Heart rate variability in drug-naïve patients with panic disorder and major depressive disorder

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A B S T R A C T

Power spectral analysis of electrocardiogram (ECG) R–R intervals is useful for the detection of autonomic dysfunction in various clinical disorders. Although both panic disorder (PD) and major depressive disorder (MDD) are known to have effects on the cardiovascular nervous system, no previous study has tested this among drug-naïve (i.e. no history of treatment) patients with MDD and PD in the same study. The purpose of this study was to compare cardiac autonomic functions among drug-naïve patients with MDD and PD and those of healthy controls. Subjects were 17 drug-naïve PD patients, 15 drug-naïve MDD patients and 15 normal controls. ECGs were recorded under both supine resting and supine deep-breathing conditions (10–12 breaths/min; 0.17–0.20 Hz). We measured the low-frequency power (LF; 0.05–0.15 Hz), which may reflect baroreflex function, the high-frequency power (HF; 0.15–0.40 Hz), which reflects cardiac parasympathetic activity, as well as the LF/HF ratio. As expected, deep breathing induced an increase in HF power and a decrease in the LF/HF ratio in healthy controls. Compared to these controls, however, the MDD group had a lower response to regular deep breathing in LF power and in LF/HF ratio. PD patients showed intermediate results between normal controls and MDD patients. The results indicate that the reactivity to deep breathing revealed diminished cardiac autonomic reactivity in drug-naïve MDD patients.

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1. Introduction

When parasympathetic activity to the heart is reduced, sympathetic tone is unopposed, thereby increasing the risk of developing lethal cardiovascular disease. Previous studies demonstrated that both patients with panic disorder (PD) (Yeragani et al., 1993; Klein et al., 1995) and those with major depressive disorder (MDD) (Rechlin et al., 1994; Guinjoan et al., 1995; Agelink et al., 2002; Udupa et al., 2007) have diminished parasympathetic activity, or an imbalance between the two systems. It is thought that this mechanism contributes to the increased rates of cardiovascular disease in patients with MDD and PD (Penninx et al., 2001; Gorman and Sloan, 2000). In fact, increased rates of cardiovascular disease cannot be used to assess sympathetic outflow to the heart (Baumert et al., 2009; Jardine et al., 2002). This would imply that the previously mentioned simplified concept, which states that the ratio of LF power to HF power (LF/HF) reflects cardiac sympathovagal balance (Perini and Veicsteinas, 2003), is also controversial.

Power spectral analysis of electrocardiogram (ECG) R–R intervals is one of the most useful methods for the detection of autonomic instabilities in various clinical disorders (Berntson et al., 1997). It is generally accepted that the high-frequency (HF; 0.15–0.40 Hz) component is mediated by cardiac parasympathetic tone, which is dependent on respiration. The measurement of augmented HF power during regular deep breathing (Driscoll and Picciardo, 2000) is of importance, because respiratory sinus arrhythmia is primarily parasympathetically mediated and allows assessment of cardiac vagal responsiveness. The relationship of low-frequency (LF; 0.05–0.15 Hz) power to cardiac sympathetic innervation and function, however, has been controversial. A recent study demonstrated that LF power reflects baroreflex function, rather than cardiac sympathetic innervations (Moak et al., 2007), and cannot be used to assess sympathetic outflow to the heart (Baumert et al., 2009; Jardine et al., 2002). This would imply that the previously mentioned simplified concept, which states that the ratio of LF power to HF power (LF/HF) reflects cardiac sympathovagal balance (Perini and Veicsteinas, 2003), is also controversial.

Using heart rate variability, the involvement of cardiac autonomic system in patients with MDD (Gorman and Sloan, 2000; Rechlin et al., 1994; Guinjoan et al., 1995; Agelink et al., 2002; Udupa et al., 2007; Yeragani et al., 1991; Licht et al., 2008) and PD (Gorman and Sloan, 2000; Yeragani et al., 1993; Klein et al., 1995; Ito et al., 1999; Garakani

Abbreviations: ECG, electrocardiogram; BMI, body mass index; HAM-D, Hamilton Depression Rating Scale; HF, high-frequency; LF, low-frequency; MDD, major depressive disorder; PD, panic disorder; STAI, Spielberger State Trait Anxiety Inventory.

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et al., 2009; Yeragani and Rao, 2003) has been studied extensively. Nevertheless, the results have been somewhat inconsistent, probably because of methodological differences, clinical heterogeneity of subjects and differences in medicament therapy. Especially psychotropic drugs are known to alter cardiac autonomic activity in diverse ways (Garakani et al., 2009; Yeragani et al., 1992; Bär et al., 2008). One previous study demonstrated that tricyclic antidepressants and selective serotonin reuptake inhibitors induced different alterations in cardiac autonomic activity (Yeragani and Rao., 2003). Therefore, findings from drug-naïve patients must be relevant for the neurophysiological nature of MDD and PD as well. To our knowledge, however, no previous study has made a direct comparison of power spectral analyses of heart rate variability among drug-naïve (i.e. no history of treatment) patients with MDD and PD. In the present study, we therefore compare cardiac autonomic responses to deep breathing among drug-naïve patients with MDD and PD with those of healthy controls. We hypothesized that patients with MDD and PD would have diminished cardiac autonomic responses to regular deep breathing (10–12 breaths/min: 0.17–0.20 Hz) compared to healthy controls.

2. Materials and methods

2.1. Subjects

As shown in Table 1, the PD group consisted of 11 men and 6 women, and the MDD group consisted of 9 men and 6 women. All patients were recruited from the psychiatric outpatient clinic of Kanazawa University Hospital. They fulfilled the DSM-IV criteria for PD or MDD. In the PD group, the mean age (±SD) was 29.4±9.5 years (range: 16–52) and the mean duration of disease (±SD) was 59.2±102.1 weeks (range: 1.5–380). Their mean state score (±SD) on the Spielberger State–Trait Anxiety Inventory (STAI: Spielberger et al., 1970) was 52.5 (±8.9) (n = 16; one participant failed). In the MDD group, the mean age (±SD) was 33.7±10.4 years (range: 20–50 years) and the mean duration of disease (±SD) was 21.5±36.3 weeks (range: 4–144 weeks). Their mean total score (±SD) on the Hamilton Depression Rating Scale (HAM-D: Hamilton, 1960) was 20.9 (±5.3). None of the patients with PD or MDD had any co-morbidity with other psychiatric disorders or any significant physical illnesses. That is, the MDD patients did not have a current or past history of anxiety disorders, and the PD patients did not have a current or past history of major depression or other psychiatric illnesses. The patients were physically healthy, and patients with cardiovascular, respiratory, endocrinological, and other physical illnesses were excluded from the studies. None of the patients had ever received medication that acts upon the central or autonomic nervous system (e.g., antipsychotics, anticholinergics, anti-depressants, anticonvulsants, anxiolytics, cerebral metabolic activators, or cerebral vasodilators).

The control subjects consisted of 15 healthy volunteers (8 men and 7 women), aged (±SD) 29.9±10.5 years (range: 21–59 years). The control group was not significantly different from the PD or MDD groups in age, gender or body mass index (BMI). The control subjects had no personal or family history of psychiatric or neurological disease. All were functioning normally and independently in their daily lives. Smokers were excluded from the studies. All subjects agreed to participate in the study with full knowledge of the experimental nature of the research. The study was performed in accordance with the rules and regulations of the hospital committee regarding personal information, and followed the Declaration of Helsinki.

2.2. ECG recording

The subjects were instructed not to drink caffeinated beverages for at least 3 h before recording. ECG was recorded in all subjects while lying in a soundproof, light-controlled recording room. Subjects were instructed to relax during the experiment. After 20 min of supine rest, an ECG was recorded for 5–10 min in the supine position (rest). Subsequently, the subject performed regular deep breathing for 4 min in the same supine position. None of the subjects complained of a panic attack or an increase in anxiety during the procedure. Deep-breathing recordings were obtained with controlled breathing at 10–12 breaths/min (0.17–0.20 Hz) using voice indication. The ECG was amplified, digitized (sampling rate 200 Hz), and stored for offline analysis. To ensure the regular deep breathing, the subjects were observed via a video monitoring system. R-peaks in the ECG waveform were detected by an automated detection algorithm and subsequently verified by visual inspection with a Hyper Wave 2.1 (Kissei Comtec, Nagano, Japan). Successive 128 R–R intervals were measured for each condition (resting and deep breathing). Power spectral analysis of the beat-to-beat time series of R–R intervals was performed using the maximum-entropy method. This analysis was performed with a Hyper Wave 2.1 (Kissei Comtec, Nagano, Japan). We measured the low-frequency power (LF; 0.05–0.15 Hz) and the high-frequency power (HF; 0.15–0.40 Hz). Data on each band power were transformed into their natural logarithms. The LF/HF ratio was also assessed.

2.3. Statistical analysis

For each physiological variable (R–R interval, LF power, HF power, LF/HF ratio), a two-way ANOVA was performed (subject group×condition). The inter-subject variable was the group (healthy control, PD, and MDD) and the intra-subject variable was the condition (rest and deep breathing). When a significant subject group effect or interaction (subject group×condition) effect was found, t-tests were performed among three groups as a post hoc test for deep-breathing condition, resting condition and response to the deep breathing (deep breathing minus resting) respectively. Relationships between the physiological variables and HAM-D total score or STAI state score were assessed using Pearson’s correlation coefficient for MDD and PD patients. Statistical significance was defined as p < 0.05.

3. Results

In the comparison of R–R interval, the two-way ANOVA (subject group×condition) showed a significant main effect of condition (F = 30.73; p < 0.001), and there was no interaction effect between group and condition (Table 3). As shown in Table 2, deep breathing shortened the R–R interval in all three groups.

In the comparison of LF power, there was no significant main effect, but a significant interaction effect was observed between group and condition (F = 3.40; p = 0.042) (Table 3). As shown in Fig. 1A, this

Table 1

Demographics.

<table>
<thead>
<tr>
<th>Total number</th>
<th>Control</th>
<th>Panic disorder</th>
<th>Major depressive disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.9 (21–59)</td>
<td>29.4 (16–52)</td>
<td>33.7 (20–50)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/7</td>
<td>11/6</td>
<td>9/6</td>
</tr>
<tr>
<td>BMIa</td>
<td>21.8 (17.1–25.6)</td>
<td>22.1 (19.2–27.2)</td>
<td>21.0 (16.7–25.1)</td>
</tr>
<tr>
<td>State anxietyb</td>
<td>52.5 (±8.9)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HAM-D scorec</td>
<td>–</td>
<td>–</td>
<td>20.9 (±5.3)</td>
</tr>
<tr>
<td>Disease duration (weeks)</td>
<td>59.2 (1.5–380)</td>
<td>21.5 (4–144)</td>
<td>–</td>
</tr>
</tbody>
</table>

Data are expressed as means (range or ±SD).

a BMI: body mass index.

b State score of Spielberger State–Trait Anxiety Inventory (n = 16; one participant failed).

c HAM-D: Hamilton Depression Rating Scale.
interaction was due to the diminished responses to deep breathing in the MDD group as compared to the control and PD groups. The t-test demonstrated the significant lower LF power in the MDD group during resting condition as compared to the control ($t = 2.47, p = 0.020$) and PD ($t = 2.54, p = 0.017$) groups, while the t-test failed to detect any significant differences during deep breathing among three groups. In the responses to deep breathing (deep breathing minus resting condition), the t-test demonstrated a significant difference between the MDD and control groups ($t = 2.51, p = 0.018$) as shown in Fig. 1A.

In the comparison of HF power, there was a significant main effect of condition ($F = 14.00; p < 0.001$), and there was no significant interaction effect between group and condition (Table 3). As shown in Table 2, deep breathing increased HF power for all three groups.

In the comparison of LF/HF ratio, there was a significant main effect of condition ($F = 10.28; p = 0.003$), and there was a significant interaction effect between group and condition ($F = 5.02; p = 0.011$) (Table 3). As shown in Fig. 1B, this interaction was due to the diminished response to deep breathing in the MDD group as compared to the control and PD groups. Although t-tests failed to detect any significant differences among groups both during resting and deep-breathing conditions, in the responses to deep breathing (deep breathing minus resting condition) the t-test demonstrated a significant difference between the MDD and control groups ($t = 3.28, p = 0.003$), and between the MDD and PD groups ($t = 2.25, p = 0.032$) as shown in Fig. 1B.

Pearson’s correlation coefficient tests did not reveal any significant correlations between physiological variables and HAM-D total score in MDD patients, or STAI state score in PD patients ($p > 0.05$).

### 4. Discussion

In previous studies on heart rate variability, many authors have reported reduced parasympathetic activity (Rechlin et al., 1994; Agelink et al., 2002) and increased sympathetic activity (Agelink et al., 2002; Udupa et al., 2007) during resting conditions in patients with MDD. However, this imbalance has not always been observed during resting conditions in patients with panic disorder (Udupa et al., 2007) during resting conditions in patients with panic disorder (Yeragani et al., 1991; Moser et al., 1998). This inconsistency may have been due to the clinical heterogeneity of subjects or the differences in clinical severity among previous studies. In fact, using direct assessment of sympathetic outflow to the heart, Barton et al. (2007) demonstrated that sympathetic nervous activity was extraordinarily high in MDD patients associated with PD. Thus, the clinical heterogeneity of subjects could indeed be a crucial factor in the assessment of cardiac autonomic functions. In addition, using spectrum analysis of heart rate variability, Agelink et al. (2002) reported higher LF/HF ratio and lower HF power in MDD patients with severe symptoms (HAM-D $> 26$ points), but not in MDD with moderately severe symptoms (HAM-D $< 25$ points). In the present study, subjects were mainly MDD patients with mild depressive symptoms (mean HAM-D score $= 20.3$) which may explain the fact that we failed to demonstrate significant group differences in HF power. History of the treatment may also underlie the inconsistencies in previous studies. Most of the previous studies included subjects who had received psychotropic drug treatment. Only one previous study tested drug-na"ive MDD patients, without any comorbidity, and demonstrated a higher LF/HF ratio in these patients as compared to normal controls (Udupa et al., 2007). Our results also show the same tendency during the deep-breathing condition.

Although there were no consistent results in previous studies, we here demonstrated lower LF power in drug-na"ive MDD patients as compared to the control and PD groups during resting condition. One recent study demonstrated that LF power is primarily a result of baroreflex sensitivity, which is a measure of the gain of the baroreflex (Moak et al., 2007). The lower LF power found in the present study may reflect lower baroreflex sensitivity which was reported in a previous study in MDD patients (Broadley et al., 2005a). Lower LF power in MDD patients may contribute to their increased cardiac risk, because reduced baroreflex sensitivity is thought to be an important, independent predictor of mortality in patients' post-myocardial infarction, and is particularly associated with sudden cardiac death (La Rovere et al., 1998). Furthermore, Broadley et al. (2005b) demonstrated the significant role of cortisol in stress-induced endothelial dysfunction and impaired baroreflex sensitivity. Although we cannot draw any definitive conclusions because cortisol levels in the present study were not measured, aberrant activity of the hypothalamic–pituitary–adrenal axis, as reported in MDD patients (Vreeburg et al., 2009), might contribute to the impaired baroreflex sensitivity and their increased cardiac risk.

In a previous study, Klein et al. (1995) demonstrated that PD patients have reduced parasympathetic activity. However, this reduced parasympathetic activity under resting conditions has not always been demonstrated in other studies (Yeragani et al., 1993; Ito et al., 1999; Garakani et al., 2009). The present study also failed to find

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### Table 2

<table>
<thead>
<tr>
<th>Group effect</th>
<th>Condition effect (rest vs deep breathing)</th>
<th>Interaction (group × condition)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>Deep breathing</td>
<td>Rest</td>
</tr>
<tr>
<td>R-R interval</td>
<td></td>
<td>F value</td>
</tr>
<tr>
<td>LF</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td>2.29</td>
</tr>
<tr>
<td>LF/HF</td>
<td></td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.047</td>
</tr>
</tbody>
</table>

Group, control vs panic disorder vs major depressive disorder; condition, rest vs deep breathing; interaction, between group and condition; LF, low-frequency (0.05–0.15 Hz); HF, high-frequency (0.15–0.40 Hz); LF/HF, ratio of LF power to HF power.

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### Table 3

Results of each physiological variable.

<table>
<thead>
<tr>
<th>Group effect</th>
<th>Condition effect (rest vs deep breathing)</th>
<th>Interaction (group × condition)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>Deep breathing</td>
<td>Rest</td>
</tr>
<tr>
<td>R-R interval</td>
<td></td>
<td>F value</td>
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obvious differences between normal controls and PD patients in any parameters of heart rate variability. Different testing methods, however, may be necessary to bring autonomic dysfunction in PD patients to light. For example, cardiac sympathetic enhancement methods, such as cardiac sympathetic enhancement methods, such as metronome breathing, may be necessary to bring autonomic dysfunction in PD patients to light.

In the present study, we increased breathing load in order to enhance the parasympathetic activity. As expected, significant increases in HF power and a decrease in LF/HF ratio were observed during deep breathing in the supine posture at 10–12 breaths/min (0.17–0.20 Hz).

These results may suggest that deep breathing changed the cardiac sympathovagal balance toward the parasympathetic direction. It is noteworthy that MDD patients showed lower cardiac autonomic reactivity to deep breathing than normal controls. This low cardiac autonomic reactivity indicates impairment of cardiovagal function in MDD, and may partly explain the increased cardiac morbidity (Bunker et al., 2003; Lett et al., 2004) and mortality of MD patients (Musselman et al., 1998). Our results suggested the usefulness of the deep-breathing task in order to enhance the physiological features in MDD patients.

There are several limitations of our study. First, deep breathing might confound LF power of heart rate variability. The deep-breathing frequency of 10–12 breaths/min (0.17–0.20 Hz) in the present study is close to the upper limit of the LF power band (0.15 Hz). i.e. deep breathing might influence LF power as a consequence of increased respiratory sinus arrhythmia. Second, as a methodological limitation, caution must be exercised when we accept the previous simplified concept that the LF/HF reflects cardiac sympathovagal balance, because a recent study demonstrated that LF power cannot be used to assess sympathetic outflow to the heart (Baumert et al., 2009; Jardine et al., 2002). Third, the sample was relatively small, yet fairly robust differences were found nonetheless.

5. Conclusions

We have found lower LF power in the MDD group during resting condition as compared to the control and PD groups. In addition, we have found that the MDD group had a lower response to regular deep breathing in LF power and in LF/HF ratio as compared to the control group. The results indicate that the deep breathing revealed diminished cardiac autonomic reactivity in drug-naive MDD patients.

References


