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Association between heart rate turbulence and anxiety symptom levels

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Abstract

General anxiety disorder (GAD) is a condition characterized by extreme, persistent, and uncontrollable worry lasting for more than six months. In addition to cognitive and behavioral symptoms, individuals with GAD also commonly exhibit physical signs and autonomic nervous system symptoms. Heart rate turbulence (HRT) is the assessment of sinus rhythm cycle fluctuation occurring in the presence of ventricular premature contraction (VPC), and is a parameter used to show autonomic dysfunction. There are no studies in the literature investigating the association between GAD and HRT. The aim of the present study was to determine the association between HRT and anxiety symptom levels. The study included 72 consecutive patients. The patients were fitted with Holter devices for 24-hr rhythm monitoring and asked to complete the Hospital Anxiety and Depression Scale (HADS) to assess their anxiety symptom levels. The study participants were grouped based on the severity of their anxiety symptoms as low (group 1) and high (group 2). Of the 72 participants, 26 had high anxiety levels and 46 had low anxiety levels. There was a significant difference between the two groups in HRT parameters. Patients in the high-anxiety group had significantly higher turbulence onset (TO) and significantly lower turbulence slope (TS) when compared with the low-anxiety group. Anxiety score was positively correlated with TO (r=0.296, p=0.01) and negatively correlated with TS (r=-0.304, p=0.009). In the present study, we found that patients with high anxiety levels showed greater abnormality in HRT parameters, indicating autonomic dysfunction.

Keywords: Heart rate turbulence, anxiety, autonomic dysfunction

Introduction

General anxiety disorder (GAD) is a condition characterized by extreme, persistent, and uncontrollable worry lasting longer than 6 months. A review of epidemiologic studies conducted in Europe reported that GAD has a prevalence of 4.3-5.9% and is seen more frequently in women and the elderly.1,2 In addition to cognitive and behavioral symptoms, individuals with GAD also commonly exhibit physical signs such as fatigue and myalgia. They often exhibit symptoms related to the autonomic nervous system such as palpitations, sweating, shivering, and hot flashes [3,4].

Ventricular premature contractions (VPC) are extra beats triggered by the myocardium in various conditions. They may occur in individuals with no heart disease, and are seen in various heart conditions, independent of disease severity. The prevalence of VPC is up to 80% in 24-hr rhythm Holter recordings in the general population and increases with advancing age [5]. Heart rate turbulence (HRT) is the assessment of sinus rhythm cycle fluctuation occurring in the presence of VPC and is a parameter used to show autonomic dysfunction [6]. HRT comprises two parameters, turbulence onset (TO) and turbulence slope (TS), which are calculated from VPCs on rhythm Holter recordings. HRT measurement can be done in individuals showing at least 5 VPCs during 24-hr rhythm Holter monitoring.

Heart rate variability (HRV), defined as cyclic changes in sinus speed over time, provides information about sympathetic/parasympathetic balance and is thus evaluated as a measure of cardiac autonomic tone and as a cardiorespiratory system indicator. Previous studies have shown that HRT is a stronger and more independent predictor of mortality than HRV [7]. Although

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HRV has been used to demonstrate autonomic dysfunction in GAD patients, there are no studies in the literature investigating the association between GAD and HRT [8]. The aim of the present study was to evaluate the relationship between anxiety levels and HRT parameters as indicators of autonomic dysfunction.

Material and Methods

Participants

The study included 72 consecutive patients between 18-80 years of age who presented to the cardiology outpatient clinic with complaints of palpitations and showed at least 5 VPCs during 24-hr rhythm Holter monitoring. Patients who were unable to sign the informed consent form, those with thyroid dysfunction, coronary artery disease, or heart failure, and those using beta blockers and antiarrhythmic drugs that may affect VPC were excluded. Other exclusion criteria were: chronic systemic disease, congenital heart disease, significant valvular heart disease, hypertrophic cardiomyopathy and cor-pulmonale [9]. The patients' demographic data, left ventricular ejection fraction measured from transthoracic echocardiographs, and blood test results were recorded. This study was approved by the local clinical research ethics committee (2017/146).

Sample size

The number of patients to include in the study was determined by power analysis. A total of 44 patients (22 patients in each group) are needed to achieve 80% power at two-sided 5% significance level (MedCalc 9.2.0.1).

Biomedical data

Venous blood samples were taken in the morning between 8:00-8:30 after a 12-hr fast. Height (cm) and weight (kg) were recorded and used to calculate body mass index (BMI). Patients' 24-hr rhythm Holter recordings were analyzed using the Cardio Track Holter Analysis System (Hangzhou, China). TO evaluates the presence of tachycardia by comparing the average interval between two normal beats before and after a VPC. A lack of this response (TO $\geq$0) is a sign of insufficient autonomic adaptation. TO reflects vagal break ability, which is necessary to compensate for acute cardiac output loss due to VPC. TS measures the degree of heart rate deceleration (bradycardia, tachycardia, return to baseline level) after a VPC. TS <2.5 is a strong indicator of autonomic dysfunction of the cardiovascular system [10]. Previous studies have shown that abnormal HRT is an indicator of cardiac autonomic dysfunction and leads to higher mortality [11-13]. TO and TS were calculated automatically by the software (Cardio Track Holter System Premier version 1.4.1.5).

Psychometric measurements

The patients were fitted with 24-hr rhythm Holter devices and asked to complete the Hospital Anxiety and Depression Scale (HADS) to assess their anxiety symptom levels. The HADS is one of the most widely used tools in the assessment and management of anxiety and depression symptoms. The HADS has separate scales for anxiety and depression. The HADS consists of two factors: the first is anxiety symptoms and the second is depression symptoms. Using receiver operating characteristic curve analysis, cut-off points for the Turkish version of the HADS were determined as 10 points for the anxiety subscale and 7 points for the depression subscale [14]. This scale was originally designed to detect symptoms of depression and anxiety in patients attending medical outpatient clinics [14]. Although the scale uses the word "hospital", it can also be used in every health establishment including outpatient polyclinics. Both the original HADS and the Turkish version have been shown to be valid and reliable in the assessment of outpatients [15,16]. A cardiology specialist measured the physiological parameters and a psychiatrist administered the HADS. After the patients in our study were fitted with 24-hr Holter monitors, they were given the HADS questionnaire form and asked to fill it in while the Holter monitor was recording. The HADS form was given after the patient was fitted with a 24-hour rhythm holter and was asked to fill out the form themselves during recording. The patients returned the HADS forms together with their Holter monitors when they returned to the outpatient clinic 24 hours later. The patients' responses were recorded by two separate psychiatric specialists who had no knowledge of the study and their anxiety and depression scores were calculated. The study participants were separated into groups based on the severity of their anxiety symptoms as low (group 1) and high (group 2). Patients without anxiety symptoms also were included in the low anxiety level group.

Statistical analysis

Statistical analyses were done using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) software package. The data were evaluated for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were expressed as percentage; numerical variables showing normal distribution (parametric) were expressed as mean ± standard deviation and those not normally distributed (non-parametric) were expressed as median and interquartile range. Student's t-test or Mann-Whitney U test was used to analyze numerical variables; chi-square ($\chi 2$) test was used for categorical variables. Correlation analysis was done with Pearson rank test for parametric variables and Spearman test for non-parametric variables. P values less than 0.05 were accepted as statistically significant.

Results

Seventy-two participants were included in the study, 26 with high anxiety levels (group 1; 18 females, mean age 45.6±16.1 years) and 46 with low anxiety levels (group 2; 27 females, mean age 47.5±16.9 years). The study participants' demographic and clinical characteristics are presented in Table I. There were no significant differences between the groups with respect to diabetes mellitus, hypertension, cigarette use, body mass index, or biochemical and hematologic parameters. Patients in the high-anxiety group had significantly higher TO (0.6 vs. -2.2, p<0.001) and significantly lower TS (1.8 vs. 3.5, p<0.001) when compared with the low-anxiety group (Table I).

When TO and TS values were classified as normal and abnormal, patients with high anxiety scores had higher rates of abnormal TO (65.3% and 19.7% respectively in the high and low anxiety groups, p<0.001) and TS (80.7% and 34.7% respectively, p<0.001) (Table II). Anxiety score was positively correlated with TO (r=0.296, p=0.01) (Figure 1) and negatively correlated with TS (r=-0.304, p=0.009) (Figure 2).

Table 1. Demographic, echocardiographic and clinical features of patients according to anxiety level.

Variable	Low anxiety level Group (n=46)	High anxiety level Group (n=26)	p
Age, year	45.6 ± 16.1	47.5 ± 16.9	0.64
Gender, male (n,%)	19, %41.3	8, %30.7	0.37
DM, present (n,%)	10, %21.7	7, %26.9	0.61
HT, present (n,%)	12, %26	7, %26.9	0.91
Creatinine, mg/dl	0.9 ±1.0	0.77±0.2	0.4
LDL Cholesterol, mg/dL	119.4±39.3	96.5±34.3	0.62
Active Smoking, (n,%)	12, %26	6, %23	0.77
TSH (µıu/mL)	1.9±1.4	1.8±0.8	0.08
Body mass index(kg/m2)	26.5±2.6	27.1±2.5	0.16
TO	-2.23±3.2	0.66±3.3	<0.001
TS	3.57±3.3	1.86±2.2	<0.001

DM; diabetes mellitus, HT; hypertension, LDL; low density lipoprotein, TSH; Thyroid stimulating hormone, TO; turbulence onset, TS; turbulence slope
p value below 0.05 was considered significant and significant parameters were shown by bold type

Table 2. The relationship with anxiety levels and abnormal heart rate turbulence.

	Low anxiety level group n=46	High anxiety level group n=26	p
Abnormal TO	9, %19.5	17, %65.3	<0.005
Abnormal TS	16, %34.7	21, %80.7	<0.005

TO; turbulence onset, TS; turbulence slope, HRT; heart rate turbulence, Abnornmal TO; TO≥0, Abnormal TS; TS≤2.5
p value below 0.05 was considered significant and significant parameters were shown by bold type

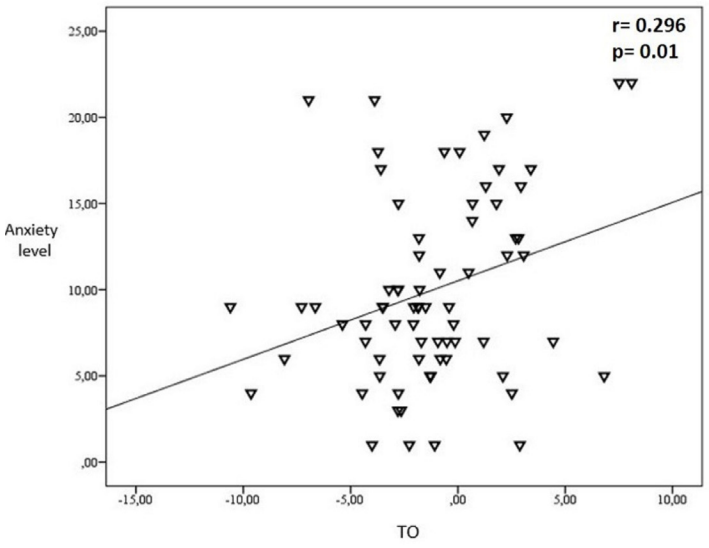

Figure 1. Correlation between turbulence onset and anxiety level (scatter dot).
TO; turbulence onset

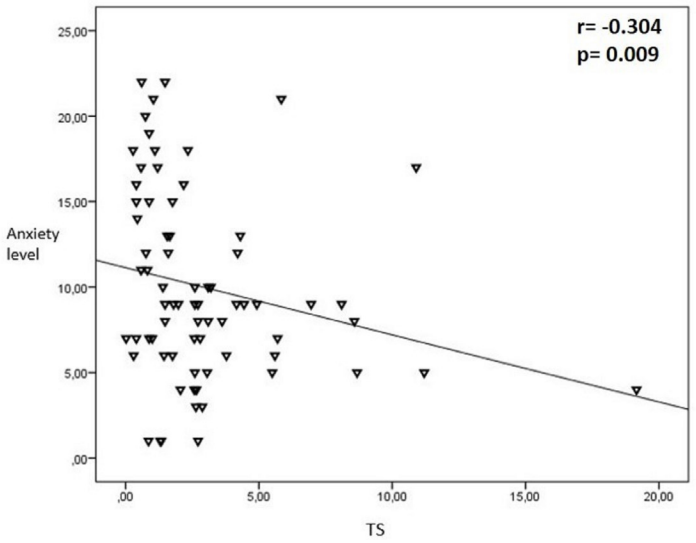

Figure 2. Correlation between turbulence slope and anxiety level (scatter dot).
TS; turbulence slope

Discussion

The effect of anxiety disorder on autonomic dysfunction was previously demonstrated in a study using HRV.8 The present study is the first in the literature to investigate the effect of anxiety level on HRT. In the present study, we found that patients with high anxiety levels showed greater abnormality in HRT parameters indicating autonomic dysfunction, and the degree of abnormality correlated with anxiety scores.

Certain psychiatric diseases have been shown to cause dysregulation of the autonomic nervous system. Kop et al. found that cardiovascular mortality was higher in patients with autonomic nervous system dysfunction detected by HRT [17]. Carney et al.

reported that patients with depression following acute myocardial infarction had a higher incidence of abnormal HRT measurement and higher mortality rate [18]. Although autonomic dysfunction has been shown in depressed patients using the HRT method, our study is the first to use HRT to demonstrate autonomic impairment in patients with GAD.

GAD and depression are distinct psychiatric disorders. Depression is described as having feelings of anguish or despair and no longer deriving pleasure from activities once enjoyed. GAD is a common condition characterized by uncontrollable, extreme agitation and anxiety. Anxiety disorders have been shown to increase the risk of cardiovascular disease by 3-4 fold, and approximately double the risk of cardiac mortality [19,20]. In previous studies, GAD was found to cause disruption between the cortical and subcortical networks [21]. This connection is believed to be an important component of the central autonomic network [22]. There are studies in the literature demonstrating autonomic dysfunction in individuals with anxiety disorder. Furthermore, meta-analyses have revealed that this autonomic disruption is independent of medication use and medical comorbidities [23]. Kim et al observed that GAD patients not under medical treatment showed greater abnormality in HRV parameters when compared with healthy individuals [24]. Abnormal HRV due to psychological stress is thought to develop secondary to reduced parasympathetic tone [25]. GAD compounded by major depression was found to have a stronger negative effect on HRV compared to GAD alone [14]. In the present study, patients presenting to a cardiology outpatient clinic with complaints of palpitations were asked to complete the HADS in order to determine their anxiety symptom levels. Zigmond and Snaith developed and demonstrated the validity and reliability of the HADS in 1983 [15].

A VPC is followed by a temporary drop in blood pressure. This results in decreased baroreceptor activity and reduced vagal stimulation, which in turn causes the heart rate to increase. Following increased myocardial contractility and blood pressure after a VPC, sinus node activity declines due to a counter effect, creating a biphasic HRT curve with increases and decreases. Abnormal HRT is a sign of autonomic dysfunction or impaired baroreflex sensitivity and increases the risk of mortality and sudden death [26]. Previous studies have reported abnormal HRT in conditions such as coronary artery disease [27], heart failure [28], metabolic syndrome [29], and polycystic ovary syndrome. Furthermore, Baydar et al showed that abnormal HRT was correlated with coronary artery disease severity [30]. There are no other studies in the literature that evaluate the relationship between anxiety level and HRT.

Limitations of Study

One of the limitations of this study is the relatively limited number of patients and correlation analysis revealing weak correlations. Groups are also heterogeneous. We believe that a thorough assessment of HRT parameters following psychiatric therapy in patients with high anxiety levels will better elucidate the relationship between anxiety and HRT.

Conclusion

Disrupted HRT function is an important indicator of autonomic dysfunction and is associated with increased mortality. HRV has been used to demonstrate the negative effects of anxiety disorders on autonomous function. In the present study, we found that patients with high anxiety levels showed greater abnormality in HRT parameters indicating autonomic dysfunction. Anxiety levels were positively correlated with TO and negatively correlated with TS. Results from this study suggest that the long-term adverse cardiovascular consequences of anxiety may be partially explained by autonomic dysfunction. Treatment of patients with anxiety by either pharmacological or psychological interventions may lead to improved long-term cardiovascular outcomes.

The manuscript was presented as a poster in the 33th. Turkish Cardiology Congress with International Participation.

Competing interests
The authors declare that they have no competing interest

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Ethical approval
Before the study, permissions were obtained from local ethical committee.

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