal blood pressure decline was calculated using the following formula:

Nocturnal BP decline (%) = (daytime BP- nocturnal BP)×100/Daytime BP.

Biochemical studies

Retrospective scanning of biochemistry lab data provided fasting glucose, urea, creatinine, total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, and cholesterol levels at the time of admission to hospital.

Echocardiographic measurements

After 15 minutes of rest, echocardiographic measurements were performed with a standard technique using the Vivid 7 with a 2.5-MHz probe (GE Medical System, Horten, Norway) in the left lateral position. All of the echocardiographic measurements were performed in 3 consecutive cycles and their average was calculated. The M-mode was recorded at 100 mm/s. According to the recommendation of the American Society of Echocardiography report, the M-mode measurements of left ventricle (LV) diastolic and systolic diameters, and left atrium systolic diameter were obtained from the image of the parasternal long axis [12]. LV ejection fraction (EF) was calculated with the Teichholz method. Doppler echocardiographic recording allowed analysis of the diastolic mitral flow velocities of the E wave (m/s), the A wave (m/s) and the E/A ratio. Tissue Doppler pulsed wave (TDI) sample volume was placed on mitral annulus at the lateral LV wall in the apical four-chamber view and the following measurements were made: Systolic myocardial velocity (Sm), peak velocity of early diastolic wave (Em), peak velocity of late diastolic wave (Am), Em/Am ratio. Tissue Doppler imaging (TDI) derived miyocardial performance index was calculated for all patients. Left ventriculer mass (LV Mass) and relative wall thickness (RWT) estimated by left ventriculer cavity dimension and wall thickness at end-diastole for all patients. RWT a value > 0.45 was considered normal for both genders. Following formulas were used to calculate LV Mass [13] and RWT [14]:

Table 1. Clinical Characteristics of Study Subjects

	Dipper (n:35)	Non dipper (n:35)	*p* value
Age (year)	55±11	56±11	NS
Gender (male/female)	9/26	10/25	NS
Height (cm)	167.2±8.1	165±7.7	NS
Weight (kg)	81.0±10.6	79.9±8.7	NS
Body mass index (kg/m^2)	29±3.4	29.4±3.5	NS
Waist circumference (cm)	96.2±11	97.6±9.9	NS
Systolic blood pressure (mmHg)	146.2±10.1	148.4±9.3	NS
Diastolic blood pressure (mmHg)	88.2±3.8	92.2±4.3	NS
Biochemical parameters			
Glucose (mg/dl)	103.3±17.27	103.6±15.76	NS
Urea (mg/dl)	18.2±4.5	17.6±3.8	NS
Creatinine (mg/dl)	0.7±0.2	0.7±0.4	NS
Triglyceride (mg/dl)	227.3±93.0	220.7±90.4	NS
Total cholesterol (mg/dl)	169.8±26.5	164.7±36.3	NS
HDL-cholesterol (mg/dl)	37.9±7.3	39.7±7.7	NS
LDL-cholesterol (mg/dl)	114.3±41.5	138.8±36.4	NS
Platelet count (×10^3/mm^3)	23.4±1.6	22.1±1.6	NS
RDW	14.3±1	13.9±1.2	NS
Blood pressure (holter) (mmHg)			
24 hours systolic	130.6±13	143.2±19.1	NS
24 hours diastolic	79.5±9.5	83.5±11.1	NS
Nighttime systolic	115.1±19.2	140.4±18.1	< 0.001
Nighttime diastolic	68.6±9.5	80.9±10	< 0.001
Daytime systolic	137.4±14	139.6±35.4	NS
Daytime diastolic	84.7±10.3	84.9±12.3	NS
Change of day and night mean pressures (%)			
Systolic pressure	12.6	4.3	0.001
Diastolic pressure	13.1	6.2	0.001

HDL: high-density lipoprotein; LDL: low-density lipoprotein; RDW: red blood cell distribution width; BMI: body mass index; Data are expressed as means±SD; NS: non significant.

LV Mass (g) = 0.8{1.04[([LVEDD+IVSd+PWd]^3-LVEDD^3)]}+0.6

RWT = 2*PWd/LVEDD

Measurement of Tp-Te, QT and QRS intervals from the 12-lead ECG

For analysis of the electrocardiographic parameters, lead II recorded at a paper speed of 50 mm/s (Nihon Kohden, Tokyo, Japan) at rest in the supine position was used. All ECGs were scanned. T wave peak to end interval, QT and corrected QT intervals and some other ECG intervals were measured by an engineer with a computer program. By using a ruler, vernier caliper or any other manual measuring tool; getting measurements off from ECG papers could be either inaccurate or slow. Therefore ECG papers were scanned and this made gathering measurements possible in digital environment. These measurements are done by a program which is generated with MATLAB (MathWorks, Natick, Massachusetts, U.S.A.) codes that written by an engineer. These codes are based on image manipulation principles. Image manipulation method could be divided into three subdivisions: image processing, image an alysis and image understanding. Image analysis is the technique that should be used to gather measurement data from ECG. Running the written code imports the image file first and then, by choice, allows user to pick points that need to be picked to get measurements or generates a matrix that consists of a dedicated numeric value of each pixel's color. Creating a matrix gives user the flexibility of using functions which predefined by program. In spite of this, hand picking is easier and has a simple interface especially for beginner level users. Algorithms are developed and used to get excellent measurements in order to tolerate differences: such are tilting during scanning process, different scanning resolutions and using different ECG. The QT interval was defined as extending from the beginning of the QRS complex to where T waves descend onto the isoelectric baseline [15]. When a U wave interrupted the T wave before returning to baseline, the

Table 2. Echocardiographic and electrocardiographic parameters of patients

	Dipper (n:35)	Non dipper (n:35)	*p* value
LVEDD (mm)	46.1±0.3	46±0.7	NS
LVESD (mm)	30±0.3	31.3±0.8	NS
EF (%)	62±3.7	60.7±6.7	NS
MPI	0.55±0.8	0.59±0.4	NS
E (cm/s)	0.6 ±0.1	0.7±0.3	NS
A (cm/s)	0.7±0.1	0.8±0.1	NS
E/A ratio	0.9±0.2	0.9±0.4	NS
LVM	179±5.58	197±40.8	NS
RWT	0.47±0,065	0.47±0.059	NS
Mitral Annulus	0.08±0.03	0.12±0.18	
Early diastolic velocity (Em)	0.09±0.01	0.10±0.02	NS
Late diastolic velocity (Am)	0.11±0.03	0.12±0.01	NS
LV (Sm)	0.81±0.11	0.79±0.21	NS
Em/Am			NS
QT	374±41,9	357±33.3	NS
QTc	416±27.7	422±42.2	NS
Tp-Te	91±12.24	74±9.96	< 0.001
Tp-Te/QT	0.24±0.027	0.20±0.025	< 0.001
Tp-Te/QTc	0.22±0.023	0.18±0.023	< 0.001

LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; EF: ejection fraction; MPI: myocardial performance index; LV (Sm): Left ventricular systolic myocardial velocity; QTc: corrected QT; QTd: QT dispersion; LVM: left ventriculer mass; RWT: relative wall thickness Data are expressed as means±SD; NS: non significant.

QT interval was measured to the nadir of the curve between the T and U waves. The QTc interval was calculated using the Bazett formula: QTc (ms) = QT measured/$\sqrt{}$RR (sec) Extended QTc interval was defined as a duration of > 440 ms. The QT dispersion [QTd] value was determined as the difference between the longest and shortest QT intervals observed from the 12 ECG leads [16]. The Tp-Te interval was defined as the interval from the peak of T wave to the end of T wave. Measurements of Tp-Te interval were performed from precordial leads [17]. Tp-Te/QT ratio was calculated from these measurements.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 for Windows. Continuous variables are presented as means±standard deviations; Categorical variables are presented as percentages. The differences between the groups for categorical varieties were compared by the chi-square or Fisher's exact test. According to the distribution, the differences between the groups for numeric parameters were compared by Student's t-test or the Mann-Whitney U test. The significance level was assumed as $P < 0.05$.

Results

Patients were divided into two groups according to the decline in systolic and diastolic blood pressures as dipper (≥ 10%; n = 35, 26 women, 9 men; mean age 55±11 years) and non-dipper (< 10%; n = 35, 25 women, 10 men; mean age 56±11 years). The two groups were similar with regard to age, sex, height, weight, body mass index, waist circumference and mean systolic and diastolic blood pressures. The night measures of blood pressure was higher in non-dipper group (140.4±18.1 mmHg vs. 115.1±19.2 mmHg and 80.9±10 mmHg vs. 68.6 ±9.5 mmHg; $p < 0.001$ consequently) (**Table 1**).

According to echocardiographic parameters; LVEDD, LVESD, ejection fraction (EF), myocardial performance index (MPI), mitral E and A waves, E/A ratio, mitral annular early (Em) and late (Am) diastolic velocity, Em/Am ratio, left ventricular systolic myocardial velocity LV (Sm) there were no differences between two groups. On the other hand, our results on surface ECG are clear and, there are not significant differences between both groups in QT, QTc. Tp-Te intervals, Tp-Te/QT ratio and Tp-Te/QTc ratio is significantly higher in non-dipper-patients with metabolic syndrome (all $p < 0.001$; **Table 2**).

Discussion

The present study showed that Tp-Te interval, Tp-Te/QT and Tp-Te/QTc ratio were prolonged in non-dipper-patients with metabolic syndrome when compared to the dippers.

Increased cardiovascular morbidity and mortality have been demonstrated in patients with non-dipper patients when compared to the dipper patients in previous studies [18, 19].

QTd has been reported to increase in patients with essential hypertension, and abnormal QTd is associated with arrythmias and sudden cardiac death. QTd has been reported to increase in left ventricular hypertrophy and hypertension [20-24]. Therefore, a reduction in QT dispersion may lead to a reduction in the rate of arrythmias and sudden cardiac death [25, 26].

In the non-dipper hypertension, left ventricular diastolic function abnormalities, evidence of conduction disturbances , cardiac autonomic dysfunction, left ventricular hypertrophia and increased the frequency of ventricular arrhythmia have been described in these patients. Moreover, increased inflammatory activity, is proposed to be associated with the pathogenesis of cardiovascular diseases and arrhythmia in these patients [27, 28].

Increased dispersion of repolarization, the disturbance of the normal orderly pattern of ventricular recovery, is generally thought to predispose to ventricular arrhythmias. Recently, the Tp-Te interval and Tp-Te/QT ratio have emerged as a novel electrocardiographic markers of increased dispersion of ventricular repolarization [9, 29]. Also, these markers may be used as an electrocardiographic index of ventricular arrhythmogenesis and sudden cardiac death [8, 15]. Previous studies showed that prolongation of Tp-Te interval was associated with increased mortality in Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy, and in patients myocardial infarction [30].

Recently Passino et al. demonstrated that QTc was significantly longer in nondippers compared to dippers or to normotensive subjects, particularly at night-time [10]. Also Demir et al. showed that Tp-Te interval, and Tp-Te/QT ratio were prolonged in nondipper patients [31].

In our study we have found significantly differences in Tp-Te interval, Tp-Te/QT and Tp-Te/QTc ratio between nondipper hypertensive patients and dipper group. Also, our findings are consistent with those of Demir et al. Conversly QT, QTc intervals were similar in both groups.

When 2 groups were compared in our study, Tp-Te interval, Tp-Te/QT and Tp-Te/QTc ratio of the patients having non-dipper hypertension were significantly higher than dipper hypertension groups.

Further studies are required to determine the relation between Tp-Te interval and Tp-Te/QT ratio and ventricular arrhythmia and non-dipper hypertensive pattern in patients with metabolic syndromes.

In conclusion, the measurement of Tp-Te interval and Tp-Te/QT ratio may be used to indicate increased risk of hypertension-related adverse cardiovascular events in patients with metabolic syndromes. Our results may contribute to pathophysiological mechanisms of increased prevalence of ventricular arrhythmias and cardiovascular mortality risk by indicating increased ventricular repolarization heterogeneity in these patients. Increased the frequency of ventricular arrhythmia and sudden cardiac death might be explained with prolonged transmural dispersion in patients with nondipper hypertension and metabolic syndromes.

Limitations

The major limitation of our study is the limited number of patients and absence of a control group. Another limitation we did not assess the association between ventricular arrhythmias with Tp-e interval and Tp-e/QT ratio. Retrospective method of study is the main handicap in this. Also study population could not be followed-up prospectively for ventricular arrhythmic episodes. Large-scale prospective studies are needed to determine the predictive value of prolonged Tp-e interval and increased Tp-Te/QT ratio in this population.

Conclusion

Our study revealed that Tp-Te interval, Tp-Te/QT and Tp-Te/QTc ratio were in non-dipper-patients with metabolic syndrome when compared to the dippers. Tp-Te interval and Tp-Te/QT ratio might be a useful marker of cardiovascular morbidity and mortality due to ventricular arrhythmias in nondipper hipertensive metabolic syndrome patients.

Disclosure of conflict of interest

None.

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