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ORIGINAL PAPER

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Dysfunctional baroreflex regulation of sympathetic nerve activity in remitted patients with panic disorder

A new methodological approach

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Abstract *Background* Many researchers have studied the abnormalities of autonomic nervous system (ANS) such as decreased heart rate variability, which is a risk factor for sudden cardiac death, in patients with panic disorder (PD). However, no consistent abnormality has been uncovered to date. One of the reasons for this controversy may be due to the fact that most of these conventional studies have analyzed each physiological variable independent of other indices. We examined the ANS in PD patients using a new method which can more directly investigate the function of the baroreflex by examining the relation between the blood pressure (BP) and heart rate (HR). *Methods* During rest and audiovisual stimulation (AS) as mental stress such as being exposed to video imaginary of experiences such as driving motor vehicles, cardiovascular parameters, HR and BP were consecutively measured in 13 remitted PD patients and twenty aged and gender-matched normal controls (NC). In this study, to assess the cardiovascular ANS function (baroreflex) in PD we used the power spectrum analysis as usual and the mean of lag time (τ) between the Mayer wave components, which was closely related to sympathetic nerve activity of vasomotor, of HR and BP variability as a new trial. *Results* The PD patients and NC did not differ with regard to the power spectrum analysis of the heart rate. We found that τ in the PD group was significantly shorter than that in the NC both before and after AS, especially before. *Conclusions* These findings suggest that remitted PD patients may have a dysfunctional baroreflex regulation of sympathetic nerve activity.

Key words panic disorder · autonomic function · heart rate · blood pressure · sympathetic · parasympathetic · audiovisual stimulation

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Introduction

The high rate of relapse in panic disorder (PD), especially after pharmacological treatment, is well-known (Noyes et al. 1989; Otto and Whittal 1995; Pollack and Smoller 1995; Gorman et al. 2000). Nagy et al. (1993) reported that over half of panic patients attempting discontinuation of imipramine experienced increased anxiety during or after taper, and more than half were unable to discontinue the medication (Nagy et al. 1993). In a study of 105 PD patients who achieved remission, Pollack (1998) found that the mean length of remission was 9.2 ± 7.0 months and that 58 % of patients experienced a relapse despite continuation of treatment (Pollack 1998). Thus, it is clinically very important to clarify why the relapse rate of PD is high.

The most common PD symptoms are cardiologic. In one sample of patients, 87 % reported shortness of breath and 61 % reported chest pain (Taylor and Arnow 1988; Shioiri et al. 1996). PD also overlaps considerably with true cardiac illness and it is especially prominent in patients with documented cardiovascular disease (CVD) (Sinha and Gorman 2003). Morris et al. (1997)

evaluated the comorbidity of PD with heart disease and the prevalence of PD in 128 out-patients presenting to a cardiologist. They found that 16 patients (12 %) met the criteria of PD, and 73 (57 %) were shown to have actual cardiac illness; of these, 10 (14 %) had PD (Morris et al. 1997). In a prospective study of 33,999 males, the risk of sudden cardiac death was significantly related to anxiety: a multivariate odds ratio of 2.96 (95 % CI: 1.02–8.55) for males who scored 1 on the Anxiety Symptom Scale compared with males who scored 0, and 4.46 (95 % CI: 0.92–21.6) for males who scored 2 or higher (Kawachi et al. 1994a, 1994b). Thus, there are many findings of significant relations between PD and CVD for male patients at least. However, the pathology is unclear (Jakubec and Taylor 1999).

It is well established that impaired autonomic nervous system (ANS) control of heart rate (HR) such as low HR variability predicts cardiac mortality (Kleiger et al. 1987; Molgaard et al. 1991; Odemuyiwa et al. 1991; Bigger et al. 1993; Watkins et al. 1999). In particular, reduced baroreceptor-mediated vagal reflex control of HR has been associated with life-threatening arrhythmias (Hohnloser et al. 1994; De Ferrari et al. 1995) and fatal cardiac event in patients (Farrell et al. 1991; Osterziel et al. 1995; La Rovere et al. 1998).

Under these circumstances, since the late 1980s a number of studies have attempted to investigate the abnormalities of ANS in PD using methods such as power spectrum analysis of HRV, but the results are controversial (Ito et al. 1999; Fleet et al. 2000; Gorman and Sloan 2000; Jeejeebhoy et al. 2000; Rao and Yeragani 2001; Yeragani et al. 2002). Some of the reasons for this controversy may be due to the fact that most of these conventional studies have analyzed each physiological variable independent of other indices (Yoshizawa et al. 2001) and the differences in pathological states of PD patients (Stein and Asmundson 1994; Seier et al. 1997; Ito et al. 1999).

From the perspective of relapse prevention, we hypothesized that there might be some abnormalities of ANS during periods of remission in remitted patients with PD. In this study, to clarify this hypothesis we used power spectrum analysis of HR variability as a usual and a new method which can more directly investigate the function of the baroreflex by examining the relation between the blood pressure (BP) and HR before and after audiovisual stimulations (AS) (Yoshizawa et al. 2001).

Subjects and methods

Subjects

The subjects were 13 male out-patients (mean ± SD age, 35.1 ± 6.6 years) who had been diagnosed as having PD according to DSM-IV criteria (American Psychiatric Association 1994). None of the patients had any comorbidity with depression, and all of them were examined after they had been in the remission phase of PD, defined as the absence of any major panic attack symptoms and agoraphobia, for at least 6 months preceding the measurement. All were receiving regular out-patient treatment including medications at the Psychiatry Clinic of the Niigata University School of Medicine Hospital. None of them was found to have any past history of head injury, neurological disorders, drug or alcohol abuse, or serious medical illnesses. Only 5 patients (38 %) were treated with paroxetine (10–40 mg/day) or fluvoxamine (50–150 mg/day) and irregularly used alprazolam.

Twenty mentally and physically healthy control subjects (NC; 36.0 ± 6.5 years), who were age and gender matched with individual patients, were selected from among a group of volunteers. All control subjects were in good physical health, and none of them had any notable history of mental disorder, neurological disease, head injury, or substance dependence, or any family history of mental disorder or substance dependence.

The psychiatric state of each patient on the day of the examination was assessed using the Sheehan patients-rated Anxiety Scale immediately before the measurement (SAS; Sheehan 1986). There was a significant group difference in SAS (PD group: 64.6 ± 19.9, NC group: 36.5 ± 2.8, $t = 3.97$, $p < 0.002$), but not in age and gender. To check their physical and mental states after the AS, simple questionnaires including 13 questions were given to all subjects, such as "Is general physical condition worse?", "Do you have headache?", "Are you less comfortable?", " Are you tired?", and so on.

Audiovisual stimulation (AS)

In this study, we used AS as a mental load including psychological stress, which must change the autonomic nervous activity and the relation between BP and HR. Subjects were exposed to video images recorded using a camera mounted on a motor vehicle such as a kart, car, motorbike, mountain-bicycle, bobsleigh or motor vessel such as a jet boat with simultaneously recorded sounds, and computer graphics such as moving balls for 17 minutes. In the middle of the video playback, they watched a scene of a tropical sea for 40 seconds as relaxation. Before and after loading the AS, 5 minutes of rest was allowed for each subject.

Images were back-projected onto an 80-in screen. Subjects sat in a chair 2 meters from the screen with a comfortable posture. Two LCD projectors (XGA, TH-L795J, Panasonic, total of 1,400 lumens) aligned together were used. Environmental conditions in the examination room were kept constant (temperature: 22 °C, intensity if illumination: 10 lux) and the time of AS was constant (16:00–17:00). The method of AS was basically similar to that described previously (Kojima et al. 2002, 2004). This study was approved by the ethical committee of Niigata University Graduate School of Medical and Dental Sciences.

Measurements and data analysis

The left radial arterial pressure signal acquired using a tonometoric pressure sensor (Nihon Corin; JENTOW 7700, JAPAN) and the ECG signal were sampled by using a data collection system (LabView, National Instruments Co., TX) and also stored on a digital tape every 1 ms. Mean blood pressure (P_{mean} [mmHg]) was obtained as the mean value of the radial arterial pressure signal over the heart beat. Heart rate (HR[min^{-1}]) was calculated from the reciprocal of the inter-R-wave interval of the ECG signal.

Each beat-to-beat variable P_{mean} and HR was interpolated by the cubic spline function to be a time-continuous function, and the function was re-sampled every $\Delta t = 469$ ms (128 points per minute). For 2 min of the 5-minute rest period before and after AS, the power of HR was calculated using the Fourier transform (256 points) on the basis of 2 min data segmented by the Hanning window from –1 min to 1 min. The low frequency (LF), high frequency (HF), and ALL were defined as the sum of the components of 0.039–0.159, 0.176–0.508 and 0–1.016 Hz, respectively. The %LF and %HF were defined as {100×(LF/ALL)} and {100×(HF/ALL)}, respectively (Yamamoto and Hughson 1991; Montano et al. 1994; Ando et al. 2002).

Each of the re-sampled P_{mean} and HR data were normalized as the mean = 0 and variance = 1, respectively. Then, they were filtered through a band-pass filter with a bandwidth between 0.08 Hz and 0.1 Hz to extract the Mayer wave component, which is a measure of a response of the ANS to psychological excitement (Akselrod et al. 1985;

Pagani et al. 1986; Baselli et al. 1988; Oka et al. 1995). For 2 min of the 5-minute rest periods before and after AS, the mean lag time (τ) of the Mayer wave components between variabilities of P_{mean} and *HR* was calculated on the basis of 2 min data segmented by the Hamming window from –1 min to 1 min (see Fig. 1).

Statistical analysis

To determine whether significant differences in the power spectrum analysis and the τ existed between the groups and/or the time (before/after AS), a two-way analysis of variance (ANOVA) with random effect was performed after logarithmic transformation. Moreover, in order to analyze the relation between clinical anxiety symptoms and the τ, we used Pearson's correlation coefficient. Values are expressed as means ± S. D. A probability level of $P < 0.05$ was regarded as statistically significant. The data were analyzed using the statistical software SPSS (release 10.07J, SPSS).

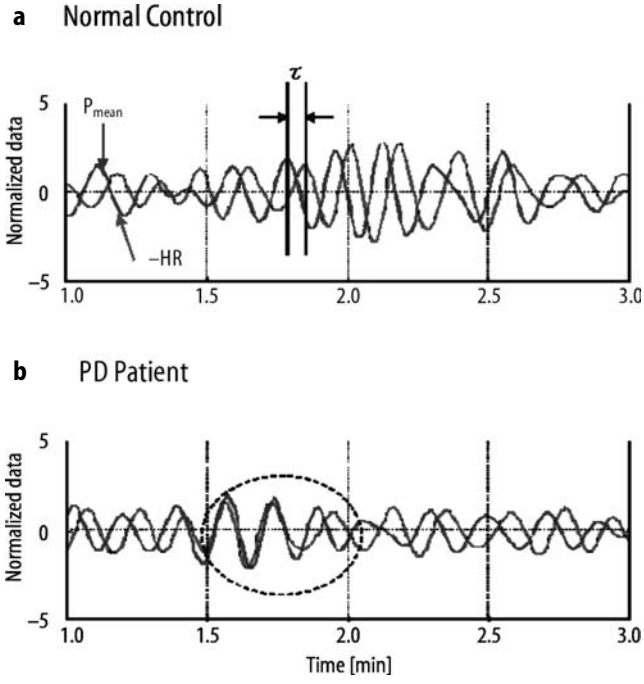

Fig. 1 Mayer wave components of P_{mean} and *HR* before audiovisual stimulation (AS) in a representative subject in each group. **a** The Mayer wave components of P_{mean} and *HR* before AS in a normal control. As for HR components, the minus sign shown in –HR was introduced to become as in phase as possible for simple interpretation. The τ is defined as the mean lag time (phase difference) of the Mayer wave components between P_{mean} and *HR*. The τ values in a normal control are constant before AS (about 3 s). **b** These waves show the representative Mayer wave components of P_{mean} and *HR* in PD patients before AS. The τs are fluctuated and the mean of τ values are about 2 s as indicated by the dotted line area where the phase differences were changed

Results

No subject in either group had any panic symptoms during the AS or noted a dislike for the AS, for example "never try it again". Table 1 shows the results of power spectrum analysis for the HR. The two-way ANOVA showed that there were no significant group or task differences, but a mild significant interaction for LF/HF ($F = 4.18$, $P = 0.049$).

Fig. 2 shows differences in τ between the PD and NC groups before and after AS. The two-way ANOVA revealed that there was a significant group difference in τ ($F = 8.35$, $P = 0.007$) and a significant interaction between the group and task ($F = 7.91$, $P = 0.008$). Before the AS, there was a mild significant correlation between SAS total scores and the τ ($R = –0.35$, $p = 0.045$) in all subjects, but not after the AS ($R = –0.10$, $p = 0.574$). However, in the PD group we could not confirm this correlation for either condition. No τ was significantly correlated with age at onset, duration of illness or medication.

Discussion

In this preliminary study, using ECG and a tonometoric pressure sensor we first tried to investigate more di-

Table 1 Power spectrum analysis of the *HR* in PD and NC groups

ANS Parameter	Before/After Audiovisual Stimulation	Groups	
		PD	NC
%LF	Before	51±18.5	54±18.6
	After	51±12.3	57±15.6
%HF	Before	0.21±0.23	0.17±0.13
	After	0.16±0.07	0.14±0.12
LF/HF	Before	5.4±3.5	5.9±4.7
	After	4.4±2.8	9.0±7.9

PD patients with panic disorder; *NC* normal controls; *LF* low frequency; *HF* high frequency

The two-way ANOVA showed that there were no significant group or task differences, but a mild significant interaction for LF/HF ($F = 4.18$, $P = 0.049$)

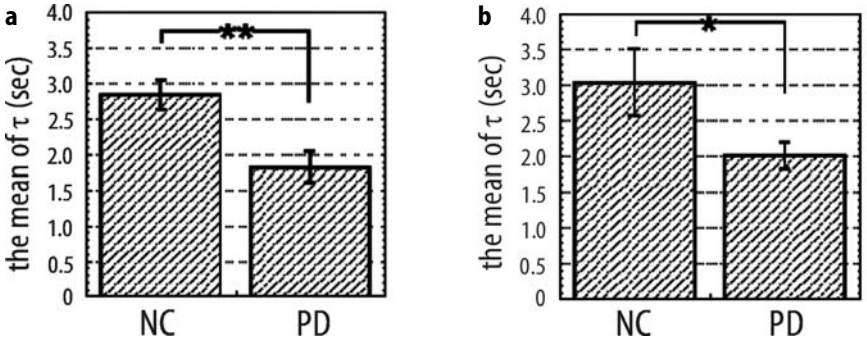

Fig. 2 Differences in τ between the PD and NC groups before (**a**) and after (**b**) AS. The ordinate and abscissa indicate the levels of the mean τ (per second) and the groups, respectively. The two-way ANOVA shows that there is a significant group difference in τ ($F = 8.35$, $P = 0.007$) and a significant interaction between the group and time ($F = 7.91$, $P = 0.008$). Using the Mann-Whitney U test, there are significant group differences before and after the AS (before; $Z = –2.78$, $P = 0.004$: after; $Z = –2.07$, $P = 0.039$)

rectly the relation between two physiological variables, BP and HR, to assess the cardiovascular ANS in PD.

In the present study, we found that there were significant group differences in τ before and after AS. Unfortunately, we cannot directly compare the present results with those of any other pathophysiological study in PD since to our knowledge this is the first study to use the new method mentioned above. In this study, τ was defined as the mean lag time of the Mayer wave components between P_{mean} and *HR*. Thus, for the new analysis, we used only this component which is closely related to sympathetic nerve activity of vasomotor (Oka et al. 1995) because of the following reasons; a) Faravelli and Paionni reported that almost all physical symptoms are due to the activation of the sympathetic nervous system because of many previous findings in PD such as elevated plasma and urinary concentrations of adrenaline, noradrenaline and their metabolites (Charney et al. 1984a, b; Ko et al. 1983), and increased activity of platelet monoamine oxidase and reductions in the number of β and α receptors (Cameron et al. 1984; Faravelli and Paionni 1999), b) in normal subjects mental stress increases plasma epinephrine and norepinephrine and HR increases markedly (Opie 1998), and c) psychological excitement can raise the dominant response in the Mayer wave component (Akselrod et al. 1985; Pagani et al. 1986; Baselli et al. 1988).

It is suggested that the τ used in the present study may become an index to detect subtle changes of cardiac sympathetic nerve function compared with usual methods because τ is a value measuring more directly the correlations between the HR and BP, while the power spectrum analysis uses only one parameter such as the R-R interval.

We hypothesized that τ would be normal before the AS and become shortened after the AS because remitted PD patients nevertheless must have an unstable ANS, especially cardiac sympathetic nerve function. In the present study, however, we found that τ in the PD group was significantly shorter than that in the NC both before and after AS, especially before. Fig. 1 shows that in the NC group the phase differences of the Mayer wave components between the HR and BP were constant (about 3 seconds), while in the PD group they were shortened in part. It is suggested that the baroreflex regulation is accurately functioning when the phase differences are constant and about 3 seconds as in the NC subjects. Thus, even during periods of remission PD patients may have dysfunctional baroreflex regulation of sympathetic nerve activity. Moreover, this finding may suggest the high rate of relapse in PD, especially after pharmacological treatment (Noyes et al. 1989; Otto and Whittal 1995; Pollack and Smoller 1995; Pollack 1998; Oakley-Browne 1999; Gorman et al. 2000), and higher cardiovascular mortality in this group (Coryell et al. 1982, 1988). To confirm this, we continue to observe the long-term outcomes for all patients that participated in this study under drug-free conditions.

The reasons why the τ in the PD group was constantly shorter before and after the AS are unclear. Recently, Cohen et al. (1998), who studied patients with post-traumatic stress disorder (PTSD), suggested that PTSD patients whose basal autonomic state was characterized by increased sympathetic and decreased parasympathetic tone demonstrated no autonomic response to the recounting of the triggering stress event (Cohen et al. 1998). In Griffin's study, there was also a suppression of autonomic physiological responses in the PTSD group (Griffin et al. 1997). Although these were PTSD studies, it is possible that patients with PD, which is also an anxiety disorder category similar to PTSD, have diminished autonomic response to stress. Further studies are needed to investigate the differences in autonomic functions between PD and PTSD. More recently, Lautenbacher (2002) investigated the discrimination between left and right visual field stimulus processing in drug-free patients with PD and concluded that PD patients appeared as disturbed in their attentional functioning (Lautenbacher et al. 2002). We are in the planning state to investigate the relationship between the abnormalities of ANS such as our finding and the central nervous system such as attention and recognition.

In this preliminary study there are a few limitations as follows. First, the sample size was relatively small, although three-fifths or greater than 50 previous studies had a similar sample size (see review; Friedman and Thayer 1998; Gorman and Solan 2000; Jeejeebhoy et al. 2000). Second, it is possible that the response to the AS in our remitted patients with PD may be due to a hyperanxious state because of the higher SAS total score in the PD patients compared to the NC and because of a mild significant correlation between SAS total scores and the τ before the AS. However, this significant correlation vanished if the NC group was excluded from this analysis since the distribution of the SAS total score shifted to the lower range compared with the PD group. Third, we could not remove the medication effects from our results completely. To confirm the present findings, as mentioned above, additional studies in drug-free patients are needed. Fourth, we could not use a video which triggered the special fears of PD patients in this study. Finally, it remains unclear whether this finding for τ is specific for PD. Therefore, it is necessary to study other anxiety and/or mood disorders using this new method.

In conclusion, we found dysfunctional baroreflex regulation of sympathetic nerve activity in remitted patients with PD using a new method. The present results may be relevant to the higher risk of relapse and cardiovascular mortality in this group. It is suggested that this new technical approach is available to measure the autonomic function in other psychiatric disorders such as PTSD, generalized anxiety disorder, social anxiety disorder, specific phobia, and depression.

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