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Original Article

Impact of anxiety level on circadian rhythm of blood pressure in hypertensive patients

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Abstract: Introduction: Considering the high prevalence rates and growing incidences of hypertension (HT) and anxiety disorders in the modern world, a full understanding of anxiety's relationship to HT is crucial. In this study we aimed to investigate the effects of anxiety level on circadian rhythm of blood pressure (BP) in hypertensive patients. Material and method: This cross-sectional study included 160 previously diagnosed essential hypertensive patients (80 female, 80 male, mean age: 55.3±15.1 years). All participants underwent 24 h ambulatory blood pressure monitoring (ABPM) and filled State-Trait Anxiety Inventory (STAI) (trait) Questionnaire. The study population was divided into 2 groups according to their STAI scores; an anxiety group (n=97; STAI ≥45) and a control group (n=63; STAI<44). Clinical characteristics, laboratory findings and ABPM measurements were compared between the groups. Results: There was no significant difference between the groups for ABPM parameters except morning blood pressure surge (MBPS). Anxiety group had a significantly higher MBPS compared to control group (14.4±17.0 vs 9.1±11.9 mmHg, P:0.03). Multivariate analysis showed that duration of HT and STAI score were the only independent predictors of MBPS. Conclusion: Patients' anxiety level is associated with MBPS which is an independent risk factor for cardiovascular complications. Assessment and control of anxiety seems to be worthy in effective treatment of hypertension.

Keywords: Hypertension, anxiety, morning blood pressure surge

Introduction

Hypertension (HT) is the leading global risk factor for morbidity and mortality, affecting over one billion people worldwide [1]. Recent trends indicate that despite improved detection and treatments, rates of HT are not decreasing [2]. To reverse this trend, we need to improve our understanding of hypertension's etiology and to determine optimal prevention strategies.

In parallel to HT, psychiatric disorders also represent a significant global health burden. Anxiety disorders-including panic disorder, generalized anxiety disorder, and others-are by far the most common mental disorders in the USA, with an estimated prevalence of 18.1% [3]. Psychological factors have been shown to be related to worse cardiovascular disease (CVD) outcomes [4, 5]. However the interaction between mood disorders and CVD is a chicken and egg problem; the causal relationship between two entities is not so clear. There is relatively strong evidence that short term anxiety is capable of increasing blood pressure (BP) in an acute fashion. However, the relationship between trait anxiety and sustained HT is more difficult to investigate and may well be bidirectional.

Regarding the clinical subtypes of HT, anxiety is a potential factor to contribute to the development of white-coat HT, masked HT and pseudopheochromocytoma. It also plays role in development of resistant HT, mainly due to resistance of patients to lifestyle changes and drug adherence as well. However, the effects of anxiety on circadian rhythm of BP is not so clear for today. Alterations in the circadian rhythm of BP, whether a loss of the nighttime dip or anexaggeration of the early morning increase thatoccurs upon rising, indicate increased cardiovascularrisk [6-8].

Investigating the role of anxiety on circadian rhythm of BP will offer a more objective basis in the interaction of anxiety-hypertension and cardiovascular outcomes. In this study we aimed to investigate the effects of anxiety level on circadian rhythm of BP in hypertensive patients.

Material and method

Study population

The study was designed as a cross-sectional study and included 160 consecutive patients with essential hypertension (80 female, 80 male, mean age: 55.3±15.1 years) who were admitted to outpatient cardiology clinic of Izmir University Medical Faculty Hospital between January-August 2013.

All demographic and clinical features were collected from medical history of the patients. Baseline examination included a questionnaire involving gender, age and smoking status. Body mass index (BMI) value was calculated as the ratio of the weight in kilograms to the height in squared meters. Hypertension was defined as systolic pressure >140 mmHg and/or diastolic pressure was >90 mmHg or if the individual was taking antihypertensive medications. The diagnosis of diabetes or cardiovascular disease was based on previous history of diabetes or cardiovascular disease treated with or without drug therapies. Routine laboratory tests including fasting blood glucose, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol and creatinine levels were also assessed.

Patients were excluded if they had presence of secondary HT, any known mood disorder requiring active treatment, cognitive dysfunction and any organic disease interrupting night time sleep of the patient.

Written informed consent was obtained from all patients with HT and control subjects prior to enrollment. The study was approved by the local ethics committee. The investigation conformed to the principles outlined in the Declaration of Helsinki.

Ambulatory blood pressure monitoring

Non-invasive ambulatory blood pressure monitoring (ABPM) measurements were taken with an oscillometric monitor (BR-102 plus, Schiller, Switzerland) every 30 min to record the systolic BP, diastolic BP and heart rate continuously over a 24-h period. Patients were instructed to follow their normal routines of daily life after leaving the physician's office, to immobilize their arms during cuff inflation and to record their bedtimes and rising times in the diary. Stored data were analyzed using commercially available software for the oscillometric monitor (MT-300, Schiller, Switzerland). Overall, diurnal and nocturnal averages of systolic-diastolic BP levels and heart rate (HR) were recorded through automatized reporting of the device. Dipping level, calculated as [(diurnal BP-nocturnal BP)/diurnal BP]; were also automatically recorded for each patient. Dipping level ≥10% were defined as dipper type HT and <10% were defined as non-dipper HT [9]. Morning blood pressure surge (MBPS) was also automatically reported by the software. The definition of MBPS used by the software, was the difference between the average of the pressures over 2 hours after rising and the average BP 2 hours preceding rising [10].

Anxiety screening scale

Anxiety level of the patients were investigated via, The Spielberger State-Trait Anxiety Inventory (trait) questionnaire contains 20 statements that are rated on 4-point Likert type scale. STAI items are divided into two groups: 10 items and 13 items, respectively, are formed to record the presence of anxiety traits and remaining items are designed to record the absence of anxiety traits and are reverse scored [11]. Higher scores on scale indicate more anxiety symptoms [12]. Scores on the STAI≥45 suggest severe anxiety [13]. Turkish translations of the STAI are used for research purposes which have been shown to be validated previously [14]. The patients were instructed to answer the questions in a short time, without too much thinking, as immediate responses tend to be more accurate and require less anxious reflection. The study population was divided into 2 groups according to their STAI scores; an anxiety group (n=97; STAI≥45) and a control group (n=63; STAI<44).

Clinical characteristics, laboratory findings, antihypertensive medications and ABPM measurements including alterations in the circadian rhythm of BP and morning blood pressure surgewere compared between the groups.

Table 1. Comparison of clinical and laboratory parameters between the groups

	Control group (n=63)	Anxiety group (n=97)	P
Age (years)º	55.0±14.4	57.4±15.4	0.07
Sex (Male/Female)	33/30	47/50	0.627
BMI (kg/m^2)º	28.0±3.8	29.2±5.6	0.09
Presence of CVD (n, %)	8 (12.7%)	18 (18.6%)	0.326
DM (n, %)	9 (14.3%)	16 (16.5%)	0.707
Current smoker (n, %)	12 (19.0%)	22/22.7%)	0.583
Serum Cre (mg/dl)º	0.94±0.18	0.98±0.21	0.561
FBG (mg/dl)º	92.8±13.6	94.9±15.7	0.466
Total Chol (mg/dl)º	220.8±18.7	225.3±20.5	0.121
Triglyceride (mg/dl)º	162.8±28.1	168.4±29.6	0.224
HDL-Chol (mg/dl)º	42.1±15.9	41.5±14.1	0.638
LDL-Chol (mg/dl)º	126.5±16.8	128.9±15.2	0.464
Statin usage (n, %)	18 (28.6%)	28 (28.9%)	0.968
Duration of HT (years)ª	2 (6.5)	2 (10)	0,208
STAI scoreª	39 (6)	52 (8)	<0.001
Antihypertensive medication			
Calcium antagonist (n, %)	28 (44.4%)	36 (37.1%)	0.355
Beta blocker (n, %)	14 (22.2%)	23 (23.7%9	0.827
Diuretics (n, %)	24 (38.1%)	38 (39.2%)	0.891

BMI: body mass index, CVD: cardiovascular disease, Cre: Creatinine, Chol: cholesterol, DM: diabetes mellitus, FBG: fasting blood glucose, HDL: high density lipoprotein, LDL: low density lipoprotein, RAAS: renin-angiotensin-aldosterone system. º: mean values ± standard deviation and student's t-test are used. ª: median values with interquartile range and Mann-Whitney-U test are used. Percentage values and chi-square test are used for the rest of the variables in the table.

Statistical analysis

Values are reported as median with interquartile range (IQR), mean ± standard deviation, and percentile value for non-parametric, parametric, and categorical variables respectively. Independent Student's t-test was used to compare means of independent continuous variables. Mann-Whitney U test was used for comparison of non-normally distributed parameters. Pearson's Chi Square was used to evaluate categorical variables. Correlation values reported are Spearman. Factors with statistical significance (P<0.05) in univariate analysis, were included in the stepwise logistic regression analysis to determine the independent predictors of morning blood pressure surge.

Results

The study population consisted of essential hypertensive patients with an average age of 55.3±15.1 years and equal distribution of sex (male/female: 80/80). Median duration of HT was 2 years among the whole group. The clinical characteristics, medications, and laboratory findings for the control group and the anxiety group are shown in **Table 1**. There were no significant differences between the groups in age, sex, body mass index, incidence of previous cardiovascular events, presence of diabetes mellitus, and usage of antihypertensive drugs or statins. Metabolic profile of the patients were similar between the groups in respect of fasting blood glucose (FBG) and lipid parameters. Smoking habits and serum creatinine levels were also similar between the groups.

Table 2 shows ambulatory blood pressure monitoring (ABPM) measurements. Averages of the 24-h, diurnal, nocturnal systolic and diastolic blood pressures, and HR were all similar between the groups. Although the prevalence rates of non-dipper HT were similar between the groups (38.1% in control group and 41.2% in anxiety group, P:0.692); Morning blood pressure surge was significantly higher in anxiety group compared to control group (14.4±17.0, 9.1±11.9 mmHg respectively, P:0.03) (**Figure 1**). The duration of HT (r=0,215, P:0.007) and STAI score were significantly correlated with MBPS (r=0.211, P:0.007)in Spearman's analysis. Age and mean systolic BP were not significantly correlated with MBPS (r=0.032, P:0.690 and r=0.060, P:0.453, respectively). Although BMI had a borderline correlation with MBPS, it was not statistically significant (r=0.153, P:0.090). The univariate and multivariate regression analyses were performed in order to identify the independent predictors of MBPS. Both analyses showed that the only independent predictors of MBPS were duration of HT and STAI score (**Table 3**).

Discussion

Considering the high prevalence rates and growing incidences of HT and anxiety disorders

Table 2. Comparison of ambulatory blood pressure monitoring findings between the groups

	Control group (n=63)	Anxiety group (n=97)	P
24 hour			
SBP (mmHg)	139.0±15.0	142.7±14.2	0.255
DBP (mmHg)	81.5±9.0	79.7±9.7	0.372
HR (beat/min)	76.5±8.9	77.1±9.4	0.672
Diurnal			
SBP (mmHg)	143.7±15.2	145.3±14.5	0.285
DBP (mmHg)	79.0±10.1	81.8±9.2	0.321
HR (beat/min)	79.1±10.1	82.2±10.3	0.07
Nocturnal			
SBP (mmHg)	128.1±13.6	131.4±15.2	0.116
DBP (mmHg)	74.2±8.0	76.8±9.1	0.342
HR (beat/min)	69.1±9.2	70.7±10.5	0.320
Circadian rhythm of BP			
Non-dipper HT (n, %)*	24 (38.1%)	40 (41.2%)	0.692
MBPS (mmHg)	9.1±11.9	14.4±17.0	0.03

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, BP: blood pressure, HT: hypertension, MBPS: Morning blood pressure surge. *: percentage values and chi-square test are used. Mean values with standard deviation and student's t-test are used for the rest of the parameters in the table.

in the modern world, a full understanding of anxiety's relationship to HT is crucial. However, a bidirectional causation, or existence of anxiety as a common-causal variable in hypertensive population limits the understanding of causal relationship between each other.

In this study the effects of anxiety level on circadian rhythm of BP was evaluated in hypertensive patients. Our results showed a direct association between morning BP surge and anxiety level of the patients. The importance of thiscircadian pattern has been proved by the extensive literature over the last two decade which showed that cardiovascular events, such as stroke, transient ischemic attacks, myocardial infarction and sudden cardiac death occur most frequently during the morning hours which coincides with the rapid rise in BP and HR [7, 8]. Successful HT management requires several steps, including timely detection, better recognition of associated conditions and identification of prognostic factors. Therefore, discovering the possible roles of mood disorders in development of HT and related cardiovascular outcomes, could alert the clinicians to be vigilant in monitoring and treating anxiety.

The relative contribution of depressive and anxiety disorders to the development of CVD remains unclear. Several hypothesis have been developed to explain this association. Psychosocial stressors associated with anxiety disorders raise autonomicarousal via the hypothalamic-pituitary-adrenal axis, which increasescirculating catecholamines. One study showed that trait anxiety was associated with higher plasma norepinephrinein patients with essential HT, suggesting achronic heightening of sympathetic activity [15]. The increased adrenergic discharge observed in patients with panic disorder may also eventually cause irreversible peripheral vasoconstriction, resulting in chronic HT. Hypertensive patients with anxiety also have been found to have reduced sinus vagal modulation compared to hypertensive patients without anxiety symptoms [16]. Other potential mechanisms include an increase in adverse behaviors due to stress and anxiety that impact health such as increased eating, smoking, alcohol use, and decreased exercise. Khatiband colleagues performed a systematic review of barriers todetection, treatment, and control of HT [17]. They identified stress, anxiety, and depression as the most commonly reported barriers hindering or delaying lifestyle modification. Moreover increasing the development of HT and causing behavioral barriers in control of HT, anxiety may also contribute to the abnormalities in circadian rhythm of BP.

Alterations in the circadian rhythm of BP, whether a loss of the nighttime dip or anexaggeration of the early morning increase that occurs upon rising, are shown to be associated with cardiovascular complications of HT, independent of the average BP level. The role of patients' anxiety level on circadian rhythm of BP is not clear for today. There is only one literature data investigating this topic; and this study showed that anxiety disorder is associated with nocturnal and early morning HT in hypertensive patients [18]. In this study, the anxiety group had a significantly greater BMI than the control group which could also contribute to the diurnal variation of BP. No multivariate analysis was performed in this study which limits making a conclusion on the net effect of anxiety on dip-

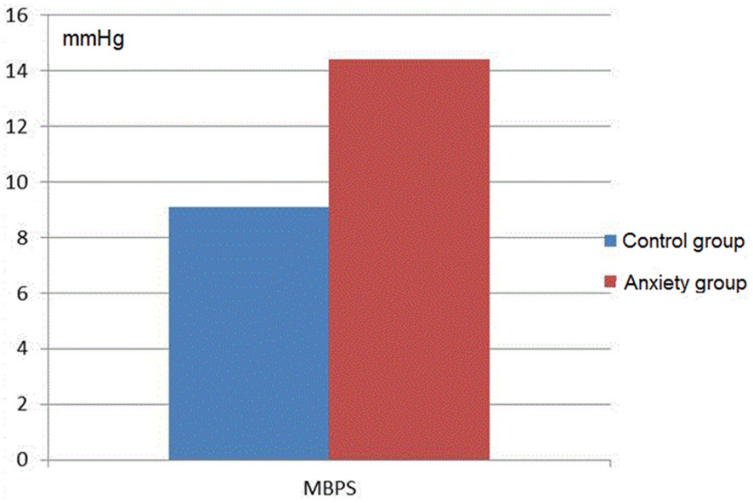

Figure 1. Comparison of morning blood pressure surges between groups.

Table 3. Univariate and multivariate regression analyses of parameters in association with morning blood pressure surge

	Univariate analysis			Multivariate analysis	
	Beta	95% CI	P	Beta	95% CI
Age (years)	0.036	-0.119-0.191	0.647		
Sex	0.031	-0.06-0.012	0.528		
BMI (kg/m^2)	0.126	-0.162-0.958	0.162		
DM	0.106	-2.822-10.258	0.262		
CVD	-0.118	-8.911-1.693	0.137		
Duration of HT (years)	0.178	0.038-0.623	0.027	0.163	0.041-0.627
HDL	0.09	-0.20-0.37	0.552		
LDL	0.15	-0.18-0.69	0.228		
RAAS blocker	-0.04	-0.29-0.22	0.761		
Beta blocker	-0.40	-0.62-0.08	0.086		
Diuretics	-0.25	-0.52-0.09	0.094		
Calcium antagonists	-0.18	-0.48-0.121	0.221		
Creatinine	0.103	-0.34-0.223	0.314		
STAI score	0.184	0.061-0.675	0.019	0.178	0.014-0.593

BMI: body mass index, CVD: presence of cardiovascular disease, DM: diabetes mellitus, HDL: high density lipoprotein, HT: hypertension, LDL: low density lipoprotein, RAAS: renin-angiotensin-aldosterone system.

ping status and morning surge as well. In the present study, the anxiety group and the control group had similar baseline clinical and metabolic profiles. So the contribution of anxiety to the morning BP surge is independent of other possible clinical and metabolic factors.

Our study group, presented a surprisingly high level of anxiety compared to the existing literature data. This high prevalence may be related to the type of the anxiety inventory and the anxiety cut-off, we used in our analyses. We used a validated anxiety inventory; STAI which is among the most widely researchedand widely used measures of general anxiety. STAI is available in many different languages including Turkish [14]. Using a cut-off level of ≥45 for high anxiety level, 97 out of 160 patients were detected to have a high level of anxiety. A cut point of 39-40 has been suggested to detect clinically significant symptoms for the S-Anxiety scale; however, other studies have suggested a higher cut score of 54-55 for older adults [11, 12]. We preferred to use a cut-off level of 45 which was already used in patient profiles similar to our study group [13]. This relatively high prevalence may also be related to social characteristics of our study population. As our group was consisted of hypertensive patients, anxiety may also be a result rather than a cause in our study group. It is also well known that anxiety scales are overly inclusive and the majority of patients with positive screening results will not meet the objective criteria for anxiety disorders [19]. So rather than labeling patients with high score as anxiety disorder, rendering them as patients with high anxiety level is more appropriate.

Among ABPM parameters, only MBPS significantly differed among groups in our study. Anxiety group had a significantly higher average of MBPS compared to control group. Averages of 24 hour-diurnal and nocturnal SBP, DBP and HR were all similar between groups. The prevalence rates of non-dipper HT were also similar between groups. There was a significant but a week correlation between MBPS and anxiety score of the patient. When the predictors of MBPS were analyzed in univariate and multi-

variate models, duration of HT and anxiety score were found as the only independent predictors of MBPS. The clinical and laboratory correlates of MBPS were identified as, age, male sex, high cholesterol levels, and high BMI in previous literatures [20]. Also beta blocker and diuretic usage were found to be associated with lower levels of MBPS [20]. In our study beta blocker and diuretic usage also showed a border line association with the decrease in MBPS, however both of them did not reach clinical significance (P:0.086 and P:0.094, respectively). Although there was no correlation between age and MBPS, duration of HT was an independent predictor of MBPS. This finding suggests that, arterial aging is more important than biological aging in respect of MBPS. Arterial stiffness which is an objective parameter of arterial aging has been shown to be correlated with MBPS in small sized studies [21]. However, larger studies are needed to make a more robust conclusion on association of arterial stiffness and morning BP surge.

Our study has several limitations. It is a single-center study with a relatively small sample size. A systematic selection bias cannotbe excluded as the patients with a higher educational degree were selected in order to accord with the study questionnaire. It is alsoimportant to note that although we controlled for important-covariates, other factors may have influenced the results. This was an observational study using claims data, we were unable to find out the conclusive mechanisms for the causal relationship. Future population based studies with larger numbers of patients are needed to make a more robust conclusion on the association of anxiety and circadian rhythm of BP. Also future studies are needed to conclude on the effects anxiety reduction on BP profiles and cardiovascular outcomes as well.

In conclusion, in order to avoid cardiovascular complications of HT, MBPS and dipper/non-dipper patterns of BP should be assessed and somehow be diminished. Identification of clinical correlates of MBPS is important in this manner to have a better control of associated conditions. The findings of present study, help us to understand the two-way and often complex relationship between anxiety and HT. Defining the role of anxiety in circadian variation of BP offers an objective finding in this association. The association of MBPS and patients' anxiety level should alert the physicians to monitor and treat anxiety in order to have a better control of cardiovascular complications.

Disclosure of conflict of interest

None.

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