Evaluation of Heart Rate Variability in Drug Free Panic Disorder Patients

Gözde Şirin DURDU¹, Meral KAYIKCIOĞLU², Şebnem PIRILDAR³, Timur KÖSE⁴

¹Department of Psychiatry, Çiğli Region Training Hospital, İzmir, Turkey

²Department of Cardiology, Ege University Faculty of Medicine, İzmir, Turkey

³Department of Psychiatry, Ege University Faculty of Medicine, İzmir, Turkey

⁴Department of Biostatistics, Ege University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Introduction: It is well-known that autonomic function is impaired in panic disorder (PD). Heart rate variability (HRV) is a reliable and noninvasive method to evaluate autonomic functions. The aim of this study is to evaluate 24-hour heart rate variability (HRV) parameters in drug-free panic disorder patients. These results are compared with those obtained from healthy controls.

Methods: Thirty-two (mean age 33.12±11.94 years, 20 female, 12 male) drug-free patients for at least 2 weeks, (for fluoxetine 3 weeks) diagnosed with panic disorder (PD) on the basis of DSM-IV criteria were included in the study. The control group comprised of 24 age and gender-matched healthy individuals (mean age 33.45±8.6 years, 17 female and 7 male) without any cardiac, endocrine (including diabetes), and neurological disease. Two groups were evaluated for any axis-I diagnosis with SCID-I. We used Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), Panic Disorder Severity Scale (PDSS) and Anxiety Sensitivity Index-3 (ASI-3) tests in both groups. After the psychiatric evaluation 24 hours Holter ECG monitoring was performed in all participants for the determination of HRV including frequency and time domain parameters.

Results: The time domain RMSSD and PNN50 values tended to be lower in panic patients but this difference did not reach significance (p=0.229,

p=0.571). There was no significant difference in mean values for all time and frequency domain HRV measures over the total 24-hours recording between patients and controls. RMSSD, pNN50 and HF was increased to reflect the parasympathetic predominance in the sleeping period (p=0.0001) but there was no significant difference between groups. However LF value which showing sympathetic activity was increased significantly in healthy control and patients in the sleeping period (p=0.0001) but there was no significant difference between two groups (p=0.905). Correlation analysis in the panic disorder patients presented a negative correlation between disease age at onset HF value (p=0.004) and positive correlation between LF/HF value (p=0.007). When both smokers and non-smokers were compared in terms of HRV values, smoking significantly decreased HRV in both groups [SDNN (p=0.18)].

Conclusion: HRV parameters of panic disorder patients were not different from healthy controls. To better clarify the effects of panic disorder on HRV, factors effecting HRV should be minimized and more Holter ECG studies with longer records should be obtained to reflect the daily life activities.

Keywords: Panic disorder, heart rate variability, Autonomic nervous system

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INTRODUCTION

Panic disorders (PD) are frequent mental disorders that significantly affect a person's life (1,2). These concomitant physical symptoms indicate impaired autonomic nervous system functions and it is asserted that autonomic functions play a role in PB etiology (3).

Cardiovascular disease (CVD) risk and mortality were reported to be higher in anxiety disorders (4,5,6). In this scope, heart rate variability (HRV) and heart rate (HR) are evaluated as the indicator of autonomic functions (7). Decrease in HRV is an independent risk factor which indicated the increased mortality for CVD (8,9,10,11). Decrease in heart rate variability is frequently used as an indicator of cardiac autonomic instability in panic disorder (12).

It was suggested that effective treatment might have positive effects on HRV and that autonomic functions may be regulated. It was reported that parasympathetic activity in PD cases had increased following 20mg/

day paroxetine treatment for 4 weeks (13). Besides, a relation between the efficiency of cognitive behavioral therapy in panic disorder and the improvement of neurocardiac control was reported (14).

In the majority of the studies regarding panic disorder, short-time provocation (Na lactate infusion, postural change, cold, various pharmacological drug infusions) or resting records were reviewed (15,16,17,18,19,20). Despite some specific findings reported, the study results are inconsistent. Particularly, the number of studies with 24-hour recording in PD patients is very small. While short-time HRV measurements may be used in the evaluation of autonomic nervous system functions, 24-hour measurements are important as they cover the daily life and sleep information. In this study, we intended to evaluate autonomic functions of drug free PD patients based on 24-hour HRV data.

Approach

Cases between the ages of 18-65 years who applied to Ege University Faculty of Medicine Psychiatry Department; who were psychotrope free for at least two weeks (3 weeks for fluoxetine), diagnosed with PD based on DSM-IV criteria; and who had a panic attack at least for once in last one month and who agreed to participate the study were included to the study following the approval of ethics committee. 39 people who met these criteria were included to the study and 33 cases agreed to participate. 2 of 6 cases who did not agree (1 male, 1 female) refused to participate as they already had Holter assessment at another center; 2 patients (male) didn't want to participate and 2 patients (1 male, 1 female) refused as they were exurbans. One case was excluded from the study because of insufficient data. 32 cases diagnosed with PD (mean age: 33.12 ± 11.94 years, age range: 21-61 years) were included to the study. The control group comprised of 25 age- and gender-matched healthy individuals (mean age 33.45 ± 8.64 years, age range: 24-55 years) without any psychiatric diagnosis or any medical diseases and who did not take any drugs other than non-steroid anti-inflammatory drugs. One person was excluded from the control group due to insufficient Holter recording time. Informed subject consent forms were obtained from the participants in patient and control groups.

3-channel Holter ECG device (DSM 300-3A, DSM Inc, USA) in Ege University Faculty of Medicine, Department of Cardiology was used for 24 hour ECG recording on all cases who participated the study. Cases were notified to continue their regular daily life as they carry the device. They were asked to record the sleep and wake-up hours during the recording period. Participants were informed not to take alcohol or benzodiazepine during the last 24 hours before the attachment of Holter, and not to have caffeine drinks (coffee, coke, energy drink, etc.) or smoke during the last 2 hours and while recording. Cases were cautioned not to take drugs other than non-steroid anti-inflammatory drugs, and to avoid any actions which may damage the device. Structure Clinical Interview for DSM IV Axial I Disorders, (SCID-I), HAM-D, HAM-A, PDSS, ASI-3 scales were applied to all participants by the psychiatrist at Ege University Psychiatry Clinic.

Measurements

At the end of 24-hour Holter recording, the recordings were transferred to the computer and the frequency and time domain parameters of HRV were automatically calculated using DSM make Cardio Scan II analysis program (DSM Inc, USA).

The time and frequency domain parameters of HRV were evaluated for the study. Within the scope of time domain parameters, SDNN (standard deviation of NN Intervals), SDANN (standard deviation of NN in All 5-Minute Segments), SDNN index (mean of five minute standard deviation of NN intervals), RMSSD (Root Mean Square of Successive NN Interval Differences) and PNN50 (proportion of NN50) were evaluated.

Within the scope of frequency domain parameters, total power (the power in all frequency intervals), VLF (power at very low frequency interval), LF (power at low frequency interval), LFnu (normalized unit of power at LF interval: $LFnu = LF / (Total\ Power - VLF) \times 100$), HF (power at high frequency), HFnu: normalized unit of power at HF interval: $HF / (Total\ Power - vlf) \times 100$) and LF/HF: ratio of LF to HF were evaluated.

Apart from the 24-hour recording time, additional analysis was conducted based on the sleep/wake-up information provided by the participants. For the sleep time, 30 minutes after the time noted on the diary by the person and for the wake-up time, 30 minutes after waking up were taken as basis. Besides, the arrhythmias observed during 24-hour recording were evaluated by the same cardiologist in terms of quality and quantity.

Statistical Analysis

Statistical analyses were performed by means of SPSS 16.0 program. As sample sizes considered sufficient, parametric methods were preferred in the comparisons between two groups and tables were summarized as average $\pm$ standard deviation. Categorical variables were determined in numbers and percentages. Student-T test was used for the group comparison of continuous variables. In the comparison of categorical variables, chi-square test and, when necessary, "Fisher-exact" test were used. Linear relation between the continuous variables was evaluated using Pearson (r) correlation analysis. Variance analysis was used for repeated measures and sleep-wake comparison was made for each group. Relations between the groups were analyzed. $p < 0.05$ value was accepted as statistically significant in all analysis.

RESULTS

Patient group was between 21-61 years. There were no significant differences between the patient group and the control group in terms of age, gender, marital status, smoking and drinking habit. In the comparison of PDSS, HAM-D, HAM-A and ASI-3 scores of panic disorder group and the control group, the scale scores of the patient group were significantly higher as expected. (Table 1) There were no statistically significant difference between the groups in terms of minimum heart rate, maximum heart rate and average RR times. In PD group, RMSSD time and pNN50 value of the time domain parameters were decreased compared to the control group, however the difference was not statistically significant. No statistically significant differences were detected between the patient and control groups in other time domain values. When frequency domain parameters were evaluated, no statistically significant differences were detected between the PD group and the health control group (Table 2). In the correlation analysis conducted, a negative correlation was found between the disease onset age in PD group and the HF value, and a weak positive correlation was found with LF/HF (Table 3).

In the comparison of sleep-awake data, RMSSD, pNN50 and HF values which indicate parasympathetic activity during sleep significantly increased in both groups, however there was no statistically significant difference between PD and control groups. Frequency domain total power and VLF values significantly increased during sleep, however there were no significant differences between two groups. Again, LF value which indicates sympathetic value increased significantly during sleep, but there were not significant differences between the groups. (Table 4)

No differences were detected between the smokers and non-smokers in PD group in terms of HRV parameters, but when the whole study group was evaluated together (PD and controls), a significant decrease in (SDNN) parameter which indicates HRV was detected in smokers (Table 5). When the presence of depression was evaluated as an additional diagnosis, no significant difference were detected between PD patients who were diagnosed with depression ($n=11$) and who were not diagnosed with depression ($n=21$) in terms of time domain HRV parameters (SDNN, SANN, RMSSD and pNN50).

Table 1. Comparison of groups with HDRS, HARS, ASI-3 and PDSS

	PD	Control	p
HDRS	21.25 ± 8.21	3.50 ± 1.71	0.0001
HARS	34.9 ± 7.67	3.58 ± 2.65	0.0001
ASI-3	36.8 ± 12.62	10.62 ± 10.78	0.0001
PDSS	18.43 ± 5.75	0.00 ± 0.00	0.0001

HDRS: Hamilton depression rate scale, HARS: Hamilton anxiety rate scale, ASI-3: Anxiety sensitivity index-3, PDSS: Panic disorder severity scale, PD: Panic disorder.

Table 2. Comparison of groups with 24 -Hours Holter Records

	PD N=32	Control N=24	p t-test
Heart Rate			
Minimal (beat/min)	47±6	45±5	0.194
Maximal	154±19	149±15	0.257
Average R-R	767±96	771±86	0.874
Total power (msn2)	3715±1897	3501±1675	0.663
VLF (msn2)	2527±1471	2309±1221	0.557
LF (msn2)	823±401	807±362	0.873
HF (msn2)	332±220	358±281	0.693
Lfnu	71±10	70±9.87	0.673
Hfnu	27±10	28±10	0.699
LF/HF	3.1±1.5	2.9±1.41	0.613
SDNN (msn)	148±38	150±28	0.866
SDANN (msn)	136±37	139±26	0.740
SDNN indeksi (msn)	59±14	59±14	0.863
RMSSD (msn)	33±9.4	36±11	0.229
pNN50 (%)	11±7.8	12±9.3	0.571

PD: panic disorder, SDNN: standard deviation of the mean of qualified NN-interval (NN), SDANN indeksi: standard deviation of average normal sinus R-R intervals for all 5-min segments, RMSSD: root mean square of the successive normal sinus R-R interval difference, pNN50: proportion of NN50, VLF: very low frequency, LF: low frequency, HF: high frequency, LFn: normalized low frequency, HFn: normalized high frequency, min: minutes, msn: milisecond, msn2: milisecond's square root
Comparison of groups with student T-test

DISCUSSION

In this study, total power and SDNN values of the HRV values recorded with 24-hour Holter ECG in PD cases were not found different than the healthy controls. RMSDD time, pNN50 value, HF value and HFn value, which are independent from diurnal variations and other influences and which reflect parasympathetic tonus, were decreased in PD group, but these differences were not statistically significant. LF and LFn values which are important indicators for the evaluation of sympathetic activity were higher in PD cases, however the difference was not statistically significant. LF/HF value used to evaluate the sympathovagal balance increased in sympathetic direction in PD cases, yet this finding was not statistically significant.

Contrary to the findings of this study, in most of the studies a decrease in HRV was reported in PD patients. However, the majority of these studies are studies with short-term laboratory resting or automated response to provocations (cold application on face, postural change, Na lactate infusion or administration of various pharmacological agents). In a study where short-term ECG findings under laboratory conditions without provocation were evaluated, HRV was detected low in PD patients, but the measurements in this study cover 5 minutes (21). There are studies which show decrease in HRV under different conditions, impairment in vagal tone and relative sympathetic system predominance. In such studies, it was suggested that vagal withdrawal decreased and sympathetic system may be more dominant in PD patients (17,18,20,19,20). All these studies were generally 5-minute short-term records and conducted under laboratory conditions and with various stimuli. As the cognitive errors may lead to HRV changes, the studies conducted under laboratory conditions in panic disorder group restrict the reliability of HRV measurements. Laboratory conditions may also stimulate anxiety in the patient. It is suggested that the decrease in HRV values detected under laboratory conditions with short-term ECG recordings may arise from the cognitive errors of the group or catastrophic misreading (22,23).

The findings of Yeragani et al. who conducted the first 24-hour Holter study in Panic Disorder conflict with our findings in some aspects. In this study where the panic disorder group and healthy controls were matched in terms of weight, height, physical activity and smoking, it was reported

Table 3. Comparison of the frequency and time dependent HRV parameters of HARS , HDRS HDRS, PDSS, Duration of disease ve age of onset

	Total Power P	VLF P	HF P	LF P	LF/HF P	SDNN P	P NN50 P	RMSS P
HARS	0.282 0.119	0.288 0.110	0.204 0.262	0.201 0.269	-0.043 0.818	0.259 0.152	0.290 0.107	0.309 0.085
HDRS	0.120 0.514	0.097 0.598	0.241 0.184	0.089 0.628	-0.043 0.817	0.053 0.774	0.198 0.277	0.214 0.240
HDRS	-0.94 0.610	-0.070 0.703	0.069 0.707	-0.012 0.950	-0.52 0.776	-0.90 0.625	0.024 0.896	-0.022 0.906
PDSS	0.127 0.490	0.162 0.376	-0.102 0.578	0.110 0.550	0.152 0.407	0.084 0.646	-0.067 0.717	-0.064 0.729
Duration of Disease	0.65 0.723	0.119 0.516	0.284 0.115	0.231 0.204	0.184 0.313	0.106 0.563	0.349 0.054	0.240 0.193
Disease onset age	-0.145 0.430	-0.005 0.977	-0.494 0.004	-911 0.112	-0.465 0.007	0.231 0.203	0.029 0.874	0.246 0.175

PD: panic disorder, SDNN: standard deviation of the mean of qualified NN-interval (NN), SDANN indeksi: standard deviation of average normal sinus R-R intervals for all 5-min segments, RMSSD: root mean square of the successive normal sinus R-R interval difference, pNN50: proportion of NN50, VLF:very low frequency, LF: low frequency, HF: high frequency, LFn: normalized low frequency, HFn: normalized high frequency, min: minutes, msn: milisecond, msn2: milisecond's square root
Comparison of groups with pearson correlation test

Table 4. Comparison of the frequency and time dependent HRV parameters of the sleep and awake

	Sleep PD N=32	Control N=24	Awake PD N=32	Control N=24	Sleep Awake f p	Group effect f p
Total Power	4115.41±2356.65	3973.36±2067.71	3392.74±1868.86	3182.29±1556.76	12.606 <0.0001	0.125 0.725
VLF	2759.48±195.14	2537.69±1471.40	2329.07±1400.96	2152.73±1185.67	5.472 0.023	0.271 0.605
LF	759.87±422.08	773.81±387.99	847.80±400.21	858.40±363.39	7.287 <0.0001	0.014 0.905
HF	462.80±331.67	537.04±450.27	248.55±178.72	234.58±154.36	49.024 <0.0001	0.177 0.676
SDNN	118.12±33.86	123.12±30.73	128.56±34.02	122.04±32.61	1.144 0.296	0.01 0.922
RMSSD	40.50±14.98	44.83±16.24	29.65±8.55	30.79±8.89	66.649 <0.000	0.796 0.376

Table 5. Comparison of frequency and time dependent HRV parameters of the smokers and non-smokers

	Smokers N=20	Non-smokers N=36	p
Total Power	3437.90±1423.31	3880.99±2149.72	0.489
VLF	2183.56±949.65	2733.86±1699.98	0.250
LF	875.64±352.05	792.11±432.97	0.557
HF	331.64±219.98	331.65±226.18	1.00
LF/HF	3.36±1.88	3.04±1.42	0.617
SDNN	125.30±23.16	144.61±35.58	0.018
SDANN ind.	138.25±26.58	155.00±36.30	0.052
RMSSD	32.70±9.38	35.44±10.98	0.330
pNN50	10.05±7.55	12.30±8.93	0.322

HRV: Heart rate variability, VLF: very low frequency, LF: low-frequency, HF: high-frequency, LF/HF: low-frequency / high-frequency, SDNN: standard deviation of the mean of qualified NN-interval (NN), SDANN indeks: standard deviation of average normal sinus R-R intervals for all 5-min segments RMSSD: root mean square of the successive normal sinus R-R interval difference, pNN50: proportion of NN50

that there was a decrease in total power, particularly significant in sleep and again, that LF and ULF values were lower significantly during sleep. We did not measure ULF value. Although the LF value was detected high in this study, there were no significant differences between PD and the control group in our study (18).

In another study where HRV was evaluated for 24 hours using Holter, a decrease in HRV value was reported in panic disorder group. In this study, it was reported that parameters indicating sympathetic system activity decreased and that there was a parasympathetic system dominance. In this study, similar to our study, physical drug use was excluded, and psychiatric comorbidity and smoking were not mentioned (24). The mean age of the groups was older than the patients in our study group. HRV is known to decrease with age (25). Therefore, the lower HRV values detected in the said study may be due to the age difference of the PD patients in both studies.

In our study there are no significant differences between two groups in terms of HRV values, but a negative correlation between disease onset age and HF value ($p: 0.004$) and a positive correlation with LF/HF ($p: 0.007$) were detected. Although this is a finding which supports the predominance of parasympathetic activity in cases with earlier onset, it is possible to mention a weak correlation.

Sleep analysis may only be obtained from 24-hour recordings. In our study, we made sleep-awake analyses and compared the data of PD cases with the control group. In the evaluation of sleep-awake data, while

values indicating sympathetic activity increased during daytime, values indicating parasympathetic activity increased during the night.

The total power value which reflects HRV increased during the night as expected, but no significant differences were detected between the PD and control groups. Considering the complex nature of sleep physiology, it is deemed more suitable to use polysomnographic ECG recordings and to even include EEG recordings to make a comment regarding HRV and, indirectly, about autonomic nervous system in terms of sleep-wake data. The aforementioned studies and our study may not be sufficient to provide information on sleep-wake and HRV difference. In a controlled polysomnographic study with panic disorder patients, no differences were detected between the patient group and the control group (26).

Anxiety sensitivity is defined as an individual's excessive fear against the sensations and symptoms associated with anxiety believed to have harmful physical and/or social outcomes (27,28). In the studies conducted it was generally determined that PD patients have higher anxiety sensitivity compared to healthy people and others with anxiety disorders, and that they scored two standard deviations more than ASI-3 (29). No significant relation was found between anxiety sensitivity and HRV parameters in our study.

Smoking is known to directly affect the heart rate and HRV. Within the minutes following smoking HRV significantly decreases (30,31). When the smokers and non-smokers are compared in our study in terms of HRV parameters, SDNN value was found significantly decreased in smokers.

Throughout the study, the patient and control groups were told not to smoke during recording, but suddenly quitting smoking may increase anxiety. When other studies in the literature are reviewed, it is seen that the influence of HRV in PD is not excluded and the smoking habit of the patients is not mentioned.

Another factor known to affect HRV is physical activity (32). This study is based on recording autonomic changes with ambulatory ECG. Although the participants were told to continue their normal daily routines, the physical activity levels of the people were not controlled. Physical activity levels might have affected the HRV parameters in our study.

The comorbidity ratio in our study was found 40.62%. MDD (34.4%) is the comorbidity with the highest ratio. The groups with and without depression were compared in terms of HRV parameters, but no significant differences were detected in any parameter. GAD+MDD was found in 2 people, GAD in 1 person and OCD+MDD was found in 1 person. Due to the small number of patients, these group were not compared in terms of HRV parameters.

Excluding the influence of drug in our study is important. There are very few studies researched the relation of antidepressant treatment and HRV in PD. In an open label study, where mirtazapine was used, HRV and LF were detected lower in cases who did not respond to the treatment, however no differences were reported in LF/HF ratio (33). In 17 PD patients treated with paroxetine, a significant increase was detected in parasympathetic component of HRV at the end of a 4-week treatment (34). In another study, it was reported that a decrease was detected in HRV both in PD and MDD cases after imipramine treatment (35). However, the number of cases in these studies are low. In the randomized placebo controlled study of Siepmann et al. where they investigated the effect of sertraline on autonomic and cognitive functions, 12 healthy subjects were administered 50mg sertraline for 14 days. At the end, sertraline was reported to cause a significant decrease in heart rate (HR). No changes were observed in HRV. This decrease in HR was detected as similar to the other SSRIs and it was reported that this might be associated with the decrease in central sympathetic system activity (36). It is understood that using antidepressants affect HRV. It is possible that the contradictory results in studies where the PD and HRV relation was analyzed may arise from the non-exclusion of drug in some studies.

Important restrictions in our study while evaluating our findings include the presence of comorbidities in PD group, exclusion of the smoking habit of the patients, not evaluating weight and physical activity levels as well as unavailability of polysomnographic recordings for sleep-wake analysis. In this research, no differences were detected between drug free PD cases and healthy control group in terms of HRV values. These data which reflect long-term daily life activities of drug free patients without comorbidities and which are obtained through 24-hour measurements are important and they should be supported with other study data and advanced researches.

Committee Approval: Approval was obtained from Ege University Medical Faculty Ethics Committee.

Informed Consent: Informed consent forms were obtained from the patients and the participants in the control group.

Peer-review: Externally peer-reviewed

Author Contributions: Concept – SP, GŞD, MK; Design –GŞD, SP, MK; Supervision – GŞD, SP, MK; Resources – GŞD; Materials – GŞD, SP, MK; Data Collection and/or Processing – GŞD; Analysis and/or Interpretation – GŞD, MK, SP, TK; Literature Search – GŞD; Writing Manuscript – GŞD; Critical Review – ŞP, MK.

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