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Analysis of 24-Hour Heart Rate Variability among Panic Disorder Patients without Previous Drug Treatment and Comorbid Disorders

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SUMMARY

Objective: One of the methods used to assess autonomic nervous system dysfunction in the etiology of panic disorder (PD) is heart rate variability (HRV). HRV is controlled by the sympathetic and parasympathetic (vagal) branches of the autonomic nervous system and reflects the capacity of autonomic stimulation by the parasympathetic system. The aim of this study was to evaluate heart rate variability (HRV) time domain parameters based on twenty four hour holter ECG analysis among drug-naive patients with panic disorder (PD) without any other medical and psychiatric comorbidity.

Method: The study group consisted of 41 patients with PD and 46 healthy controls. Participants were evaluated with SCID-1 for psychiatric diagnoses. Then Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), Panic Disorder Severity Scale (PDSS) and Clinical Global Impression Scale (CGI-S) were applied to participants. Twenty four hour Holter ECG outcomes were analyzed on a computer program and time domain parameters were evaluated.

Results: Among the parameters analyzed from HRV, SDANN was significantly higher ($p < 0.001$); duration of RMSSD, NN50 and pNN50 were lower in PD group than the control group ($p = 0.003$, $p = 0.005$, $p = 0.047$, respectively). In the correlation analysis, there was a moderate negative correlation between CGI-S and NN50 and pNN50. In logistic regression analysis, the increase in SDNN was found to increase the probability of PD by 1.11 (95% CI, 1.010-1.209); the increase in SDANN was found to decrease the probability of PD by 0.892 (95% CI, 0.818-0.973), and the increase in pNN50 was found to decrease the probability of PD by 0.523 (95% CI, 0.342-0.801).

Conclusion: The data obtained in our study confirm that there is a decrease in some HRV parameters like RMSSD, NN50 and pNN50 reflecting parasympathetic activity among patients with PD.

Keywords: Panic disorder, heart rate variability, autonomic nervous system, spectral analysis

INTRODUCTION

Panic disorder (PD) is a disease that presents with repeated and unexpected panic attacks which severely affect the quality of life. The typical symptoms of panic attack include chest pain, palpitations, sweating, respiratory difficulties, feeling of drowning, and flushes suggesting autonomic nervous system (ANS) function disorders (McCraty et al. 2001).

Among the many studies reporting ANS function disorder in the aetiology of PD, some have measured catecholamine or its metabolites in plasma or urine to evaluate sympathetic nervous system activity (Gurguis and Uhde 1998, van Megen et al. 1996), and others have examined heart rate or blood pressure responses after autonomic stimulation such as orthostatic provocation (Yeragani et al. 1990).

Heart rate variability (HRV) is another approach evaluating ANS by measuring heart rate variations (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) and was

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initially used in the field of cardiology to assess especially the severity of ischemic heart diseases. In healthy individuals with normal sinus rhythm, continuous change in the duration of intervals between heart beats is caused by the physiological fluctuations of respiration, thermoregulation and a range of baroreflex mechanisms. Heart rate and rhythm is affected by ANS (Kayıkçıoğlu and Payzın 2001, Friedman and Thayer 1998). HRV is directed by the parasympathetic and sympathetic cardiac innervation and reflects the suppressive capacity of the parasympathetic system on the autonomic stimulation (Carney et al. 2000, Frasure-Smith et al. 1995). Thus, high HRV reflects a healthy ANS responding to the variable environmental conditions (Thayer and Lane 2007), whereas reduced HRV is regarded as a marker reflecting autonomic function disorder in a variety of clinical disorders (Bloomfield et al. 1997, Thayer and Lane 2000).

HRV can be analyzed on the short term 5-minute or the long-term 24-hour recordings by the non-invasive method of electrocardiography (ECG) (McCraty et al. 2001). Calculation of the HRV parameters is based on the analysis of the R waves measured by ECG. Many methods have been developed to determine the R-R interval. After ECG records are obtained, HRV parameters are calculated with statistical methods using special computer software. HRV analyses are investigated with time measurements or frequency measurements based on separate assumptions and approaches (Yang et al. 2010). The time measurement method used in our study is based on the analysis of the interval between two consecutive normal beats (the NN interval) emanating from the sinus node during the 24-hour Holter ECG recordings. Many indices have been developed based on the values thus calculated (Kayıkçıoğlu and Payzın 2001). In this study, the time domain measures of SDNN (standard deviation of NN interval), SDANN (standard deviation of the average NN), SDNN index, RMSSD (root mean square successive difference) ,the NN_{50} value and pNN50 (percentage of differences of successive NN intervals greater than 50 ms) for HRV were used (Berntson et al. 1997, Berntson et al. 2005, Kayıkçıoğlu and Payzın 2001). Throughout the investigation, SDNN, as the standard deviation of all NN intervals, shows the general status of ANS balance and SDANN is the standard deviation of mean NN intervals in the 5-minute recordings. The SDNN index is the mean of standard deviations of NN intervals recorded every 5 minutes during the 24-hour recording. RMSSD is the square root of the total squared values of the differences between consecutive NN intervals recorded during 24-hours and reflects the parasympathetic activity. RMSSD shows the changes in heart rate in response to respiratory processes. The NN_{50} value is the count of the changes of more than 50 milliseconds between every two NN intervals. The pNN50 is the ratio of the NN50 count to the total NN interval count expressed in percentage terms and reflects parasympathetic activity (Berntson et al. 1997, Berntson et al. 2005, Kayıkçıoğlu and Payzın 2001). The time-dependent parameter of SDNN shows the general status of the autonomic nervous system balance, while pNN50 and RMSSD predominantly reflect parasympathetic activity (Kayıkçıoğlu and Payzın 2001). Another method for HRV evaluation depends on frequency measurements by spectral analysis using the 2-5 minute 'short-term' and the 24-hour 'long-term' recordings. From both short and long time records, 3 basic spectral parameters of very low frequency (VLF), low frequency (LF) and high frequency (HF) can be calculated. (Kayıkçıoğlu and Payzın 2001). In clinical studies, LF, HF and the LF/HF ratio are used. LF shows sympathetic activity and HF indicates parasympathetic activity. The LF/HF ratio is a marker of sympathovagal balance (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In the literature, majority of the studies assessing HRV in PD patients used frequency measurements (Yeragani et al. 1993, Klein et al.1995, Hovland et al. 2012), while very few studies used time measurement methods (Petrowski et al. 2016, Petrowski et al. 2010, Durdu et al. 2018).

Although there is not a consensus for the use of HRV in research on autonomic function disorder in mental disorders, HRV continues to be investigated as a candidate biomarker for a variety of mental disorders including anxiety disorders led by PD (Kotianova et al. 2018, Perini and Veicsteinas 2003), post-traumatic stress disorder (PTSD) and depression (Boettger and Hoyer 2006, Ito et al. 1999, Nahshoni et al. 2004, Udupa et al. 2007, Peschel et al. 2016, Friedman 2007, Shinba 2017). Research has demonstrated increased heart rate in patients with PD diagnosis at rest compared to healthy controls (Martinez et al. 2010, Friedman and Thayer 1998, Cohen et al. 2009, Garakini et al. 2009, Wise et al. 2011), reduction in HRV (McCraty et al. 2001, Hovland et al. 2012, Martinez et al. 2010, Wise et al. 2011, Yeragani et al. 2003, Diveky 2012), reduced vagal tonus and a relative increase in sympathetic system efficacy (McCraty et al. 2001, Yeragani et al. 1993, Klein et al. 1995, Friedman and Thayer 1998, Chalmers and Quintana 2014, Cohen and Benjamin 2006). Furthermore, an association was reported between the anxiety level and the reduction in frequency dependent parameters, such as HF, that reflect parasympathetic activity in HRV (Miu et al. 2009). A study by Hovland et al. (2012) found the reduction in HRV to be associated with the severity of PD symptoms. Based on these data, HRV is considered to be an important biomarker for evaluating symptom severity in PD patients (Garakini et al. 2009, Diveky 2012, Yeragani et al. 1999).

There are also studies reporting PD to be associated with increased risk of cardiac disease and mortality (Albert et al. 2005, Katerndahl 2008, Tully and Baune 2014, Gomez-Caminero et al. 2005); and a strong link between PD and cardiovascular disease was reported by Tully and Baune

(2014). A population-based study on the correlation between PD and coronary artery disease (CAD) reported the CAD risk was doubled in PD patients (Gomez-Caminero et al. 2005). This finding and the reduced HRV in PD patients suggest that HRV can be used as a biomarker (Cohen and Benjamin 2006, Tsuji et al. 1996).

Most studies in the literature have used short-term frequency measurements in assessing HRV in PD patients (Petrowski et al. 2016, Martinez et al. 2010, Diveky 2012), with few studies having evaluated HRV with the 24-hour Holter approach (McCraty et al. 2001, Durdu et al. 2018, Yeragani 1998). In a majority of these studies, comorbid psychiatric disorders, physical diseases and cigarette smoking, known to affect HRV, were not excluded. (Durdu et al. 2018, Kobayashi et al. 2005, Shinba 2017). Therefore, it was decided in this study to make time-based measurements using the 24-hour Holter method in order to compare HRV in healthy individuals with PD patients who did not have any comorbid psychiatric disorder diagnosis, were not on any psychotropic agents and were not cigarette smokers. The main hypotheses of our study are that, as compared to the controls, the time dependent HRV parameters reflecting parasympathetic activity are reduced in PD patient and that this decrease is related to PD severity.

METHOD

Participants

The study included 41 patients with PD diagnosis on the criteria of the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; American Psychiatric Association 1994) attending the psychiatry outpatient clinic in Erzurum Training and Research Hospital between March 2016 and September 2016. Hospital staff, consisting of 46 healthy individuals, without any current psychiatric treatment or regular drug use for any physical illness and, also, age and gender matched with the patients were recruited as the control group.

The exclusion criteria for the PD group were the presence of any neurological diseases affecting cognitive functions including previous cerebrovascular disease; epilepsy, demyelinating diseases such as multiple sclerosis; heart diseases such as HT, rhythm disorder, heart valve defects; endocrine disorders including DM, hypothyroidism, hyperthyroidism; alcohol and/or drug intoxication or lifelong drug/alcohol use disorder; lifelong psychotic disorders comorbid psychiatric disorders including bipolar disorder, current depression; anxiety disorders, PTSD, obsessive compulsive disorder; using any medication other than antidepressant, antipsychotic or mood stabilising agents; pregnancy and lactation; having used benzodiazepines , propranolol or alcohol in the previous 24-hours and caffeine in the previous 2 hours. Medical records of patients known to have consulted the emergency services with panic attack were investigated and those who had been given benzodiazepines or propranolol in the previous 24 hours were also excluded from the study.

Written informed consent of the participants were acquired prior to the study which was approved by Erzurum District Training and Research Hospital local Ethics Committee.

Patients who had consulted the psychiatry outpatient clinic and were diagnosed with PD on the basis of the SCID-I interviews (First et al. 1996) were asked to complete the Panic Disorder Severity Scale (PDSS), the Hamilton Anxiety Rating Scale (HAM-A), the Hamilton Depression Rating Scale (HAM-D) and the Clinical Global Impressions (CGI) Scale. After the interviews, the patients were directed to the cardiology polyclinic with the request to complete the tests for a haemogram, fasting or sated blood sugar, liver function tests (LFT), renal function tests (RFT), thyroid function tests (TFT) and electrolyte levels. Further, hospital records of the patients were controlled and their medical records were investigated. Patients with normal tests were subsequently examined by ECG and ECO and fitted with the 24-hour Holter equipment. The recorded data were automatically loaded to the computer program to be analysed for the time-dependent parameters of HRV.

Of the 51 patients referred to the cardiology polyclinics with preliminary PD diagnosis, 3 with TFT anomalies, 2 with heart valve defects detected on the ECO, 1 with scleroderma diagnosis made 3 months previously, and 4 who had removed the Holter device before completion of the 24-hour period were excluded from the study. Hence, a total of 41 patients who met the inclusion criteria were enrolled in the study and were started on treatment procedures immediately after the investigations with the Holter-ECG use.

Data Acquisition

The Sociodemographic Form: This included sociodemographic data on age, gender, marital status and educational level of the participants.

The Structured Clinical Interview Form For DSM IV- Axis I Disorders (SCID-I): The SCID-I, designed as a structured clinical diagnosis tool (American Psychiatric Association 1994) ensures research into any first axis diagnosis in the past and/or the last 1 month according to the DSM diagnostic criteria. Developed by First et al. (1996), the adaptation and reliability study for the Turkish language version of the SCID-I was performed by Özkürkçügil et al. (1999).

The Panic Disorder Severity Scale: This measures the severity of PD, frequency of panic attacks, limited symptom episodes, severity of expectation anxiety, phobic avoidance and functional impairment. It comprises a total of 7 items. Each item has a score range of 0-4 and the total score is calculated by adding the scores on the 7 items. The scale was developed

by Shear et al. (1997) and the validity and reliability studies of the Turkish language version was completed by Monkul et al. (2004).

The Hamilton Anxiety Rating Scale: This is a scale that is completed by the clinician with the aim of determining anxiety levels and symptom distribution. It contains a total of 14 questions encompassing subdimensions inquiring about both somatic and psychic anxiety symptoms. Scores on each item are added to obtain the total score. Developed by Hamilton (1959), the validity and reliability in the Turkish language was determined by Yazıcı et al. (1998).

The Hamilton Depression Rating Scale: This scale, completed by the clinician, measures the level and the changes in the severity of depression in a patient. It comprises structured questions and each question has a score range of 0-4. Scores of ≥16 are indicative of depression. Developed by Hamilton (1960), the validity and reliability in the Turkish language was determined by Akdemir et al. (1996).

The Clinical Global Impression Scale (CGI): This is a three-dimensional scale, developed by Guy et al. (1976) with the aim of assessing progress of all psychiatric diseases at all ages for clinical research purposes. The first dimension evaluates disease severity, the second is on healing and the third assesses the severity of medication side effects. In this study, the disease severity section of the scale was used. The clinician assesses the severity, from mild to severe, of the present disease with a Likert-type rating between 1 and 7.

Holter Electrocardiography: All volunteering participants of the study underwent the 24-hour Holter ECG procedure provided by the cardiology clinic. Both PD and the control groups were connected to a 3-band Holter ECG device (DSM 300-3A, DSM Inc, USA). At the end of the 24-hour recording, the data were uploaded to a DSM brand Cardio Scan II analysis program (DSM Inc. USA) on the computer and the HRV time-dependent parameters were automatically calculated.

All of the participants of the study were requeasted to continue daily life activities without any physical limitations, to refrain from taking the banned caffeinated drinks, using mobile telephones and making movements that may damage the equipment while carrying the Holter device for 24. The participants were also asked not to use any benzodiazepines in the 2 last hours before being fitted with the Holter device. Compliance with these conditions were based on the statements of the participants and their relations; and 4 noncompliant pariticpants were excluded from the study.

The 24-hour Holter-ECG procedure was started at the cardiology clinic after completion of the psychiatric assessments. The data were automatically up-loaded to the the computer program to analyse the HRV time dependent parameters.

Statistical Analyses

The Shapiro Wilks test was used to assess whether or not the variables of interest were normally distributed. The data with normal distribution in descriptive statistics are expressed in terms of the mean ± standard deviation, while variables without normal distribution are presented as the median ± interquartile range. Parametric methods were used for comparing the group means of variables with normal distribution, and non-parametric methods were used for those without normal distribution. Whether the Holter data predicted the PD group was assessed by logistic regression analysis whereby the initial and final classification tables and the Nagelkerke R^2 variation were investigated. Significant variables were interpreted with the Odds ratio (Exp B). All statistical comparisons were performed on the SPSS 16 software and the $p \leq 0.05$ value was accepted as significant.

RESULTS

The study included 41 patients with PD diagnosis and a healthy control group of 46 individuals. Among the PD patients participating in the study 21(51.3%) were females, while 25 (54.3%) of the healthy controls were females (p=0.332). The mean age in the patient group was 33.18 ± 10.88 years, while the mean age in the healthy control group was 36.04 ± 11.55 years (p=0.078). In the PD group 22(53.7%) patients were married, while in the healthy control group 33 (60.0%) were married (p=0.082). In the PD group 11(26.9%) patients were primary school graduates, while in the healthy control group 8 (42.1%) participants were primary school graduates (p=0.809). Table 1 shows that the demographic variables

Table 1. Sociodemografic Characteristics of the Study Group

	Healthy Controls (N=46)	PD (N=41)	Statistics
Gender (female,%)	25(%54.3)	21(%51.3)	χ^2=2.21, df=2, p= 0.332
Marital status (married, %)	33 (%60.0)	22(%53.7)	χ^2=4.99, df=2, p= 0.082
Education (elementaryschool,%)	8 (%42.1)	11 (%26.9)	χ^2=3.00, df=6, p= 0.809
Age	36.04±11.55	33.18±10.88	F=2.630, df=2, p=0.078

PD: PanicDisorder

Table 2. Comparison of Holter Data of the PD Patients and the Healthy Control Group

	Healthy Controls (N=46) (Mdn ±IR)	PD (N=41) (Mdn ±IR)	Statistics (Kruskal Wallis test)
SDNN	142.5±60.75	151.5±75.75	χ^2=5.885, df=2, p= 0.053
SDANN	117.0±54.0	36.0±23.50	χ^2=47.781, df=2, p<0.001
RMSSD	58.50±33.25	35.0±23.00	χ^2=11.654, df=6, p= 0.003
SDNN index	71.0±34.50	68.50±27.00	χ^2=1.062, df=2, p= 0.588
NN50	16126.0±1282934.75	7902.50±12286.75	χ^2=10.714, df=2, p= 0.005
PNN50 %	15.795±14.83	6.66±11.92	χ^2=6.095, df=2, p= 0.047

PD: Panic Disorder, SDNN: Standard deviation of NN interval, SDANN: Standard deviation of the average NN, RMSSD: Root mean square successive difference, PNN50 %: Percentage of differences of successive NN intervals greater than 50 ms

Table 3. Correlation of Holter Data and Psychometric Scale Scores (N=41)

	SDNN (ms)	SDAN (ms)	RMSSD (ms)	SDNN index ms	SDSD ms	NN50	PNN50 (%)
HAM-A	-0.065	-0.252	-0.097	-0.205	-0.035	0.021	-0.031
HAM-D	-0.109	-0.084	-0.029	-0.143	0.092	0.218	0.128
CGI	0.145	-0.033	0.182	0.041	0.253	0.493**	-0.372*
PDSS	0.091	-0.006	0.000	-0.052	0.179	0.254	0.096

Spearman correlationanalysis,
**significant at 0.01 level, * significant at 0.05 level
HAM-A: Hamilton Anxiety Rating Scale, HAM-D: Hamilton Depression Rating Scale, CGI: Clinical Global Impression Scale, PDSS: Panic Disorder Severity Scale, SDNN: Standard deviation of NN interval, SDANN: Standard deviation of the average NN, RMSSD: Root mean square successive difference, PNN50 %: Percentage of differences of successive NN intervals greater than 50 ms

of gender, age, educational level and marital status, did not differ significantly between the two groups.

Comparison of the Holter data on the PD and the control groups showed significant differences between the values of the time dependent variables SDANN, RMSSD, NN_{50} and pNN_{50}. In the PD group, the values for SDANN (p<0.001), RMSSD (p= 0.003), NN_{50} (p= 0.005) and pNN50 (p= 0.047) were determined to be significantly lower compared to the healthy control group. Statistically significant differences were not found between the SDNN (p= 0.053) and SDNN index values (p= 0.588) in the two groups (Table 2).

Correlation analysis between the data on psychometric tests and the Holter procedure in the PD group showed a significant negative correlation of moderate level between the CGI data and part of the Holter data (Table 3). Also, there were significant negative correlations of moderate level between the CGI score and the pNN_{50} and the NN_{50} values.

It was observed that the participants with PD and the healthy controls could be discriminated on the basis of the Holter data. A logistic regression equation explaining 85.2% of the variance was created (Nagelkerke R^2). By using the Holter data and the sociodemographic variables such as age and gender which affected the Holter data, it was observed that the logistic regression analysis accurately classified 100% of the PD cases and 97.7% of the whole group (Table 4). The SDNN, SDANN and pNN50 values were significantly predictive of PD. The Odd's ratio and 95% CI for all variables are given in Table 5. Disease duration was not included in the analyses.

The increase in the SDNN values by 1 unit increased the probability of PD risk by 1.11 fold, while increases in the SDANN values and pNN50 values by 1 unit reduced the probability of PD risk (0.892 and 0.523, respectively).

It was found by logistic regression analysis that an increase in SDNN values by 1 unit increased the probability of PD by 1.11 times (95% CI, 1.010-1.209); while an increase of SDANN values by 1 unit reduced the probability of PD by 0.892 fold (95% CI, 0.818-0.973) and an increase of 1 unit in pNN50 reduced the probability of PD by 0.523 fold (95% CI, 0.342-0.801).

Table 4. Classification Table Estimated by Logistic Regression

	Estimated		
	Healthy Controls	PD	Adjusted Percentage
Healthy Controls	44	2	95.7
PD	0	41	100.0
General Percentage			97.7

PD: Panic Disorder

Table 5. Logistic Regression Holter Data Predicting PD

	B	S.E.	Wald	df	Sig	Exp (B)	95.0% C.I. for Exp(B)	
							Lower	Upper
SDNN	0.100	0.046	4.723	1	0.030	1.105	1.010	1.209
SDAN	-0.114	0.044	6.707	1	0.010	0.892	0.818	0.973
RMSSD	0.030	0.048	0.410	1	0.522	1.031	0.939	1.132
SDNNindex	0.055	0.40	1.909	1	0.167	1.056	0.977	1.142
SDSD	-0.016	0.42	0.141	1	0.707	0.984	0.907	1.069
NN50	0.000	0.000	3.505	1	0.061	1.000	1.000	1.001
PNN50	-0.648	0.217	8.904	1	0.003	0.523	0.342	0.801
Gender (1)	1.349	1.218	1.227	1	0.268	3.852	0.354	41.893
Age	-0.041	0.045	0.824	1	0.364	0.960	0.879	1.048
Constant	-3.889	3.723	1.092	1	0.296	0.020		

PD: Panic Disorder, SDNN: Standard deviation of NN interval, SDANN: Standard deviation of the average NN RMSSD: Root mean square successive difference, PNN50 %: Percentage of differences of successive NN intervals greater than 50 ms

DISCUSSION

This study investigated HRV in patients with PD diagnosis without comorbid medical or psychiatric diseases and compared the acquired data with those of healthy controls. PD patients with active symptoms and not using psychotropic medications and the healthy control participants were tested by the 24-hour long-term Holter ECG recording and the results were compared. In our study, the values of the time-dependent HRV variables of SDANN, RMSSD, NN_{50} and pNN_{50}determined by 24-hour Holter ECG were found to differ in PD and the healthy control groups. The study also investigated the effects of the time dependent HRV variables on the risk of presenting with PD. It was found that PD risk increased with increase in the SDNN values, and the risk decreased with increases in the SDANN and PNN50 values.

In the relevant literature, most studies assessing HRV in patients with PD diagnosis reported results based on short-term frequency measurements, generally performed under laboratory conditions using a variety of stimulants (Petrowski et al. 2016, Martinez et al. 2010, Divek 2012, Kikuchiet al. 2009). In these studies the majority of the measurements were made on short durations around 5 minutes which do not reflect the actual variation in the daily life of the patients. Assessments using 5-minute measurements found reductions in RMSSD values (Petrowski et al. 2016), HRV (Petrowski et al. 2016, Martinez 2010) and HF rates (Diveky 2012) which reflect the parasympathetic activity, increases in the LF ratio which is a marker for sympathetic activity (Martinez 2010, Diveky 2012) and a reduction in the LF/HF ratio, which is a marker for sympathovagal balance (Petrowski et al. 2016). On the other hand, using the 24-hour Holter ECG recording method provides detailed information related to autonomic functioning in daily lives of individuals.

There are fewer studies assessing HRV with the 24-hour Holter ECG method (McCraty et al. 2001, Durdu et al. 2018, Yeragani et al. 1998). The first study using the 24-hour Holter measurement reported lowered HRV in PD (McCraty et al. 2001, Yeragani et al. 1998). A thesis study carried out in Turkey, using the 24-hour Holter ECG method, did not find any significant difference between the HRV values of the PD patients and the controls. SDNN values did not differ between the two groups. Although the RMSSD duration and the pNN50 value of the PD group were lower, these differences were not statistically significant (Durdu et al. 2018).

It is notable that the unique results obtained by using Holter ECG in studies with PD patients are conflicted. Contrary to the studies reporting reductions in HRV in PD cases (Klein et al. 1995, Ito et al. 1999, Seier et al. 1997, Pitting et al. 2013, Blechert et al. 2007), there are studies not reporting similar obsrvations (Durdu et al. 2018, Yeragani et al. 1998, Rechlin et al. 1994). Reviews of the studies in this area (Rottenberg 2007, Kemp 2011) proposed that these contradictions may arise from not controlling some factors that may affect HRV. These factors can be summarized as (1) not excluding PD patients with comorbid cardiovascular diseases and physical diseases like DM; (2) not excluding PD patients using psychotropic medication, such as mirtazapine (Slapp et al. 2002), paroxetine (Tucker et al. 1997) and imipramine (Yeragani et al. 1992), which alter HRV; (3) not excluding comorbidity with at least one other anxiety disorder; and (4) not excluding the diagnosis of comorbid depression (Kemp et al. 2012). These four basics precautions were included in the basic methodological approach of our study. The exclusion criteria of our study included factors known to affect HRV, including diagnosis of comorbid depression,

anxiety disorders other than PD, psychotropic agent use, HT, DM, cardiovascular diseases such as rhythm disorders and heart valve diseases, epilepsy, MS, chronic neurological diseases including previous CVE and alcohol and/or drug use. Our study has also excluded cigarette smoking reported to affect HRV (Kobayashi et al. 2005). Despite the effects of medical treatment on HRV (Shinba 2017), very few studies have excluded the effect of medication as in our study (McCraty 2001, Durdu et al. 2018, Yeragani et al. 1998). Studies, similar to ours, with the 24-hour ECG recording that better reflects daily life, are important for evaluating these conflicting findings.

In our study, RMSSD duration, NN50 and pNN_{50}values, independent of the diurnal alterations in heart rate and reflecting the parasympathetic tonus, were found to be significantly lower in the PD group compared to the healthy control groups. This, in agreement with the medical literature, reflects the reduced parasympathetic activity, or the vagal tonus, and dominance of the sympathetic system in the PD group (Petrowski et al. 2016, Petrowski et al. 2010). Reduced HRV is one of the significant markers of the impairment in autonomic functions (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). The time-dependent RMSSD and a number of the frequency-dependent HRV parameters appear to be significant markers for determining autonomic function disorders in a variety of clinical disorders (Bloomfield 1997). By using the Trier social stress test (TSST) in PD patients, Petrowski et al. (2010) showed that the time dependent HRV parameter RMSSD was reduced by imposed psychosocial stress. During psychosocial stress the mean heart rate was increased and the vagally controlled HRV components, especially RMSSD, were reduced in both the PD patients and the healthy controls (Petrowski et al. 2016).

Our data support the view that the cardiovascular system traits in PD cases differ from those of the healthy controls. Many studies have shown increased risk of cardiovascular diseases and death due to cardiovascular causes in PD (Gomez-Caminero 2005, Fleet et al. 2000, Walters et al. 2008). Given its association with the increased risk of cardiac disease and mortality in PD, the reduced HRV has clinical importance (Tsuji et al. 1996). Patients experience panic attacks characterized by autonomic stimulation symptoms of palpitation, hyperventilation, dizziness, shaking, sense of compression in the chest, sweating and hot and cold flushes (Woodward et al. 2009). ANS appears to be associated with the occurrence and duration of panic attacks (Friedman et al. 1998). The increase in cardiac disease risk related with PD is associated with autonomic system function disorder and especially variations in heart rate and HRV (Diveky 2012). Therefore, reduced HRV emerging as a result of the reduced vagal tonus, impairment of autonomic function and reduced parasympathetic activity may constitute a common etiological factor for PB and the related cardiac diseases (Thayer and Lane 2007). Considering the assumption that HRV is an important marker for this relationship between PD and cardiac disease, early detection of the HRV reduction in PB would enable reduction of cardiac mortality incidences (Shinba 2017). In our study, determination of moderate negative correlations between the CGI score and the pNN_{50} and NN_{50} values in PD patients indicate, in agreement with the medical literature, that decrease in parasympathetic activity is associated with PD severity (Martinez et al. 2010, Agelink et al. 2002). By using the CGI scale, as in our study, Martinez et al**.** (2010) reported lower HRV parameters in PD patients with increased disease severity. Also, a decrease in the parasympathetic function indicants among the frequency dependent HRV parameters was reported in PD of increased severity (Agelink et al. 2002). These data further demonstrate a possible correlation between anxiety severity and the sympatovagal balance level, meaning that there may be a greater risk of cardiac disease (Martinez et al. 2010).

The regression analysis used in this study demonstrated the significance of the SDNN value that reflects the ANS balance, and the SDANN and pNN50 values, reflecting the parasympathetic activity, for predicting PD. Despite having concluded that HRV time-dependent parameters of SDNN, SDANN and pNN50 could be used to predict PD, there is a need for studies in this area with larger participant groups.

Strong aspects of our research are including patients not using medication, excluding diagnoses of comorbidities and smoking, and making 24-hour Holter ECG recordings which reflect long-term daily life activities. Nevertheless, there are limitations to this study. Although physical activity was known to affect HRV (Rennie et al. 2003), it was not evaluated in our participants and the frequency dependent parameters of HRV were not investigated. Another important limitation is not having repeated the sleep and wake analyses of HRV, shown to differ significantly by a limited number of studies (McCraty et al. 2001, Hovland et al. 2012, Durdu et al. 2018, Yetkinet al. 2014). One of the basic limitations of this study is not evaluating the respiratory rate of PD patients which has been recommended since especially the time dependent RMSSD component of HRV shows difference with respiratory frequency (Berntson et al. 1997, Berntson et al. 2005). Lastly, the small number of PD group participants may also be taken as an important limitation.

Data obtained in our study, although confirming that PD patients have HRV parameters differing from those of healthy controls, indicate that there is need for further long-term Holter studies evaluating HRV and autonomic functions in PD cases under daily life conditions.

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