ORIGINAL ARTICLE

Heart rate variability spectral analysis in patients with panic disorder compared with healthy controls

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Abstract

OBJECTIVES: 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 test in patients with panic disorder and a comparison with healthy controls.

METHODS: We measured HRV in 31 patients with panic disorder and 20 healthy controls. Diagnosis was done according to the ICD-10 research diagnostic criteria confirmed with MINI (MINI international neuropsychiatric interview). Autonomic nervous system (ANS) has been evaluated during orthostatic change in three positions. Intensity of symptoms was assessed using psychiatric scales.

RESULTS: There were highly statistically significant differences between panic patients and control group in all components of power spectral analysis in 2nd and 3rd VLF components and in HF components of 2nd. We have found highly statistically significant negative correlations between level of dissociation measured by DES and some parameters of ANS. We found negative correlations between the age of the patient and activity of ANS, and negative correlations between activity of ANS and duration and onset of disorder and dosage of antidepressants.

CONCLUSION: These findings demonstrate a lower parasympathetic activity and higher sympathetic/parasympathetic ratio in panic disorder patients measured during the changes of postural position in comparison with healthy controls. Autonomic dysregulation is associated with panic disorder and has the relation with the level of dissociation, the age of patiens and age of onset of disorder.

INTRODUCTION

Panic disorder is a severe and often disabling condition with a lifetime prevalence rate of 4.1% to 8.8% (Bandelow 2003). Patients experience panic attacks characterized by symptoms of autonomic activation such as palpitations, hyperventilation, dizziness, tremor, chest discomfort, sweating, and hot and cold flashes and gastrointestinal problems. Patients with panic disorder were found to be unique in their familial aggregation, development of agoraphobia and panic-induction responsiveness to sodium lactate infusion. There are two main approaches to the treatment of panic disorder: pharmacotherapy and cognitive-behavioral therapy (Prasko *et al.* 2004). But more than 1/3 of patients have a chronic and/ or recurrent form of the disorder, which can be resistant to the treatment with both main modalities. The understanding of causes for treatment resistance is limited (Prasko *et al.* 2005). Many different approaches have been used to overcome it, sometime without any success (Prasko *et al.* 2007). Better understanding of the biological markers of panic disorder could help with this issue.

Autonomic nervous system (ANS) dysfunction and reduced heart rate variability (HRV) have been reported in a wide variety of psychiatric disorders (Klein *et al.* 1995; Ito *et al.* 1999; Carney *et al.* 2005; Blechert *et al.* 2007; Latalova *et al.* 2010; Prasko *et al.* 2011). Patients with panic disorder have higher baseline heart rate and periods of tachycardia which coincide with panic symptoms (Freedman *et al.* 1985; Liebowitz *et al.* 1985). Increased cardiac mortality and morbidity have been suggested in these patients (Katerndahl 2008).

HEART RATE VARIABILITY (HRV) MEASUREMENTS

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 exhibit alterations in HR and cause oscillation of the R–R interval around its mean value (HRV). Increasingly refined calculations have been developed to measure HRV. Respiration has a strong influence on HR changes and is commonly included as a covariate in statistical analysis of the relation between stress and HRV changes (Bernston *et al.* 1997). Respiratory sinus arrhythmia (RSA) is one of basic mechanisms participating on heart rate variability origin. RSA is known as an index of cardiac parasympathetic activity and usually decreases under acute psychological stress (Houtveen *et al.* 2002).

More recently, there have been attempts to detect more elaborate physiological abnormalities that could be attributed to dysfunction of either the vagal or the SNS (sympathetic nervous system) by analyzing heart rate variability. Power spectral analysis of electrocardiogram (ECG) R-R intervals (PSR-R) is known to be a particularly successful tool in the detection of autonomic instabilities in various clinical disorders (Ponikowsky *et al.* 1997; Bernston *et al.* 1997). PSR-R yields high-frequency (HF), low-frequency (LF), and very low-frequency (VLF) components. It is proposed that the instantaneous balance between sympathetic and parasympathetic activities can be captured by the ratio between low frequency band power (LF, 0.04–0.15 Hz) and high frequency band power (HF, >0.15 Hz); the latter represents primarily respiratory components. 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 (Bernston *et al.* 1997). Some new research showed that LF power could reflect baroreflex function, not exactly the only sympathetic innervation (Moak *et al.* 2009) . Hence, the ratio of LF power to HF power (LF/HF) is generally accepted as an index of cardiac sympathovagal balance (Task Force 1996), but recently, this ratio is discussed. VLF power may indicate thermoregulation or vasomotor activity, although this has been disputed; it may involve a parasympathetic component, possibly engage the rennin-aldosterone system (Ponikowsky *et al.* 1997; Bernston *et al.* 1997; Virtanen *et al.* 2003).

Studies on healthy individuals show that acute stress increases LF/HF and decreases HF, suggesting activation of the SNS as well as reduction of PNS (parasympathetic nervous system) activity under stress (Pagani *et al.* 1997). However, it is not clear that the LF/HF ratio represents a relative sympathetic modulation (Eckberg *et al.* 1997).

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 interval of 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) found 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 VLF and a higher relative power in the band of 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.

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) at the beginning of the treatment. 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. Prasko *et al.* (2011) in small study with 19 panic patients and 18 healthy volunteers 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. Tonhajzerova *et al.* (2009) found that HRV is lower in adolescent patients with major depressive disorder (MDD) especially in the HF frequency band component. These findings were supported in the next study, where authors on a group of 20 adolescent girls with a major depressive disorder (MDD) compared to 20 healthy controls found significantly reduced HRV complexity in a supine rest and after posture change, especially in the standing position (Tonhajzerova *et al.* 2010).

AIM OF THE STUDY

The aim of our study is to measure VLF, LF and HF frequency band components of R-R interval in patients with panic disorder and in healthy controls, compare both groups, and test the relation between HRV components and level of dissociation in the patients group. We hypothesized that: (a) there are differences between HRV components in patients and healthy controls; (b) The value of VLF, LF a HF decrease with the age of the patient and the same picture will be in healthy controls; (c) The value of VLF, LF and HF is negatively correlated with age of onset of panic disorder; (d) The value of VLF, LF and HF is negatively correlated with the dosage of psychotropic medication; (e) The value of VLF, LF and HF in panic patients is negatively correlated with the level of dissociation measured by DES.

METHODS

Subjects

Patients were recruited from the inpatients department of the Psychiatry department University hospital Olomouc. All patients have been hospitalized for panic disorder. After study enrolment, patients were assessed during the first two days of hospitalization. Inclusion criteria were: (a) ICD-10 research criteria for panic disorder or for panic disorder with agoraphobia; (b) Nonresponders 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. The diagnosis of panic disorder was confirmed according to the clinical interview by two experienced clinicians. 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. The severity of the disorder was assessed with CGI (Clinical Global Impression) (Guy 1976), BAI (Beck Anxiety Inventory) (Beck & Emery 1985), BDI (Beck Depression Inventory) (Beck *et al.* 1961). Psychological dissociative symptoms were examined using the Dissociative Experiences Scale (DES) (Carlson *et al.* 1991; Carlson *et al.* 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 (Waller *et al.* 1996). After the evaluation by the psychiatrist, patients filled in their demographic data. Their written consent to participate in the research was given. Demographic data, including age, sex, age of the onset of the disorder, duration of disorder, were obtained in the 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). The control group was recruited from healthy subjects, without any psychopathological complaints. They were also not used any psychopharmacological medication and the HRV measures were made strictly same as in the patients group.

HRV measurement

The patients were examined in following order : supine – standing – supine. The functioning of the ANS has been measured by the diagnostic systems that are using the power spectral analysis which quantifies the heart rate variability. This procedure has been used frequently over the past decades as a noninvasive, simple and sensitive method to examine the autonomic regulation of the heart. There are three frequency bands detected by the fast Fourier transformation in heart rate variability (HRV) (Javorka 2008).

- The high frequency band – HF (0.15–0.40 Hz) represents the parasympathetic activity.
- The low frequency band – LF (0.04–0.15 Hz) represents not exactly the sympathetic activity. A relative increase can be found after physical activities or mental stress. This frequency band can be influenced also by the baroreceptor acitivity, parasympathetic activity, vasomotor activity or in orthostatic test.
- The very low frequency band – VLF (0.0033–0.04 Hz) represents also the sympathetic activity, but there are some research findings that this frequency can be influenced also by thermoregulation, oscillations of the blood vessel tone and especially the renin – angiotensin – aldosteron system (Klieger *et al.* 2005).

To examine the short-term heart rate variability 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. This system evaluates HRV by spectral (frequency) analysis, using the fast Fourier transformation algorithm. Because the distribution of variance of the frequency bands exhibited skewness, we used natural logarithmic transformation to adjust this skewness and also it is recommended for appropriate statistical analysis using parametric tests (Kuo *et al.* 1999).

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.

Statistical analysis

Demographic and baseline clinical characteristics were analyzed using column statistics. Normal distribution of the demographic and clinical variables was determined by the Shapiro-Wilk W test. Group differences between patients with panic disorder and healthy controls were analyzed using unpair t-tests. The chi^2 test or Fisher´s exact test were used for the analyses of categorical data. The relationships between variables with normal distribution were calculated using Pearson correlation analysis, while Spearman rank correlation was used for variables with non-normal distribution. GraphPad PRISM version 5.0 was used and the level of significance was set at 5% (http://www.graphpad.com/prism/prism.htm).

Tab. 1. Demographic and clinical characteristics of the patients and controls.

	Patients (n=31)	Controls (n=20)
Age	39.45 ± 10.32	35.33 ± 12.11
Sex:		
Males	9	5
Females	22	15
Age of the disorder onset	32.71 ± 11.48	
Length of the disorder	6.74 ± 7.14	
Antidepressants index	23.27 ± 8.825 (n=26)	
Benzodiazepine index	12.50± 7.071 (n=16)	
Antipsychotics index	3.5 ± 2.380 (n=4)	
CGI	4.13 ± 1.23	
BAI	27.41 ± 13.38	
BDI	20.48 ± 11.38	
DES	8.75 ± 10.06	

CGI = Clinical Global Impression-Severity of disorder;
DES=Dissociative Experience Scale; BAI=Beck Anxiety Inventory;
BDI=Beck Depression Inventory

RESULTS

Demographic and clinical characteristics of the patients and healthy controls

Thirty one patients with panic disorder (74.2% females) between age 20 and 57 years (mean age 39. 45 ± 10.32 were included into the study. The age at the disorder onset was 32.71 ± 11.48 years; duration of the disorder 6.74 ± 7.14 years (Table 1). All patients used psychotropic medication:

- antidepressants (n=26; /escitalopram, paroxetine, venlafaxin, clomipramine, sertraline/ mean defined daily dosage of antidepressant was 23.27 ± 8.825 mg of daily paroxetine equivalent);
- and some patients also used antipsychotics (n=4, / quetiapine, chlorprotixen, olanzapine/, mean defined daily dosage of antipsychotics was 3.5 ± 2.380 mg of daily haloperidol equivalent)

- and benzodiazepines (n=16; /buspirone, mirtazapine, bromazepam, dosulepine/ mean defined daily dosage of benzodiazepines was 12.5 ± 7.071 mg of daily diazepam equivalent).

Twenty healthy controls (76.2% females) between age 25 and 54 years (mean age 35.33 ± 12.11) were included into the study. There were no statistical difference between mean ages (unpair t-test: t=0.8044 df=49: n.s.) and gender distribution (Fisher exact test: n.s.) of the patients and controls. The control group underwent the same HRV measurements procedure as the patients group.

Data describing the activity of autonomic nervous system

There were highly statistically significant differences between panic patients and control group in all components of power spectral analysis in 2nd and 3rd VLF components (standing and supine position) and in HF components of 2nd (standing) of experiment (Table 2) (Figure 1). We can also see the decrease in all three frequency components in the second (standing) position of the orthostatic test (Figure 1).

There was also a statistically significant difference between these two groups in LF/HF ratio in standing position (2nd), but not in supine (Figure 2).

Correlation between demographic and clinical data, and autonomic nervous system

There were no correlations between age of the patient and parameters of ANS. The negative correlations between age and VLF-1 (supine), VLF-3 (supine), LF-3 (supine) were found in healthy control group (Table 3). There were statistically significant correlations between age of the disorder onset and LF-2 (standing) and HF-2 (standing) bands in second position.

The BDI scores statistically significantly negatively correlated with the HF-2 (supine) power spectra component (Spearman r=–0.4033; $p<0.05$) but not with other bands in other positions. There was also statistically significant positive correlation between BDI score and ratio LF/HF-3 (supine) (Pearson r=0.418; $p<0.05$)

The rating scale BAI, which is more appropriate for the measurement of anxiety, was not statistically significant positive correlations with HRV power spectra components. There were also no statistically significant correlations between CGI and CGI change and HRV power spectra components.

The dosages of antidepressants were positively correlated with BDI (Spearman r=0.5154; $p<0.01$) and negatively correlated with LF-1 (Spearman r=–0.4265; $p<0.05$), LF-2 (Spearman r=–0.476; $p<0.05$), LF-3 (Spearman r=–0.6084; $p<0.001$), HF-1 (Spearman r=–0.5803; $p<0.005$), HF-2 (Spearman r=–0.4914; $p<0.05$), HF-3 (Spearman r=–0.7258; $p<0.0001$), and positively with LF/HF-1 (Spearman r=0.4842; $p<0.05$) and LF/HF-3 (Spearman r=0.5994; $p<0.005$). There

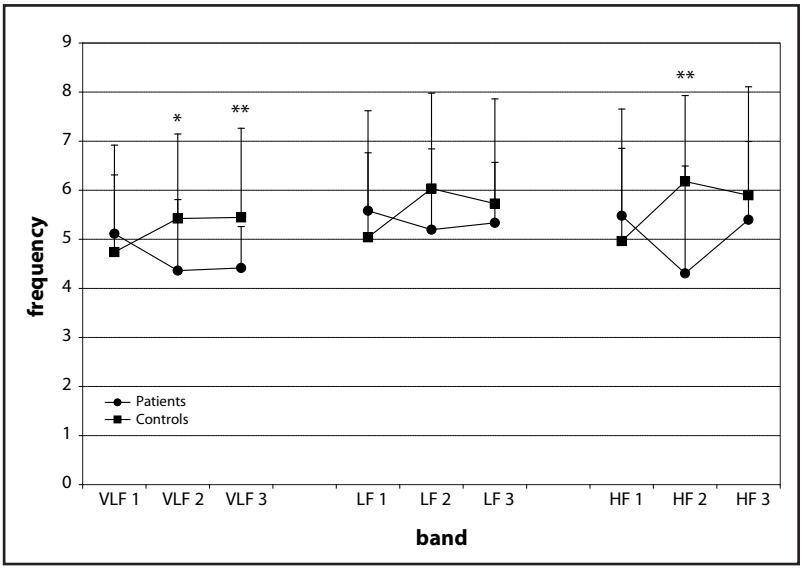

Figure 1. Changes of very low-frequency (VLF), low-frequency (LF), and high-frequency (HF) components during orthostatic changes in panic disorder and healthy controls. VLF= very low frequency band (0.0033–0.04 Hz); LF= low frequency band (0.04–0.15 Hz); HF= high frequency band (0.15–0.40 Hz); 1= supine 5 minutes; 2= standing 5 minutes; 3= supine 5 minutes, *unpair t-test: $p<0.05$ ** unpair t-test $p<0.05$

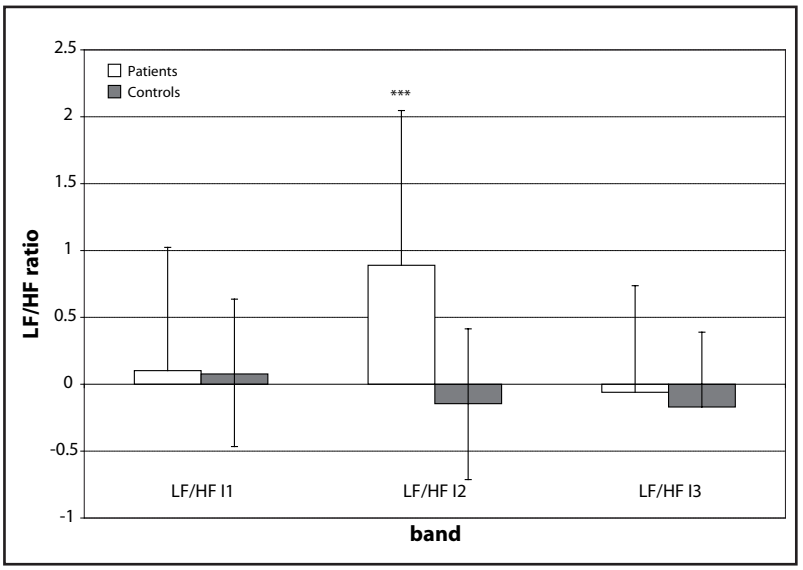

Figure 2. LF/HF ratio of healthy controls in comparison with panic disorder patiens. *** unpair t-test $p<0.0005$

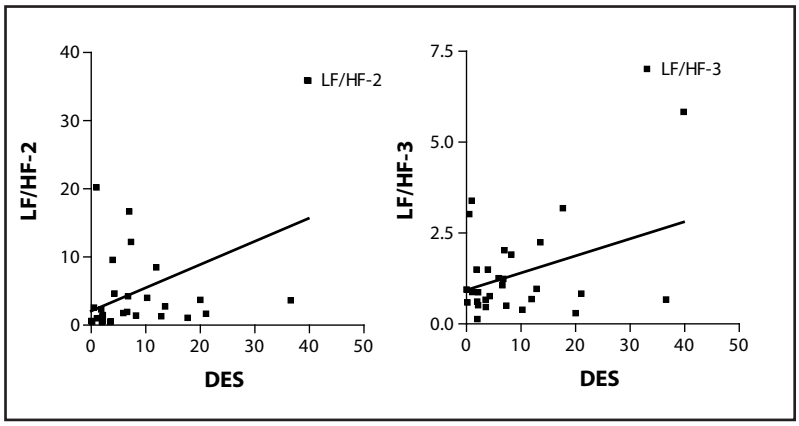

Fig. 3. Linear regression DES versus LF/HF-2 and DES versus LF/HF-3.

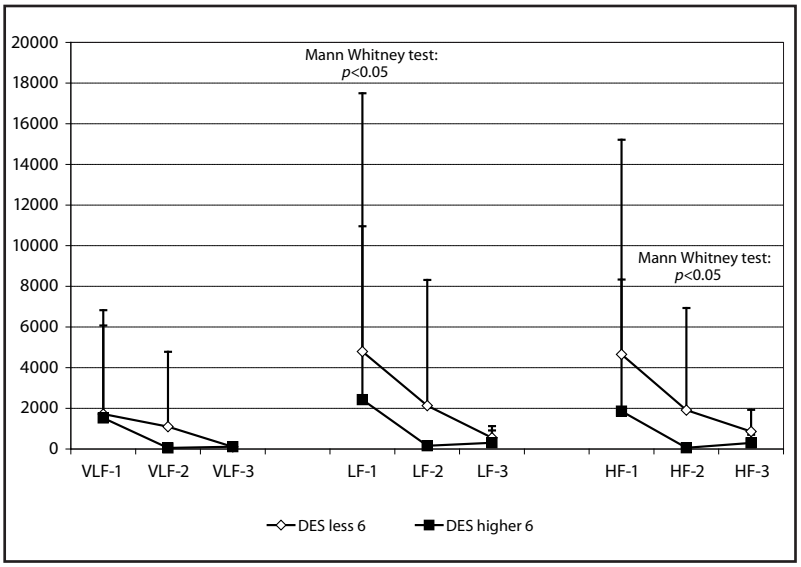

Fig. 4. Vegetative system measurements in panic patients with DES less or higher than 6. VLF= very low frequency band (0.0033–0.04 Hz); LF= low frequency band (0.04–0.15 Hz); HF= high frequency band (0.15–0.40 Hz); 1= supine 5 minutes; 2= standing 5 minutes; 3= supine 5 minutes. Mann-Whitney U test $p<0.05$

were no statistically significant correlations between dosages of anxiolytics or antipsychotics and HRV power spectra components.

Relation between dissociation and autonomic nervous system

There were highly statistically significant negative correlations between level of dissociation measured by DES and LF-1, HF-1 and HF-3 (Table 4).

The group of patients was divided into two subgroups according the DES scores: patient with lower level of dissociation (DES less than 6), and patients with higher level of dissociation (DES higher than 6). There was statistically significant difference in orthostatic position LF I1 (supine) and HF I2 (standing) between groups with lower (less than 6) and higher (higher than 6) level of dissociation (Table 5) (Figure 4).

There was other highly statistically significant difference between LF/HF-2 (standing) in group with lower and higher level of dissociation (Figure 5). It means that patients with higher level of dissociation have LF/HF ratio significantly lower than patients with lower level of dissociation in second orthostatic position (LF/HF-2: unpaired t-test; t=3.974 df=27: $p<0.0005$). There were no statistically significant difference between these two subgroups in first and third orthostatic position (LF/HF-1: unpaired t-test; t=1.067 df=27: p=n.s.; LF/HF-3: unpaired t-test; t=0.9256 df=27: p=n.s.).

Tab. 2. Vegetative system measurements in panic patients and healthy controls.

		VLF-1	VLF-2	VLF-3	LF-1	LF-2	LF-3	HF-1	HF-2	HF-3
Patients	Mean	5.115	4.363	4.415	5.583	5.196	5.337	5.482	4.307	5.399
	Standard deviation	1.804	1.448	0.8453	2.039	1.646	1.23	2.173	2.188	1.593
Controls	Mean	4.74	5.425	5.446	5.04	6.033	5.727	4.964	6.178	5.897
	Standard deviation	1.573	1.722	1.816	1.724	1.946	2.136	1.889	1.753	2.212
Mann Whitney test:										
Mann Whitney U		285.0			276.0			268.0		
p-value		0.6364			0.5181			0.4233		
Unpair t-test:										
t, df			t=2.375 df=49	t=2.743 df=49		t=1.651 df=49	t=0.8296 df=49		t=3.213 df=49	t=0.9349 df=49
p-value			**0.0215**	**0.0085**		0.1051	0.4108		**0.0023**	0.3544

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: $p<0.05$

DISCUSSION

Cautious statements can be made at this point about the physiological significance and interpretation of our findings, because how we describe in the introduction, the physiological relevance especially of LF and VLF bands and their relation to sympathetic and parasympathetic nervous system is not fully clear.

Orthostatic test revealed spectral activity decline in all frequency bands – HF, LF, VLF indicating altered cardiac regulation in panic disorder at rest and during active orthostasis, as well. Decrease in LF band was not significant and this tendency toward to decreasing in all positions could confirm the suggestion that sympathetic activity is not dominant in LF band (Goldstein *et al.* 2011). Therefore, the increase or decrease of LF spectral activity depends on current interaction of physiological subsystems including vasomotor activity, central sympathetic oscillator, cardiovagal activity associated with baroreflex function. According to other studies the LF was not pure index of sympathetic activity (Elghozi *et al.* 2007; Moak *et al.* 2009).

Contrary, the ratio LF/HF was significantly higher in response to standing in panic disorder compared to controls. It seems that decrease of parasympathetic activity was dominant and higher in

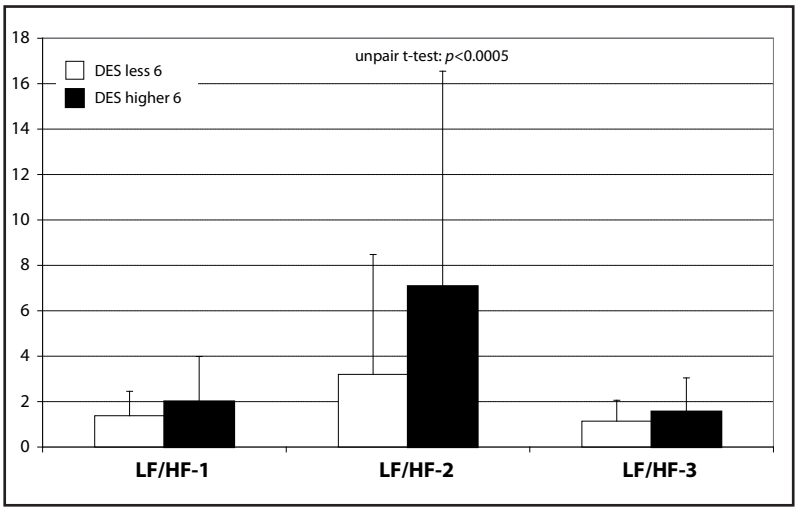

Fig. 5. Ratio LF/HF in patients with DES less or higher than 6.

Tab. 3. Ratio LF/HF of panic disorder patients in comparison with healthy controls.

	LF/HF-1	LF/HF-2	LF/HF-3
Patients	0.1016	0.8891	–0.06025
Standard deviation	0.922	1.157	0.7977
Controls	0.07679	–0.1453	–0.1699
Standard deviation	0.5597	0.5419	0.5673
Unpair t-test:			
t, df	t=0.1079 df=49	t=3.732 df=49	t=0.5331 df=49
p-value	0.9146	**0.0005**	0.5964

Tab. 4. Correlation of demographic and clinical characteristics and parameters of ANS in panic patients and healthy controls.

		VLF-1	VLF-2	VLF-3	LF-1	LF-2	LF-3	HF-1	HF-2	HF-3
Age - controls	r	–0.4905^{S}	–0.3812^{P}	–0.7252^{S}	–0.2863^{S}	–0.3722^{P}	–0.477^{P}	–0.2445^{S}	–0.3932^{P}	–0.3989^{P}
	p	**0.0281**	0.0973	**0.0003**	0.2211	0.1061	**0.0335**	0.2988	0.0863	0.0815
Age - patients	r	–0.1157^{S}	–0.0838^{S}	0.3176^{P}	–0.2258^{S}	–0.3334^{S}	–0.1125^{S}	–0.0059^{S}	–0.2454^{S}	–0.167^{S}
	p	0.5353	0.654	0.0816	0.222	0.0668	0.5469	0.9751	0.183	0.3692
Age of disorder onset	r	–0.2131^{S}	–0.2087^{S}	0.0440^{P}	–0.2861^{S}	–0.3961^{S}	–0.2133^{S}	–0.0591^{S}	–0.3842^{S}	–0.2761^{S}
	p	0.2497	0.26	0.8143	0.1186	**0.0274**	0.2493	0.752	**0.0328**	0.1328
BDI	r	0.001^{S}	–0.0252^{S}	0.1962^{P}	–0.1349^{S}	–0.2059^{S}	–0.1009^{S}	–0.164^{S}	–0.4033^{S}	–0.1682^{S}
	p	0.9959	0.8969	0.3077	0.4853	0.2838	0.6026	0.3952	**0.0301**	0.3831
BAI	r	0.1191^{S}	0.1104^{S}	0.1878^{P}	0.2707^{S}	0.1632^{S}	0.1634^{S}	0.192^{S}	0.0885^{S}	0.2463^{S}
	p	0.5384	0.5685	0.3293	0.1556	0.3976	0.3969	0.3183	0.648	0.1978
CGI-S	r	–0.1578^{S}	–0.146^{S}	0.00254^{P}	–0.141^{S}	–0.1514^{S}	0.05664^{S}	–0.0302^{S}	–0.0539^{S}	–0.0494^{S}
	p	0.3964	0.4333	0.9892	0.4494	0.4163	0.7622	0.8719	0.7732	0.7921

r: P=Pearson r; S=Spearman r; *p*= *p*-value; ns=no significant; AD index=antidepressants index; AP index=antipsychotic index; AX index=anxiolytics index; BDI=Beck Depression Inventory; BAI=Beck Anxiety Inventory; CGI-S=Clinical Global Impression-Severity

Tab. 5. Correlation of DES and parameters of ANS in panic disorder patients.

		VLF-1	VLF-2	VLF-3	LF-1	LF-2	LF-3	HF-1	HF-2	HF-3
DES	r	−0.2924[S]	−0.3648[S]	0.0750[P]	−0.3811[S]	−0.3523	−0.3138	−0.3705	−0.4254	−0.2929
	p	0.1237	0.0517	0.6989	0.0414	0.0609	0.0973	**0.0479**	**0.0214**	0.1231

DES=Dissociative Experience Scale; P=Pearson r; S=Spearman r
There were also statistically significant correlation between DES and LF/HF ratio in second position - standing (LF/HF-2; Spearman r=0.4126; $p<0.05$) and third position – supine (LF/HF-3; Pearson r=0.3878; $p<0.05$). There were no correlations between dissociation and dosages of medication (all components of power spectra analysis n.s.).

Tab. 6. Vegetative system measurements in panic patients with DES less or higher than 6.

		VLF-1	VLF-2	VLF-3	LF-1	LF-2	LF-3	HF-1	HF-2	HF-3
DES less than 6	Mean	1722	1098	105.8	4796	2132	556.3	4658	1916	861.6
	Standard deviation	4352	3683	85.7	12702	6185	568.8	10552	5020	1066
DES higher than 6	Mean	1527	55.38	115.5	2430	156.8	305.7	1863	60.72	297.8
	Standard deviation	5301	25.82	116.4	8527	165.7	607.9	6474	55.86	399.6
Mann Whitney test:										
Mann Whitney U		79	70		57	69	72	60	52	67
p-value		0.2658	0.1322		**0.03282**	0.1214	0.1561	0.0522	**0.022**	0.1018
Unpair t-test:										
t, df				t=0.2572 df=27						
p-value				0.799						

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. Mann-Whitney U test $p<0.05$

comparison with spectral activity in LF band, therefore, we suggest that LF/HF was relatively higher. Based on the work of Lucini *et al.* (2005) we could expect higher LF/HF ratio in response to orthostatic test.

Our hypotheses were mostly been confirmed:

(a) There are differences between HRV components in patients and healthy controls.

The main differences are seen in second position of orthostatic test (standing after supine) in VLF and HF bands and in third position (supine after standing) in VLF band. There was also difference in LF/HF ratio in second position. It seems, that patient with panic disorder react differently to orthostatic changes than healthy controls and the main characteristic is decrease baroreceptor activity and decrease of parasympathetic components and therefore relative increase of the ratio between sympathetic and parasympathetic systems.

(b) The value of VLF, LF a HF decrease with the age of the patient and the same picture will be in healthy controls.

This hypothesis was fulfilling only partially. There were statistically significant correlations between the age and two VLF bands in supine position (-1, -3) and also third position in LF band in healthy controls. It seems than in healthy people there is decreasing of activity of cardiovascular system within the age (Latalova *et al.* 2010). The ability of the system to react to stress and return to the beginning state changes during life. These findings can be interpreted to mean that the activity of the parasympathetic nervous system could decrease during the lifetime. But this pattern was not recognized in patients group. But this could be due to insufficient number of patients with different ages in the study and high standard deviations of HRV measurements. Other explanation of this finding is unclear, but it is possible, than in panic patients the activity of all bands is reduced in earlier age and therefore the age decreasing trajectory is reduced. Much more patients with different age groups we need to clarify this question.

(c) The value of VLF, LF and HF is negatively correlated with age of onset of panic disorder.

There were statistically significant negative correlations between age of the onset of the disorder and two bands in second orthostatic position (standing after supine) in LF-2 and HF-2, no in other bands and positions. It is difficult to interpret these findings, but one can speculate that these data, which partially reflected the activity of sympathetic and parasympathetic nervous systems while standing after supine, show a decreased ability to calm down the ANS, which can be factor for higher reactivity to distress (Hynynen *et al.* 2011). Why this mechanism developed is unknown.

It could be hypothetically explain by two possibilities: the first possibility is that people with premorbid lower cardiovascular flexibility to orthostatic change develop panic disorder earlier than people with higher flexibility; the second is that less flexible cardiovascular system is due to earlier development of panic disorder. We do not 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 indicating that lower vagal recovery and higher negative affectivity were associated with maladaptive emotion regulation responses to frustration (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 ANS recovery developed during the medication intake. But there were no significant correlations between the duration of the disorder and the dosages of medications and VLF-3 or HF-3 values in our study.

(d) The value of VLF, LF and HF is negatively correlated with the dosage of psychotropic medication.

Other hypothesis that the activity of VLF, LF and HF is negatively correlated with the dosage of psychotropic medication was confirmed in most HRV spectra components except VLF part of spectra. There were positive correlation between dosages of antidepressants and LF/HF ratio in first and third orthostatic positions. It seems, that suppression of value of LF and HF in patients with panic disorder can be connected or with higher BAI scores or with dosages of antidepressants. It is hardly to say from our data if the reason is seriousness of the disorder or dosages of antidepressants. The other design of the study with drug free patients could be help to better understanding in future. There were no statistically significant negative correlations between dosages of antipsychotics or benzodiazepines in our group of patients.

(e) The value of VLF, LF and HF in panic patients is negatively correlated with the level of dissociation measured by DES.

The last but most important hypothesis was that the activity of VLF, LF and HF in patients with panic disorder is negatively correlated with the level of dissociation measured by DES. This hypothesis reflects old view that people who repressed or dissociate their primary emotions frequently suffer with mood disorders and with the findings, that people with mood and anxiety disorders have higher incidents of hypertension and heart diseases (Esler *et al.* 2008). The level of dissociation statistically significant negatively correlate with the activity of cardiovascular system in LF-1 and HF-1 bands first position (supine), and in HF-2 (standing). It is probable, that high level of dissociation is in relation with low level of activity and flexibility of autonomous nervous system. 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). We have several indirect arguments for these views in confirming higher level of dissociation in anxiety disorders (Pastucha *et al.* 2009a; Pastucha *et al.* 2009b), OCD (Prasko *et al.* 2009; Raszka *et al.* 2009), borderline personality disorder patients (Pastucha *et al.* 2009c), some findings about decreased heart rate variability in depression, anxiety disorders and bipolar disorders (Todder *et al.* 2005; Henry *et al.* 2010; Latalova *et al.* 2010), and substantial evidence for higher incidents of heart disease in affective and anxiety disorders (Esler *et al.* 2008). But there has not been any information about connection between dissociation and autonomic nervous system activity. In our study, there were highly significant negative correlations between the level of dissociation and some parameters of ANS. It seems that higher level of dissociation is related to a lower level of ANS activity in three frequency bands and with higher ratio LF/HF in second and third position. These findings have several interpretations. One could think about another possibility, which is not easy to discount, that both DES and changed autonomic activity is the result of pharmacotherapy. But there was no correlation between dissociation and dosages of psychotropic medication. All patients used psychotropics. Both changed autonomic activity and dissociation could be also the results of another third process, like panic disorder itself. Only studies of drug naive patients with panic disorder could confirm or disconfirm this speculation. Other possibilities are that dissociation as a psychological process leads to decreased parasympathetic activity and relative increase of sympathetic activity or, the opposite that decreased parasympathetic and relatively increased sympathetic activity leads to dissociation. These possibilities are hard to support without future experiments.

Our results are in accord with findings of other authors in previous studies, which found decreased HRV and substantial reduction of HF in patients with panic disorder (Klein *et al.* 1995), exaggerated cardiac vagal withdrawal during lactate infusions (Yeragani *et al.* 1994).

Our study has substantial limitations that should be considered. The most important limitation is the relative small number of subjects. Our sample may not be representative of the population of patients with panic disorder. Generalization of findings is doubtful especially in a situation where the variability of ANS responses is very high. 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.

Limitation of our study is the influence of medication on HRV caused by psychotropic drug treatment and the combinations of psychotropic drugs especially antidepressants, anxiolytics and antipsychotics. Latalova *et al.* (2010) in a studie of bipolar patients found that only benzodiazepines can influence HRV especially VLF and HF band. There were found no significant influence of antidepressants (SSRI) and

antipsychotics 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 . With respect to the short-term recording studies there was only reliable change in HRV was a marginally significant increase in SDNN (Rechlin 1995; Volkers *et al.* 2004; Straneva *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 (Lederbogen *et al.* 2001; Khaykin *et al.* 1998).

However the outcome validity could be limited by combinations of psychotropic drugs. Further research with drug naive patients or patients with only one medication is needed.

Prospective studies of cardiovascular changes in panic disorder patients are needed to evaluate 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.

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REFERENCES

1 Ariyo AA, Haan M, Tangen CM, Rutledge JC, Cushman M, Dobs A (2000). Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans: Cardiovascular Health Study Collaborative Research Group. Circulation. **102**: 1773–79.

2 Baker B, Khaykin Y, Devins G, Dorian P, Shapiro C, Newman D (2003). Correlates of therapeutic response in panic disorder presenting with palpitations: Heart rate variability, sleep, and placebo effect. Canadian J Psychiatry. **48**(6): 381–87.

3 Bandelow B (2003). Epidemiology of depression and anxiety. In: Kasper S, ed. Handbook on Depression and Anxiety. New York, NY: M. Dekker. pp 49–68

4 Beck AT, Emery G (1985). Anxiety disorders and phobias: A cognitive perspective. New York, Basic Books.

5 Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961). An inventory for measuring depression. Arch Gen Psychiatry. **4**: 561–71.

6 Berntson GG, Bigger JT Jr. Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, van der Molen MW (1997). Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology. **34**: 623–48.

7 Blechert J, Michael T, Grossman P, Lajtman M, Wilhelm FH. (2007). Autonomic and respiratory characteristics of posttraumatic stress disorder and panic disorder. Psychosom Med. **69**(9): 935–43.

8 Carlson EB, Putnam FW (1993). An update on the Dissociative Experience Scale: An update on the Dissociative. Dissociation. **6**: 16–27.

9 Carlson EB, Putnam FW, Ross CA, Anderson GG, Clark P, Torem Coons P, Bowman E, Chu JA, Dill D, Loewenstein RJ, and Braun BG (1991). Factor analysis of the Dissociative Experiences Scale: A multicenter study. In BG Braun & EB Carlson (Eds.). Proceedings of the Eighth International Conference on Multiple Personality and Dissociative States. Chicago: Rush.

10 Carney RM, Freedland KE, Miller GE, Jaffe AS (2002). Depression as a risk factor for cardiac mortality and morbidity: A review of potential mechanisms. J Psychosom Res. **53**: 897–902.

11 Carney RM, Freedland KE, Veith RC. (2005). Depression, the autonomic nervous system, and coronary heart disease. Psychosom Med. **67**(Suppl 1): S29–33.

12 Eckberg DL (1997). Sympathovagal balance: a critical appraisal. Circulation. **96**: 3224–32.

13 Elghozi JL, Julien C (2007). Sympathetic control of short-term heart rate variability and its pharmacological modulation. Fundam Clin Pharmacol. **21**(4): 337–47.

14 Esler M, Eikelis N, Schlaich M, Lambert G, Alvarenga M, Kaye D, El-Osta A, Guo L, Barton D, Pier C, Brenchley C, Dawood T, Jennings G, Lambert E (2008). Human sympathetic nerve biology: parallel influences of stress and epigenetics in essential hypertension and panic disorder. Ann N Y Acad Sci. **1148**: 338–48.

15 Freedman RR, Ianni P, Ettedgui E, Puthezhath N (1985). Ambulatory monitoring of panic disorder. Arch Gen Psychiatry. **42**: 244–48.

16 Goldstein DS, Bentho O, Park MY, Sharabi Y (2011). LF power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol. **96**(12): 1255–1261.

17 Guy W (1976). ECDEU Assessment manual for psychopharmacology. Rockville, U.S. DHEW.

18 Henry BL, Minassian A, Paulus MP, Geyer MA, Perry W (2010). Heart rate variability in bipolar mania and schizophrenia. J Psychiatr Res. **44**(3): 168–76.

19 Houtveen JH, Rietveld S, de Geus EJ (2002). Contribution of tonic vagal modulation of heart rate, central respiratory drive, respiratory depth, and respiratory frequency to respiratory sinus arrhythmia during mental stress and physical exercise. Psychophysiology **39**: 427–36.

20 Hynynen E, Konttinen N, Kinnunen U, Kyröläinen H, RuskoH (2011). The incidence of stress symptoms and heart rate variability during sleep and orthostatic test. Eur J Appl Physiol. **111**: 733–41.

21 Ito T, Inoue Y, Sugihara T, Yamada H, Katayama S, Kawahara R (1999). Autonomic function in the early stage of panic disorder: Power spectral analysis of heart rate variability. Psychiatry and Clinical Neurosciences. **53**: 667–72

22 Javorka K (2008). Heart Rate Variability. Mechanisms, classification, clinical utilization. Osveta, Martin.

23 Katerndahl DA (2008). The association between panic disorder and coronary artery disease among primary care patients presenting with chest pain: an updated literature review. Prim Care Companion J Clin Psychiatry. **10**: 276–85.

24 Khaykin Y, Dorian P, Baker B, Shapiro C, Sandor P, Mironov D, Irvine J, Newman D (1998). Autonomic correlates of antidepressant treatment using heart-rate variability analysis. Can J Psychiatry. **43**: 183–86.

25 Kleiger RE, Stein PK, Bigger TJr (2005). Heart Rate Variability: Measurement and Clinical Utility. Ann Noninvasive Electrocardiol. **10**(1): 88–101

26 Klein E, Cnaani E, Harel T, Braun S, Ben-Haim SA (1995). Altered heart rate variability in panic disorder patients. Biol. Psychiatry. **37**: 18–24.

27 Kuo TBJ, Lin T, Yang CCH, Li CL, Chen CF and Chou P (1999). Effect of aging on gender differences in neural control of heart rate. Am J Physiol. **277**: H2233–39.

28 Latalova K, Prasko J, Diveky T, Grambal A, Kamaradova D, Velartova H, Salinger J, Opavsky J (2010). Autonomic nervous system in euthymic patients with bipolar affective disorder. Neuroendocrinol Lett. **31**(6): 829–836.

29 Lavoie KL, Fleet RP, Laurin C, Arsenault A, Miller SB, Bacon SL (2004). Heart rate variability in coronary artery disease patients with and without panic disorder. Psychiatry Research. **128**(3): 289–99.

30 Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, Janavs J, Dunbar GC (1997). The MINI-international neuropsychiatric interview (M.I.N.I.): a short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry. **12**: 224–31.

31 Lederbogen F, Gernoth C, Weber B, Colla M, Kniest A, Heuser I, Deuschle M (2001). Antidepressive treatment with amitriptyline and paroxetine: comparable effects on heart rate variability. J Clin Psychopharmacol. **21**: 238–39.

32 Liebowitz MR, Gorman JM, Fyer A J, Levitt M, Dillon D, Levy G, Appleby IL, Anderson S, Palij M, Davies SO, Klein DF (1985). Lactate provocation of panic attacks. II. Biochemical and physiological findings. Arch Gen Psychiatry. **42**: 709–19.

33 Lucini D, Gaetana DF, Parati G, Pagani M (2005). Impact of Chronic Psychosocial Stress on Autonomic Cardiovascular Regulation in Otherwise Healthy Subjects. Hypertension. **46**: 1201–06.

34 Moak JP, Goldstein DS, Eldadah BA, Saleem A, Holmes C, Pechnik S, Sharabi Y (2009). Supine Low Frequency Power of Heart Rate Variability Reflects Baroreflex Function, Not Cardiac Sympathetic Innervation. Cleveland Clinic Journal of Medicine. **76**(2): 51–59.

35 Pagani M, Montano N, Porta A, Malliani A, Abboud FM, Birkett C, Somers VK (1997). Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation. **95**: 1441–48.

36 Pastucha P, Prasko J, Diveky T, Grambal A, Latalova K, Sigmundova Z, Tichackova A (2009c). Borderline personality disorder and dissociation – comparison with healthy controls. Activitas Nervosa Superior Rediviva. **51**(3–4): 146–49.

37 Pastucha P, Prasko J, Grambal A, Latalova K, Sigmundova Z, Tichackova A (2009a). Panic disorder and dissociation – comparison with healthy controls. Neuroendocrinol Lett. **30**(6): 774–78.

38 Pastucha P, Prasko J, Grambal A, Latalova K, Sigmundova Z, Tichackova A (2009b). Dissociative disorder and dissociation – comparison with healthy controls. Neuroendocrinol Lett. **30**(6): 769–73.

39 Ponikowski P, Chua TP, Piepoli M, Amadi AA, Harrington D, Webb-Peploe K, Volterrani M, Colombo R, Mazzuero G, Giordano A, Coats AJ (1997). Chemoreceptor dependence of very low frequency rhythms in advanced chronic heart failure. Am. J. Physiol. **272**: H438–47.

40 Prasko J, Bares M, Horacek J, Kopecek M, Novak T, Paskova B (2007). The effect of repetitive transcranial magnetic stimulation (rTMS) add on serotonin reuptake inhibitors in patients with panic disorder: A randomized, double blind sham controlled study. Neuroendocrinol Lett. **28**: 33–38.

41 Prasko J, Horacek J, Zalesky R, Kopecek M, Novak T, Paskova B, Skrdlantova L, Belohlavek O, Hoschl C (2004). The change of regional brain metabolism (18FDG PET) in panic disorder during the treatment with cognitive behavioral therapy or antidepressants. Neuroendocrinology Letters. **25**: 340–48.

42 Prasko J, Houbova P, Novak T, Zalesky R, Espa-Cervena K, Paskova B, Vyskocilova J (2005). Influence of personality disorder on the treatment of panic disorder. Comparison study. Neuroendocrinology Letters. **26**: 667–74.

43 Prasko J, Latalova K, Diveky T, Grambal A, Kamaradova D, Velartova H, Salinger J, Opavsky J, Silhan P (2011). Panic disorder, autonomic nervous system and dissociation – changes during therapy. Neuro Endocrinol Lett. **32**(5): 641–651.

44 Prasko J, Raszka M, Adamcova K, Grambal A, Koprivova J, Kudrnovska H, Latalová K, Vyskocilova J (2009). Predicting the therapeutic response to cognitive behavioral therapy in patients with pharmacoresistant obsessive-compulsive disorder. Neuroendocrinol Lett. **30**(5): 615–23.

45 Ptacek R, Bob P, Paclt I, Pavlat J, Jasova D, Zvolsky P, Raboch J (2007). Psychobiology of dissociation and its clinical assessment. Neuro Endocrinol Lett. **28**(2): 191–98.

46 Raszka M, Prasko J, Koprivova J, Novak T, Adamcova K (2009). Psychological dissociation in obsessive-compulsive disorder is associated with anxiety level but not with severity of obsessive-compulsive symptoms. Neuroendocrinol Lett. **30**(5): 624–28.

47 Rechlin T (1995). The effects of psychopharmacological therapy on heart-rate variation. Nervenarzt. **66**(9): 678–85.

48 Santucci AK, Silk JS, Shaw DS, Gentzler A, Fox NA, Kovacs M (2008). Vagal tone and temperament as predictors of emotion regulation strategies in young children. Dev Psychobiol. **50**(3): 205–16.

49 Slaap BR, Boshuisen ML, van Roon AM, den Boer JA (2002). Heart rate variability as predictor of nonresponse to mirtazapine in panic disorder: a preliminary study. International Clinic Psychopharmacology. **17**(2): 69–74.

50 Slaap BR, Nielen MMA, Bohuisen ML, van Roon AM, den Boer JA (2004). Five-minute recording of heart rate variability in obsessive-compulsive disorder, panic disorder and healthy volunteers. J Affective Disorders. **78**(2): 141–48.

51 Straneva-Meuse PA, Light KC, Allen MT, Golding M, Girdler SS (2004). Bupropion and paroxetine differentially influence cardiovascular and neuroendocrine responses to stress in depressed patients. J Affect Disord. **79**: 51–61.

52 Task force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology (1996). Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation **93**: 1043–65.

53 Todder D, Bersudsky Y, Cohen H (2005). Nonlinear analysis of RR interval in euthymic bipolar disorder. Auton Neurosci. **117**(2): 127–31.

54 Tonhajzerova I, Ondrejka I, Javorka K, Turianikova Z, Farsky I, Javorka M (2010). Cardiac autonomic regulation is impaired in girls with major depression. Progress in Neuro-Psychopharmacology & Biological Psychiatry. **34**: 613–18

55 Tonhajzerova I, Ondrejka I, Javorka M, Adamik P, Turianikova Z, Kerna V, Javorka K, Calkovska A (2009). Respiratory sinus arrhythmia is reduced in adolescent major depressive disorder. Eur J Med Res. **14(**Suppl 4): 280–3.

56 van Zyl LT, Hasegawa T, Nagata K (2008). Effects of antidepressant treatment on heart rate variability in major depression: A quantitative review. BioPsychoSocial Medicine **2**: 12.

57 Virtanen R, Jula A, Salminen JK, Voipio-Pulkki LM, Helenius H, Kuusela T, Airaksinen J (2003). Anxiety and hostility are associated with reduced baroreflex sensitivity and increased beat-to-beat blood pressure variability. Psychosomatic medicine. **65**(5): 751–56.

58 Volkers AC, Tulen JH, van den Broek WW, Bruyn JA, Passchier J, Pepplinkhuizen L (2004). Effects of imipramine, fluvoxamine and depressive mood on autonomic cardiac functioning in major depressive disorder. Pharmacopsychiatry. **37**: 18–25.

59 Waller NG, Putnam FW, Carlson EB (1996). Types of dissociation and dissociative types: A taxonometric analysis of dissociative experiences. Psychological Methods. **1**(3): 300–21.

60 Yeragani VK, Pohl R, Berger R, Balon R, Ramesh C, Glitz D, Srinivasan K, Weinberg P (1993). Decreased heart rate variability in panic disorder patients: A study of power-spectral analysis of heart rate. Psychiatry Res. **46**: 89–103.

61 Yeragani VK, Srinivasan K, Balon R, Ramesh C, Berchou R (1994). Lactate sensitivity and cardiac cholinergic function in panic disorder. Am. J. Psychiatry. **151**: 1226–28.