Panic disorder, autonomic nervous system and dissociation – changes during therapy

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Abstract

OBJECTIVES: Alarming somatic symptoms and in particular the cardiovascular symptoms, are the characteristic features of panic attacks. Increased cardiac mortality and morbidity have been proposed in these patients. Power spectral analysis of electrocardiogram R-R intervals is known to be a particularly successful tool in the detection of autonomic instabilities in various clinical disorders. Heart rate variability (HRV) has been found to be the outcome of rapidly reacting cardiovascular control systems. The aim of our study is to measure very low frequency band (VLF), low frequency band (LF) and high frequency band (HF) components of R-R interval during orthostatic experiment in patients with panic disorder before and after treatment and compares it with healthy controls.

METHODS: We assessed heart rate variability in 19 patients with panic disorder before and after 6-weeks treatment with antidepressants combined with cognitive behavioral therapy (CBT) and in 18 healthy controls. Diagnosis was done according to the ICD-10 research diagnostic criteria confirmed with MINI (MINI international neuropsychiatric interview). Patients were treated with CBT and psychotropics. They were regularly every week assessed using CGI (Clinical Global Impression), BAI (Beck Anxiety Inventory) and BDI (Beck Depression Inventory). Heart rate variability was assessed during 3 positions (1st – 5 min supine; 2nd – 5 min standing; 3rd – 5 min supine) before and after the treatment. Power spectra were computed for very low frequency – VLF (0.0033–0.04 Hz), low-frequency – LF (0.04–0.15 Hz) and high frequency – HF (0.15–0.40 Hz) bands using fast Fourier transformation.

RESULTS: Nineteen panic disorder patients resistant to pharmacological treatment entered a 6-week open-label treatment study with combination of SSRI and CBT. The combination of CBT and pharmacotherapy proved to be an effective treatment in these patients. The patients significantly improved during the study period in all

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rating scales. There were highly statistical significant differences between panic patients and control group in all components of power spectral analysis in 2nd (VLF, LF and H in standing) and in two component of 3rd (LF and HF in supine) positions. There was also a statistically significant difference between these two groups in LF/HF ratio in standing position (2nd). During therapy there was a tendency increasing values in all three positions in components of HRV power spectra, but HF in 1st supine position was the only component where the increase reached the level os statistical significance. **CONCLUSIONS:** These findings demonstrate a lower autonomic activity in panic disorder patients measured during the changes of postural position in comparison with healthy controls and tendency to increase this autonomic power during the treatment.

INTRODUCTION

Panic disorder is chronic psychiatric malady. Patients experience panic attacks characterized by symptoms of autonomic activation such as palpitations, hyperventilation, dizziness, tremor, chest discomfort, sweating, and hot and cold flashes (Woodward *et al.* 2009). Alarming somatic symptoms and cardiovascular symptoms in particular, are among the hallmarks of panic attacks, along with the intense fear of dying and loss of control which are so often described by many patients (Katerndahl 2008). The autonomic nervous systems seem to be intimately involved in the initiation and manifestation of panic attacks. Patients with panic disorder have higher baseline heart rate (Liebowitz *et al.* 1985) and periods of tachycardia which coincide with panic symptoms (Freedman *et al.* 1985). Increased cardiac mortality and morbidity have been suggested in these patients (Coryell *et al.* 1989; Fleet *et al.* 2000; Katerndahl 2008). Variety of studies has been performed to examine autonomic nervous system in panic disorder. These studies have measured the variety of sympathetic nervous system functions, including heart rate or blood pressure responses to autonomic stimuli such as orthostatic challenge (Yeragani *et al.* 1990a; Stein & Asmundson 1994; Roy-Byrne *et al.* 1997; Alvarenga *et al.* 2006), plasma or urinary catecholamines or catecholamine metabolites (Villacres *et al.* 1987) and mental stress (Wilkinson *et al.* 1998).

Power spectral analysis of electrocardiogram

Heart rate variability has been found to be the outcome of rapidly reacting cardiovascular control systems, namely, the sympathetic and parasympathetic branches of the autonomic nervous system (Pagani *et al.* 1997). Continuous changes in sympathetic and parasympathetic neural impulses cause alterations in heart rate including oscillation of the R–R interval around its mean value (HRV). Power spectral analysis of heart rate variability offers reliable assessment of cardiovascular autonomic responses, providing a "window" onto interaction of peripheral sympathetic and parasympathetic tone. Alterations in HRV are associated with various physiological and pathophysiological processes, and may contribute to morbidity and mortality (Lucini *et al.* 2002; La Rovere *et al.* 1998; Filipovic *et al.* 2005). Diabetes mellitus (Guo *et al.* 2000), coronary artery disease (Huikuri *et al.* 1996), end-stage heart failure (Guzzetti *et al.* 2000), and myocardial infarction, are some of the most clear-cut examples in which HRV was found to be associated with survival. Power spectral analysis of electrocardiogram R-R intervals yields of high-frequency (HF, 0.15–0.40 Hz), low-frequency (LF, 0.05–0.15 Hz), and very low-frequency (VLF, 0.0033–0.04 Hz) components (Billman *et al.* 1990, Ponikowski *et al.* 1997, Yeragani *et al.* 2000, Cohen *et al.* 2000, Kumar *et al.* 2009, Salinger and Gwozdziewicz 2008). This analysis is known to be a particularly successful tool for the detection of autonomic instabilities in various clinical disorders (Akselrod *et al.* 1981; Ponikowski *et al.* 1997; Berntson *et al.* 1997; Tucker *et al.* 1997; Bloomfield *et al.* 1997). It is generally accepted that the HF component is mediated by cardiac parasympathetic tone, which depends on respiration, while the LF component is mediated by both cardiac sympathetic and parasympathetic tones (Akselrod *et al.* 1981; Saul 1990; Berntson *et al.* 1997; Houtveen *et al.* 2002). Hence, the ratio of LF power to HF power (LF/HF) was generally accepted as an index of cardiac sympathovagal balance (Pagani *et al.* 1997; Task force of ESC and NAPE 1996; Virtanen *et al.* 2003; Alvarenga *et al.* 2006), but Moak *et al.* (2009) in their study showed that LF power could reflect baroreflex function, not cardiac sympathetic innervation. VLF power may indicate thermoregulation or vasomotor activity, although this has been disputed (Taylor *et al.* 1998); it may involve a parasympathetic component (Taylor *et al.* 1998), possibly engage the rennin-aldosterone system (Ponikowski *et al.* 1997; Berntson *et al.* 1997; Taylor *et al.* 1998; Virtanen *et al.* 2003).

Studies on healthy individuals show that acute stress increases LF/HF and decreases HF, suggesting activation of the sympathetic nervous system as well as reduction of parasympathetic activity under stress (Pagani *et al.* 1997). However, data suggesting that the LF/HF ratio represents a relative sympathetic modulation are far from being unequivocal (Eckberg 1997). Moreover, a major proportion of HRV occurs over a large frequency span showing broad, noise-like, irregular variability (Kobayashi & Musha 1982). Such evidence supports critics who argue that the proposed rigid scheme of the frequency bands cannot cope with the complex and variable interactions between the different rhythms (Grasso *et al.* 1997; Lambertz & Langhorst 1998; Perlitz *et al.* 2004).

Power spectral analysis of electrocardiogram in panic disorder

Klein *et al.* (1995) studied resting electrocardiographic recordings in panic disorder and controls using power spectrum analysis of the beat-to-beat heart rate. Patients with panic disorder had decreased heart rate variability and substantial reduction in the high-frequency peaks (HF) of the power spectrum densities. Yeragani *et al.* (1993; 1994) found out that patients with panic disorder showed decreased standard deviation and mean consecutive difference of the R-R intervals, especially in standing posture. In a later study, they investigated power spectral analysis in patients with panic disorder and found that these patients had a significantly lower power in the band of 0.01–0.05 Hz (VLF) and a higher relative power in the band of 0.04–0.15 Hz (LF) in standing posture. They also found that patients with panic disorder had an exaggerated cardiac vagal withdrawal during lactate infusions compared with normal controls (Yeragani *et al.* 1994). Klein *et al.* (1995) described a higher resting LF/HF in patients with panic disorder compared with normal controls. Seier *et al.* (1997) found that person in whom lactate infusion induced panic ("lactate-induced panickers") had a significant enhancement of the HF power, and a lower sympathovagal ratio (LF/HF) during lactate infusions compared with non-panickers. Ito *et al.* (1999) compared autonomous nervous system activity in untreated patients in the early stage of panic disorder with control subjects using power spectral analysis of electrocardiogram R-R intervals in supine rest and during a head-up tilt. In the tilt position the patients with panic disorder had significantly higher values of all components of power spectral analysis of electrocardiogram R-R intervals only in the tilt position total power, LF, and HF than did the control subjects. However, the LF/HF ratio did not differ significantly between the two groups in tilt position. Cohen *et al.* (2000) described an analysis of HRV at rest and after psychological stress in panic disorder patients, PTSD patients and in healthy control subjects. While both patients groups had elevated HR and LF components of HRV at baseline, PTSD patients, unlike panic disorder patients and controls, failed to respond to the recall stress with increased in heart rate and LF. McCraty *et al.* (2001) retrospective study employed 24-hours HRV analysis of Holter records to compare autonomic function in panic disorder patients with healthy, age- and gender- matched controls. The SDNN index (he standard deviation of all normal to normal intervals), 5-min total power, VLF and LF power were significantly lower in panic patients relative to controls over the 24-h period. Hourly means were significantly lower during some of the waking hours as well as the latter part of the sleep cycle. In contrast, the mean RR interval, RMSSD (square root of the mean of the squared differences between adjacent normal to normal intervals) and HF power were comparable in patients and controls. The authors concluded that sympathetic activity is depressed in panic disorder patients under usual life conditions, leading to a relative predominance of vagal tone. Slaap *et al.* (2002) reported that patients with panic disorder, who did not respond to pharmacotherapy, were characterized at baseline by a higher heart rate. Five minute HRV recording was obtained in medication free panic patients before 12-week open-label treatment with mirtazapine and were analyzed using spectral analysis. The total spectrum and low frequency power of responders to mirtazapine were significantly higher that those of nonresponders. These findings suggest that nonresponders to short-term mirtazapine treatment are characterized as baseline by a lower output of the ANS (autonomic nervous system). Baker *et al.* (2003) in a double blind randomized 4 week study with clonazepam or placebo performed standard sleep measures and recorded HRV from 24-hour Holter samples acquisitions at baseline and end of study. None of HRV measures correlated with response, but compared with placebo, clonazepam led to a decrease in all the time and frequency domain of HRV. Lavoie *et al.* (2004) evaluated HRV in coronary artery disease patients with and without panic disorder by 48h electrocardiographic monitoring. Power spectral analysis of HRV indicated that coronary artery disease patients with panic disorder exhibited significantly lower LF/HF ratios, which according the authors may reflect lower sympathetic modulation, compared with non panic disorder patients. Total power in panic disorder patients was made up of a significant higher proportion of HF power and a significant lower proportion of VLF power than in non-panic disorder patients. Slaap *et al.* (2004) used spectral analysis of HRV in drug free panic disorder patients, OCD patients and normal controls. The results showed that neither OCD patients nor panic disorder patients were characterized by a reduced HRV, as compared to normal controls. Blechert *et al.* (2007) studied electrodermal, cardiovascular, and respiratory psychophysiology in panic disorder patients, PTSD, and healthy individuals at baseline and during a threat of shock. Panic disorder patients exhibited lower PCO_2 and higher cardiovascular sympathetic activation compared with healthy controls.

Aim of the study

The aim of our study was to study power spectral analysis of heart variability of R-R interval in patients with panic disorder before and after treatment, and compare the data before treatment with healthy controls. Second aim was to test the relation between the results of power spectral analysis and the level of psychopathology and dissociation in the panic disorder patients.

METHODS

The subjects were 19 inpatients with panic disorder. Inclusion criteria were (a) ICD-10 research criteria for panic disorder or for panic disorder with agoraphobia; (b) Non-responders on SSRIs (at least 6 weeks

treatment before the screening into the study; (c) Age 18–60 years; (d) Written informal consensus. Excluding criteria were: (a) Major depressive disorder; (b) High risk of suicidality; (c) Organic psychiatric disorder; (d) Psychotic disorder in history; (e) Abusus of alcohol or other drugs; (f) Serious somatic disease; (g) Pregnancy or lactation. Inclusion and exclusion criteria were confirmed by 2 independent raters.

Assessment

After study enrolment, patients were assessed during the first two days of hospitalization before the beginning of treatment with combination of SSRIs and cognitive behavioral therapy. Diagnosis was confirmed with M.I.N.I. (MINI-international neuropsychiatric interview; Lecrubier *et al.* 1997). The assessment focused on psychopathology was carried out using rating scales. General psychopathology was assessed by Clinical Global Impression-Severity of illness (CGI-S) by clinician; and self-measurements Beck Anxiety Inventory (BAI) and Beck Depression inventory (BDI). Rating scales were administered before the beginning of the treatment, then weekly during the 6 weeks treatment and at the end of the treatment. Psychological dissociative symptoms were examined using the Dissociative Experiences Scale (DES, Carlson *et al.* 1991; 1993). The DES is a self-administered 28-item inventory of psychological dissociation, where participants are asked to indicate on a visual analog scale how often they experience the dissociative symptoms (in percentage of time). The Czech version of the scale is comparable to the original version in terms of its test-retest reliability, validity and factor structure (Ptacek *et al.* 2007). Pathological DES was measured by a Dissociative Experiences Scale Taxon (DES-T) based on the items of DES number 3, 5, 7, 8, 12, 13, 22, and 27. These items measure identity alteration, depersonalization, derealization, discontinuation of awareness, dissociative amnesia, and auditory hallucinations (Waller *et al.* 1996). Patients´ written consent to participate in the research was given. Demographic data, including age, sex, age of the onset of the disorder, duration of disorder, and the number of psychiatric hospital admissions were obtained in an interview. In order to compare the antidepressants we converted the doses of individual drugs to the equivalents of an antidepressant (paroxetine 20 mg = citalopram 20 mg or fluoxetin 20 mg or sertralin 50 mg or fluvoxamin 50 mg or escitalopram 10 mg or venlafaxin 75 mg), or an anxiolytic (alprazolam 0.75 mg = clonazepam 0.5 mg or diazepam 15 mg or oxazepam 20 mg).

Autonomic nervous system measurements

The functioning of the autonomic nervous system has been measured by the diagnostic systems that are using the power spectral analysis of the beat-to-beat time series, which quantifies the heart rate variability. Heart rate variability was assessed during 3 positions (1st – 5 min supine; 2nd – 5 min standing; 3rd – 5 min supine) before and after the treatment, recording beat-to-beat photoplethysmographic finger systolic arterial pressure and diastolic arterial pressure obtaining during paced breathing. Power spectra are computed using a fast Fourier transformation for very low frequency (VLF: 0.0033 – 0.04 Hz), low-frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.40 Hz) powers (Weise *et al.* 1987; Lipsitz *et al.* 1990; Ponikowski *et al.* 1997; Virtanen *et al.* 2003; Javorka *et al.* 2008). To examine of short heart rate we used the microcomputer system VarCor PF7 which enables radio transmission of the ECG signal to the receiver connected by an USB cable to the PC. Data were processed by a software program (VarCor Medical PC).

Treatment approaches

Patients were treated using combination of group cognitive-behavioral therapy and SSRIs in usual range of dosages. A structured CBT program established on the ward consisted of 18 CBT group sessions (vicious circle of panic disorder and agoraphobia, cognitive restructuring, interoceptive exposure, exposure in vivo, communication training, practical problem solving and adjustment of cognitive schemes), ergo-therapy, and physical exercises. Pharmacotherapy was more variable, because patient typically used several antidepressants and tranquillizers before study enrolment. The drugs and their dosages were adjusted using clinical judgment.

Ethical issues

Investigation was carried out in accordance with the latest version of the Declaration of Helsinki and the written informed consent was obtained from all subjects after the nature of the procedures had been fully explained. The local ethic Committee of University Hospital Olomouc approved this project.

Statistics

Demographic and baseline clinical characteristics were analyzed using column statistics. All data are presented as the mean and standard deviation. Normal distribution of the demographic and clinical variables was determined by the Shapiro-Wilk W test. Differences between patients and healthy controls were analyzed using unpair t-tests for independent groups and the Mann-Whitney test according the data distribution. Differences between patients´ data before and after treatment were analyzed using pair t-test or Wilcoxon signed rank test respectively. Spearman Rank Correlation coefficients or Pearson correlation analysis were obtained to examine relationships between physiological variables and scores of rating scales. The correlation was considered significant when a p value smaller than 0.05 was observed. No correction for multiple testing was applied. STATISTICA version 9.0 was used and the level of significance was set at 5%.

RESULTS

Demography and treatment outcome

Nineteen patients with panic disorder (68.4 % females) between age 20 and 54 years (mean age 37.37 ± 9.60) were included into the study. The age of the disorder onset was 30.95 ± 11.81 years; duration of the disorder 7.11 ± 7.48 years. All patients used psychotropic medication: antidepressants (n=19; mean defined daily dosage of antidepressant was 28.42 ± 12.59 mg of daily equivalent); and some of them also used benzodiazepines (n=8; mean defined daily dosage of benzodiazepines was 18.13 ± 10.33 mg of daily equivalent). Eighteen healthy controls (72.2 % females) between age 23 and 54 years (mean age 35.22 ± 12.08) were included into the study. There were no statistical difference between age of patients and controls.

Panic disorder patients were improved significantly during the treatment program (Table 1 and Figure 1). Time path of BAI and BDI scores – general subjective scales for anxiety and depressive symptoms – were similar to those of objective scale CGI-S. Clinical response as determined as decrease of psychopathology at least of 30% in BAI was achieved in 62.6% of patients. The remission determined as CGI-S of 1 or 2 at the end of the study, was achieved in 43.8% of patient.

HRV measurements – Comparison of healthy control and panic disorder patients

The healthy controls group consisted of 18 people (72.2% females) with age between 23 to 54 years (mean age 35.22 ± 12.02 years). There was no statistically significant difference between mean age of controls and

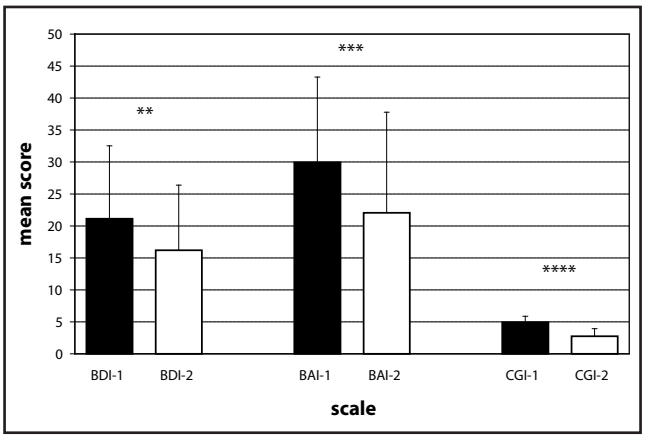

Fig. 1. Changes during the therapy in rating scales. CGI = Clinical Global Impression; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory.
pair t-test: ** $p<0.01$; *** $p<0.005$; **** $p<0.0001$.

Tab. 1. Changes during the therapy in rating scales.

	CGI-S-1	CGI-S-2	BAI-1	BAI-2	BDI-1	BDI-2
Mean	2.75	1.563	29.94	22.06	21.13	16.19
SD	1.183	1.365	13.35	15.72	11.41	10.19
pair t-test:	t=6.855; df=15; $p<0.0001$		t=3.516; df=15; $p<0.005$		t=2.209; df=15; $p<0.01$	

CGI-S = Clinical Global Impression-Severity of illness; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory

Tab. 2. Comparison of healthy controls with patients before treatment in all frequency components.

	VLF 1	VLF 2	VLF 3	LF 1	LF 2	LF 3	HF 1	HF 2	HF 3	LF/HF 1	LF/HF 2	LF/HF 3
Controls	577.4	798.6	1032	1108	1650	1357	1131	1519	1769	1.283	1.043	0.9788
Standard deviation	± 1354	± 1331	± 1871	± 3360	± 2684	± 1817	± 3135	± 2092	± 2646	± 0.7253	± 0.5988	± 0.6304
Panic disorder	172.4	95.59	114.2	293	294.8	301.2	235.2	96.3	432.1	1.591	4.147	1.027
Standard deviation	± 152.2	± 82.68	± 83.24	± 367.2	± 314	± 288	± 205	± 83.39	± 523	± 1.546	± 4.229	± 0.7143
Mann Whitney test:												
Mann Whitney U	162		94	165			167					
p-value	n.s.		$p<0.05$	n.s.			n.s.					
Unpair t-test:												
t, df		t=2.299 df=35			t=2.186 df=35	t=2.212 df=35		t=2.964 df=35	t=2.160 df=35	t=0.7684 df=35	t=3.082 df=35	t=0.2184 df=35
p-value		$p<0.05$			$p<0.05$	$p<0.05$		$p<0.005$	$p<0.05$	n.s.	$p<0.005$	n.s.

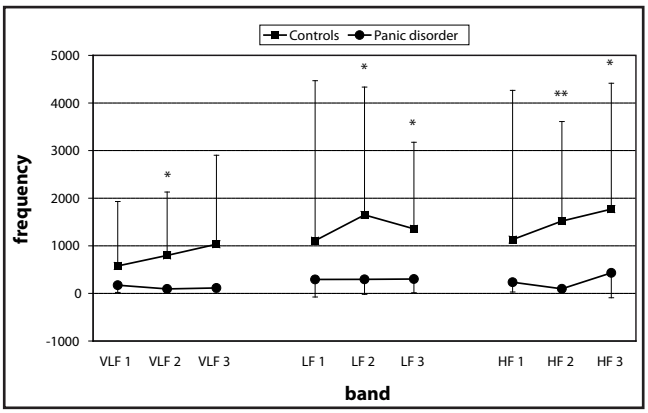

Fig. 2. Comparison of healthy controls with patients before treatment in all frequency components. VLF= very low frequency band (0.0033–0.04 Hz); LF= low frequency band (0.04–0.15 Hz); HF= high frequency band (0.15–0.40 Hz); 1= supine 5 minutes; 2= standing 5 minutes; 3= supine 5 minutes, unpair t-test: * $p<0.05$. ** $p<0.01$.

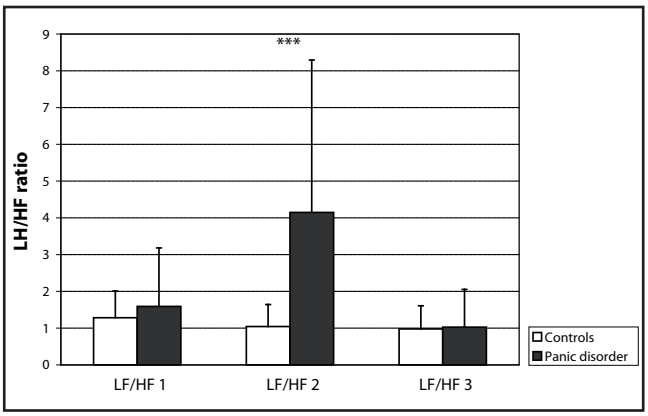

Fig. 3. Ratio LF/HF of healthy controls in comparison with panic disorder patients.
unpair t-test *** $p<0.005$.

patients (unpair t-test; t=0.6009; df=35; p=0.5518). The control group underwent the same HRV measurements procedure as the patients´ group. The activity of the autonomic nervous system fluctuated between each measurement (1st – supine; 2nd – standing position; 3rd – supine) in all three components (VLF, LF and HF). There were highly statistically significant differences between panic patients and control group in all components of power spectral analysis in 2nd (VLF, LF and HF in standing position) and in LF and HF component of 3rd (supine) of experiment (Table 3 and Figure 2). There was also a statistically significant difference between these two groups in LF/HF ratio in standing position (2nd), but not in supine (Figure 3).

HRV measurements – Comparison of panic disorder patients before and after therapy

During therapy there was tendency to increasing values in all three orthostatic positions in all components of HRV power spectra, but there was statistically significant increase only in HF1 component (supine posture: pair t-test; t=2.216; df=18; $p<0.05$) (Table 3 and Figure 4).

Correlation of demographic and clinical data with HRV measurements

There was a statistical significant correlation of the age and VLF3 (Spearman r=–0.6639; $p<0.05$) of HRV power spectra components in healthy control group. There was no other correlation of the age and other power spectra components of HRV.

In the patients group there was only statistically significant negative correlations between the age of the patient and LF2 component of power spectra analysis (Pearson r=–0.5069; $p<0.05$) and LF sum (Pearson r=–0.4934; $p<0.05$). There were no other statistically

Tab. 3. Means of HRV power spectra components during three positions before and after treatment of panic disorder.

	VLF 1	VLF 2	VLF 3	LF 1	LF 2	LF 3	HF 1	HF 2	HF 3	LF/HF 1	LF/HF 2	LF/HF 3
Before treatment	172.4	95.59	114.2	293	294.8	301.2	235.2	96.3	432.1	1.591	4.147	1.027
standard deviation	± 152.2	± 82.68	± 83.24	± 367.2	± 314	± 288	± 205	± 83.39	± 523	± 1.546	± 4.229	± 0.7143
After treatment	174.1	234.9	220.7	645.9	520.6	399	826.4	298	1100	1.642	4.245	1.953
standard deviation	± 261.6	± 308.6	± 361.3	± 1495	± 774.5	± 500.7	± 1215	± 553.3	± 2038	± 2.207	± 3.74	± 2.579
Wilcoxon signed rank test:												
Sum of signed ranks (W)	26		2	–42				–38	–42			
p-value	n.s.		n.s.	n.s.				n.s.	n.s.			
Pair t-test:												
t, df		t=1.900 df=18			t=1.992 df=18	t=0.7787 df=18	t=2.216 df=18			t=0.1673 df=18	t=0.086 df=18	t=1.757 df=18
p-value		$p<0.05$			n.s.	n.s.	$p<0.05$			n.s.	n.s.	n.s.

significant correlations between age and other power spectra component during three measured body positions. There was no correlation between the age of the disorder onset and disorder duration.

The BDI mean score before treatment negatively correlated with the HF2 (standing position) power spectra component (Pearson r=–0.5745; $p<0.05$). BDI change during the therapy negatively correlated with LF3 (supine position) power spectra component (Pearson r=–0.5557; $p<0.05$)

The rating scale BAI, which is more appropriate for the measurement of anxiety, was significantly positive correlated with LF1 (Pearson r=0.5824; $p<0.01$), LF2 (Pearson r=0.603; $p<0.05$), LF sum (Pearson r=0.57; $p<0.05$), and HF1 (Pearson r=0.5182; $p<0.05$). These results can be interpreted to mean that both sympathetic and parasympathetic activities are increased in more anxious patients.

There were no statistically significant correlations between CGI and CGI change and HRV power spectra components.

The dosages of antidepressants were negatively correlated with the VLF-1 (Spearman r=–0.6395; $p<0.005$), VLF-2 (Spearman r=–0.5526; $p<0.05$), HF-1 (Spearman r=–0.5216; $p<0.05$), HF-2 (–0.5545; $p<0.05$), HF-3 (Spearman r=–0.7071; $p<0.001$), and positively with the HF/LF-1 ratio (Spearman r=0.6501; $p<0.001$) and the HF/LF-3 ratio (Spearman r=0.853; $p<0.0001$) in the second measurement after treatment. There were no statistically significant correlations between dosages of anxiolytics and HRV power spectra components. Also, there were no statistically significant correlation between DES or pathological DES and HRV power spectra components.

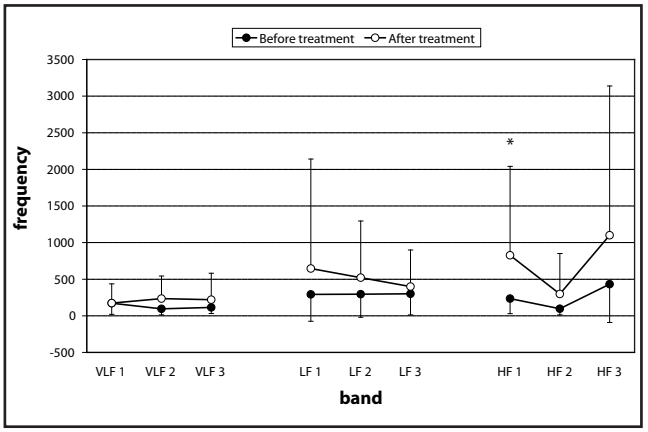

Fig. 4. Means of HRV power spectra components during three orthostatic positions before and after treatment of panic disorder. VLF= very low frequency band (0.0033–0.04 Hz); LF= low frequency band (0.04–0.15 Hz); HF= high frequency band (0.15–0.40 Hz); 1= supine 5 minutes; 2= standing 5 minutes; 3= supine 5 minutes, pair t-test: * $p<0.05$.

DISCUSSION

Cautious statements can be made at this point about the physiological significance of our findings. As mentioned before, the higher-frequency components (HF) could reflect parasympathetic activity. Our findings may thus suggest that in panic disorder patients, resting cardiac activity is characterized by alterations in sympathovagal balance which result primarily from a reduction in parasympathetic tone. Traditionally, it has been postulated that increased noradrenergic activity in panic disorder results in increased activity of the sympathetic nervous system (Ko *et al.* 1983; Charney *et al.* 1984; Villacres *et al.* 1987). Our data suggest, that in comparison with the healthy volunteers the patients with panic disorder could have decreased sympathetic and parasympathetic activity and also decreased parasympathetic activity and decreased LF/HF ratio. However, since the parasympathetic system modulates the effects of the sympathetic system on the heart via tonic inhibition (Berne & Levy 1986), reduction in LF/HF ratio could result in increased noradrenergic activity on the heart (Lundberg and Hokfelt 1983, Berne and Levy 1986).

There were significant negative correlations between age and HF 2 and HF 3. These finding can be interpreted to mean that the activity of parasympaticus could decrease during the lifetime course in our patients. But it could be true for healthy people (Yeragani *et al.* 1997). The ability of the system to react to stress and come back to the resting state changes during the life. Surprisingly, we did not find decrease of the VLF and LF (reflected mostly sympathetic activity) with the age. This could be due to insufficient number of patients in the study and high standard deviations of VLF and LF measurements.

The second hypothesis was also partly confirmed. The activities of VLF 3 and HF 3 were negatively correlated with the age of disorder onset. It is difficult to interpret these findings, but one can speculate, that these data, which partially reflected the activity of sympaticus and parasympaticus in the situation of lying down after standing, show the decreased ability to calming down the autonomic nervous system, can be factor of higher vulnerability to distress. We don´t know, if the patients had lower sympathetic and vagal recovery before the onset of the disorder, but this speculation could be supported by a finding in children, in which the lower vagal recovery and higher negative affectivity were associated with maladaptive emotion regulation responses to frustration in children (Santucci *et al.* 2008). Other interpretation of these findings could be that patients with earlier onset of the disorder used medication longer and the lower autonomic nervous system recovery developed during the medication intake. But there were not significant correlations between the duration of the disorder and the dosages of medications and VLF 3 or HF 3 values in our study.

The third hypothesis that the activity of VLF, LF and HF is negatively correlated with the dosage of psychotropic medication was partially confirmed. There were statistically significant negative correlations between dosages of antidepressants and baroreceptor activity in the first (VLF-1) and second position (VLF-2) and between the parasympathetic activity in the second (HF-2) and third position (HF-3) and positive correlation in the parasympathetic/sympathetic ratios in the first (LF/HF-1) and third (LF/HF-3) position after treatment. These results can be interpreted to mean that higher dosages of antidepressants decrease more the activity of baroreceptors and parasympaticus during the treatment than lower dosages but increase the ratio between the parasympathetic/sympathetic activities, which could reflect the higher level of adaptability of the autonomic nervous system to orthostatic changes. But the medication did not substantially change during the study and all patients used medication for at least 6 weeks before the study. Furthermore at the 1st measurements of HRV there were not any correlation between dosage of antidepressants and HRV parameters. That is why we could speculated, that the changes between 1st and 2nd measurement could reflect other factor, than the medication itself, mostly a decrease of psychopathology. There were not correlations with dosages of anxiolytics and HRV power spectra components. But we must take into consideration that the number of patients with benzodiazepinem is limited and not enough for generalization.

The last but most important our hypothesis was that the activity of VLF, LF and HF in panic patients is negative correlated with the level of dissociation measured by DES. This hypothesis reflects the old view that people who repressed or dissociate their primary emotions frequently suffer from mood disorders and with the findings, that people with mood and anxiety disorders have higher incidents of hypertension and heart diseases (Zellweger *et al.* 2004; Esler *et al.* 2008). This hypothesis is also consistent with our findings of higher level of dissociation in patients with bipolar affective disorder (Latalova *et al.* 2010), panic disorder, dissociative disorder (Pastucha *et al.* 2009a,b), obsessive compulsive disorder (Prasko *et al.* 2009; 2010; Raszka *et al.* 2009), and borderline personality disorder patients (Pastucha *et al.* 2009c), and other findings about decreased heart rate variability in depression, anxiety disorders and bipolar disorders (Cohen *et al.* 2003; Todder *et al.* 2005; Gruber *et al.* 2008). However, our current results did not confirm this hypothesis. There were no correlations between the level of dissociation and the HRV power spectra components.

Our current findings confirmed the decreased vagal function in patients with panic disorder in comparison with healthy controls. Decreased cardiac vagal function is linked with increased cardiac mortality and depression is associated with decreased heart rate variability (Ariyo *et al.* 2000; Carney *et al.* 2002).

Although the reason for the differences between the present and previous studies (Ito *et al.* 1999; Yeragani *et al.* 1992; 1993; 1995) is not entirely clear, we speculate that differences in the stage of illness (i.e., duration of illness or clinical grade) might contribute to the divergence of autonomic nervous system activity in panic disorder patients. The patients in the study of Ito *et al.* (1999) had a relatively short duration of illness, less than 1 year without phobic avoidance or depression. All patients in their study could be considered to be in the early stage of panic disorder and decreased HRV is connected with the chronicity in many disorders. Our group of patients had a much longer duration of illness, and most of them suffer also from agoraphobia.

Another important question is the influence of medication on HRV. Rechlin (1995) found that HRV parameters significantly decreased in depressive patients under amitriptyline treatment, but not under paroxetine treatment. Also in the study of van Zyl *et al.* (2008) tricyclic antidepressants (TCAs) in patients with major depression were associated with declines in most measures of HRV and significant increase in heart rate (HR) in patients with major depression studied with short recording intervals. No significant changes were found for longer recording times. Although the effect of SSRIs on HRV is weaker than for TCAs, evidence shows that SSRIs are associated with a small decrease in HR, and an increase in one measure of HRV.

Papers investigating HRV response to SSRI treatment yielded a total of seven comparisons. The medications investigated in these studies were fluvoxamine, paroxetine, and fluoxetine. In five of the comparisons, HRV parameters were obtained from short recordings and in two studies 24-hour recording methods were employed (review van Zyl *et al.* 2008). With respect to the short-term recording studies there was only reliable change in HRV was a marginally significant increase in SDNN (Rechlin *et al.* 1994 a,b,c; Rechlin *et al.* 1995; Volkers *et al.* 2004; Straneva-Meuse *et al.* 2004). The very wide range of values for the different parameters and the small number of studies limits the power of this analysis. The long-term studies were markedly contradictory (Leberbogen *et al.* 2001; Khaykin *et al.* 1998).

There are several limitations of our study that need to be mentioned. There is a small group size. Another limitation is that we used self-report questionnaires to asses the level of dissociation. Further studies in this area need to be undertaken. Other limitation is that to assess the level of dissociation, we used self-report questionnaires. Future research should corroborate these questionnaires with clinician-rated instruments.

Prospective studies of cardiovascular changes in panic disorder are needed to evaluate a psychopathological state in connection with cardiovascular changes and cardiac morbidity and mortality and to test the extent to which processing of positive emotion contributes to the course of symptoms and heart rate variability in panic disorder.

Little work has been published about the role of the parasympathetic and central cholinergic system in anxiety in general and in panic disorder in particular; these findings suggest that this area needs further investigation. The question of the specificity of these findings to panic disorder patients remains open at this point.

CONCLUSION

These findings may provide a useful measure that could be of help in the diagnosis and follow-up of patients with panic disorder. However, to determine whether these findings are specific to panic disorder or nonspecifically reflect states of increased anxiety and arousal, other patient groups need to be studied. Such group should include patients with other anxiety disorders such as generalized anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder, need to be studied.

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