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COMPARISON OF HEART RATE VARIABILITY IN PATIENTS WITH PANIC DISORDER DURING COGNITIVE BEHAVIORAL THERAPY PROGRAM

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SUMMARY

Background: *Many authors suggest that there is low reactivity of autonomic nervous system and reduced heart rate variability in patients with panic disorder. The patients are therefore exposed to increased cardiac mortality. Power spectral analysis is a successful tool in detecting autonomic instabilities in many disorders.*

Subjects and methods: *The aim of our study is to monitor the activity of the autonomic nervous system through heart rate variability measured in the beginning and end of a therapeutic cognitive behavioral therapy (CBT) program in patients with panic disorder. We measured 31 patients with panic disorder in the beginning (1st measurement) and end of a therapeutic CBT program (2nd measurement). The autonomic nervous system (ANS) has been evaluated in three positions (supine – standing – supine). The evaluated parameters of the HRV linear analysis were: RR interval, HF, LF, VLF band and VLF + LF / HF ratio.*

Results: *Spectral activity in the very low frequency band was significantly higher in the 2nd measurement compared to the 1st measurement in the standing position. The ratio of the spectral activity at lower frequencies (VLF+LF) to high frequency (HF) was significantly lower in the supine position.*

Conclusion: *This study demonstrated an improvement of neurocardiac control regulation after a therapeutic CBT program in patients suffering from panic disorder.*

Key words: *autonomic nervous system - sympathicus - parasympathicus - heart rate variability - power spectral analysis - cognitive behavioral therapy*

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INTRODUCTION

The prevalence of panic disorder is 4.1% to 8.8% (Bandelow 2003). Panic disorder is a serious disorder that can influence common daily wellbeing in the patients suffering from this disorder. It is characterized by unexpected panic attacks, which are not exactly bounded to a specific situation. There are specific physiological and psychological symptoms characterrizing the panic disorder and the physiological symptoms are often associated with autonomic activation controlled by autonomic activation - hyperventilation, palpitations, 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. The most useful treatment approach in treating panic disorder is combination of pharmacotherapy and psychotherapy – especially cognitive behavioral psychotherapy – CBT (Prasko et al. 2004).

Many authors suggest that there is an autonomic dysfunction and reduced heart rate variability in patients with panic disorder (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 a higher baseline heart rate and periods of tachycardia which coincide with panic symptoms (Freedman et al. 1985, Liebowitz et al. 1985). The autonomic imbalance could be an important pathophysiological mechanism leading to increased cardiac mortality and morbidity in panic disorder (Katerndahl 2008).

Respiration has a strong influence on HR changes and is commonly included as a covariate in statistical analysis of the relationship between stress and HRV changes (Berntson et al. 1997). Respiratory sinus arrhythmia (RSA) is one of the basic mechanisms participating in 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).

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 on the sinoatrial node exhibit alterations in HR and cause oscillations of the R–R interval around its mean value (HRV). Increasingly refined calculations have been developed to measure HRV.

The most used method to quantify heart rate variability oscillations is linear - spectral analysis. This conventional method is known to be a particularly successful tool in the detection of autonomic instabilities in various clinical disorders (Berntson et al. 1997).

The spectral analysis can provide information about physiological mechanisms influencing three frequency bands - high frequency (HF), low frequency (LF) and very low frequency (VLF). The most important problem is how to interpret these frequency bands according to the function of branches of the autonomic nervous system – sympathicus and parasympathicus. There are clear suggestions that the HF represents parasympathethic activity (Task Force, 1996), but we must be cautious in the interpretation of the LF and VLF frequencies. Some authors (Malliani et al. 1994, Pagani et al. 2009) suggested that the LF represents the activity of sympathicus, but actual research shows, that this is not so clear. Other authors suggest, that the LF band represents both sympathicus and parasympathicus activity (Moak et al. 2009, Goldstein et al. 2011), especially because of the baroreflex activity, but there are other factors that influence LF – central oscillator, vasomotor noise etc. The physiological interpretation of the VLF frequency is also ambiguous. It is hypothesized to be under the influence of thermoregulation, peripheral vasomotoric tone and the rennin – angiotenzine – aldosterone system.

There are many studies that reflect heart rate variability in patients with psychiatric disorders (Yeragani et al. 1994, Klein et al. 1995, Slaap et al. 2002, Tonhajzerova et al. 2009, Prasko et al. 2011, Latalova et al. 2011). These studies indicated the reduced heart rate variability in patients with mental disorders, especially with panic disorders.

The aim was to study the effect of 6-weeks of cognitive behavioral therapy on cardiac autonomic control using short-term heart rate variability spectral analysis in adult patients suffering from panic disorder.

SUBJECTS AND METHODS

Evaluation of psychopathological symptoms

After study enrolment, patients were assessed during the first two days of hospitalization. Inclusion criteria were: (a) precisely defined diagnosis of panic disorder according to ICD-10; (b) Non-responders on SSRIs (at least 6 weeks treatment before the screening into the study; (c) Age 18-60 years;

Excluding criteria were: (a) Comorbid psychiatric diagnoses (e.g. major depression); (b) High risk of suicidality; (c) Organic psychiatric disorder; (d) Psychotic disorder in history; (e) Abuse 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 using M.I.N.I. (MINI-international neuropsychiatric interview; Lecrubier et al. 1997). The severity of the disorder was assessed using the 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, 1993). The measurements were done in three changing positions (supine – standing – supine) in an interval of 5 min. change.

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.

Data recording and analysis

The HRV measurement was done with microcomputer HRV system VarCor PF 7 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 (HF, LF, VLF) exhibited skewness, we used natural logarithmic transformation to adjust this skewness. This was also recommended for appropriate statistical analysis using parametric tests (Kuo et al. 1999).

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 unpaired 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).

RESULTS

Demographic data

31 subjects (74.2% females) were recruited from the inpatients department of the Psychiatry Department University Hospital Olomouc. All patients had been hospitalized for panic disorder. The diagnosis was confirmed after detailed examination by a specialist. The mean age of the patients was 39.45±10.32 years. The age at the disorder onset was 32.71±11.48 years; the duration of the disorder was 6.74±7.14 years. All patients used psychotropic medication. This included antidepressants (n=26; mean defined daily dosage of antidepressant was 23.27±8.825 mg of daily paroxetine equivalent); and some patients also used antipsychotics (n=10, mean defined daily dosage of antipsychotics was 1.87±1.984 mg of daily haloperidol equivalent) and benzodiazepines (n=20; mean defined daily dosage of benzodiazepines was 11.5±6.708 mg of daily diazepam equivalent) (Table 1). Doses of drugs were converted to defined daily doses using data provided by the Czech State Institute of Drug Control (SÚKL 2010).

HRV measures

There were no correlations between age of the patient and the parameters of the autonomic nervous system.

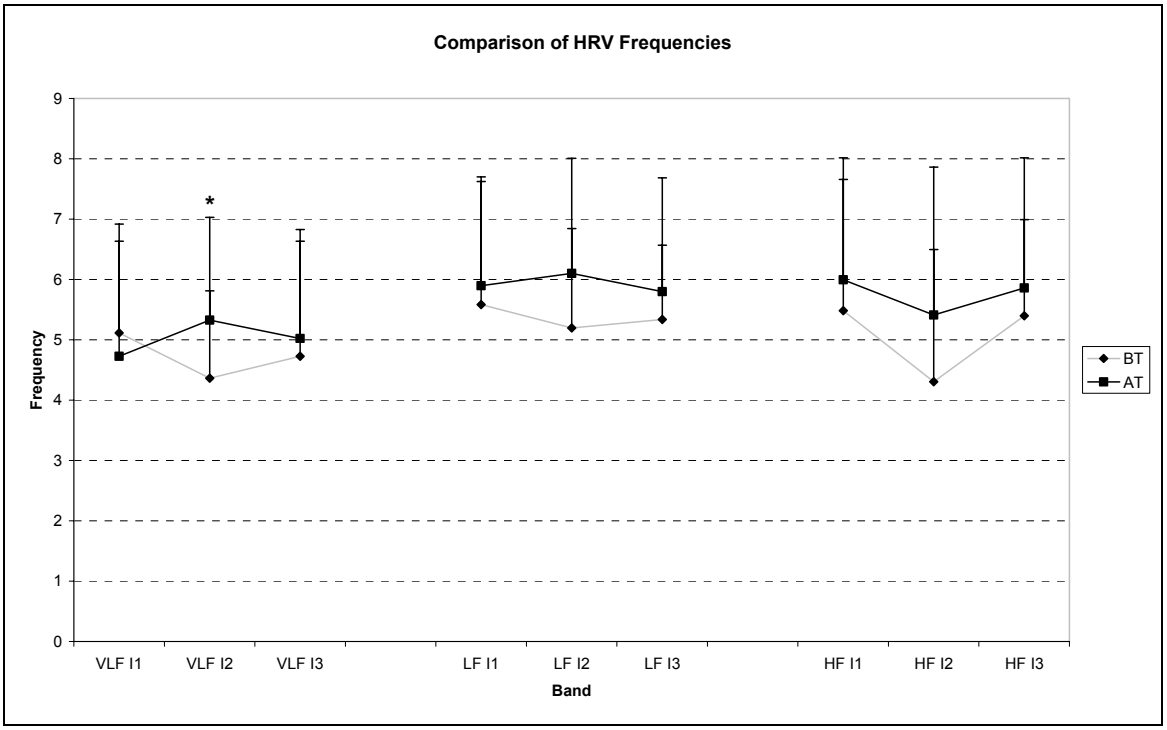
We have found statistically significant differences in HRV frequencies before and after the CBT program in VLF in the standing position (Figure 1).

We have also found statistically significant differences in HRV frequency ratios in the third position in the case of a decrease in VLF + LF / HF ratio. We can also see decreasing activity in VLF and LF band in the standing position in the 1st measurement and an increase in VLF and LF band in the standing position in the 2nd measurement (Figure 2).

Table 1. Demographic and clinical characteristics of the patients

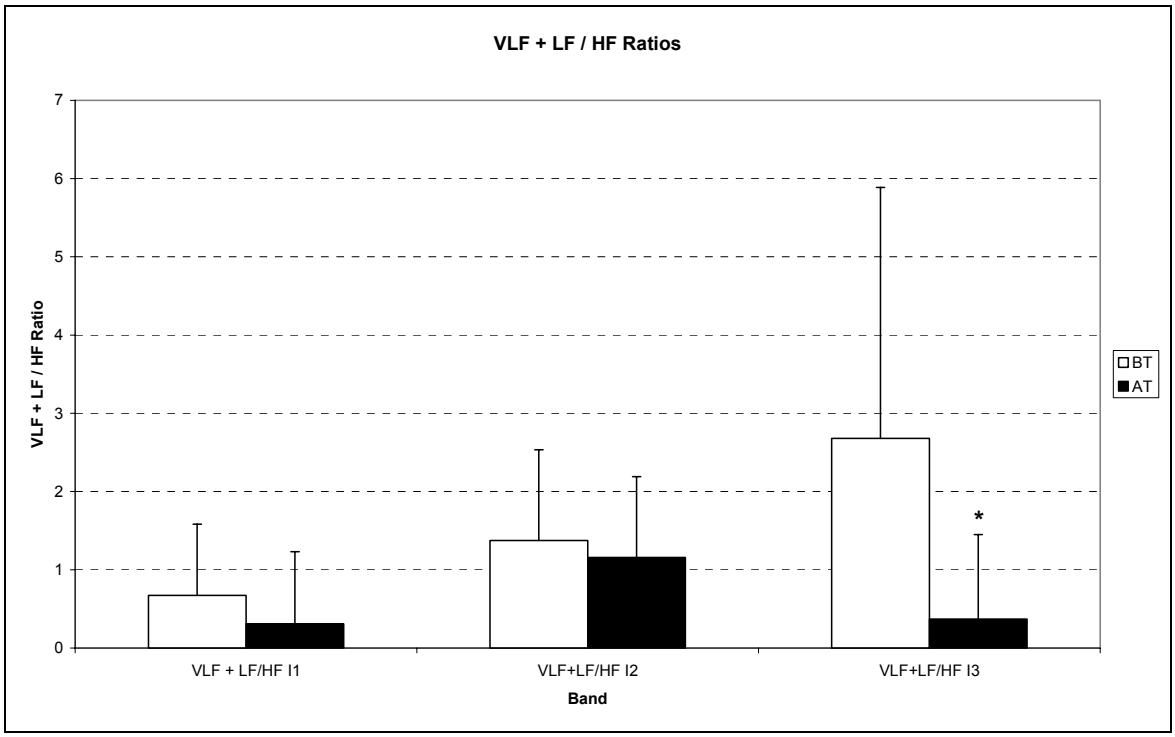
	Patients (n=31)
Age	39.45±10.32
Sex:	
Males	9
Females	22
Age of the disorder onset	32.71±11.48
Length of the disorder	6.74±7.14
Antidepressants index	23.27±8.825 (n=26)
Benzodiazepine index	11.5±6.708 (n=20)
Antipsychotics index	1.87±1.984 (n=10)
CGI	4.13±1.23
BAI	27.41±13.38
BDI	20.48±11.38
DES	8.75±10.06

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



BT = Before Treatment; AT = After Treatment; 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); I1= supine; I2= standing; I3= supine; *unpair t-test: $p<0.05$

Figure 1. Comparison of HRV frequencies before and after treatment



BT = Before Treatment; AT = After Treatment; 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); I1= supine; I2= standing; I3= supine, *unpair t-test: $p<0.05$

Figure 2. Comparison of HRV frequencies ratios before and after treatment

DISCUSSION

We should be cautious in interpreting the data from the HRV measures. We have relevant information that the HF band represents parasympathethic activity (Task Force, 1996), but the relevance of the LF and VLF frequency bands is still unclear. Some studies refers that the LF band represents sympathetic activity (Malliani et al. 1994, Pagani et al. 2009), but we do not comment on these findings. In our study we have found that all three frequency bands tend to decrease during orthostasis (there were no statistical significance, but we can see a decreasing trend.) before treatment. In case of expected higher sympathetic activity in panic disorder, that is shown in some studies, we could expect a higher value of the LF band. But the LF band has decreased. In case of these findings we could suggest with other authors (Moak et al. 2009, Goldstein et al. 2011), that the LF band is probably also influenced by parasympathetic activity. Therefore, the LF is probably not a pure index of sympathetic activity. One can interpret the decrease in HF, LF and VLF before treatment as a reduction in the autonomic nervous system activity and therefore a reduced HRV in patients with panic disorder, so we can concur with the studies that refer to reduced autonomic activity in patients with psychiatric disorders (Tonhajzerova et al. 2009, Prasko et al. 2011, Latalova et al. 2011). We have found only one statistically significant difference after treatment – in VLF in the second supine position. At this point it is difficult to interpret what this increase means in the functioning of the autonomic nervous system, because the physiological importance of VLF in HRV measures is unclear. We can speculate that it is because of higher sympathetic activity in the second supine position. We can also see that the LF in the second supine position tended to increase, while the HF tended to decrease, but this was not statistically significant. One can speculate that patients with panic disorder react differently to posture changes before and after treatment. In this case, the sympathetic activity tended to be higher in the second position after treatment but further research is needed to elucidate these statements.

While suggesting that the LF band does not represent clear sympathic activity, but is also influenced by the parasympathic, we can postulate, that the LF/HF ratio, used in many studies as an index of sympathovagal balance is not exact. Therefore we tried to add the VLF band into the LF/HF ratio, so we extended the ratio as VLF+LF/HF to find out if this ratio could not be a better marker of sympathetic activity. We added the VLF to the LF band, because of the lower frequency range in power spectral analysis of the HRV. We have found interesting results with this ratio in comparing these ratios before and after treatment. Before treatment the ratio tended to increase in all three positions, but without any statistical significance. After treatment we have found that there

was a statistically significant difference between the ratios in the third position in the case of decrease of the VLF+LF/HF ratio. One can interpret this result as a higher participation of parasympathic activity in the third position after treatment and therefore we can speculate that this ratio can be a better marker of sympathetic activity. An increase of VLF and LF band in the 2nd measurement (after therapy) is also interesting. This can be interpreted as an improvement of sympathetic activity and better physiological response to the posture change and an improvement of baroreflex sensitivity.

The index of VLF+LF could provide information about potential sympathetic effects on the sinoatrial node activity. The physiological mechanisms influencing these spectral activities in the stated frequency bands need to be elucidated. We need further research to confirm these results, but this can be a chance to better interpret the ratio of sympathovagal balance. Short term HRV suggests changes in autonomic regulation – this is questionable because of physiological mechanisms or the influence of subjective improvement. It seems to be affected by the interaction of all factors.

CONCLUSION

In conclusion, this study revealed an improvement of neurocardiac control regulation after a therapeutic CBT program in patients suffering from panic disorder.

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Conflict of interest: None to declare.

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