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Assessment of the relationship between non-dipping phenomenon and heart rate turbulence

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Abstract

Background: *The aim of this cross-sectional study was to evaluate cardiac autonomic function by heart rate turbulence (HRT) indices in normotensive and hypertensive individuals with either non-dipper or dipper type circadian rhythm of blood pressure (BP).*

Methods: *A total of 122 patients were allocated into four groups: normotensive/dipper, n = 33; normotensive/non-dipper, n = 31; hypertensive/dipper, n = 29; and hypertensive/non-dipper, n = 29. HRT indices (turbulence slope [TS] and turbulence onset [TO]) were calculated from 24-h ambulatory electrocardiographic recordings.*

Results: *TS values were higher (TS = 10.0 ± 3.4* vs *8.0 ± 1.5, p = 0.004) and TO values were lower (TO = –2.9 [–3.6, –2.2]* vs *–2.0 [–2.3, –1.9], p = 0.037) in the dipper subgroup of normotensive cases than in the non-dipper subgroup of normotensive cases. Similarly, TS values were higher (TS = 8.4 ± 3.5* vs *6.2 ± 2.9, p = 0.012) and TO values were lower (TO = –2.1 [–3.4, –2.0]* vs *–1.6 [–1.9, –0.2], p = 0.003) in the dipper subgroup of hypertensive cases than in the non-dipper subgroup of hypertensive cases. Spearman's correlation analyses revealed a high positive correlation between percentage of dipping and TS (r = 0.600, p = 0.001) and a higher negative correlation between percentage of dipping and TO (r = –0.653, p = 0.001).*

Conclusions: *Blunting of the nocturnal fall in BP is associated with impaired HRT indices in both normotensive and hypertensive groups.* (Cardiol J 2012; 19, 2: 140–145)

Key words: ambulatory blood pressure, heart rate turbulence, dipper

Introduction

Arterial blood pressure (BP) exhibits a circadian type rhythm. This 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, a phenomenon known as the dipping pattern [3]. A number of studies have demonstrated that the lack of nocturnal BP fall, known as non-dipping, is associated with more serious and increased frequency of target organ damage compared to dipping pattern individuals [4, 5]. The underlying mechanisms responsible for blunted nocturnal fall in BP are not completely understood. Nevertheless, there is some evidence to suggest that non-dippers show impairment in the autonomic system that includes abnormal parasympathetic and increased sympathetic nervous system activity which might explain the increase in cardiovascular risk (CV) in non-dipper subjects [6–8].

Initial acceleration and a subsequent deceleration of sinus rhythm following a ventricular premature beat (VPB) with a compensatory pause has

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been termed heart rate turbulence (HRT) [9]. It has been acknowledged by the European Cardiac Society that HRT is a marker of cardiac autonomic regulation and represents a measure of vagal activity [10]. Similarly ventricular repolarization abnormalities are also associated with sympatho-vagal imbalance characterized by vagal withdrawal and relative sympathetic dominance [11, 12]. The relationship between circadian BP type and HRT indices has not been evaluated yet. Therefore, the aim of the present cross-sectional study was to evaluate HRT indices in normotensive and hypertensive individuals with either non-dipper or dipper type circadian rhythm of BP.

Methods

Study population

One hundred and twenty nine 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 a history of CV, cerebrovascular or other systemic disease were excluded. Eventually, out of 129 patients, 122 subjects were enrolled in the current study. Six patients were excluded due to lack of ventricular premature contraction (VPC), and one patient was excluded because of having diabetes mellitus. The study was approved by the local ethics committee and patients gave informed written consent.

Patients were divided into four groups according to the presence of hypertension and circadian BP pattern as follows: (1) normotensive/dipper, n = 33; (2) normotensive/non-dipper, n = 31; (3) hypertensive/dipper, n = 29; and (4) hypertensive/ /non-dipper, n = 29. Thus, dipper and non-dipper cases were compared with their respective groups.

Ambulatory blood pressure monitoring

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-min intervals during the day, and at 30-min intervals during the night. Recordings were accepted only if more than 85% of the raw data was valid. The absolute decrease and the percentage of the decrease in night--time systolic BP *vs* daytime systolic BP were calculated in all subjects. Time in bed was defined based on a patient-kept diary that documented the exact times of getting into and getting out of bed. The average BP for this time in bed was calculated from the ambulatory monitoring data (and was termed night-time BP). Daytime BP was defined as the average BP during the remainder of the 24-h period. Mean BP was calculated as the diastolic pressure plus one-third of the pulse pressure. The percentage decline in night-time BP was calculated as follows: (mean daytime BP – mean night-time BP/mean daytime BP × 100). Patients with a decline in mean night-time BP of less than 10% were accepted as non-dippers. Patients were accepted as hypertensive if the following were present: (i) current use of antihypertensive drugs; (ii) presence of resting systolic BP of 140 mm Hg and/or diastolic BP of 90 mm Hg; and (iii) an average 24-h BP value above 130/80 mm Hg.

Analysis of HRT

HRT indices were obtained with a three channel analog recorder (ELA Medical) and analyzed with ELATEC Holter software. Recordings were eligible if they had much more than 18 h of analyzable data. After manual review of the recorded data, singular VPB followed by 20 or more normal sinus beats were selected. The 20 subsequent R-R intervals in the beats following a VPB were measured automatically and HRT onset and slope were calculated according to Schmidt's method [13]. Turbulence onset (TO) shows the initial phase of sinus rhythm acceleration, and turbulence slope (TS) shows the deceleration phase. TO can be defined as the percentage difference between the mean of first two R-R intervals after a VPB and the last two sinus R-R intervals before VPB. TS is defined as the maximum positive slope of a regression line assessed over any of five consecutive R-R intervals within the first 20 sinus R-R intervals after VPB. TO was calculated for all ventricular premature beats separately and then the average was calculated, whereas TS was calculated based on an average local tachogram. The optimal cut-off value assigned for TS is 2.5 ms/R-R interval. A TS value below 2.5 ms/R-R interval is considered abnormal. TO > 0% indicates sinus deceleration after a VPB and TO < 0% indicates acceleration after a VPC. The cut-off value for TO has been taken to be 0%, meaning that a positive value is considered abnormal [14]. Patients having at least one VPB during the 24-h ECG recording were eligible for HRT analysis.

Transthoracic echocardiography

Standard imaging was performed in the left lateral decubitus position using a commercially availa-

Table 1. Demographic characteristics and clinical parameters of normotensive group.

Variable	Normotensive/dipper (n = 33)	Normotensive/non-dipper (n = 31)	P
Age	44.7 ± 5.0	45.2 ± 4.6	NS
Gender (male/female) [%]	54/46	58/42	NS
Smokers [%]	33.3	32.2	NS
Basal heart rate [bpm]	74.9 ± 8.4	71.0 ± 8.8	NS
Left ventricular ejection fraction [%]	65.1 ± 3.4	66.2 ± 3.5	NS
Average systolic 24-h ABPM [mm Hg]	120.6 ± 4.4	118.2 ± 6.3	NS
Average diastolic 24-h ABPM [mm Hg]	76.2 ± 3.9	72.1 ± 5.1	0.001
Decline in night-time blood pressure [%]	14.8 ± 2.8	4.5 ± 3.0	0.001

Numeric variables with a normal distribution were presented as the mean ± standard deviation; ABPM — ambulatory blood pressure monitoring

Table 2. Demographic characteristics and clinical parameters of hypertensive group.

Variable	Hypertensive/dipper (n = 29)	Hypertensive/non-dipper (n = 29)	P
Age	46.4± 5.0	47.6± 4.3	NS
Gender (male/female) [%]	56/44	45/55	NS
Smokers [%]	35	31	NS
Basal heart rate [bpm]	72.8 ± 11.8	70.4 ± 10.1	NS
Left ventricular ejection fraction [%]	63.5 ± 2.8	64.7 ± 2.2	NS
Average systolic 24-h ABPM [mm Hg]	135.8 ± 3.0	137.4 ± 4.4	NS
Average diastolic 24-h ABPM [mm Hg]	86.0 ± 4.9	89.8 ± 3.5	0.002
Decline in night-time blood pressure [%]	13.5 ± 2.1	4.7 ± 2.6	0.001

Numeric variables with a normal distribution were presented as the mean ± standard deviation; ABPM — ambulatory blood pressure monitoring

ble 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 (LVEF) 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 [15].

Statistical analysis

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 χ^2 test and Fischer's exact χ^2 test were used for comparisons of categorical variables. Multivariate linear regression analysis was performed to evaluate the effects of variables such as age, gender, basal heart rate (BHR), systolic and diastolic BP, smoking status, LVEF, LVEDD, LVESD, average systolic (AvSBP) and average diastolic (AvDBP) 24-h ambulatory BP monitoring values on HRT indices. The correlation between the decline in night-time BP and HRT indices was examined with Spearman's correlation analysis. Two-tailed p values below 0.05 were considered as significant.

Results

The demographic characteristics, distribution of conventional risk factors, BP and exercise test parameters of the groups are summarized in Tables 1 and 2. The dipper and non-dipper subgroups of normotensive and hypertensive cases were similar with respect to age, gender distribution, smoking status, BHR, LVEF and AvSBP. Nevertheless, in the normotensive/dipper and hypertensive/ /dipper groups, AvDBP values were significantly

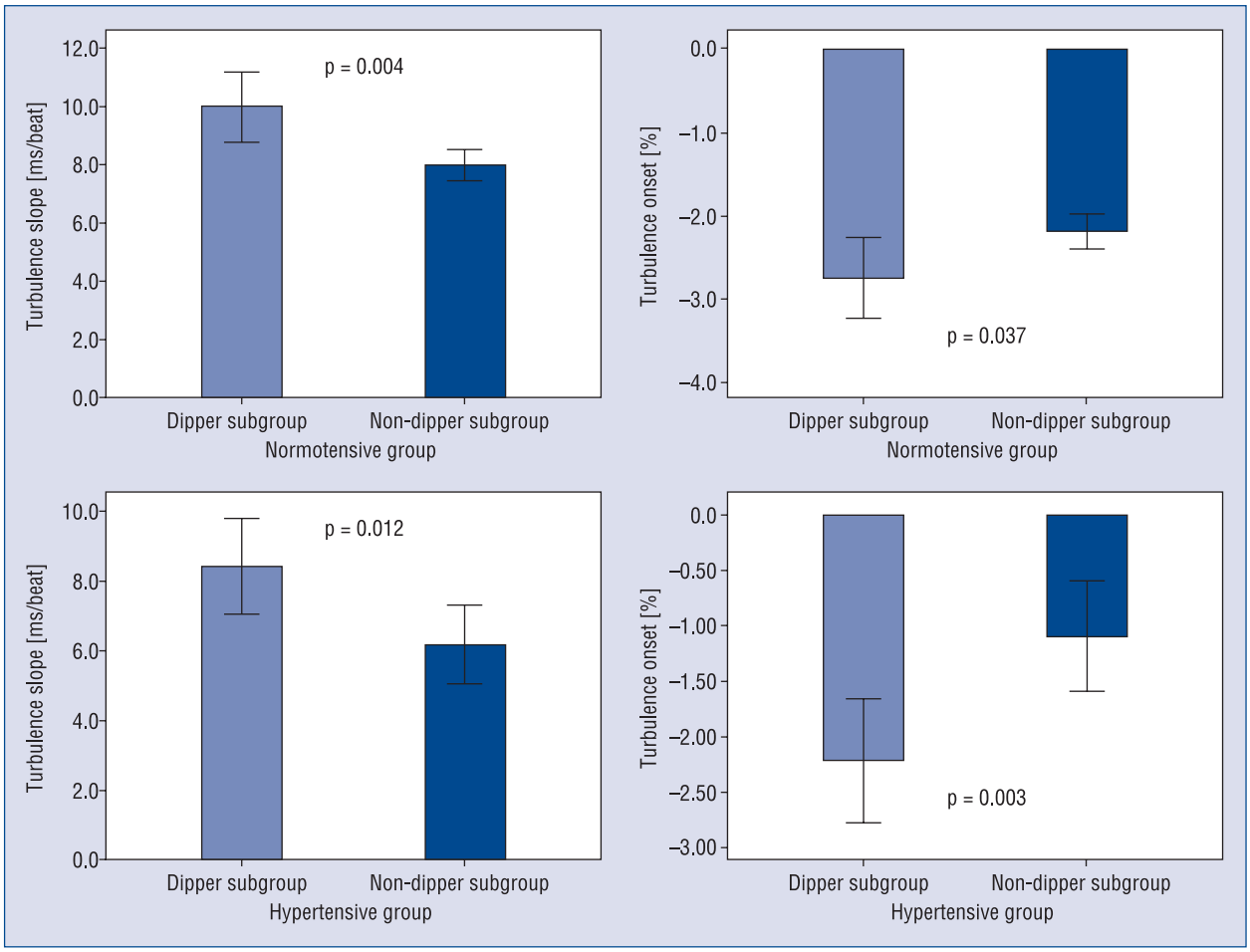

Figure 1. Distribution of turbulence slope and turbulence onset indices among two subgroups of normotensive and hypertensive groups according to dipping status.

lower than in the normotensive/non-dipper group (p = 0.001) and the hypertensive/non-dipper group (p = 0.002), respectively.

TS values were higher (TS = 10.0 ± 3.4 *vs* 8.0 ± ± 1.5, p = 0.004) and TO values were lower (TO = = –2.9 [–3.6, –2.2] *vs* –2.0 [–2.3, –1.9], p = 0.037) in the dipper subgroup of normotensive cases than in the non-dipper subgroup of normotensive cases (Fig. 1). Similarly, TS values were higher (TS = 8.4 ± ± 3.5 *vs* 6.2 ± 2.9, p = 0.012) and TO values were lower (TO = –2.1 [–3.4, –2.0] *vs* –1.6 [–1.9, –0.2], p = 0.003) in the dipper subgroup of hypertensive cases than in the non-dipper subgroup of hypertensive cases (Fig. 1).

The effects of age, BHR, AvSBP, AvDBP, and decline in night-time BP on TS were examined in a multivariate linear regression analysis, and it was determined that the degree of dipping and AvDBP were independent predictors of TS. In this model, the influence of night-time dipping on TS was found to be more prominent than the other factors (p = = 0.001, β = 0.443). The effects of age, BHR, AvSBP, AvDBP, and decline in night-time BP on TO were also examined in a multivariate linear regression analysis, and it was determined that the degree of dipping and age were independent predictors of TO. In this model, the influence of night-time dipping on TO was found to be more prominent than the other factors (p = 0.001, β = –0.418). Spearman's correlation analyses revealed a high positive correlation between the percentages of nocturnal fall in BP and TS (r = 0.600, p = 0.001; Fig. 2). Spearman's correlation analyses revealed a higher negative correlation between the percentages of nocturnal fall in BP and TO (r = –0.653, p = 0.001; Fig. 3).

The correlation coefficients for degree of night--time dipping and HRT indices were higher in the hypertensive group than the normotensive group (for TS: r = 0.691, p = 0.001 in hypertensive group and r = 0.620, p = 0.001 in normotensive group; for TO: r = –0.767, p = 0.001 and r = –0.638, p = 0.001, respectively).

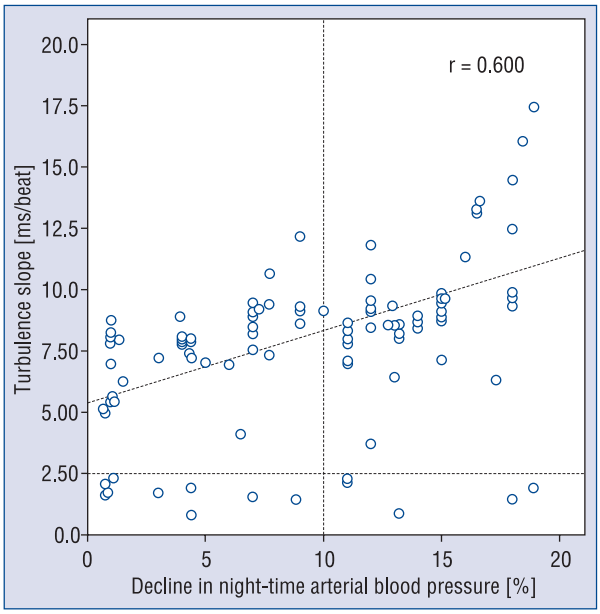

Figure 2. Correlations for turbulence slope indices and decline in night-time blood pressure in all the study population.

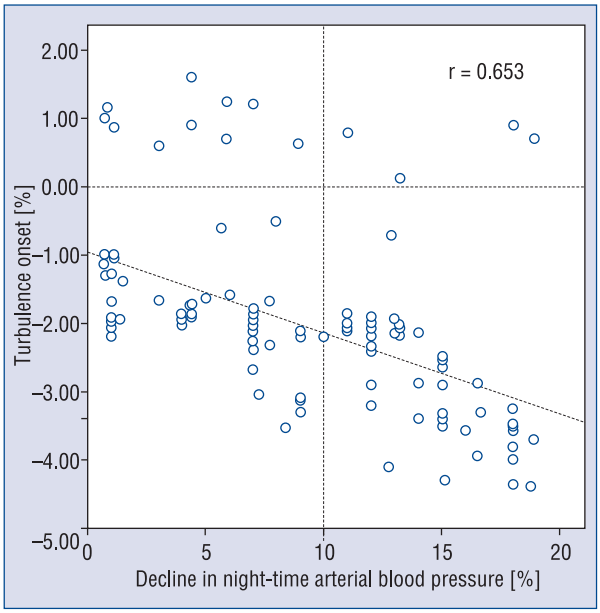

Figure 3. Correlations for turbulence onset indices and decline in night-time blood pressure in all the study population.

When the recommended cut-off values for TO and TS indices were assessed in the normotensive group, although the frequencies of abnormal TS (< 2.5 ms/beat, 3.0% *vs* 6.5%, p = 0.607) and abnormal TO (> 0, 0% *vs* 9.7%, p = 0.108) were higher in the non-dipper subgroup, it did not reach statistical significance. Similarly, when the recommended cut-off values for TO and TS indices were assessed in the hypertensive group, the frequencies of abnormal TS (< 2.5 ms/beat, 24.1% *vs* 13.8%, p = 0.252) and abnormal TO (> 0, 24.1% *vs* 13.8%, p = 0.252) were similar in both subgroups, despite the presence of higher values in the non-dipper subgroup.

Discussion

To the best of our knowledge, our study is the first to evaluate the relationship between circadian BP rhythm and HRT indices. We have found that the degree of non-dipping, which means inadequate fall of night-time BP, is correlated with abnormal HRT indices. A higher degree of non-dipping is associated with lower values of TS and higher values of TO, regardless of normotensive or hypertensive individuals.

Nocturnal dipping of arterial BP is part of the normal circadian pattern, and its absence, which is called non-dipping, is associated with more severe end-organ damage and increased risk of CV events, especially in hypertensive patients [1, 16]. Left ventricular hypertrophy [17], microalbuminuria [18] and cerebrovascular damage [19] tend to be more common in patients whose 24-h BP profile is blunted. Although the underlying mechanisms of nocturnal decrease of BP are not yet fully understood, there is some evidence to suggest that non-dippers show impairment in the autonomic system that includes abnormal parasympathetic and increased sympathetic nervous system activity [6, 7]. Recently, increasing interest has focused on new risk factors for CV disease, especially in the area of non-invasive assessment [16]. The absence of a nocturnal BP decrease is emerging as an index for future target organ damage.

Assessment of HRT is an inexpensive and simple method that allows selection of patients with an increased risk of future cardiac events [20]. The evaluation of HRT is totally non-invasive and can be performed using routine ambulatory 24 h ECG recording. Following a VPB with a compensatory pause, there is known to be an initial acceleration and a later deceleration of sinus rhythm. This sequence is termed HRT and it is thought to be a measure of the autonomic response to perturbations of arterial BP invoked by a VPC [9]. HRT has been shown to be an independent and powerful predictor of mortality after myocardial infarction (MI). Prognostic values of TO and TS were analyzed in

two large and independent populations of post-MI survivors: the Multicenter Post-Infarction Program (MPIP) study and the placebo arm of the European Myocardial Infarction Amiodarone Trial (EMIAT) study [13]. In these studies, both HRT parameters were found to be strong predictors of mortality in post-MI patients.

Durability of circadian BP rhythm seems to be related to durability of ANS. Withdrawal of sympathetic nervous system and dominance of the parasympathetic system play an important role in nighttime BP fall and *vice versa* in daytime. Therefore, some novel risk assessment tool in cardiology practice which is non-invasive and affected by the same physiological mechanism as circadian BP rhythm may have a significant relationship with dipper/non-dipper status. A recently published study evaluating a similar relationship between exercise heart rate recovery (HRR) and circadian BP pattern, revealed that blunting of the nocturnal fall in BP is associated with a delayed recovery of heart rate after graded maximal exercise in both normotensive and hypertensive groups [21].

Just like HRR indices, in our study we found that a similar correlation exists between blunted circadian BP pattern and abnormal HRT indices, not only in hypertensive non-dipper patients but also in normotensive non-dipper patients. It has been hypothesized that HRT is a vagal phenomenon, since atropine eliminates it completely, whereas intravenous esmolol does not alter it [22]. Others believe that the importance of a sympathetic role cannot be ruled out [23]. Both divisions of the autonomic nervous system interact with each other. It seems that vagal predominance is stronger than in the absence of sympathetic tone [24]. Since circadian BP rhythm and HRT indices are affected by the same controller, it could be argued that in the presence of any ANS instability, both of them will show a similar defect.

The major limitations of the present study are the relatively small number of patients and that the results are based on a single center. In our study, when the recommended cut-off values for TO and TS indices were assessed in both groups, although the frequencies of abnormal TS and abnormal TO were higher in the non-dipper subgroups, it did not reach statistical significance. This might be due to the relatively small population size. However, it is more appropriate to use and compare these indices as a continuous variable and this is the main strength of the study. In patients with atrial fibrillation or paced rhythm, HRT indices could not be evaluated and that may be another limitation of this study.

Conclusions

Blunting of the nocturnal fall in BP was associated with abnormal HRT indices, both in normotensive and hypertensive groups. When the prognostic significance of HRT is considered, hypertensives and normotensives with a non-dipping pattern should be followed closely for adverse CV outcome.

Conflict of interest: none declared

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