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

Jan Prasko 1,2, Klara Latalova 1,2, Tomas Dively 1,2, Ales Grambal 1,2, Dana Kamaradova 1,2, Hana Velartova 1,2, Jiri Salinger 3, Jaroslav Opavsky 4, Petr Silhan 1,5

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 Cybernetics, Faculty of Physical Culture, Palacky University Olomouc, Czech Republic
4 Department of Physiotherapy, Faculty of Physical Culture, Palacky University Olomouc, Czech Republic
5 Department of Psychiatry, University Hospital Ostrava, Czech Republic

Correspondence to: Prof. Jan Prasko, MD., PhD.
Department of Psychiatry, Faculty of Medicine and Dentistry, Palacky University Olomouc, University Hospital Olomouc
I.P. Pavlova 6, 775 20 Olomouc, Czech Republic
TELE: +420 588 443 5030; E-MAIL: prasko@fnol.cz

Submitted: 2011-08-05 Accepted: 2011-08-28 Published online: 2011-11-12

Key words: heart rate variability (HRV); panic disorder; power spectral analysis; autonomous nervous system; very low frequency band (VLF); low frequency band (LF); high frequency band (HF)

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 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.

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

To cite this article: Neuroendocrinology Letters 2011; 32(5):641–651
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/HP) 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 panicers”) had a significant enhancement of the HF power, and a lower sympathovagal ratio (LF/HF) during lactate infusions compared with non-panicers. 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. McCratty *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 PCO₂ 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 20mg = citalopram 20 mg or fluoxetine 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

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

<table>
<thead>
<tr>
<th></th>
<th>CGI-S-1</th>
<th>CGI-S-2</th>
<th>BAI-1</th>
<th>BAI-2</th>
<th>BDI-1</th>
<th>BDI-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2.75</td>
<td>1.563</td>
<td>29.94</td>
<td>22.06</td>
<td>21.13</td>
<td>16.19</td>
</tr>
<tr>
<td>SD</td>
<td>1.183</td>
<td>1.365</td>
<td>13.35</td>
<td>15.72</td>
<td>11.41</td>
<td>10.19</td>
</tr>
<tr>
<td>pair t-test:</td>
<td>t=6.855; df=15; p&lt;0.0001</td>
<td>t=3.516; df=15; p&lt;0.005</td>
<td>t=2.209; df=15; p&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th></th>
<th>VLF 1</th>
<th>VLF 2</th>
<th>VLF 3</th>
<th>LF 1</th>
<th>LF 2</th>
<th>LF 3</th>
<th>HF 1</th>
<th>HF 2</th>
<th>HF 3</th>
<th>LF/HF 1</th>
<th>LF/HF 2</th>
<th>LF/HF 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>577.4</td>
<td>798.6</td>
<td>1032</td>
<td>1108</td>
<td>1650</td>
<td>1357</td>
<td>1131</td>
<td>1519</td>
<td>1769</td>
<td>1.283</td>
<td>1.043</td>
<td>0.9788</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>± 1354</td>
<td>± 1331</td>
<td>± 1871</td>
<td>± 3360</td>
<td>± 2684</td>
<td>± 1817</td>
<td>± 3135</td>
<td>± 2092</td>
<td>± 2646</td>
<td>± 0.7253</td>
<td>± 0.5988</td>
<td>± 0.6304</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>172.4</td>
<td>95.59</td>
<td>114.2</td>
<td>293</td>
<td>294.8</td>
<td>301.2</td>
<td>235.2</td>
<td>96.3</td>
<td>432.1</td>
<td>1.591</td>
<td>4.147</td>
<td>1.027</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>± 152.2</td>
<td>± 82.68</td>
<td>± 83.24</td>
<td>± 367.2</td>
<td>± 314</td>
<td>± 288</td>
<td>± 205</td>
<td>± 83.39</td>
<td>± 523</td>
<td>± 1.546</td>
<td>± 4.229</td>
<td>± 0.7143</td>
</tr>
</tbody>
</table>

Mann Whitney test:

<table>
<thead>
<tr>
<th></th>
<th>Mann Whitney U</th>
<th>162</th>
<th>94</th>
<th>165</th>
<th>167</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>n.s.</td>
<td>p&lt;0.05</td>
<td>n.s.</td>
<td>n.s.</td>
<td></td>
</tr>
</tbody>
</table>

Unpair t-test:

<table>
<thead>
<tr>
<th></th>
<th>t, df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLF 1</td>
<td>t=2.299, df=35</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>VLF 2</td>
<td>t=2.186, df=35</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>VLF 3</td>
<td>t=2.212, df=35</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>LF 1</td>
<td>t=2.964, df=35</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td>LF 2</td>
<td>t=2.160, df=35</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td>LF 3</td>
<td>t=0.7684, df=35</td>
<td>n.s.</td>
</tr>
<tr>
<td>HF 1</td>
<td>t=3.082, df=35</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td>HF 2</td>
<td>t=0.2184, df=35</td>
<td>n.s.</td>
</tr>
<tr>
<td>LF/HF 1</td>
<td>t=3.082, df=35</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td>LF/HF 2</td>
<td>t=0.2184, df=35</td>
<td>n.s.</td>
</tr>
<tr>
<td>LF/HF 3</td>
<td>t=0.2184, df=35</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
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 significant correlations of the age and other power spectra components of HRV.

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

<table>
<thead>
<tr>
<th></th>
<th>VLF 1</th>
<th>VLF 2</th>
<th>VLF 3</th>
<th>LF 1</th>
<th>LF 2</th>
<th>LF 3</th>
<th>HF 1</th>
<th>HF 2</th>
<th>HF 3</th>
<th>LF/HF 1</th>
<th>LF/HF 2</th>
<th>LF/HF 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>172.4</td>
<td>95.59</td>
<td>114.2</td>
<td>293</td>
<td>294.8</td>
<td>301</td>
<td>235.2</td>
<td>96.3</td>
<td>432.1</td>
<td>1.591</td>
<td>4.147</td>
<td>1.027</td>
</tr>
<tr>
<td>standard deviation</td>
<td>± 152.2</td>
<td>± 82.68</td>
<td>± 83.24</td>
<td>± 367.2</td>
<td>± 314</td>
<td>± 288</td>
<td>± 205</td>
<td>± 83.39</td>
<td>± 523</td>
<td>± 1.546</td>
<td>± 4.229</td>
<td>± 0.7143</td>
</tr>
<tr>
<td>After</td>
<td>174.1</td>
<td>234.9</td>
<td>220.7</td>
<td>645.9</td>
<td>520.6</td>
<td>399</td>
<td>826.4</td>
<td>298</td>
<td>1100</td>
<td>1.642</td>
<td>4.245</td>
<td>1.953</td>
</tr>
<tr>
<td>standard deviation</td>
<td>± 261.6</td>
<td>± 308.6</td>
<td>± 361.3</td>
<td>± 1495</td>
<td>± 774.5</td>
<td>± 500.7</td>
<td>± 1215</td>
<td>± 553.3</td>
<td>± 2038</td>
<td>± 2.207</td>
<td>± 3.74</td>
<td>± 2.579</td>
</tr>
</tbody>
</table>

**Wilcoxon signed rank test:**

<table>
<thead>
<tr>
<th>Sum of signed ranks (W)</th>
<th>26</th>
<th>2</th>
<th>–42</th>
<th>–38</th>
<th>–42</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

**Pair t-test:**

<table>
<thead>
<tr>
<th>t, df</th>
<th>t=1.900</th>
<th>t=1.992</th>
<th>t=0.7787</th>
<th>t=2.216</th>
<th>t=0.1673</th>
<th>t=0.086</th>
<th>t=1.757</th>
</tr>
</thead>
<tbody>
<tr>
<td>df=18</td>
<td>df=18</td>
<td>df=18</td>
<td>df=18</td>
<td>df=18</td>
<td>df=18</td>
<td>df=18</td>
<td>df=18</td>
</tr>
<tr>
<td>p-value</td>
<td>p&lt;0.05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p&lt;0.05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

**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.
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.

**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 sympathetic 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 measurement 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 benzodiazepinism 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 negatively correlated with the level of dissociation measured by DES. This hypothesis reflects the old view that people who repress or dissociate their primary emotions frequently suffer from mood disorders and with the findings, that people with mood and anxiety disorders have higher incidences 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; Yeraganti 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 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 (Leerbogen 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 assess 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.

ACKNOWLEDGEMENT

Supported by the IGA MZ CR NS 10301-3/2009.

REFERENCES


Jan Prasko, Klara Latalova, Tomas Diveky, Ales Grambal, Dana Kamaradova, Hana Velartova, Jiri Salinger, Jaroslav Opavsky, Petr Silhan


