Autonomic nervous system in euthymic patients with bipolar affective disorder

Klara Latalova [1,2], Jan Prasko [1,2], Tomas Diveky [1,2], Ales Grambal [1,2], Dana Kamaradova [1,2], Hana Velartova [1,2], Jiri Salinger [3], Jaroslav Opavsky [4]

1 Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic
2 Department of Psychiatry, University Hospital Olomouc, Czech Republic
3 Department of Biomechanics and Technical Cyberentics, Faculty of Physical Culture, Palacky University Olomouc, Czech Republic
4 Department of Physiotherapy, Faculty of Physical Culture, Palacky University Olomouc, Czech Republic

Correspondence to: Klara Latalova,
Faculty of Medicine and Dentistry,
Palacky University Olomouc, Czech Republic.
e-mail: klaralat@centrum.cz

Submitted: 2010-09-07 Accepted: 2010-11-01 Published online: 2010-12-29

Key words: **bipolar disorder; remission; controls, autonomic nervous system**

Neuroendocrinol Lett 2010; **31**(6):829–836 **PMID:** 21196931 NEL310610A19

Abstract

BACKGROUND: Autonomic nervous system (ANS) dysfunction and reduced heart rate variability (HRV) have been reported in a wide variety of psychiatric disorders, but have not been well characterized in bipolar patiens in remission. We recorded cardiac activity and assessed HRV in bipolar outpatients in remission.
AIMS: Ascertain if ANS decrease with the age of the patient; ascertain relation between activity of ANS and level of dissociation, and other components (age of patients, and age of disorder, dosage of psychotropic medication)
METHODS: Autonomic nervous system (ANS) has been evaluated during orthostatic change in three positions (1 – lie down 5 minutes, 2 – stand up 5 minutes, 3 – lie down 5 minutes). 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 (HRV) was assessed using time domain, frequency domain, and nonlinear analyses in 23 bipolar patients in remission.
RESULTS: We found highly statistically significant negative correlations between level of dissociation measured by DES (Dissociative Experience Scale) and most of 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.
CONCLUSIONS: Autonomic dysregulation is associated with bipolar disorder in remission and has relation to level of dissociation and probably to age of patiens and age of onset and duration of disorder.

INTRODUCTION

Autonomic nervous system (ANS) dysfunction and reduced heart rate variability (HRV) have been reported in a wide variety of psychiatric disorders (Blechert *et al.* 2007; Carney *et al.* 2005; Ito *et al.* 1999; Klein *et al.* 1995), but there are only few works which characterized ANS in bipolar disorder (Voss *et al.* 2006; Chen *et al.* 2006; Cohen 2003, Henry *et al.* 2010).

ORIGINAL ARTICLE

Correlations between electrodermal and heart rate indices of autonomic nervous system (ANS) activity and measures of state and trait anxiety were examined in 22 high-risk subjects, who had a parent with bipolar affective disorder, and in controls (Zahn *et al.* 1991). Relatively consistent and significant correlations between anxiety and ANS "arousal" at rest and under stress were found in high-risk subjects, but not in controls. Relationships between electrodermal laterality and anxiety, and between electrodermal activity and heart rate, were also observed only in the high-risk group. The data suggest a unique concordance between various manifestations of anxiety in high-risk persons which may effectively increase the salience of stressful events and the sensitization to stress.

Cohen *et al.* (2003) studied 39 euthymic bipolar patients and 39 controls, matched for age and sex. A high-resolution electrocardiogram was obtained during complete rest. Spectral analysis of R-R intervals was performed by the fast Fourier transform algorithm. Euthymic bipolar patients at rest were characterized by markedly low HRV, independent of specific drug treatments.

Todder *et al.* (2005) studied 32 euthymic bipolar patients and 24 controls. A high-resolution electrocardiogram was obtained during complete rest. There was no statistically significant difference in the nonlinear analysis of the heart rate variability, between the euthymic bipolar patients and controls, in the rest situation. Authors conclude that the nonlinear analysis of heart rate variability did not support the notion that there is a disturbance in the autonomic nervous system of bipolar patients in the euthymic state.

Gruber *et al.* (2008) used a multimethod approach to examine positive emotional disturbance by comparing participants at high and low risk for episodes of mania, which involves elevations in positive emotionality. Ninety participants were recruited into a high or low mania risk group according to responses on the Hypomanic Personality Scale. Participants' subjective, expressive, and physiological emotional responses were gathered while they watched two positive, two negative, and one neutral film clip. Results suggested that participants at high risk for mania reported elevated positive emotion and irritability and also exhibited elevated cardiac vagal tone across positive, negative, and neutral films.

Henry *et al.* (2009) recorded cardiac activity and assessed HRV in acutely hospitalized manic bipolar (BD) and schizophrenia (SCZ) patients compared to age- and gender-matched healthy comparison (HC) subjects. HRV was assessed using time domain, frequency domain, and nonlinear analyses in 23 manic BD, 14 SCZ, and 23 HC subjects during a 5min rest period. Psychiatric symptoms were assessed by administration of the Brief Psychiatric Rating Scale (BPRS) and the Young Mania Rating Scale (YMRS). Manic BD patients demonstrated a significant reduction in HRV, parasympathetic activity, and cardiac entropy compared to HC subjects, while SCZ patients demonstrated a similar, but non-significant, trend towards lower HRV and entropy. Reduction in parasympathetic tone was significantly correlated with higher YMRS scores and the unusual thought content subscale on the BPRS. Decreased entropy was associated with increased aggression and diminished personal hygiene on the YMRS scale.

HEART RATE VARIABILITY (HRV) MEASUREMENTS

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 (Berntson *et al.* 1997). Respiratory sinus arrhythmia (RSA) is the HRV in synchrony with respiration and represents the difference between the longest and the shortest heart period within the respiratory cycle (Berntson *et al.* 1997). 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 (Akselrod *et al.* 1981; Pomeranz *et al.* 1985; Ponikowski *et al.* 1997; Berntson *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, 0.05–0.15 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 (Akselrod *et al.* 1981; Pomeranz *et al.* 1985; Berntson *et al.* 1997). Hence, the ratio of LF power to HF power (LF/HF) is generally accepted as an index of cardiac sympathovagal balance (Pagani et al. 1986; Malliani *et al.* 1991; Task force of ESC and NAPE 1996). The VLF component of heart rate variability has been speculated to relate to function of the baroreflex, sensitivity in the chemoreflex, or renin–angiotensin system (Akselrod *et al.* 1981; Ponikowski *et al.* 1997; Berntson *et al.* 1997).

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, 1997). Moreover, a major proportion of HRV occurs over a large frequency span showing broad, noise-like, irregular variability (Kobayashi and 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 and Langhorst, 1998; Perlitz *et al.* 2004).

AIM OF THE STUDY

The aim of our study is to measure VLF, LF and HF components of R-R interval in patients with bipolar affective disorder in clinical remission and test the relation between these components and level of dissociation of the patient. We hypothesized that: (a) The amount of VLF, LF a HF decrease with the age of the patient; (b) The amount of VLF, LF and HF is negatively correlated with age of onset of bipolar disorder; (c) The amount of VLF, LF and HF is negatively correlated with the dosage of psychotropic medication; (d) The amount of VLF, LF and HF in bipolar patients in remission is negatively correlated with the level of dissociation measured by DES.

METHODS

Patients were recruited from the outpatients department of the Psychiatry department University hospital Olomouc. All patients had been hospitalized for bipolar disorder. The diagnosis of lifetime bipolar disorder was confirmed according to the patients´ documentation and clinical interview. The ICD research criteria for bipolar disorder (ICD-10 1996) in remission were checked by trained psychiatrists. Diagnosis was confirmed with M.I.N.I. (MINI-international neuropsychiatric interview; Lecrubier *et al.* 1997). At the time of evaluation all the patients were in clinical remission (Clinical Global Impression – Severity; CGI-S one or two). Psychiatric symptoms were assessed with the Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HAMD). 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, number of psychiatric hospital admissions, numbers of manic and depressive episodes, were obtained in the interview. Doses of drugs were converted to defined daily doses using data provided by the Czech State Institute for Drug Control (2010).

Autonomic nervous system (ANS) has been evaluated during orthostatic change in three positions (1 – lie down 5 minutes, 2 – stand up 5 minutes, 3 – lie down 5 minutes). 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 (FFT) in heart rate variability (HRV) (Javorka, 2008).

- The low frequency band – LF (0.04–0.15 Hz) represents the sympathetic activity. A relative increase can be found after physical activities or mental stress. This frequency band can be influenced also by the parasympathetic activity, by the tone of blood vessels 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 the parasympathical activity. Oscillations of the blood vessel tone and especially the rennin – angiotensin – aldosteron system are the major factors that have an impact on this frequency band.
- The high frequency band – HF (0.15–0.40) represents the parasympathetic activity and it is influenced by oscillation of the vagal activity.

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.

Statistical analysis

Demographic and baseline clinical characteristics were analyzed using column statistics. Normal distribution of the demographic and QoL variables was determined by the Shapiro-Wilk W test. Time changes within diagnostic groups (bipolar patients and healthy controls separately) were analyzed using repeated measures ANOVA. In case of nonparametric distribution of data, Friedman test with post test Dunn's multiple comparison test was used. Group differences between patients with bipolar disorder and healthy controls were analyzed using two-way ANOVA (to compare the changes in both groups in time) and pair t-tests (to compare differences between pairs of diagnostic groups). The χ^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. STATISTICA version 9.0 was used and the level of significance was set at 5%.

RESULTS

Demographic and clinical characteristics of the patients

Twenty three patients with bipolar disorder (52.2% females) in clinical remission between age 23 and 70 years (mean age 46.17 ± 14.11) were included into the study. The age at the disorder onset was 32.78 ± 8.09 years; duration of the disorder 13.52 ± 9.15 years; number of previous manic episodes 2.61 ± 2.15; depressive episodes 2.65 ± 1.82, and the number of hospitalization was 2.65 ± 2.85 (Table 1). The mean duration of the current remission was 1.48 ± 2.57 years. All patients used psychotropic medication, mood stabilizers (n=21; mean defined daily dosage of mood stabilizers was 0.91 ± 0.45 of daily equivalent); antipsychotics (n=17; mean defined daily dosage of antipsychotics was 1.01 ± 0.56 of daily equivalent); antidepressants (n=10; mean defined daily dosage of antidepressant was 1.33 ± 0.56 of daily equivalent); and some patients also used benzodiazepines (n=8; mean defined daily dosage of benzodiazepines was 0.91 ± 0.53 of daily equivalent).

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

Age	46.17 ± 14.11
Sex	
Male	11
Female	12
Education	
Basic	7
Secondary - without graduation	3
Secondary - with graduation	8
University	5
Marital status	
Single	8
Married	12
Unmarried living with partner	0
Divorced	3
Widower	0
Employment	
Yes	10
No	13
Age of the disorder onset	32.78 ± 8.09
Length of the disorder	13.52 ± 9.15
Number of manias	2.61 ± 2.15
Number of depressions	2.65 ± 1.82
Number of hospitalizations	2.65 ± 2.85
Length of the clinical remission	1.48 ± 2.57
Number of suicidal attempts (n=10)	0.57 ± 0.73
+Thymostabilisers index (n=21)	0.91 ± 0.45
+Antipsychotics index (n=17)	1.01 ± 0.56
+Antidepressants index (n=10)	1.33 ± 0.56
+Benzodiazepine index (n=8)	0.91 ± 0.53
HAMD	3.17 ± 1.70
YMRS	1.13 ± 1.42
DES	13.25 ± 9.23
Pathological DES	1.71 + 2.82

HAMD=Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; DES=Dissociative Experience Scale

Data describing the activity of autonomic nervous system

The activity of ANS fluctuated between each measurement (I1-lie down; I2-stand up; I3-lie down) in all three components (VLF, LF and HF) with typical decrease in the second position in all components (Table 2). There were no statistically significant differences in measurements between the three positions in VLF and LF, but there were highly significant differences between the three positions in HF (Friedman test: FS=18.87, $p<0.0001$; Dunn's multiple comparison test: HF|1 vs HF|2: $p<0.001$; HF|2 vs HF|3: $p<0.001$) (Figure 1).

Relation between demographic and clinical data, and autonomic nervous system

We found negative correlations between the age of the patient and HF|2 and HF|3 and age of disorder onset and VLF|3 and HF|3 (Table 3). One can interpret these findings to mean that the activity of parasympathetic nervous system could decrease during the lifetime course and that the people with an earlier onset of the disorder have lower activity of sympathetic and parasympathetic nervous system which is seen mostly in orthostatic change between position |2 (stand up) and |3 (lie down). There were no correlations between duration of the disorder, number of maniacs episodes, depressive episodes, hospitalizations, dosages of mood stabilizers, antipsychotics and antidepressants and measured parameters of ANS. But there were statistically significant correlations between dosage of benzodiazepines and VLF|1 and HF|1 which reflects sympathetic and parasympathetic activity in first position |1 (lie down) before the orthostatic experiment.

Relation between dissociation and autonomic nervous system

There were highly statistically significant negative correlations between level of dissociation measured by DES and most of parameters of ANS: VLF|1,2,3; LF|1,3 and

Tab. 2. Vegetative system measurements in bipolar patients in remission.

	VLFI1	VLFI2	VLFI3	LFI1	LFI2	LFI3	HFI1	HFI2	HFI3
Mean	212.5	132.6	196.9	313.7	260.8	350.6	313.5	59.0	256.1
Standard deviation	± 315.7	± 156.0	± 222.0	± 561.8	± 373.5	± 719.7	± 361.8	± 67.5	± 297.7

Tab. 3. Correlation of demographic and clinical characteristics and parameters of ANS in bipolar patients in remission.

		VLF|1	VLF|2	VLF|3	LF|1	LF|2	LF|3	HF|1	HF|2	HF|3
Age	r	−0.12^{P}	0.06^{P}	−0.32^{P}	−0.31^{S}	−0.23^{P}	−0.36^{S}	−0.40^{P}	−0.43^{P}	−0.47^{S}
	p	ns	ns	ns	ns	ns	ns	ns	*p*<0.05	*p*<0.05
Age of disorder onset	r	−0.14^{P}	0.03^{P}	−0.45^{P}	−0.26^{S}	−0.10^{P}	−0.30^{S}	−0.38^{P}	−0.37^{P}	−0.43^{S}
	p	ns	ns	*p*<0.05	ns	ns	ns	ns	ns	*p*<0.05
Mood stabilizer index	r	−0.30^{P}	−0.35^{P}	−0.21^{P}	−0.35^{S}	−0.01^{P}	−0.37^{S}	−0.19^{P}	−0.22^{P}	−0.20^{S}
	p	ns	ns	ns	ns	ns	ns	ns	ns	ns
Antipsychotic index	r	0.01^{P}	−0.28^{P}	0.23^{P}	0.26^{S}	0.25^{P}	−0.04^{S}	0.13^{P}	0.20^{P}	0.11^{S}
	p	ns	ns	ns	ns	ns	ns	ns	ns	ns
Antidepressant index	r	−0.01^{P}	−0.26^{P}	−0.33^{P}	−0.25^{S}	−0.56^{P}	−0.11^{S}	0.23^{P}	−0.12^{P}	0.17^{S}
	p	ns	ns	ns	ns	ns	ns	ns	ns	ns
Benzodiazepine index	r	0.77^{P}	0.68^{P}	0.06^{P}	0.20^{S}	−0.21^{P}	0.51^{S}	0.82^{P}	0.33^{P}	0.63^{S}
	p	*p*<0.05	ns	ns	ns	ns	ns	*p*<0.05	ns	ns

P=Pearson r; S=Spearman r; ns=no significant

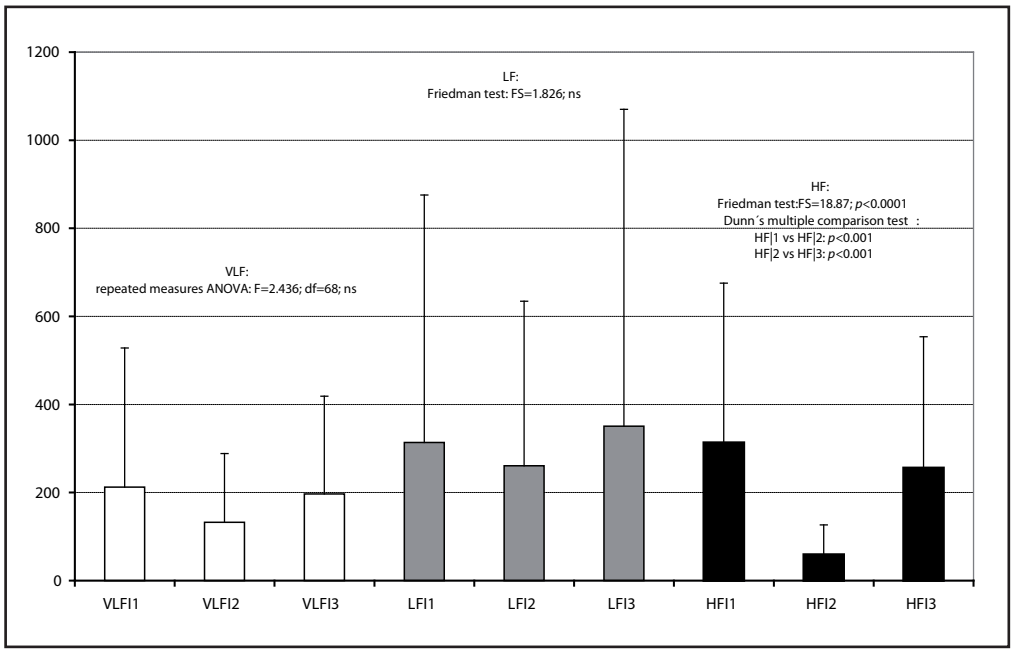

Fig. 1. Time changes of high-frequency (HF), low-frequency (LF), and very low-frequency (VLF) components during orthostatic experiment.
VLF = very low frequency band (0.0033–0.04 Hz); LF = low frequency band (0.04 – 0.15 Hz); HF= high frequency band (0.15–0.40 Hz)
Measured conditions: |1= lie down 5 minutes; |2= stand up 5 minutes; |3= lie down 5 minutes

HF|1,3 (Table 4). Also there were highly statistically significant negative correlations between pathological DES and LF|1 and LF|3.

When we summed the spectral power for low and very low frequency band (0.0033–0.15 Hz) in all positions (VLF|1+ VLF|2+ VLF|3+ LF|1+ LF|2+ LF|3) which can reflect mainly sympathetic activity during orthostatic experiment and correlated it with DES, the negative correlation was statistically significant (Pearson´s r=−0.5441; $p<0.01$). Also the correlation with the high frequency band (0.15–0.40), which can reflect mainly parasympathetic activity during the experiment, is statistically significant (Pearson´s r=−0.5278; $p<0.01$). The linear regression of DES with the sum of VLF and LF, and linear regression of DES with sum of HF is on Figure 2.

DISCUSSION

Our hypotheses were mostly confirmed. There were significant negative correlations between age and HF|2 and HF|3. These findings can be interpreted to

Tab. 4. Correlation of DES and parameters of ANS in bipolar patients in remission.

		VLF|1	VLF|2	VLF|3	LF|1	LF|2	LF|3	HF|1	HF|2	HF|3
DES	r	−0.60^{P}	−0.46^{P}	−0.57^{P}	−0.72^{S}	−0.21^{P}	−0.75^{S}	−0.54^{P}	−0.26^{P}	−0.54^{S}
	p	*p*<0.005	*p*<0.05	*p*<0.005	*p*<0.0001	ns	*p*<0.0001	*p*<0.01	ns	*p*<0.01
Pathological DES	r	−0.31^{P}	−0.26^{P}	−0.30^{P}	−0.72^{S}	−0.34^{P}	−0.53^{S}	−0.38^{P}	−0.29^{P}	−0.29^{S}
	p	ns	ns	ns	*p*<0.0001	ns	*p*<0.01	ns	ns	ns

P=Pearson r; S=Spearman r; ns=no significant

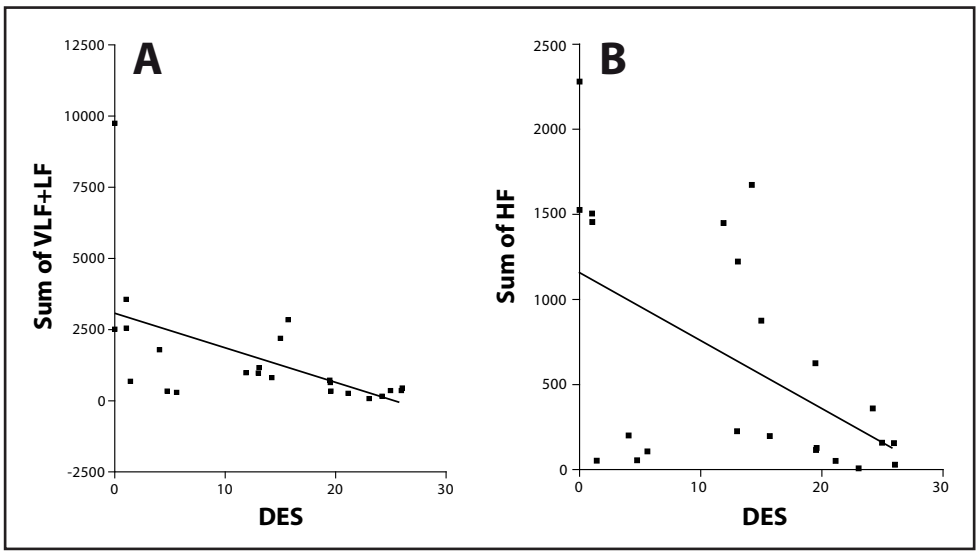

Fig. 2. Linear regression of DES to sum of VLF and LF (low and very low frequency band) and DES to sum of HF (high frequency band). **A:** Linear regression: Sum VLF+LF to DES: F=8.831, DFn, DFd = 1.000, 21.00; *p*<0.01. **B:** Linear regression: Sum HF to DES: F=8.109; DFn,DFd=1.000, 21; *p*<0.01

mean that the activity of the parasympathetic nervous system could decrease during the lifetime course in our patients. But this could also be true for healthy people (Yeragani *et al.* 1997). The ability of the system to react to stress and return to the beginning state changes during life. Surprisingly, we did not find a decrease of the VLF and LF (reflecting mostly sympathetic activity) with age. But 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 activity of VLF|3 and HF|3 were negatively correlated with the age of onset. 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 lying down after standing, show a decreased ability to calm down the ANS, which can be factor in a higher vulnerability to distress. 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.

The third hypothesis that the activity of VLF, LF and HF is negatively correlated with the dosage of psychotropic medication was not confirmed. There were no statistically significant negative correlations between dosages of mood stabilizers, antipsychotics, antidepressants or benzodiazepines in our group of patients. To the contrary, there were positive correlation between dosages of benzodiazepines and VLF|1 and HF|1. But we must take into consideration that the number of patients in any type of medication is limited and not enough to allow generalization.

The last but most important hypothesis was that the activity of VLF, LF and HF in bipolar patients in remission 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 disor-

ders 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). 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, b), OCD (Prasko *et al.* 2009; 2010, 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 (Cohen *et al.* 2003; Todder *et al.* 2005; Gruber *et al.* 2008; Henry *et al.* 2009), and substantial evidence for higher incidents of heart disease in affective and anxiety disorders (Zellweger *et al.* 2004; Esler *et al.* 2008). But there has not been any information about connection between dissociation and autonomic nervous system activity. In out study, there were highly significant negative correlations between the level of dissociation and most of the parameters of ANS. It seems that higher level of dissociation is related to a lower level of ANS activity in all frequency bands. These findings have several interpretations. One possibility, which is not easy to discount, it that both DES and decreased autonomic activity is the result of pharmacotherapy. All patients used psychotropics and it is ethically problematic to have patients with bipolar disorder in remission without prophylactic pharmacotherapy. Both decreased autonomic activity and dissociation could be also the results of another third process, like the bipolar disorder itself. Only studies of drug naive bipolar patients could confirm or disconfirm this speculation. The studies of ANS in manic, depressed and euthymic patients show the same patterns of autonomic activity which could be interpreted to mean that mood fluctuations in bipolar disorder have no differential impact on autonomic functions (Cohen *et al.* 2003; Todder *et al.* 2005; Henry *et al.* 2009). Other possibilities are that dissociation as a psychological process leads to decreased autonomic activity or, the opposite, that decreased autonomic activity leads to dissociation. These possibilities are hard to support without future experiments.

Our study has substantial limitations that should be considered. The most important limitation is the small number of patients. Our sample may not be representative of the population of bipolar patients in remission. 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.

Prospective studies of cardiovascular changes in mania and depression 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 bipolar disorder.

ACKNOWLEDGEMENT

Supported by the NT11047 IGA MZ ČR

REFERENCES

1 Agelink MW, Klimke A. Cordes J, Sanner D, Kavuk I, Malessa R, Klieser E, Baumann B (2004). A functional-structural model to understand cardiac autonomic nervous system (ANS) dysregulation in affective illness and to elucidate the ANS effects of antidepressive treatment. Eur J Med Res. **9**(1): 37–50.

2 Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ (1981). Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. Science. **213**: 220–222.

3 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**: 1773–1779.

4 Beauchaine T (2001). Vagal tone, development, and Gray's motivational theory: toward an integrated model of autonomic nervous system functioning in psychopathology. Dev Psychopathol. Spring. **13**(2): 183–214.

5 Berntson GG, Bigger JT Jr, Eckberg DL *et al.* (1997). Heart rate variability: Origin, methods, and interpretive caveats. Psychophysiology. **34**: 623–648.

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**: 623–648.

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): 935–943.

8 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.

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

10 Cohen H, Kaplan Z, Kotler M, Mittelman I, Osher Y, Bersudsky Y (2003). Impaired heart rate variability in euthymic bipolar patients. Bipolar Disord. **5**(2): 138–143.

11 Czech State Institute for Drug Control. List of covered drugs and foods for special medical purposes. Online: <http: //www.sukl.cz/file/2631/>.

12 Eckberg DL (1997). Sympathovagal balance: a critical appraisal. Circulation. **96**: 3224–3232.

13 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**: 338–348.

14 Grasso R, Schena F, Gulli G, Cevese A (1997). Does low-frequency variability of heart period reflect a specific parasympathetic mechanism? J Auton Nerv Syst. **63**: 30–38.;

15 Gruber J, Harvey AG, Johnson SL (2009). Reflective and ruminative processing of positive emotional memories in bipolar disorder and healthy controls. Behav Res Ther. **47**(8): 697–704.

16 Gruber J, Johnson SL, Oveis C, Keltner D (2008). Risk for mania and positive emotional responding: too much of a good thing? Emotion. **8**(1): 23–33.

17 Henry BL, Minassian A, Paulus MP, Geyer MA, Perry W (2010). Heart rate variability in bipolar mania and schizophrenia. J Psychiatr Res. **44**(3): 168–176.
18 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**: 427–436.
19 Chen CH, Lennox B, Jacob R, Calder A, Lupson V, Bisbrown-Chippendale R, Suckling J, Bullmore E (2006). Explicit and implicit facial affect recognition in manic and depressed States of bipolar disorder: a functional magnetic resonance imaging study. Biol Psychiatry. **59**(1): 31–39.
20 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 Clin Neurosci. **53**: 667–672
21 Javorka KI (2008). Heart Rate Variability. Mechanisms, classification, clinical utilization. Osveta, Martin.
22 Klein E, Cnaani E, Harel T, Braun S, and Ben-Haim SA (1995). Altered Heart Rate Variability in Panic Disorder Patients. Biol Psychiatry. **37**: 18–24.
23 Kobayashi M, Musha T (1982). 1/f fluctuation of heartbeat period. IEEE Trans Biomed Eng. **29**: 456–457.
24 Köbele R, Koschke M, Schulz S, Wagner G, Yeragani S, Ramachandraiah CT, Voss A, Yeragani VK, Bär KJ (2010). The influence of negative mood on heart rate complexity measures and baroreflex sensitivity in healthy subjects. Indian J Psychiatry. **52**(1): 42–47.
25 Lambertz M, Langhorst P (1998). Simultaneous changes of rhythmic organization in brainstem neurons, respiration, cardiovascular system and EEG between 0.05 Hz and 0.5 Hz. J Auton Nerv Syst. **68**: 58–77.
26 Lecrubier Y, Sheehan DV, Weiller E, *et al.* (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**: 224–231.
27 Malliani A, Pagani M, Lombardi F, Cerutti S (1991). Cardiovascular neural regulation explored in the frequency domain. Circulation. **84**: 482–492.
28 Oosterman M, De Schipper JC, Fisher P, Dozier M, Schuengel C (2010). Autonomic reactivity in relation to attachment and early adversity among foster children. Dev Psychopathol. Winter. **22**(1): 109–18.
29 Pagani M, Lombardi F, Guzzetti S *et al.* (1986). Power spectral density of heart rate and arterial pressure variability as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res. **59**: 178–193.
30 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**: 1441–1448.
31 Pastucha P, Praško J, Diveky T, Grambal A, Latalova K, Sigmundová Z, Ticháčkova A (2009c). Borderline personality disorder and dissociation – comparison with healthy controls. ANSR. **51**(3–4): 146–149.
32 Pastucha P, Praško J, Grambal A, Látalová K, Sigmundová Z, Ticháčková A (2009a). Panic disorder and dissociation – comparison with healthy controls. Neuro Endocrinol Lett. **30**(6): 774–778.
33 Pastucha P, Praško J, Grambal A, Látalová K, Sigmundová Z, Ticháčková A (2009b). Dissociative disorder and dissociation – comparison with healthy controls. Neuro Endocrinol Lett. **30**(6): 769–773.
34 Perlitz V, Lambertz M, Cotuk B, Grebe R, Vandenhouten R, Flatten G, Petzold ER, Schmid-Schönbein H, Langhorst P (2004). Cardiovascular rhythms in the 0.15 Hz band: common origin of identical phenomena in man and dog in the reticular formation of the brain stem? Pflügers Arch. **448**: 579–591.
35 Pomeranz B, MaCauly RJB, Caudill MA *et al.* (1985). Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol. **248**: H151–153.
36 Ponikowski P, Chua TP, Piepoli M *et al.* (1997). Chemoreceptor dependence of very low frequency rhythms in advanced chronic heart failure. Am J Physiol. **272**: H438–447.
37 Prasko J, Raszka M, Diveky T, Grambal A, Kamaradova D, Koprivova J, Latalova K, Pastucha P, Sigmundova Z (2010). Obsessive compulsive disorder and dissociation – comparison with healthy controls. Biomed Pap Med Fac Univ Palacky Olomouc. **154**: 179–183.
38 Praško J, Raszka M, Adamcová K, Grambal A, Kopřivová J, Kudrnovská H, Látalová K, Vyskočilová J (2009). Predicting the therapeutic response to cognitive behavioral therapy in patients with pharmacoresistant obsessive-compulsive disorder. Neuro Endocrinol Letters. **30**(5): 615–623.
39 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. Neuro Endocrinol Letters. **30**(5): 624–628.
40 Salinger J, Gwozdziewicz M (2008). Systémy používané pro vyšetření krátkodobé variability srdeční frekvence. In Javorka, K. *et al.*: Variabilita frekcencie srdca. Martin, Osveta
41 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): 205–216.
42 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**: 1043–1065.
43 Todder D, Bersudsky Y, Cohen H (2005). Nonlinear analysis of RR interval in euthymic bipolar disorder. Auton Neurosci. **117**(2): 127–131.
44 Voss A, Baier V, Schulz S, Bar KJ (2006). Linear and nonlinear methods for analyses of cardiovascular variability in bipolar disorders. Bipolar Disord. **8**(5 Pt 1): 441–452.
45 Yeragani VK, Sobolewski E, Kay J, Jampala VC, Igel G (1997). Effect of age on long-term heart rate variability. Cardiovasc Res. **35**: 35–42.
46 Zahn TP, Nurnberger JI Jr, Berrettini WH, Robinson TN Jr (1991). Concordance between anxiety and autonomic nervous system activity in subjects at genetic risk for affective disorder. Psychiatry Res. **36**(1): 99–110.
47 Zellweger MJ, Osterwalder RH, Langewitz W, Pfisterer ME (2004). Coronary artery disease and depression. Eur Heart J. **25**: 3–9.