ORIGINAL ARTICLE

Effect of fluoxetine and psychotherapy on heart rate variability in children and adolescents diagnosed with panic disorder: 24-hour Holter monitoring study before and after treatment

Panik bozukluk tanısı konulan çocuklar ve adölesanlarda kalp hızı değişkenliği üzerine fluoksetin ve psikoterapinin etkisi: Tedavi öncesi ve sonrası 24 saat Holter monitorizasyon çalışması

Mustafa Argun, M.D.,[1] Hesna Gül, M.D.,[2] Selahattin Çelebi, M.D.,[3] Ferhan Elmalı, M.D.,[4] Nazmi Narin, M.D.[5]

[1]Department of Pediatric Cardiology, Necip Fazıl City Hospital, Kahramanmaraş, Turkey; [2]Department of Pediatric Psychiatry, Necip Fazıl City Hospital, Kahramanmaraş, Turkey; [3]Department of Pediatrics, Necip Fazıl City Hospital, Kahramanmaraş, Turkey; [4]Department of Biostatistics and Medical Informatics, Erciyes University Faculty of Medicine, Kayseri, Turkey; [5]Department of Pediatric Cardiology, Erciyes University Faculty of Medicine, Kayseri, Turkey

ABSTRACT

Objective: Panic disorder (PD) is now recognized as a common and important problem in children, and particularly adolescents, and one that can negatively affect daily well-being and educational performance. The aim of this study was to investigate the relationship between heart rate variability (HRV) and the severity of symptoms before and after treatment with psychotherapy and fluoxetine.

Methods: The PD study group consisted of 23 children diagnosed with PD and the healthy control (HC) group comprised 27 healthy children. Panic-anxiety symptoms were measured using 2 assessments performed before and after treatment. HRV was evaluated with a 24-hour Holter examination.

Results: According to the analysis of the 24-hour, all-day Holter device recordings, the high frequency (HF) and parasympathetic (%) scores in the PD group were lower than those of the HC group ($p<0.05$). The low frequency (LF)/HF ratio and sympathetic (%) scores in the PD group were higher than those of the HC group ($p<0.05$). The analysis of daytime readings indicated that the HF values of the PD group were lower than those of the HC group ($p<0.05$), while the very LF/HF ratio and LF/HF ratio were higher than those of the HC group ($p<0.05$). Analysis of nighttime Holter results revealed that the rMSSD, pNN50, and HF readings of the PD group were lower than those of the HC group ($p<0.05$), while the LF/HF ratio in PD patients was higher than that seen in the HC group ($p<0.05$).

Conclusion: In children and adolescents with PD, increased sympathetic activity can cause changes in some HRV parameters. Some of these changes may return to normal with treatment.

ÖZET

Amaç: Günümüzde panik bozukluk (PB), çocuklarda ve özellikle de adölesanlarda sık görülen, günlük iyilik halini olumsuz etkileyen ve okul başarısını düşüren önemli bir sağlık problemidir. Bu çalışmanın amacı PB tanısı konulan çocuklar ve adolesanlarda fluoksetin ve psikoterapi tedavisi öncesi ve sonrası belirtilerin şiddeti ve kalp hızı değişkenliği ilişkisini araştırmaktı.

Yöntemler: PB grubu, PB tanısı konulan 23 çocuktan ve sağlıklı kontrol grubu 27 sağlıklı çocuktan oluştu. Panik-anksiyete semptomları, 6-8 haftalık bilişsel davranış terapisi ve selektif serotonin geri alım inhibitörü (fluoksetin) tedavisinden önce ve sonra iki ölçüm ile değerlendirildi. Kalp hızı değişkenliği 24-saat Holter incelemesi kullanılarak değerlendirildi.

Bulgular: Tüm gün analizlerinde, PB grubunda, yüksek frekans ve parasempatik skor (%) sağlıklı kontrol grubundan düşüktü ($p<0.05$). PB grubunda, düşük frekans/yüksek frekans oranı ve sempatik skor (%) sağlıklı kontrol grubundan yüksekti ($p<0.05$). Gündüz analizlerinde, PB grubunda, yüksek frekans sağlıklı kontrol grubundan düşüktü ($p<0.05$). PB grubunda, çok düşük frekans/yüksek frekans oranı ve düşük frekans/yüksek frekans oranı sağlıklı kontrol grubundan yüksekti ($p<0.05$). Gece analizlerinde, PB grubunda, ardışık gelen normal sinüs iletili NN intervalleri farklılıklarının ortalama değerinin karekökü, 50 milisaniyeyi aşan ardışık NN intervalleri sayısının yüzdesel değeri ve yüksek frekans sağlıklı kontrol grubundan düşük, düşük frekans/yüksek frekans oranı ise sağlıklı kontrol grubundan yüksekti ($p<0.05$).

Sonuç: PB'li çocuklarda, artmış sempatik aktivite bazı kalp hızı değişkenliği parametrelerinde değişime neden olmaktadır. Kalp hızı değişkenliğinde azalmayı gösteren bu değişikliklerden bir kısmı tedavi ile normale dönmektedir.

Received: May 15, 2018 *Accepted:* February 13, 2019

Correspondence: Dr. Mustafa Argun. Kayseri Şehir Hastanesi, Çocuk Kardiyoloji Kliniği, Kayseri, Turkey.
Tel: +90 352 - 315 77 00 e-mail: dr.margun@hotmail.com

Panic disorder (PD) is a clinical and socioeconomic problem characterized by recurrent unexpected panic attacks chracterized by symptoms of autonomic arousal, hyperventilation, dizziness, tremor, chest discomfort, sweating, and hot/cold flushes.[1] The lifetime prevalence has been reported to be about 4.7% in adults and 0.5% to 5% in children and adolescents.[2] Psychotherapy, especially cognitive behavioral therapy (CBT) and pharmacotherapy, particularly with selective serotonin reuptake inhibitors (SSRIs) is considered effective first-line treatment for patients with PD. But, only some 11% of adult patients with PD receive CBT or SSRI treatment, and the figure is not much higher in children.[3–5]

Abbreviations:

BAI	*Beck Anxiety Inventory*
CBT	*Cognitive behavioral therapy*
HC	*Healthy control*
HF	*High frequency*
HR	*Mean heart rate*
HRV	*Heart rate variability*
LF	*Low frequency*
PD	*Panic disorder*
pNN50	*The percentage of successive NN intervals greater than 50 milliseconds*
rMSSD	*The root mean square of successive differences between normal sinus RR intervals*
SSRI	*Selective serotonin reuptake inhibitors*
STAI	*State-Trait Anxiety Inventory*
SDNN	*The mean RR interval, the standard deviation of all normal sinus RR intervals over 24 hours*
SDNN index	*The mean of the SDNN*
SDANN index	*The mean of the standard deviation of all averaged normal sinus intervals for each 5-minute segment in the 24-hour recording*
VLF	*Very low frequency*

An increased risk of cardiac events associated with PD has been linked to an abnormal or dysregulated autonomic system and alterations in heart rate variability (HRV) in adults.[6–10]

HRV is a measurement of the beat-to-beat difference in heart rate. It is controlled by the activity of the autonomic nervous system and reflects the capacity for parasympathetic inhibition of autonomic arousal. HRV may be considered a noninvasive measurement of the activity of the sympathetic and parasympathetic nervous systems. Spectral analysis is the most commonly used method for HRV analysis. It provides information about 3 separate frequency bands: high frequency (HF), low frequency (LF), and very low frequency (VLF). The HF component of HRV reflects parasympathetic activity and the LF component reflects both sympathetic and parasympathetic activities. HRV indicates dominance of the sympathetic or parasympathetic system rather than the relationship between the 2 systems.[5]

A normal HRV reflects a healthy autonomic nervous system response to changing circumstances. However, a decreased HRV is an expression of the impairment of this response and may be correlated with the severity of cardiac disorders, especially in young patients with ischemic heart diseases.[11] In recent years, there has been significant research about HRV abnormality without heart disease in various mental disorders, including depression, PD, eating disorders, and schizophrenia in adult patients,[12–15] but to our knowledge, no study to date has examined treatment effectiveness and HRV using all-day, daytime, nighttime parameters with 24-hour Holter monitoring in children and adolescents with mental disorders, particularly those with PD.

The objective of this study was to evaluate whether HRV was associated with the severity of PD symptoms in children and adolescents.

METHODS

Participants and procedures

The PD group consisted of 23 children and adolescents, and a healthy control (HC) group was made up of 27 healthy children and adolescents. PD was diagnosed based on clinical criteria and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Patients with PD had no additional psychopathology. The Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version assessment was not used in the diagnostic phase.

The research protocol was approved by the Research Ethics Board of Kahramanmaras Sutcu Imam University. Participants in the study group were recruited from newly diagnosed children with PD who were referred to the Necip Fazıl City Hospital Child and Adolescent Psychiatry between January and June 2015. The aim and procedures of the study were explained to all of the children and their parents, and written informed consent was obtained. The members of the PD group were aged between 7 and 16 years. The healthy, age and gender-matched control group was aged between 8 and 17 years.

A physical examination, hemogram, thyroid function tests, electrocardiography, and transthoracic

echocardiography (TTE) were performed for all of the participants before initiating treatment. The exclusion criteria of the study were infection, anemia, thyroid dysfunction, or cardiac defect and valve insufficiency observed in the TTE examination.

Measurement of severity of anxiety level in panic disorder group

The psychopathological burden and severity of panic-anxiety symptoms were evaluated before and after 6 to 8 weeks of CBT and SSRI (fluoxetine) treatment. Two assessment tools were used: the Beck Anxiety Inventory (BAI), which is a 21-item, self-report instrument to measure the severity of anxiety, and the State-Trait Anxiety Inventory (STAI), which is a commonly used 4-point scale that consists of 20 items to assess trait anxiety and 20 items to evaluate state anxiety.[16,17]

Treatment

At the outset of this longitudinal study, all of the children were treated with both CBT and fluoxetine. The CBT was conducted by a child and adolescent psychiatrist in weekly sessions lasting 45 minutes for 6 to 8 weeks. The types of CBT used included psychoeducation, breathing retraining, progressive muscle relaxation, cognitive restructuring, interceptive exposure, and situational exposure.[18] Fluoxetine was administered at 20 mg daily for the first 2 weeks and increased to 40 mg daily if the response was determined to be inadequate.

Evaluation of heart rate variability

HRV was assessed using time domain and frequency domain analysis with a 24-hour Holter device examination of the PD patients recorded before and after treatment and in the healthy group. To evaluate the HRV in this study, the following time domain parameters were used: mean heart rate (HR), the mean RR interval, the standard deviation of all normal sinus RR intervals over a 24-hour period (SDNN), the mean of the SDNN (SDNN index), the mean of the standard deviation of all averaged normal sinus intervals for each 5-minute segment in the 24-hour recording (SDANN index), the root mean square of successive differences between normal sinus NN intervals (rMSSD), and the percentage of successive NN intervals greater than 50 milliseconds (pNN50). In addition, the following frequency domain parameters were used: the total spectral power, very low frequency (VLF; 0.0033–0.04 Hz), low frequency (LF; 0.04–0.15 Hz), high frequency (HF; 0.15–0.40 Hz), VLF/HF ratio, LF/HF ratio, sympathetic activity (%), parasympathetic activity (%), and sympathetic activity/parasempathetic activity ratio.[13–15]

Statistical analysis

The study data were analyzed with the IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) statistical software package. The normality of the distribution of numeric variables was tested using the Shapiro-Wilk test and Q-Q graphics. Statistical comparisons between the patient and control groups were conducted with an independent samples t-test for variables with normal distribution and the Mann-Whitney U test for the data that did not follow a normal distribution. The correlation between anxiety scale score and HRV parameters was examined using Spearman's correlation analysis. Comparison of repeated measurements was conducted with a paired sample t-test or the Wilcoxon test. A value of $p<0.05$ was considered statistically significant.

RESULTS

The PD patients were aged between 7 and 16 years (mean: 13.1±2.8 years). The HC group was aged between 8 and 17 years (mean: 13.2±2.1 years). There were no significant differences between the groups

Table 1. Anxiety scale scores of the groups

	Healthy controls (n=27)	Before treatment panic patients (n=23)	After treatment panic patients (n=23)
	Mean±SD	Mean±SD	Mean±SD
BAI	13.0±1.4	30.9±8.1*	15.9±7.8**
STAI-S	22.4±1.6	43.6±8.2*	38.3±4.7**
STAI-T	30.5±1.18	55.0±7.2*	41.5±4.2**

*Indicates a significant difference compared to control group, $p<0.01$. **Indicates a significant difference compared to before treatment panic disorder, $p<0.01$. BAI: Beck Anxiety Inventory; STAI: State-Trait Anxiety Inventory; SD: Standard deviation.

in terms of gender, age, weight, height, or body mass index.

The members of the PD group had significantly higher BAI, STAI-S, and STAI-T scores when compared with the control group (p<0.01) (Table 1). All of the anxiety scale scores decreased after treatment (p<0.01).

Change in heart rate variability parameters in panic disorder patients

The HRV parameters for all-day, daytime, and nighttime were measured. The 24-hour, all-day analyses of HF and parasympathetic (%) scores in the PD group were significantly lower than those of the HC group (p<0.05). The LF/HF ratio and sympathetic (%) scores in the PD group were higher than those of the HC group (p<0.05). After treatment, there was a statistically significant decrease in the LF/HF ratio (p<0.01) (Table 2).

According to the daytime HRV analyses, the HF scores of PD patients were significantly lower than those of the HC group (p<0.05), while the VLF/HF ratio and LF/HF ratio in PD patients were higher than those of the HC group (p<0.05). After treatment, there was a statistically significant decrease in the LF/HF ratio (p<0.01) (Table 3).

The nighttime analyses indicated that the rMSSD, pNN50, and HF of the PD group were significantly lower than those of the HC group (p<0.05), while the LF/HF ratio in the PD patients was higher than those recorded in HC subjects (p<0.05). After treatment, there was a statistically significant increase in rMSSD and pNN50 (p<0.01) (Table 4).

Correlation between anxiety scale score and heart rate variability parameters

Prior to treatment, the BAI of the PD patients demonstrated significant negative correlations with the

Table 2. Differences in all-day heart rate variability parameters between groups

All day	Healthy controls (n=27)	Before treatment panic patients (n=23)	After treatment panic patients (n=23)
	Mean±SD	Mean±SD	Mean±SD
Mean heart rate (BPM)	85.1±17.1	85.8±9.6	84.1±8.3
Mean RR interval (ms)	730.3±115.5	706.5±88.5	723±73.5
SDNN (ms)	161.9±53.0	152.7±42.5	151.2±35.5
SDNN index (ms)	72.2±21.9	66.2±20.2	66.7±16.7
SDANN index (ms)	139.9±45.1	137.1±38.0	135.3±32.8
rMSSD (ms)	46.8±17.4	39.3±15.2	41.1±12.2
pNN50 (%)	22.0±12.3	15.6±10.4	17.9±7.9
Total spectral power (ms^2)	5434±3272	4447±3334	4612±2413
VLF (ms^2)	3639±2640	3138±2680	3129±1847
LF (ms^2)	1069±456	942±439	933±955
HF (ms^2)	679±331	449±246*	509±264
VLF/HF ratio	5.59±3.11	7.29±4.13	7.35±4.25
LF/HF ratio	1.84±0.96	2.38±1.03*	2.12±0.98**
Sympathetic (%)	86.3±5.0	89.3±3.8*	88.5±4.4
Parasympathetic (%)	13.6±5.02	10.7±3.7*	11.4±4.4
Sympathetic/parasympathetic ratio	7.5±3.7	9.8±4.8	9.4±5.1

BPM: Beats for minute; ms; Miliseconds; SDNN: The mean RR interval, the standard deviation of all normal sinuses RR interval over 24 h; SDANN: The mean of the standard deviation of all averaged normal sinus intervals for each 5-min segment in the 24-h recording; rMSSD: The root mean square of successive differences between normal sinus RR intervals; pNN50: The percentage of successive NN intervals greater than 50 milliseconds; VLF: Very low frequency: LF: Low frequency; HF: High frequency; SD: Standard deviation.

*Indicates a significant difference compared to control group, p<0.05. **Indicates a significant difference compared to before treatment panic disorder, p<0.01.

Table 3. Differences in daytime heart rate variability parameters between groups

Day time	Healthy controls (n=27)	Before treatment panic patients (n=23)	After treatment panic patients (n=23)
	Mean±SD	Mean±SD	Mean±SD
SDNN (ms)	126.9±42.8	137.1±45.3	135±34.9
rMSSD (ms)	39.8±14.9	34.4±14.4	35.8±10.4
pNN50 (%)	17.5±10.5	12.08±9.44	13.13±7.07
Total spectral power (ms^2)	5061±3210	4533±3247	4264±2361
VLF (ms^2)	3455±2585	3183±2625	2968±1834
LF (ms^2)	1062±486	939±429	876±429
HF (ms^2)	499±251	348±226*	382±190
VLF/HF ratio	7.10±3.41	9.40±3.88*	8.74±4.71
LF/HF ratio	2.35±0.91	3.04±1.06*	2.49±0.95**

ms: Miliseconds; SDNN: The mean RR interval, the standard deviation of all normal sinuses RR interval over 24 h; rMSSD: The root mean square of successive differences between normal sinus RR intervals; pNN50: The percentage of successive NN intervals greater than 50 milliseconds; VLF: Very low frequency: LF: Low frequency; HF: High frequency; SD: Standard deviation.
*Indicates a significant difference compared to control group, $p<0.05$. **Indicates a significant difference compared to before treatment panic disorder, $p<0.01$.

Table 4. Differences in nighttime heart rate variability parameters between groups

Night time	Healthy controls (n=27)	Before treatment panic patients (n=23)	After treatment panic patients (n=23)
	Mean±SD	Mean±SD	Mean±SD
SDNN (ms)	121.2±39.0	125.0±44.0	128.0±34.0
rMSSD (ms)	61.6±23.0	46.2±19.2*	51.8±19.4**
pNN50 (%)	36.5±17.0	22.3±15.5*	28.5±14.3**
Total spectral power (ms^2)	6100±3602	4757±3902	5291±2820
VLF (ms^2)	3948±2906	3152±3269	3450±2095
LF (ms^2)	1077±484	954±530	1043±461
HF (ms^2)	1017±531	600±326*	750±470
VLF/HF ratio	4.63±2.83	6.13±4.78	6.25±4.48
LF/HF ratio	1.41±0.97	1.90±1.14*	1.82±1.17

ms: Miliseconds; SDNN: The mean RR interval, the standard deviation of all normal sinuses RR interval over 24 h; rMSSD: The root mean square of successive differences between normal sinus RR intervals; pNN50: The percentage of successive NN intervals greater than 50 milliseconds; VLF: Very low frequency: LF: Low frequency; HF: High frequency; SD: Standard deviation.
*Indicates a significant difference compared to control group, $p<0.05$. **Indicates a significant difference compared to before treatment panic disorder, $p<0.05$.

all-day rMSSD, all-day pNN50, daytime rMSSD, daytime pNN50, and nighttime HF ($p<0.05$), and a significant positive correlation with the all-day LF/HF ratio ($p<0.05$). After the treatment, the BAI score of the panic attack patients revealed negative correlations with the all-day rMSSD, all-day pNN50, nighttime rMSSD, nighttime pNN50, and nighttime HF ($p<0.05$). There was no correlation between other anxiety scores and HRV parameters (Table 5).

DISCUSSION

The use of 24-hour Holter monitoring in children with panic disorder revealed that the all-day sympathetic

Table 5. Correlation between the Beck Anxiety Index and some heart rate variability parameters

Variables	Before treatment BAI		After treatment BAI	
	r	*p*	r	*p*
All day rMSSD (ms)	-0.439	<0.05	-0.427	<0.05
Day time rMSSD (ms)	-0.437	<0.05	-0.199	>0.05
Night time rMSSD (ms)	-0.410	>0.05	-0.488	<0.05
All day pNN50 (%)	-0.448	<0.05	-0.537	<0.05
Day time pNN50 (%)	-0.434	<0.05	-0.346	>0.05
Night time pNN50 (%)	-0.387	>0.05	-0.675	<0.001
All day low frequency/high frequency ratio	0.428	<0.05	0.270	>0.05
Night time high frequency (ms^2)	-0.452	<0.05	-0.450	<0.05

BAI: Beck Anxiety Inventory; ms: Miliseconds; rMSSD: The root mean square of successive differences between normal sinus RR intervals; pNN50: The percentage of successive NN intervals greater than 50 milliseconds.

activity and LF/HF ratio were elevated, parasympathetic activity and HF were decreased and there was a reduction in LF/HF ratio with treatment. Daytime HF was reduced, while the VLF/HF ratio and LF/HF ratio were increased, and there was a reduction in LF/HF ratio with treatment. Nighttime rMSSD, pNN50, and HF values were reduced, while the LF/HF ratio was increased, and there were rMSSD, and pNN50 were increased with treatment. We found a correlation between the BAI anxiety scale and some HRV parameters. These results implied that in children with PD, increased sympathetic activity leads to a decrease in HRV. Not all, but some of the HRV parameters, returned to normal with treatment.

There are many studies indicating that psychiatric disorders like major depression, anxiety disorders, and post-traumatic stress syndrome can lead to a reduction in HRV in adults.[19] Furthermore, a number of studies have provided evidence of increased susceptibility to ventricular fibrillation, ventricular tachycardia, and sudden cardiac death among patients with coronary artery disease and depression.[20]

In children, PD usually starts after puberty, and it is more common among girls. The most common physical symptoms are palpitations, chest pain, light-headedness, and shivering. Lipsitz et al.[21] found that psychiatric disorders were prevalent among young people referred to pediatric cardiologists for evaluation of chest pain. Psychological symptoms, such as a fear of dying or losing self-control, may be present. Patients with PD are at increased risk of comorbid psychiatric disorders and suicide attempts. As it can have a negative effect on the daily state of well-being, PD should be treated with CBT and/or pharmacotherapy.[5]

According to a meta-analysis published by Chalmers et al.,[22] a decrease in HRV was associated with reduced pNN50, rMMSD, and HF values with an increased LF/HF ratio in patients diagnosed with anxiety disorders.[22] Our results were similar to those reported in the literature demonstrating a decrease in rMSSD and pNN50 at night, increased LF/HF ratios over the 24-hour monitoring period, as well as during the day and night, and decreased HF values seen in the all-day, daytime and nighttime measurements in children with PD. Our research revealed no published study evaluating the relationship between childhood PD and HRV using 24-hour Holter monitoring.

Our results indicated no significant difference between daytime and all-day rMSSD and pNN50 values. The nighttime rMSSD and pNN50 values were statistically significantly lower in the PD group. This sensitivity may be an important indicator of impaired sleep quality in PD.

The BAI correlated negatively with rMSSD, pNN50 and nighttime HF and positively with the LF/HF ratio. We think that these parameters may be more sensitive in PD than other HRV parameters. In our study, some HRV parameters improved after CBT and fluoxetine treatment in children with PD.

In children and adolscents with PD, increased sympathetic activity can cause changes in some HRV parameters. Some of these changes may return to normal with treatment.

Limitations

This study was conducted with a relatively small sample population. CBT and pharmacotherapy were not separately compared; hence, no evidence was obtained that could determine which treatment was more effective. Also, the absence of a 24-hour Holter follow-up examination in the control group is another limitation of this study.

Conclusion

In children with PD, increased sympathetic activity causes changes in some HRV parameters. Some of these changes that create a decrease in HRV may return to normal with treatment. We think that such HRV data and the different effects seen during the day and at night may provide valuable information in the diagnosis of PD and its response to treatment.

Ethics Committee Approval: The study protocol was approved by Kahramanmaras Sutcu Imam University Ethics Committee.

Peer-review: Externally peer-reviewed.

Funding source: None

Conflict-of-interest: None.

Authorship contributions: Concept: M.A.; Design: M.A., H.G., S.Ç.; Supervision: M.A., N.N.; Materials: M.A., H.G., S.Ç.; Data: M.A., H.G., Analysis: F.E; Literature searh: M.A., H.G, S.Ç.; Writing: M.A., H.G.; Critical Revision: M.A., N.N.

REFERENCES

1. Woodward SH, Arsenault NJ, Voelker K, Nguyen T, Lynch J, Skultety K, et al. Autonomic activation during sleep in posttraumatic stress disorder and panic: a mattress actigraphic study. Biol Psychiatry 2009;66:41–6. [CrossRef]
2. Goodwin RD, Faravelli C, Rosi S, Cosci F, Truglia E, de Graaf R, et al. The epidemiology of panic disorder and agoraphobia in Europe. Eur Neuropsychopharmacol 2005;15:435–43.
3. Cuijpers P, Gentili C, Banos RM, Garcia-Campayo J, Cristea IA. Relative effects of cognitive end behavioral therapies on generalized anxiety disorder, social anxiety disorder and panic disorder: A meta-analysis. J Anxiety Disorder 2016; 43:79–89. [CrossRef]
4. Goisman RM, Warshaw MG, Keller MB. Psychosocial treatment prescriptions for generalized anxiety disorder, panic disorder, and social phobia,1991–1996. Am J Psychiatry 1999;156:1819–21.
5. Garakani A, Martinez JM, Aaronson CJ, Voustianiouk A, Kaufmann H, Gorman JM. Effect of medication and psychotherapy on heart rate variability in panic disorder. Depression and Anxiety 2009;26:251–8. [CrossRef]
6. Vural M, Acer M, Akbaş B. The scores of Hamilton depression, anxiety, and panic agoraphobia rating scales in patients with acute coronary syndrome. Anatol J Cardiol 2008;8:43–7.
7. Fleet R, Lavoie K, Beitman BD. Is panic disorder associated with coronary artery disease? A critical review of the literature. Journal of Psychosomatic Research 2000;48:347–56.
8. Katerndahl DA. The association between panic disorder and coronary artery disease among primary care patients presenting with chest pain: an updated literature review. Prim Care Companion J Clin Psychiatry 2008;10:276–85. [CrossRef]
9. Smoller JW, Pollack MH, Wassertheil-Smoller S, Jackson RD, Oberman A, Wong ND, et al. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women's Health Initiative Observational Study. Arch Gen Psychiatry 2007;64:1153–60. [CrossRef]
10. Friedman BH. An autonomic flexibility–neurovisceral integration model of anxiety and cardiac vagal tone. Bioll Psychol 2007;74:185–99. [CrossRef]
11. Kayıkçıoğlu M, Payzın S. Heart Rate Variability. Turk Kardiol Dern Ars 2001;29:238–45.
12. Boettger S, Hoyer D, Falkenhahn K, Kaatz M, Yeragani VK, Bär KJ. Altered diurnal autonomic variation and reduced vagal information flow in acute schizophrenia. Clin Neurophysiol 2006;117:2715–22. [CrossRef]
13. Ito T, Inoue Y, Sugihara T, Yamada H, Katayama S, Kawahara R. Autonomic function in the early stage of panic disorder: power spectral analysis of heart rate variability. Psychiatry Clin Neurosci1999;53:667–72. [CrossRef]
14. Nahshoni E, Aravot D, Aizenberg D, Singler M, Zalsman G, Strasberg B, et al. Heart rate variability in patients with major depression. Psychosomatics 2004;45:129–34. [CrossRef]
15. Udupa K, Sathyaprabha TN, Thirthalli J, Kishore KR, Lavekar GS, Raju TR, et al. Alteration of cardiac autonomic functions in patients with major depression: a study using heart rate variability measures. J Affect Disord 2007;100:137–41.
16. Donzuso G, Cerasa A, Gioia MC, Caracciolo M, Quattrone A. The neuroanatomical correlates of anxiety in a healthy population: differences between the State-Trait Anxiety Inventory and the Hamilton Anxiety Rating Scale. Brain Behav 2014;4:504–14. [CrossRef]
17. Raymond JG, Steele JD, Series P. Modeling trait anxiety: From computational processes to personality. Front Psychiatry 2017;8:1. [CrossRef]
18. Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination

for panic disorder: A randomized controlled trial. Jama 2000;283:2529–36. [CrossRef]

19. Wood SK. Cardiac autonomic imbalance by social stress in rodents: understanding putative biomarkers. Front Psychol 2014;5:950(1-7). [CrossRef]
20. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, et al. Depression, heart rate variability, and acute myocardial infarction. Circulation 2001;104:2024–28.
21. Lipsitz JD, Hsu DT, Apfel HD, Marans ZS, Cooper RS, Albano AM, et al. Psychiatric disorders in youth with medically unexplained chest pain versus innocent heart murmur. J Pediatrics 2012;160:320-4. [CrossRef]
22. Chalmers JA, Quintana DS, Anne-Abbott MJ, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta analysis. Front Psychiatry 2014;11:80. [CrossRef]

Keywords: Adolescent; fluoxetine; heart rate variability; panic disorder; psychotherapy.

Anahtar sözcükler: Adölesan; fluoksetin; kalp hızı değişkenliği; panik bozukluk; psikoterapi.