Assessment of the Relationship Between Non-dipping Phenomenon and Ventricular Repolarization Dynamics

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Objective: The aim of the present cross-sectional study was to evaluate ventricular repolarization dynamics by QT dynamicity in normotensive and hypertensive individuals with either non-dipper or dipper type circadian rhythm of blood pressure.

Methods: A total of 103 patients were allocated into 4 groups according to the presence of hypertension and circadian BP pattern as follows: (1) normotensive/dipper, n=28; (2) normotensive/non-dipper, n=26; (3) hypertensive/dipper, n=25; and (4) hypertensive/non-dipper, n=24.

Results: QTapex/R-R and QTend/R-R slopes were higher in non-dipper subgroup of normotensive cases with respect to the dipper subgroup of normotensive cases (QTapex/R-R= 0.171±0.017 vs. 0.127±0.023, p=0.001; QTend/R-R= 0.159±0.015 vs. 0.133±0.025, p=0.001). QTapex/R-R and QTend/R-R slopes were higher in non-dipper subgroup of hypertensive cases with respect to the dipper subgroup of hypertensive cases (QTapex/R-R= 0.187±0.019 vs. 0.133±0.019, p=0.001; QTend/R-R= 0.183±0.018 vs. 0.147±0.022, p=0.001). Spearman’s correlation analyses revealed a higher negative correlation between percentage of nocturnal fall in BP and QTapex/R-R (r=-0.638, p=0.001). There was also a moderate negative correlation between percentage of nocturnal fall in BP and QTend/R-R (r=-0.504, p=0.001).

Conclusion: Blunting of the nocturnal fall in blood pressure associates impaired QT dynamicity indices in both normotensive and hypertensive groups.

Keywords
Arterial, biological clocks, blood pressure, dipping, non-dipping, QT dynamicity
Non-dipping Fenomeni ile Ventriküler Repolarizasyon Dinamikleri Arasındaki İlişkinin Değerlendirilmesi

Introduction

Arterial blood pressure (BP) exhibits a circadian type rhythm which refers to the daily variation of BP that is generally higher during the day than at night (1,2). Most people have an average night-time BP that is 10–20% lower than their average daytime BP, which is called a dippder pattern (3). A number of studies have demonstrated that the lack of nocturnal BP fall which is called non-dipping is associated with more serious and increased frequency of target end organ damages when compared dipping pattern individuals (4,5). The underlying mechanisms responsible for blunted nocturnal fall in BP are not completely understood. Nevertheless, there are some evidences to suggest that non-dippers show impairment in the autonomic system that includes abnormal parasympathetic and increased sympathetic nervous system activity (6,7). Since, there are several studies depict that both increased sympathetic and decreased parasympathetic activity have been associated with an increased risk for overall mortality, the decline in vagal tone and increased sympathetic tone might explain the increase in cardiovascular risk in non-dipper subjects (8).

QT dynamicity is the one of the relatively novel methods that could be used to assess ventricular repolarization dynamics (9,10). Abnormal QT dynamicity, which means abnormal rate adaptation of
ventricular repolarization has been considered to reflect the diminished cardiac autonomic functions that may be associated with a worse cardiovascular outcome (11,12). Ventricular repolarization heterogeneity has been previously assessed in non-dippers with QT dispersion. However, the relationship between circadian blood pressure type and QT dynamicity has not been evaluated yet. Therefore, the aim of the present cross-sectional study was to evaluate QT dynamicity in normotensive and hypertensive individuals with either non-dipper or dipper type circadian rhythm of BP.

Methods

**Study Population**

One hundred and ten patients were evaluated in our study. All patients underwent 24-hour ambulatory BP and electrocardiographic monitoring. Transthoracic echocardiographic examination was performed in all patients. Patients with history of cardiovascular, cerebrovascular or other systemic disease were excluded. The study was approved by the local ethics committee and patients gave informed written consent.

**Ambulatory BP Monitorization**

Ambulatory BP monitoring studies were carried out using a Tracker NIBP2 (Del Mar Reynolds Medical Ltd, Hertford, UK) monitoring device. The first hour was discarded from analysis. BP readings were obtained automatically at 15-minute intervals during the daytime and 30-minute intervals during the nighttime. Recordings were accepted only if more than 85% of the raw data were valid. The absolute and the percentage of the decrease of nighttime systolic BP vs daytime systolic BP were calculated in all subjects. Time in bed was defined based on the patient-kept diary that documented the exact time of getting into and arising from bed. The average BP for this time in bed was calculated from the ambulatory monitoring data (termed nighttime BP). Daytime BP was defined as the average BP during the remainder of the 24-hour period. Mean BP was calculated as the diastolic pressure plus one-third of the pulse pressure. The percentage decline in nighttime BP was calculated as follows: (mean daytime BP – mean nighttime BP / mean daytime BP x 100). Patients with a decline in mean nighttime BP of less than 10% were accepted as nondippers. Patients were accepted as hypertensive if the following were present: (i) current use of antihypertensive drugs; (ii) presence of resting systolic BP of 140 mmHg and/or diastolic BP of 90 mmHg; and (iii) an average 24-hour BP value above 130/80 mmHg.

**Analysis of QT Dynamicity**

QT dynamicity parameters were obtained with a three channel analog recorder (ELA Medical Limited) and analyzed with ELATEC Holter software. Recordings were eligible if they had much more than 18 hours of analyzable data. To investigate QT dynamicity all 24-hour periods were used to investigate QT dynamicity. The T apex was determined by fitting a parabola through the peak of the T wave, whereas the end of the T wave was determined by the intersection of the tangent of the down slope of the T wave with the isoelectric baseline. The software thereafter computed linear regression (QTend/R-R and QTapex/R-R) and provided the slope and correlation coefficient of these linear regressions.

**Transthoracic Echocardiography**

Standard imaging was performed in the left lateral decubitus position using a commercially
available system (Vingmed System Five GE ultrasound, Horten, Norway). Images were obtained using a 2.5-3.5 MHz transducer in the parasternal and apical views. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters and left ventricular ejection fraction were determined with M-mode echocardiography under two-dimensional guidance in the parasternal long-axis view, according to the recommendations of the American Society of Echocardiography (13).

**Statistical Analyses**

Statistical analyses were performed using SPSS for Windows 15 (SPSS Inc., Chicago, IL, USA). Numerical variables with a normal distribution were presented as the mean ± standard deviation and numerical variables with a skewed distribution were presented as the median (minimum and maximum) and categorical variables were presented as percentages. For numerical variables, an independent sample t-test and Mann-Whitney U test were used for inter-group comparisons. A chi-square test and Fischer’s exact chi-square test were used for comparisons of categorical variables. Multivariate linear regression analysis was performed to evaluate the effects of various variables, such as age, gender, basal heart rate (BHR), systolic and diastolic blood pressure, smoking status, LVEF, LVEDD, LVESD, average systolic (AvSBP) and average diastolic (AvDBP) 24-hour ambulatory BP monitoring values on QT dynamicty indices. The correlation between the decline in night-time BP and HRT and QT dynamicty was examined with Spearman’s correlation analysis. Two-tailed p values below 0.05 were considered as significant.

**Results**

Out of 110 patients, 103 subjects were enrolled in the current study. Four patients were excluded because of atrial fibrillation, 2 patients were excluded because of permanent pacemaker and 1 patient was excluded because of diabetes mellitus. Patients divided into 4 groups according to the presence of hypertension and circadian BP pattern as follows: (1) normotensive / dipper, n=28; (2) normotensive / nondipper, n=26; (3) hypertensive / dipper, n=25; and (4) hypertensive / nondipper, n=24. Thus, dipper and non-dipper cases were compared with their respective groups. Demographic characteristics, distribution of conventional risk factors, blood pressure and exercise test parameters of the groups are summarized in Table 1 and Table 2.

The dipper and non-dipper subgroups of normotensive cases were similar with respect to age (45.2 ± 4.4 vs. 44.8 ± 4.7 years), gender distribution ([male/female] 16/12 vs. 14/12), smoking status (32% vs. 31%), BHR (72.5 ± 8.3 vs. 74.7 ± 8.5 beats/minute), left ventricular ejection fraction (LVEF) (66.1 ± 3.8 vs. 65.1 ± 3.4%) and AvSBP (117.6 ± 6.2 vs. 120.3±4.4). In normotensive / dipper group AvDBP (72.2 ± 5.4 vs. 76.3 ± 3.8, p=0.003) values were significantly lower than the normotensive / non-dipper group. QTapex/R-R and QTend/R-R slopes were higher in non-dipper subgroup of normotensive cases with respect to the dipper subgroup of normotensive cases (QTapex/R-R= 0.171±0.017 vs. 0.127±0.023, p=0.001; QTend/R-R= 0.159±0.015 vs. 0.133±0.025, p=0.001)(Figure 1).

The dipper and non-dipper subgroups of hypertensive cases were similar with respect to age (46.9±5.0 vs. 47.2±4.3 years), gender distribution ([male/female] 13/12 vs. 10/14), smoking status (32% vs. 33%), BHR (72.8 ± 12.7 vs. 71.9 ± 10.3 beats/minute), left ventricular ejection
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**TABLE 1**

Demographic Characteristics and Clinical Parameters of Normotensive Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive / Dipper (n=28)</th>
<th>Normotensive / Nondipper (n=26)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45.2±4.4</td>
<td>44.8±4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male / female, %)</td>
<td>57/43</td>
<td>54/46</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>32</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Basal heart rate, bpm</td>
<td>72.5±8.3</td>
<td>74.7±8.5</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>66.1±3.8</td>
<td>65.1±3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Average systolic 24-h ABPM, mmHg</td>
<td>117.6±6.2</td>
<td>120.3±4.4</td>
<td>NS</td>
</tr>
<tr>
<td>Average diastolic 24-h ABPM, mmHg</td>
<td>72.2±5.4</td>
<td>76.3±3.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Decline in nighttime BP (%)</td>
<td>15.3±2.7</td>
<td>4.8±3.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Numeric variables with a normal distribution were presented as the mean ± standard deviation. Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; bpm, beats per minute; NS, not significant.

**TABLE 2**

Demographic Characteristics and Clinical Parameters of Hypertensive Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive / Dipper (n=25)</th>
<th>Hypertensive / Nondipper (n=24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.9±5.0</td>
<td>47.2±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male / female, %)</td>
<td>52/48</td>
<td>42/58</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>32</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Basal heart rate, bpm</td>
<td>72.8±12.7</td>
<td>71.9±10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>63.4±3.0</td>
<td>64.5±2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Average systolic 24-h ABPM, mmHg</td>
<td>135.8±6.0</td>
<td>137.4±6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Average diastolic 24-h ABPM, mmHg</td>
<td>85.9±5.0</td>
<td>89.6±3.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Decline in nighttime BP (%)</td>
<td>13.2±2.1</td>
<td>4.3±2.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Numeric variables with a normal distribution were presented as the mean ± standard deviation. Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; bpm, beats per minute; NS, not significant.

**FIGURE 1**

Distribution of QT dynamicity indices among 2 subgroups of normotensive groups according to dipping status.
fraction (LVEF) (63.4 ± 3.0 vs. 64.5 ± 2.3%) and AvSBP (135.8 ± 6.0 vs. 137.4±6.8). In hypertensive / dipper group AvDBP (85.9 ± 5.0 vs. 89.6 ± 3.8, p=0.005) values were significantly lower than the hypertensive / non-dipper group. QTapex/R-R and QTend/R-R slopes were higher in non-dipper subgroup of hypertensive cases with respect to the dipper subgroup of hypertensive cases (QTapex/R-R= 0.187±0.019 vs. 0.133±0.019, p=0.001; QTend/R-R= 0.183±0.018 vs. 0.147±0.022, p=0.001)(Figure 2).

Effects of age, BHR, AvSBP, AvDBP, and decline in night-time BP on QTapex/R-R were examined in a multivariate linear regression analysis and it was determined that the degree of dipping and AvDBP were independent predictors of QTapex/R-R. In this model, the influence of nighttime dipping on QTapex/R-R was found to be more prominent than the other factors (P=0.001, β=-0.582). Effects of age, BHR, AvSBP, AvDBP, and decline in night-time BP on QTend/R-R were also examined in a multivariate linear regression analysis and it was determined that the degree of dipping and AvDBP were independent predictors of QTend/R-R. In this model, the influence of nighttime dipping on QTend/R-R was found to be more prominent than the other factors (P=0.001, β=-0.404). Spearman’s correlation analyses revealed a higher negative correlation between percentage of nocturnal fall in BP and QTapex/R-R (r=-0.638, p=0.001). There was also a moderate negative correlation between percentage of nocturnal fall in BP and QTend/R-R (r=-0.504, p=0.001)(Figure 3).

The correlation coefficients for degree of nighttime dipping and QT dynamicity indices were higher in hypertensive group than the normotensive group (for QTapex/R-R= r=-0.691, P=0.001 in hypertensive group and r=-0.590, P=0.001 in normotensive group; for QTend/R-R= r=-0.575, P=0.001 in hypertensive group and r=-0.438, P=0.001 in normotensive group).

**Discussion**

To the best of our knowledge our study is the first to evaluate the relationship between circa-

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**FIGURE 2**

*Distribution of QT dynamicity indices among 2 subgroups of hypertensive groups according to dipping status.*
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Dian blood pressure rhythm and QT dynamicity. We have found that the degree of nighttime dipping moderate to highly correlated with QT dynamicity parameters both in normotensive and hypertensive individuals. As would expected, degree of impairment such indices was found more pronounced in non-dipper subgroups of hypertensive patients.

Recently a growing amount of interest has focused on new risk factors for cardiovascular disease, especially in the area of non-invasive assessment and electrocardiographic measurements (14). The blunted nocturnal BP decline is emerging as an index for future target organ damage. Left ventricular hypertrophy (15), microalbuminuria (16) and cerebrovascular damage (17) tend to be more common in patients whose 24-hour BP profile is blunted. Although the underlying mechanisms of nocturnal decrease of BP are not yet fully understood, there are some evidences to suggest that non-dippers show impairment in the autonomic system that includes abnormal parasympathetic and increased sympathetic nervous system activity (6,7).

We recently evaluated the relationship between exercise HRR and circadian blood pressure pattern both in hypertensive and normotensive individuals (18). We found that the blunting of the nocturnal fall in BP was associated with a delayed recovery of heart rate after graded maximal exercise in both normotensive and hypertensive groups. This relationship was more prominent in the hypertensive group. We concluded that when the prognostic significance of HRR is considered, hypertensives and normotensives with a non-dipping pattern should be followed closely for adverse cardiovascular outcomes. Corroborating these results, Polonia and colleagues (19) have also reported an association between the blunting of the nocturnal fall of BP and delayed HRR after graded maximal exercise, but different from the previous study normotensive individuals were not involved.

Ventricular repolarization is a critical time in the cardiac cycle, playing a considerable ro-
le in the pathophysiology of malignant arrhythmias and the QT interval from the standard resting 12-lead electrocardiogram is considered as a marker of ventricular repolarization. The lengthening of QT interval corrected by heart rate (QTc) has been associated with increased risk of either ventricular arrhythmias or sudden cardiac death (20,21). QT dispersion (QTd) which is derived from 12 lead surface electrocardiogram is the difference between the maximum and minimum QT interval. Increased QT dispersion is associated with arrhythmic events in various clinical settings, such as long QT syndrome, heart failure, coronary artery disease, post-myocardial infarction or hypertrophic cardiomyopathy (22). However, the ability of QTd to identify cardiac patients at high risk of sudden death remains uncertain due to conflicting findings. This could be due to the fact that ECG parameters poorly reflect the complexity of the ventricular repolarization process depending on different dynamic components as transmembrane ion currents, heart rate, and autonomic nervous system activity (23).

QTc interval is also affected by the autonomic nervous system (24). Sympathovagal imbalance leads to increase in QT dispersion. Because underlying pathophysiological mechanism is similar, there are several studies have been researched the association between non-dipping BP pattern and QT dispersion. Passino et al. (9) have found that QTc interval is prolonged in non-dipper hypertensive patients. Kohno et al. (25) have found that the maximum QTc interval and QTc dispersion were longer in non-dippers than in dippers.

QT dynamicity is a relatively novel method that could be used for assessment of ventricular repolarization dynamics (23). QT dynamicity offers an advantage in evaluation of QT changes by measuring the differences in QT intervals rather than absolute values (26). A steeper slope of the QT/RR regression line has been related to unfavourable prognosis. QT dynamicity has been shown to have a prognostic value in some cardiac pathologies such as heart failure (27), ischemic cardiomyopathy (28) and ventricular fibrillation without a structural heart disease (29). Our study is the first to assess the relationship between circadian blood pressure rhythm and QT dynamicity indices. We found that both normotensive and hypertensive non-dipper individuals show an abnormal QT/R-R relationship with increased slopes of QT/RR regression line for QTapex/RR and QTend/RR.

The main strength of the present study was the selection of patients from the most frequently encountered patients in the daily practice of cardiology. The major limitations of the present study are the relatively small number of patients and that the results are based on a single center. Another limitation for QT dynamicity is patients with atrial fibrillation, paced rhythm with abnormal ventricular repolarization could not be evaluated.

**Conclusion**

The blunting of the nocturnal fall in BP was associated with the abnormal QT dynamicity indices both in normotensive and hypertensive groups. This relationship was more prominent in the hypertensive group. When the prognostic significance of QT dynamicity is considered, hypertensives and normotensives with a nondipping pattern should be followed closely for adverse cardiovascular outcomes especially related to arrhythmic events.
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