Association between Heart Rate Variability Indices and Depressed Mood in Patients with Panic Disorder

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Objective: Heart rate variability (HRV) reflects the regulation of the autonomic nervous system. Panic disorder is highly associated with autonomic dysfunction, and is often accompanied by depression. The aim of this study is to determine the association between depression and HRV indices in patients with panic disorder.

Methods: A total of 110 outpatients diagnosed with panic disorder participated in this study. The medical records of patients with panic disorder who visited the outpatient clinic of Konkuk University Hospital between December 2018 and March 2020 were retrospectively reviewed. Measurements used in this study include the Panic Disorder Severity Scale-Self Report, Beck Depression Inventory (BDI-II), Insomnia Severity Index, and HRV. Patients were divided into depressive and non-depressive groups based on their BDI-II scores. The association between HRV indices and depressive symptoms was statistically analyzed.

Results: The low frequency/high frequency (LF/HF) ratio was reduced in patients with depression (mean = −0.095, p = 0.004 in the above moderate depressive group, mean = −0.120, p = 0.020 in the severe depressive group). Significant correlations were found between depressive symptoms and standard deviation of NN interval (SDNN) (ms) (−0.19, p = 0.044), very low frequency (VLF) (ms²/Hz) (−0.22, p = 0.021), LF (−0.25, p = 0.008), HF (−0.19, p = 0.043), and LF/HF (−0.25, p = 0.009). Multiple linear regression analysis showed that BDI predicted SDNN (ms), VLF (ms²/Hz), LF, HF, and LF/HF.

Conclusion: We confirmed that the LF/HF ratio decreases when depression is accompanied by panic disorder. HRV indices may be useful markers for detecting depressive symptoms in patients with panic disorder.

KEY WORDS: Panic disorder; Depression; Heart rate variability.

INTRODUCTION

Panic disorder is characterized by a sudden and recurring surge in anxiety and avoidance of potential future panic attacks, which can include throbbing, sweating, trembling, shortness of breath, numbness, or the feeling that something terrible is about to happen [1]. Panic disorder is one of the most common anxiety disorders, with a lifetime prevalence rate of 2.1−4.7% in the general population [2,3]. It is a chronic disease with various courses. Adequate pharmacotherapy and cognitive behavioral therapy are effective in more than 85% of cases, either individually or in combination. Patients with good premorbid function tend to have a good prognosis. About 10−20% of patients continue to show significant symptoms [4]. Panic disorders often coexist with a wide range of other mental disorders. The most frequent comorbid psychiatric disease is depressive disorder, followed by other anxiety disorders [5]. In patients with panic disorder, the lifetime prevalence of major depressive disorders increases up to 50−60% [6]. Patients with comorbid depression are more likely to have poorer psychopathologies and prognoses than those without depression [7]. They have more severe symptoms of each disease, longer durations of illness, frequent hospitalizations, as well as decreased social skills and occupational function [8]. In addition, patients with comorbid depressive disorder showed a higher level of suicidality [9,10], and was a predictor of suicide attempts in the near future [11]. Therefore, it is important to evaluate whether depressive symptoms are present in patients.
One of the most typical and painful symptoms of panic disorder are autonomous neurological symptoms, such as palpitations, hyperventilation, dizziness, tremors, chest discomfort, sweating, as well as hot and cold flushes [12]. The autonomic nervous system seems to be closely related to the onset and expression of panic attacks [13]. The increased risk of cardiac events associated with panic disorder is related to dysregulated autonomous systems, especially heart rate (HR) and heart rate variability (HRV) [14]. HRV is the variation in the time interval between adjacent heartbeats [15] and reflects the regulation of autonomic balance, blood pressure, gas exchange, internal organs, as well as heart and vascular tone adjustments [16]. A high HRV reflects a healthy autonomous nervous system that can respond to changing environments. In contrast, reduced HRV indicates stress from exercise, psychological events, or other internal or external stressors. In addition, reduced HRV is widely used as a sign of cardiac autonomous flexibility related to diseases such as panic disorder.

There has been various studies on HRV changes in patients with depression, but no consistent results have been reported. Patients with major depressive disorder showed significantly lower standard deviation of NN interval (SDNN), root mean square of the successive differences (RMSSD), high frequency (HF), and very low frequency (VLF), and higher low frequency/high frequency (LF/HF) ratio [17,18]. On the contrary, some studies reported that there was no difference in HRV between depressive patients and normal people [19]. In panic disorder, reduced HF, increased LF and increased LF/HF ratio were observed due to an increase in sympathetic activity [20,21]. However, in some studies, LF/HF ratio was decreased [22], or did not change at all compared to normal people [23]. Although many studies have been conducted on HRV changes in patients with panic disorder and depression, few studies have attempted to identify the association of comorbid depression with HRV in patients with panic disorder.

Measuring HRV as a diagnostic purpose has an obvious advantage compared to existing psychological tests. It is a non-invasive biomarker that enables objective evaluation of patients’ symptoms and treatment responses as biomarkers, while conventional psychological tests rely on subjective reporting. Based on the results of previous HRV studies on depression, we hypothesized that patients with panic disorder accompanying depressive symptoms would show different HRV profiles than those without depression. For example, depressive patients have negative symptoms such as decreased level of energy, decrease motivation, and etc., which can be considered as a result of parasympathetic activity. Therefore, it can be assumed that when depression is accompanied by panic disorder, the proportion of parasympathetic activation increases compared to that of panic disorder only, resulting in a decrease in LF/HF ratio. Considering that coexisting depression has a significant effect on the treatment and prognosis of patients with panic disorder, analyzing these differences is of great clinical significance. Therefore, the aim of this study is to determine how HRV is associated with depressive symptoms in patients with panic disorder by comparing HRV indices between patients with and without depression.

**METHODS**

**Study Population**

A retrospective review of electronic medical records was conducted among outpatients who visited the psychiatry department at Konkuk University Hospital from December 2018 to March 2020. The inclusion criteria were as follows: patients who (1) were diagnosed as panic disorder based on The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5); (2) were aged greater than or equal to 18; and (3) had completed Panic Disorder Severity Scale-Self Report (PDSS-SR), Beck Depression Inventory (BDI-II), and HRV at the initial visit. Patients who had other psychiatric, neurological, cardiovascular, or respiratory diseases were excluded from this study. Out of 276 eligible individuals, 165 were excluded from the statistical analyses because they did not meet the inclusion criteria. The final sample consisted of 111 participants. This study was approved by the Institutional Review Board (IRB) of Konkuk University Hospital (approval number: KUMC 2021-03-035), and written informed consent was waived by the IRB due to the retrospective nature of the study.

**Measures**

**PDSS-SR**

The PDSS-SR is a self-report diagnostic measure of pan-
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Panic disorder, and can be used to measure the severity of the symptoms in the last week (e.g., "During the past week, how much have you worried or felt anxious about when your next panic attack would occur or about fears related to attacks?") [15]. It has seven items that can measure all panic disorder dimensions, including panic attack frequency, anticipatory anxiety, agoraphobic fear or avoidance, fear of panic-related bodily sensations, and work and social impairment [16,24]. Items are rated on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("most severe"). The Korean version of PDSS-SR was confirmed to have good reliability and validity in a previous study [25].

BDI-II
The BDI is a self-rated scale with 21-items which assess symptoms of depression persisting over a 2-week period. Each item is rated on a 4-point Likert scale ranging from 0 (symptom absent) to 3 (severe). The total score ranges from 0 to 63, with 0−13 considered minimal range, 14−19 mild, 20−28 moderate, and 29−63 severe. The BDI was originally developed by Beck in 1961 [26] with BDI-II being the most recent version of the BDI, which was developed in 1996 in response to changes in the DSM-IV criteria for the diagnosis of depressive symptom [27]. The Korean version of the BDI-II showed good internal consistency (Cronbach’s alpha = 0.89) and test-retest reliability, and was strongly correlated with other depression-related self-report measures, such as the Patient Health Questionnaire-9 (PHQ-9) (r = 0.75) [28]. In this study, the criteria for depression were set based on a score of 20 or higher.

ISI
The Insomnia Severity Index (ISI) is a simple self-report questionnaire that measures patients' perception of insomnia severity [29]. The Korean version of the Insomnia Severity Index (ISI-K) was used to assess sleep disorders in the Korean population, and was found to be a reliable and effective evaluation tool [30]. The index consists of seven questions: (1) Difficulty falling asleep? (2) Any problems that occur too early? (3) How satisfied are you with your current sleep patterns? (4) How much do you think your sleep problems affect your quality of life? (5) How worried are you? Any current sleep problems? (6) To what extent do you think sleep problems interfere with your current day-to-day function? These questions use a five-point Likert scale, with each question scoring from 0 to 4 (e.g., 0 = no problem, 4 = very serious problem). The sum of these seven scores totals from 0 to 28.

HRV
HRV is a physiological phenomenon occurring over the time interval between heartbeats. This value was measured as the variation in the beat-to-beat interval. It is a useful indicator of mortality and cardiovascular events in heart diseases [31]. Since HRV reflects the heart’s ability to adapt to its environment, an analysis of HRV is useful for evaluating autonomic neuronal imbalance by quantifying the state of the autonomic nervous system that regulates cardiac activity. Unlike most autonomic neurological tests that require patients’ cooperation, analysis of spontaneous heart rate is physiological, non-invasive, and can be done without the need for strict patients’ cooperation [32]. Various time and frequency domain parameters were used for measuring HRV [33]. Time domain measurements included SDNN, RMSSD, and pNN50. SDNN represents both sympathetic and parasympathetic activities, while RMSSD and pNN50 are more sensitive to parasympathetic tone. The frequency domain represents various spectral components, low frequency (LF: 0.04 to 0.15 Hz), high frequency (HF: 0.15 to 0.4 Hz), and LF/HF ratio. LF is regulated by sympathetic and parasympathetic activities, and HF reflects parasympathetic activities. The LF/HF ratio measures the balance between sympathetic and parasympathetic modulation [34]. Methods used to detect beats include an electrocardiogram (ECG), blood pressure, ballistocardiograms, and brainwave signals. ECG is preferred because it provides a clear waveform, making it easier to exclude heartbeats that do not occur in the sinoatrial node [35].

Statistical Analyses
HRV indices were logarithmically transformed because of skewed distribution. To investigate the differences in HRV between depressive and non-depressive patients, we classified participants into two groups according to the BDI score. First, we divided patients into the "above moderate depression" group and the control group based on a BDI score of 20. Then, patients were once more divided into a "severe depression" group and control group based on a BDI score of 29. Analysis of covariance (ANCOVA) was used to compare the differences between the groups,
with covariates of age, sex, and PDSS-SR scores. In addition, partial correlations were used to adjust for age, sex, and PDSS-SR score. Multiple linear regressions with age, sex, PDSS-SR score, and BDI as covariates were applied to all HRV indices. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 17 (SPSS Inc., Chicago, IL, USA), with significance established at $p < 0.05$.

**RESULTS**

Table 1 summarizes the participants’ characteristics of the participants among the observations. The sample consisted of approximately the same number of male and female participants (male:female = 57:54), with a mean age of 35 years (mean = 34.95, standard deviation = 12.91). Nearly half of the patients with panic disorder showed significant symptoms of depression (49.1% for moderate to severe depression and 46.0% for severe depression). The results of ANCOVA are presented in Tables 2, 3. The LF/HF ratio was lower in the group with moderate to severe depression ($p = 0.004$) (Table 2) and in the group with severe depression than in the control group ($p = 0.020$) (Table 3). In addition, LF was lower in patients with severe depression than in the control group ($p = 0.035$) (Table 3). Figure 1 shows the data visualized as a histogram comparing the LF/HF ratio for each group, as shown in Tables 2, 3.

The results of correlation analysis to determine the correlation between depressive symptoms and HRV while

| Table 1. Sample characteristics of 111 patients with panic disorder |
|---------------------------------------------------------------|
| **Variables** | **Frequencies (%)** | **Mean** | **Standard deviation** |
|----------------|---------------------|----------|-----------------------|
| **Sex**        |                     |          |                       |
| Male           | 57 (51.4)           | 34.95    | 12.91                 |
| Female         | 54 (48.7)           |          |                       |
| **Age**        |                     | 34.95    | 12.91                 |
| **PDSS-SR**    |                     |          |                       |
| 8 ≤ Sum of score < 10 | 32 (28.8) | 9.03    | 0.82                  |
| 11 ≤ Sum of score < 15 | 39 (35.1) | 12.80   | 1.30                  |
| 16 ≤ Sum of score | 40 (36.0) | 19.85   | 3.22                  |
| **BDI-II**     |                     |          |                       |
| Sum of score ≤ 13 | 23 (20.7) | 9.52    | 3.62                  |
| 14 ≤ Sum of score ≤ 19 | 14 (12.6) | 17.21   | 1.58                  |
| 20 ≤ Sum of score ≤ 28 | 23 (20.7) | 23.35   | 2.50                  |
| 29 ≤ Sum of score | 51 (46.0) | 40.33   | 7.52                  |
| **ISI**        |                     |          |                       |
| Sum of score ≤ 15 | 56 (50.1) | 8.71    | 3.46                  |
| 15 ≤ Sum of score | 54 (49.1) | 20.70   | 3.62                  |

PDSS-SR, Panic Disorder Severity Scale-Self Report; BDI-II, Beck Depression Inventory-II; ISI, Insomnia Severity Index.

| Table 2. Differences of logarithmically transformed heart rate variability indices between patients with above moderate depression and the controls |
|---------------------------------------------------------------|
| **Source** | **Sum of squares** | **df** | **Mean square** | **F** | **p value** |
|----------------|---------------------|-------|----------------|------|-------------|
| Log NN50      | 2.367               | 1     | 2.367          | 1.394| 0.241       |
| Log pNN50     | 10.167              | 1     | 10.167         | 3.483| 0.065       |
| Log RMSSD (ms)| 2.150               | 1     | 2.150          | 0.951| 0.332       |
| Log VLF (ms²/Hz) | 14.668   | 1     | 14.668         | 1.756| 0.188       |
| Log LF        | 18.494              | 1     | 18.494         | 2.052| 0.155       |
| Log HF        | 5.607               | 1     | 5.607          | 0.680| 0.412       |
| Log LF/HF     | 6.046               | 1     | 6.046          | 8.779| 0.004*      |
| Log SDNN (ms) | 1.990               | 1     | 1.990          | 1.270| 0.262       |

RMSSD, root mean squares of the successive differences; LF, low frequency; HF, high frequency; VLF, very low frequency; SDNN, standard deviations of the NN intervals.

Age, sex, and Panic Disorder Severity Scale (PDSS) were adjusted.

*Statistically significant ($p < 0.05$).
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Table 3. Differences of logarithmically transformed heart rate variability indices between patients with severe depression and the controls

| Source       | Sum of squares | df | Mean square | F     | p value |
|--------------|----------------|----|-------------|-------|---------|
| Log NN50     | 0.033          | 1  | 0.033       | 0.019 | 0.891   |
| Log pNN50    | 6.294          | 1  | 6.294       | 2.128 | 0.148   |
| Log RMSSD (ms) | 3.725         | 1  | 3.725       | 1.659 | 0.201   |
| Log VLF (ms²/Hz) | 21.991       | 1  | 21.991      | 2.655 | 0.106   |
| Log LF       | 39.983         | 1  | 39.983      | 4.539 | 0.035*  |
| Log HF       | 17.313         | 1  | 17.313      | 2.127 | 0.148   |
| Log LF/HF    | 3.924          | 1  | 3.924       | 5.537 | 0.020*  |
| Log SDNN (ms) | 2.392          | 1  | 2.392       | 1.529 | 0.219   |

RMSSD, root mean squares of the successive differences; LF, low frequency; HF, high frequency; VLF, very low frequency; SDNN, standard deviations of the NN intervals.

Age, sex, and Panic Disorder Severity Scale (PDSS) were adjusted.

*Statistically significant (p < 0.05).

Fig. 1. Visualized histogram of logarithmically transformed LF/HF ratio between each group shown in Tables 2 and 3. (A) Differences of logarithmically transformed heart rate variability indices between patients with above moderate depression and the controls. (B) Differences of logarithmically transformed heart rate variability indices between patients with severe depression and the controls.

Table 4. Correlations between Beck Depression Inventory (BDI) and logarithmically transformed heart rate variability indices

| Variable       | BDI        | Log SDNNms | Log NN50 | Log pNN50 | Log RMSSDms | Log VLFms/Hz | Log LF | Log HF | Log LF/HF |
|----------------|------------|------------|----------|-----------|-------------|--------------|--------|--------|-----------|
| BDI            | -0.194*    | -0.045     | -0.155   | -0.187    | -0.222*     | -0.255**     | -0.195*| -0.252**| -0.025    |
| Log SDNN (ms)  | -0.045     | 0.379***   | -0.108   | 0.412***  | 0.260***    | 0.331**      | 0.444***| 0.332***| 0.080     |
| Log NN50       | -0.155     | 0.040      | -0.108   | -0.046    | -           | -            | -      | -      | -         |
| Log pNN50      | -0.187     | 0.982***   | 0.412*** | 0.046     | -           | -            | -      | -      | -         |
| Log RMSSD (ms) | -0.222*    | 0.942***   | 0.260*** | 0.072     | 0.904***    | 0.921***     | 0.956***| 0.956***| 0.956***  |
| Log VLF (ms²/Hz) | -0.255**   | 0.938***   | 0.331**  | 0.047     | 0.921***    | 0.953***     | -      | -      | -         |
| Log LF         | -0.195*    | 0.948***   | 0.444*** | 0.067     | 0.956***    | 0.913***     | 0.956***| 0.956***| 0.956***  |
| Log HF         | -0.252**   | 0.169      | -0.281** | -0.025    | 0.074       | 0.332***     | 0.353***| 0.353***| 0.080     |
| Log LF/HF      | -0.025     | -0.321     | -0.281** | -0.025    | 0.074       | 0.332***     | 0.353***| 0.353***| 0.080     |

RMSSD, root mean squares of the successive differences; LF, low frequency; HF, high frequency; VLF, very low frequency; SDNN, standard deviations of the NN intervals.

Partial correlations were controlled for age, sex, and Panic Disorder Severity Scale (PDSS) scores.

*Statistically significant at p < 0.05, **statistically significant at p < 0.01, ***statistically significant at p < 0.001.
controlling for age, sex, and PDSS-SR scores are shown in Table 4. There were significant correlations between depressive symptoms (represented as BDI) and SDNN (ms) (correlation coefficient = −0.19, p = 0.044), VLFms2Hz (correlation coefficient = −0.22, p = 0.021), LF (correlation coefficient = −0.25, p = 0.008), HF (correlation coefficient = −0.19, p = 0.043), and LF/HF (correlation coefficient = −0.25, p = 0.009). No significant correlations were found between depressive symptoms and other HRV indices. Multiple linear regression analysis revealed that higher BDI scores were associated with lower levels of SDNN (ms) (p = 0.044), VLFms2Hz (p = 0.021), LF (p = 0.063), HF (p = 0.008), and LF/HF (p = 0.009) (Table 5).

| Dependent variable | Independent variables | Coefficient B | Standard error | p value |
|--------------------|----------------------|---------------|----------------|---------|
| Log SDNN (ms)      | (Constant)           | 4.849         | 0.567          | 0.000   |
|                    | Age                  | −0.005        | 0.010          | 0.595   |
|                    | Sex                  | −0.059        | 0.237          | 0.805   |
|                    | PDSS                 | 0.045         | 0.027          | 0.096   |
|                    | BDI                  | −0.020        | 0.010          | 0.044*  |
| Log NN50           | (Constant)           | 3.981         | 0.633          | 0.000   |
|                    | Age                  | −0.014        | 0.011          | 0.189   |
|                    | Sex                  | 0.369         | 0.257          | 0.155   |
|                    | PDSS                 | −0.030        | 0.029          | 0.295   |
|                    | BDI                  | 0.005         | 0.011          | 0.654   |
| Log pNN50          | (Constant)           | −0.039        | 0.843          | 0.963   |
|                    | Age                  | −0.006        | 0.014          | 0.678   |
|                    | Sex                  | 0.132         | 0.338          | 0.696   |
|                    | PDSS                 | −0.021        | 0.039          | 0.582   |
|                    | BDI                  | −0.022        | 0.014          | 0.123   |
| Log RMSSD (ms)     | (Constant)           | 4.986         | 0.680          | 0.000   |
|                    | Age                  | −0.005        | 0.011          | 0.670   |
|                    | Sex                  | −0.069        | 0.284          | 0.809   |
|                    | PDSS                 | 0.048         | 0.032          | 0.139   |
|                    | BDI                  | −0.023        | 0.012          | 0.052   |
| Log VLF (ms²/Hz)   | (Constant)           | 7.682         | 1.303          | 0.000   |
|                    | Age                  | −0.023        | 0.022          | 0.301   |
|                    | Sex                  | −0.183        | 0.544          | 0.738   |
|                    | PDSS                 | 0.135         | 0.061          | 0.029   |
|                    | BDI                  | −0.053        | 0.022          | 0.021*  |
| Log LF             | (Constant)           | 7.993         | 1.344          | 0.000   |
|                    | Age                  | −0.027        | 0.023          | 0.230   |
|                    | Sex                  | −0.436        | 0.561          | 0.439   |
|                    | PDSS                 | 0.144         | 0.063          | 0.024   |
|                    | BDI                  | −0.063        | 0.023          | 0.008*  |
| Log HF             | (Constant)           | 7.428         | 1.296          | 0.000   |
|                    | Age                  | −0.019        | 0.022          | 0.390   |
|                    | Sex                  | −0.309        | 0.541          | 0.570   |
|                    | PDSS                 | 0.121         | 0.061          | 0.049   |
|                    | BDI                  | −0.046        | 0.022          | 0.043*  |
| Log LF/HF          | (Constant)           | 0.540         | 0.383          | 0.162   |
|                    | Age                  | −0.009        | 0.006          | 0.191   |
|                    | Sex                  | −0.146        | 0.160          | 0.364   |
|                    | PDSS                 | 0.025         | 0.018          | 0.163   |
|                    | BDI                  | −0.018        | 0.007          | 0.009*  |

RMSSD, root mean squares of the successive differences; LF, low frequency; HF, high frequency; VLF, very low frequency; SDNN, standard deviations of the NN intervals; PDSS, Panic Disorder Severity Scale; BDI, Beck Depression Inventory.

*Statistically significant at p < 0.05.
DISCUSSION

In this study, we investigated the association between depression and HRV in patients with panic disorder. Our results showed that HRV indices were reduced in patients with depression. In particular, the LF/HF ratio was significantly associated with depressive symptoms in both comparative and regression analyses. HRV has long been a focus of research as a biological marker for depression [36], and promising attempts have been made to utilize HRV as a diagnostic or predictive biomarker of depression. However, to our knowledge, this is the first study to analyze the differences in HRV indices from depression in patients with panic disorder.

Studies that identify the relationship between HRV and mood disorders generally suggest that reduced HRV is associated with negative outcomes [37]. The severity of depression has been associated with a decrease in parasympathetic activity [38]. In patients with depression, parasympathetic responses were lower during the resting state and task performance than in patients with anxiety disorders. As a result, SDNN, RMSSD, and HF were found to be low [17], while LF/HF was found to be high [18]. In particular, SDNN, RMSSD, HF, and VLF reflect parasympathetic activity, which is reduced in patients with depression [39]. A reduction in parasympathetic HRV indices has also been reported in anxiety disorders, such as generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, and panic disorder [13,40-43]. In patients with posttraumatic stress disorder, there were relatively consistent results showing low RMSSD, HF, and high LF [44-47].

With regard to panic disorder, the results of previous studies are inconsistent. In a study comparing HRV differences between patients with panic disorder and healthy controls, the results showed lower HF, high LF, and LF/HF in patients with panic disorder [20]. Similarly, decreased HF and increased LF/HF and LF were observed in patients with panic disorder, suggesting the presence decreased parasympathetic activity and increased sympatho-vagal balance [21]. In a study analyzing HRV and plasma norepinephrine kinetics in patients with panic disorder, LF was found to be unremarkable. This is because LF does not strictly measure the firing rate of sympathetic nerves [48]. Another study showed completely opposite results. In patients with panic disorder, LF/HF ratios and LF were significantly lower, whereas HF was significantly higher [22]. In a study of patients with an early stage of panic disorder, there was no significant difference LF/HF ratios between patients and controls [23]. Similarly, several other studies did not show significant differences in HRV [49,50]. These studies have shown that HRV may vary even in patients with the same disease.

We observed a significant decrease in the LF/HF ratio in patients with depression. The LF/HF ratio reflects the balance between sympathetic and parasympathetic activities. An increase in the LF/HF ratio represents low vagal activity [51]. In general, sympathetic activity increases in stressful situations, such as depression and anxiety. In a large-scale meta-analysis of patients with major depressive disorder, depressive patients showed significantly higher LF/HF ratios than control groups [38,52]. However, some studies have found no significant differences in HRV indices between patients with depression and controls, and the results have all been heterogeneous in several other clinical studies [17,19,53-55]. The causes of this heterogeneity include differences in data acquisition techniques, lack of consensus on standards for HRV analyses prior to 1996, cross-sectional versus longitudinal research methods, and adverse effects of antidepressants on the autonomic nervous system. In general, the LF/HF ratio is higher in patients with MDD or panic disorder, suggesting increased sympathetic activity and a reciprocal decrease in parasympathetic activity. However, the changes in the autonomic nervous system during depression in patients with panic disorder are not yet known.

It is highly possible that the presence or absence of co-morbid depressive symptoms has a great influence on the heterogeneity of previous HRV studies in patients with panic disorder. Interestingly, our results showed that, along with a decrease in HRV indices representing parasympathetic activity, a reduced LF was also observed. Every time the BDI 1 point increased, the LF decreased more significantly (coefficient = −0.063) than the HF (coefficient = −0.046), and as a result, the total value of the LF/HF decreased. Generally, the LF/HF ratio is reduced in patients with depression. However, in a previous study involving healthy subjects, it was observed that the LF/HF ratio decreased in the group reporting depressive symptoms, and the LF/HF ratio was found to increase after the depressive symptoms improved [56]. This is contrary to most other studies comparing patients with depression
and healthy subjects. As such, it seems that the pattern of LF/HF ratio according to depressive symptoms may vary depending on the baseline disease condition of the study subjects. Our study was conducted on patients with panic disorder who showed increased sympathetic activity due to high tension and anxiety [57]. However, when parasympathetic activity overrides, it can lead to lethargy, loss of normal motivation, and depression [58]. In this context, it is assumed that when depression is present in patients with panic disorder, a significant decrease in the LF index representing sympathetic activity can be expected.

This study has several limitations. First, this study was conducted with a relatively small sample size. A small sample size increases variability and bias, thus affecting the reliability of the results. Second, several studies have shown that antidepressants affect HRV indices [38,59]. However, in this study, no information was provided about patients’ medication use. This is a limitation of this study because patients’ medication use can affect the results of the study. Third, this study was conducted without healthy control group. Even though we compare panic disorder patients with and without depression, it is still important to include healthy control participants in the study design. Healthy control group allows discrimination of patient outcomes caused by other variables, as well as it helps generalize the research results.

The advantage of this study is that standardized tools were used to test for comorbid depression in patients with panic disorder, and psychological test scales were administered and HRV measurements taken at the initial visit. Furthermore, the association between depressive symptoms and HRV indices could be more accurately analyzed, as HRV was tested before treatment began. This is of great importance, given that HRV can be highly sensitive to external environments. In this study, HRV was measured at the same location each time, and all tests were performed by one inspector, which provided uniformity to the measurement and interpretation of the findings. It is well known that many patients with panic disorder have comorbid depression, which is important for treatment and prognosis. However, to the best of our knowledge, there is still a lack of research on the relationship between HRV and depression, especially in patients with panic disorder. Through this study, it was possible to show that the change in heart rate due to depression in patients with panic disorder differs from that in the general population. In this study, we showed that the LF/HF ratio decreased when depression was accompanied by panic disorder. This is probably due to the specificity of patients with panic disorder, with depressive symptoms noted to lead to an increase in parasympathetic nerve activity. The clinical implication of this study is that its results can be used as important biomarkers for the evaluation and treatment of patients with panic disorder.

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