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Threat-induced autonomic dysregulation in panic disorder evidenced by heart rate variability measures

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ABSTRACT

Objective: The objective was to compare autonomic response to threatening stimuli between patients with panic disorder (PD) and healthy volunteers by using 5-min recordings of heart rate variability (HRV).
Methods: Twenty-seven patients with PD and 20 healthy controls were recruited. The first 5-min measurement of HRV was conducted at resting state. HRV measurement during threatening stimuli was conducted while participants were viewing 15 threatening pictures. Spectral analyses measures included high-frequency (HF; 0.15–0.4 HZ) component, low-frequency (LF; 0.04–0.15 Hz) component and LF/HF ratio.
Results: There was no significant HRV difference between the two groups at the resting state. During threatening stimuli, the PD group had significantly higher LF power and LF/HF ratio and significantly lower HF power than the healthy controls (for all, $P<.01$). A two-way analysis of variance was employed to determine the effect of group (patient and control) and condition (threatening and resting) on all three HRV measures. The analysis showed a significant main effect of group ($F=12.21$; $P<.01$), condition ($F=14.21$; $P<.001$) and interaction effect between group and condition ($F=4.83$; $P<.05$) on LF/HF ratio.
Conclusions: The findings from the present study suggest that patients with PD exhibit a sympathetic predominance when faced with threatening stimuli compared with normal control subjects.

1. Introduction

Panic disorder (PD) is characterized by sudden and unexpected attacks of fear accompanied by severe anxieties and alarming somatic symptoms [1–3]. The cognitive–psychological model suggests that the manner in which threat-relevant information is perceived, encoded and recalled plays an important role in PD [4]. Patients with PD tend to show attentional bias toward threatening cues [5] and have excessive response to these threat-related stimuli [6]. The excessive response to threat-related stimuli in PD patients can be expressed via bodily sensations or somatic symptoms [2,7]. The somatic symptoms include chest pain, heart pounding, tachycardia, shortness of breath, sweating and dizziness [8]. These physical responses of PD may suggest dysfunction of autonomic nervous system (ANS). Accordingly, previous studies indicate that autonomic dysregulation plays an important role in the pathophysiology of PD [9,10].

Heart rate variability (HRV) is primarily controlled by interactions between sympathetic and parasympathetic activity [11]. Thus, many recent studies used HRV analysis to investigate autonomic dysregulation of PD. There are two major measures of HRV analysis, namely, frequency domain and time domain measures [12]. Spectral analysis of HRV has been especially useful in providing information on sympathovagal change after exposure to various stimuli. Accordingly, the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (ESC/NASPE) recommend using frequency domain analysis for short-term electrocardiogram (ECG) recordings of 5 min and time domain analysis for 24-h ECG recordings [3].

In spectral analysis of HRV, three major components ranging from 0 to 0.4 Hz are often distinguished. It is generally acknowledged that high-frequency (HF; 0.15–0.4 HZ) component reflects parasympathetic activity [13]. Although it is still a controversy, studies suggest that low-frequency (LF; 0.04–0.15 Hz) component reflects sympathetic activity [3,12]. Accordingly, the LF/HF ratio is generally computed as a measure of the sympathovagal balance toward sympathetic activity [14]. The physiological role of very low frequency (VLF; 0.01–0.04 Hz) component is not yet known [3]. Moreover, VLF component assessed from short-term ECG recordings is generally not used because it is a dubious measure.

Large bodies of research generally suggest that patients with PD exhibit decreased HRV, reduced vagal activity and increased sympathetic tone at resting state [15]. A study reported that patients with PD have a decreased HF component and an increased LF component

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compared with control subjects [16]. Klein et al. [17] also reported that patients with PD showed a lowering in the HF peak. A more recent research extended the previous findings and showed that reduced vagal activity in HRV is not only associated with symptom severity but is also correlated with cognitive dysfunction in patients with PD [18]. Many recent studies have focused on investigating short-term HRV changes in response to diverse panic-evoking stimuli. A study performed spectral analysis of HRV in PD patients before and after infusing isoproterenol, which is a beta-adrenergic agonist. The results showed that sympathovagal ratios were significantly increased only in the PD group after isoproterenol administration [19]. Yeragani et al. [20] also showed that sodium lactate infusions significantly decreased HF power and increased sympathovagal ratios in patients with PD. In addition, compared with healthy volunteers, PD patients showed higher startle responses to threat of shock (fear-potentiated startle) and greater startle potentiations to aversive imagery of standard panic attack scenarios [21,22]. Studies using postural change, orthostatic challenge, pharmacological challenge using yohimbine, hyperventilation, deep breathing and traumatic recall also showed similar findings [9,16,23–26]. Threatening stimulus, as discussed earlier, is another important panic-evoking stimulus [27]. However, no studies conducted so far have investigated the effect of threatening stimuli on the ANS by using HRV. Furthermore, most of the previous studies have used biological or physical panic-evoking stimuli rather than psychological stimuli. Nevertheless, psychological stimuli, such as threat-related stimuli, are more frequently encountered than contrived agents such as various pharmacological challenges, hyperventilation and deliberate traumatic recall in real-life situations.

The purpose of the present study is to compare autonomic response to threatening stimuli between patients with PD and healthy volunteers by using 5-min recordings of HRV. We hypothesized that patients with PD would have higher sympathetic activity, evidenced by higher sympathovagal ratios (LF/HF), in response to threatening stimuli.

2. Methods

2.1. Subjects

Twenty-seven patients with PD and 20 healthy volunteers aged 18–65 participated in the present study. Patients with PD were recruited from the outpatient psychiatry clinic at Uijeongbu St. Mary's Hospital, The Catholic University of Korea. Participants of the control group were recruited from the general community via self-referral from advertisements and collaborating clinicians. A board-certified psychiatrist carefully assessed the participants of both groups using the Diagnostic and Statistical Manual of Mental Disorders semistructured interview. A comprehensive psychiatric interview was completed to rule out patients with bipolarity, psychotic symptoms, cognitive deficits and neurological conditions. All patients in the PD group met the diagnosis of PD with or without agoraphobia. Participants of the control group were free of current or previous history of psychiatric disorders or cardiac disorders. All subjects agreed to participate in the present study by giving their written informed consent. This study was approved by the Institutional Review Board of Uijeongbu St. Mary's Hospital, The Catholic University of Korea.

2.2. Procedure

All subjects completed both demographic data and clinical measures before performing the experimental task. Demographic data included age, gender, marital status, religion, socioeconomic status and education level. Clinical measures included the State Anxiety Inventory (SAI) and the Trait Anxiety Inventory (TAI) [28]. The PD group completed the Panic Disorder Severity Scale (PDSS) in addition to the SAI and TAI [29].

The ECG was recorded with a limb lead placed in the index finger by using a digital arterial pulse-wave analyzer (McPulse, Meridian, Seoul, Korea). The participants sat in a semisupine position with their back leaning comfortably to allow visual contact to a computer screen. After resting quietly for 5 min in the chair, the first ECG was recorded for 5 min in the semisupine position (resting state). After 1 min of rest for stabilization, participants were shown 15 threatening pictures (e.g., a picture showing a person with severe injury in the leg), each lasting 10 s, on a computer screen while recording a 5-min ECG. After another 1 min for stabilization, a third 5-min ECG recording was conducted while the subjects were viewing another set of 15 similar threatening pictures (during threatening stimuli). The second 5-min ECG recording was not included in the analysis because HRV tends not to be stationary within the first 3 min of stimulus exposure [19,20]. Pictures were presented using the E-Prime software package (Psychology Software Tools Inc., Pittsburgh, PA, USA). Participants were instructed not to drink caffeinated beverages for at least 8 h before the ECG recordings. All participants completed the procedure at a similar time of the day (i.e., late morning to early afternoon).

2.3. HRV indices

Fast Fourier transformation was used to reveal the peak of major frequency ranges. Frequency ranges for spectral analysis were set based on ESC/NASPE guidelines [3]. Two spectral measure components included LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz). LF and HF can be measured in absolute values of power (ms^2) and in normalized units (NUs) [8,30]. NU was used in the present study because NU better reflects the controlled and balanced behavior of the two branches of the ANS. The ratio of LF/HF was also computed based on NU.

2.4. Statistical analysis

All statistical analyses were performed using SAS/PC version 9.2 (SAS Institute Inc., Cary, NC, USA). Comparisons of demographic findings between the panic and the control groups were evaluated on the basis of the χ^2 test for categorical variables and the Student's t test for continuous variables. Differences in HRV measures between two groups were analyzed using Student's t test. For all three HRV measures, a two-way analysis of variance (ANOVA) was performed (subject group × condition). The between-subject variable was the group (PD vs. control), and the within-subject variable was the condition (resting state vs. during threatening stimuli). Correlations between HRV measures with symptom severity measures (PDSS, SAI and TAI) and with duration of illness in patients with PD were analyzed using Pearson correlation. Statistical significance was defined as $P<.05$ (two-tailed).

3. Results

3.1. Participant characteristics

Demographic and clinical data of the subjects are summarized in Table 1. The two groups did not differ in age, gender, marital status, religion and socioeconomic status. Mean SAI and TAI scores were significantly higher in the PD group than in the control group (for both, $P<.01$). In the PD group, 8 patients were drug-naïve, and 19 patients had been taking medication for at least 1 month before participating in the present study. Among 19 patients taking medication, 9 patients were prescribed paroxetine (12.5–37.5 mg/day), 4 patients were prescribed escitalopram (10–20 mg/day), and 6 were prescribed other medications (sertraline, n=2; venlafaxine, n=2; mirtazapine, n=1; imipramine, n=1).