Normalization of Heart Rate Variability in Post-Traumatic Stress Disorder Patients Following Fluoxetine Treatment: Preliminary Results

Hagit Cohen PhD, Moshe Kotler MD, Mike Matar MD and Zeev Kaplan MD

Mental Health Center, and Anxiety and Stress Research Unit, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

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Abstract

Background: Spectral analysis of heart rate variability has been shown to be a reliable non-invasive test for quantitative assessment of cardiovascular autonomic regulatory responses, providing a window reflecting the interaction of sympathetic and parasympathetic tone. Alterations in autonomic function are associated with a variety of physiologic and pathophysiologic processes and may contribute substantially to morbidity and mortality. Our previous study shows that patients with post-traumatic stress disorder have significantly lower HRV compared to controls, reflecting a basal autonomic state characterized by increased sympathetic and decreased parasympathetic tone.

Objectives: To apply this tool to PTSD patients treated with selective serotonin re-uptake inhibitors in order to assess the impact of such treatment on the autonomic dysregulation characterizing these patients.

Methods: Standardized heart rate analysis was carried out in nine PTSD patients treated with SSRI agents and compared to that in a matched control group of nine healthy volunteers and in nine untreated PTSD patients, based on a 15 minute resting electrocardiogram.

Results: Our preliminary results show that the HRV parameters indicating autonomic dysregulation, which characterize PTSD patients at rest, are normalized in responding patients by use of SSRIs. Neither the clinical implications of these findings nor their physiological mechanisms are clear at present, although we presume that they reflect a central effect, since the peripheral autonomic effects of SSRIs are relatively negligible.

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Post-traumatic stress disorder is a chronic condition, defined by DSM-IV criteria as resulting from exposure to an extreme traumatic experience. DSM-IV criteria for PTSD include a state of constant hyperarousal and vigilance, vivid re-experiencing of the traumatic event, emotional numbing, changes in personality, and behavior and avoidant behavior [1]. Mood and anxiety-related symptoms are integral to the clinical syndrome.

The PTSD syndrome has repeatedly been shown to have a strong physiologic component, principally of hyperarousal, as demonstrated by peripheral physiologic parameters. Tachycardia, increased blood pressure, tachypnea, tremor, and excessive sweating have all been described [2]. No characteristic ECG abnormalities have been demonstrated in these patients. PTSD patients exposed to simulated combat noise, individualized scripts portraying stressful combat experiences, or hypnotically induced imagery of a traumatic event, showed increased physiological responses as compared to combat veterans without PTSD [3]. The physiological component of the syndrome can thus be regarded as being based on changes in autonomic nervous system function at two distinct levels: the basal tone and the reaction to stress-related cues. PTSD patients demonstrate hyperalertness, and higher basal heart rate and blood pressure than control subjects [4]. It may thus be presumed that autonomic function is altered in PTSD patients.

Spectral analysis of heart rate variability is a simple non-invasive method for quantifying the activity of the autonomic nervous system functions [5]. Power spectral analysis of HRV has been used to explore dynamic mechanisms in the cardiovascular system and appears to provide a quantitative evaluation of the sympathovagal interaction that modulates cardiovascular function [5]. It has been shown that harmonic oscillations in heart rate are concentrated into at least two distinct bands. The one referred to as the low frequency band is affected by the oscillatory rhythm of the baroreceptor system and is mediated by sympathetic influences. In the other, the high frequency band, respiration is the primary rhythmic stimulus and is mediated by changing levels of parasympathetic tone. Heart rate variability involves a complex interaction between several mechanisms working

HRV = heart rate variability
PTSD = post-traumatic stress disorder
SSRI = selective serotonin re-uptake inhibitor

to maintain heart rate and blood pressure within normal limits [6].

Using HRV analysis, the results of our preliminary study in a group of untreated PTSD patients demonstrate an electrophysiologic profile distinct from that of normal control subjects. The PTSD patients at rest demonstrated significantly lower HRV, with significantly lower HF and higher LF components than controls. This was interpreted as reflecting a disordered-basal autonomic state characterized by increased sympathetic and decreased parasympathetic tone [7,8].

There is no definitive pharmacotherapy for PTSD, although multiple agents have been studied and have resulted in various degrees of improvement in PTSD symptoms and/or the associated anxiety and depressive symptoms [9,10]. These include antidepressants (monoamine oxidase inhibitors, tricyclic antidepressants, and selective serotonin re-uptake inhibitors), adrenergic agonists and antagonists (clonidine, propenolol), mood-stabilizing drugs (carbamazepine, lithium, valproic acid), and benzodiazepines (alprazolam). The SSRIs have been the focus of considerable attention in the study of pharmacologic treatment of PTSD in recent years [11,12].

The present study aimed to address the following questions: Does treatment of post-traumatic stress disorder with an SSRI (fluoxetine) change autonomic components of HRV (which have been shown to be abnormal in PTSD in several studies)? If so, which components will be changed? And, is there an association between symptom improvement and HRV parameters? In the present study we applied power spectrum analysis of HRV in PTSD patients treated with SSRIs in order to assess the relevance of HRV analysis in the assessment of clinical response.

Methods

Sixteen consecutive medication-free patients (8 men and 8 women) fulfilling the DSM-IV diagnostic criteria for PTSD were recruited from the outpatient treatment program at the Beer Sheva Mental Health Center. Six were non-smokers and 10 were smokers.

The normal control group comprised 16 healthy volunteers (8 men and 8 women) matched for age, gender, smoking status, and time of day of ECG recordings. Control subjects had no known diagnosable medical conditions. The healthy control subjects were recruited from among the staff in the Department of Psychiatry and from students in the Department of Psychology at the Ben-Gurion University. All subjects gave their consent to participate, and possible side effects were explained to them. All subjects were physically healthy, with no known diagnosable medical conditions, no medical or cardio-vascular illness according to history and examination, and no abnormalities on ECG or known history of structural cardiac abnormalities, such as mitral valve prolapse. No subjects had been exposed for at least 2 weeks to drugs that might affect the cardiovascular system. In addition, none had been on any psychotropic medication, including SSRIs, for at least 2 weeks. All patients were free of any major cognitive impairment or psychotic symptoms and were in ongoing treatment programs.

ECG recording data collection

Heart rate was determined while subjects were at rest in a reclining position. To minimize extraneous stress, the room was quiet with the temperature maintained at 25°C (to prevent activation of thermoregulatory mechanisms that affect power spectra). A detailed explanation of the procedure was given. After allowing 5 minutes for stabilization, a 10 minute ECG recording was done ("resting"). Subjects were instructed to breathe normally, and respiratory rate was measured in order to control for possible effects of respiration on HRV [5].

Segments of lead II ECG were amplified, digitized, and stored using a personal computer-based software system (unpublished manuscript, available on request). ECG data were digitized at a rate of 250 Hz (width pass 0.05–35 Hz). The ECG signal was converted into an event series, which required the measurement of R-R intervals. Representing this series as a function of the R-wave time of occurrence created a non-uniformly sampled event series. Therefore, the second phase of the algorithm was interpolated. Finally, analyses of HRV, Fast-Fourier Transform, power spectrum density (calculated as milliseconds squared/Hz) [6] were performed using signal processing software. The power spectrum was divided into two major frequency ranges: LF bands (0.04–0.15 Hz) and HF bands (0.15–0.5 Hz). The integral of the power spectrum within each region was calculated (Simpson integration) [6].

The HRV of subjects in the study group was assessed at two time points: before treatment (baseline) and 4 months after the initiation of treatment with flouxetine 20–60 mg/day. Each participant was clinically assessed by means of the following validated measures:

- *The Clinical Global Impression Improvement scale* [13]. Primary emphasis was placed on the patient's PTSD *symptoms*, but overall function was also taken into account. The final CGI-I scores were used as the basis for distinguishing treatment responders and non-responders. Responders were defined as those with final CGI-I scores of either 1 or 2 (i.e., much or very much improved), whereas non-responders were defined on the basis of having a final CGI-I score of 3,4,5, or 6 (i.e., minimally improved, no change, minimally worse, much worse, respectively). By this means, patients with minimal or equivocal response were excluded from the "responders."

HF = high frequency
LF = low frequency

CGI-I = Clinical Global Impression Improvement scale

- *The Impact of Event Scale* [14]. This measure is a self-report scale with two subscales, "intrusion" and "avoidance." Seven of the items reflect the presence of intrusive thoughts, images and feelings, or dreams of the event, and the eight other items reflect the tendency to deny, repress or avoid memories or situations related to the trauma.
- *The Symptom Check List* [15]. This comprised 90 items measuring 9 clinical subscales that developed as a measure of general psychiatric symptom severity and a descriptive measure of psychopathology (and has been found to perform well in the assessment of neurotic symptoms). The present study used the four subscales of depression, anxiety, interpersonal sensitivity and somatization, which are common associated features of PTSD.

In addition, all patients completed a background questionnaire on demographic data, marital status, place of birth, education, place of residence, and the type of trauma that led to the seeking of help. During the course of the entire study protocol, patients did not receive any new or additional treatments, including other psychotropic medications.

Statistical analysis

As all HRV indices were skewed, a natural logarithmic transformation was used to normalize the data adequately. To examine main effects in groups (PTSD vs. control) each variable was assessed by analysis of covariance (ANCOVA), with age status as the covariate. Age was entered as a covariate since HRV decreases with increasing age (r=- 0.73; r^2=0.53; $F(1,8)$= 7.83; P< 0.02). Post hoc comparisons employed Scheffe's test.

Results

The demographic data on the 16 patients treated with fluoxetine are summarized in Table 1. The patients were designated as responders or non-responders according to changes in the CGI scores. Table 2 shows the means and standard deviation for the 16 subjects in the psychological parameters. As can be seen from the table there was a significant improvement in the Clinical Global Impression. There was a significant lowering in the Impact of Event scores, avoidance subscale (PTSD core symptoms). Regarding the SCL-90, the subscales measuring anxiety and depression showed significant results: after 4 months the anxiety and depression scores were significantly lower than at baseline. No significant differences were observed regarding the subscales of somatization and interpersonal sensitivity.

Table 3 shows the means and standard errors for the 16 subjects in the HRV parameters. Heart rate was significantly higher in PTSD populations as compared to controls (P=0.0034, F=7.45). There was no significant difference in heart rate between treated and untreated PTSD patients.

The untreated PTSD patient group was found to have significantly lower HRV, with significantly higher LF and lower HF components, than the treated PTSD patients or the controls. There were no significant differences between the control group and the treated PTSD patients in any of these parameters.

In our sample there were no changes in the respiratory rate (13–15 cyclic/min) either in the PTSD population or in control subjects. This implies that the hemodynamic changes, which could affect HF recording, would be equivalent in both settings, so that any significant

Table 1. Data for 16 patients included in the study

Patients	Study week dose (mg/day)	Gender	Age	Type of trauma	Time since trauma (yr)	Response
A	20	M	24	Car accident	1.5	NR
B	40	M	28	War	2	NR
C	40	F	34	Act of terror	4	R
D	40	F	42	Prisoner of war	6	R
E	20	M	46	Car accident	1	NR
F	20	F	21	Car accident	0.5	NR
G	20	F	33	Act of terror	2	R
H	60	M	38	War	23	NR
I	60	F	34	War	17	NR
J	40	M	49	Act of terror	12	NR
K	40	M	56	Act of terror	15	NR
L	40	M	52	Act of terror	7	R
M	40	F	46	Car accident	5	R
N	40	M	41	Car accident	4	R
O	40	F	36	War	4	NR
P	20	F	34	Car accident	3	R

NR = non-responder, R = responder.

Responders were those with final CGI-I scores of either 1 or 2 (i.e., much or very much improved), whereas non-responders were defined on the basis of having a final CGI-I scores of 3,4,5, or 6 (i.e., minimally improved, no change, minimally worse, much worse, respectively).

Table 2. Means and standard deviations and analyses of variance for the CGI, IES and the SCL-90 at baseline and 4 months after treatment with SSRI was initiated

Variable	PTSD patients before treatment	Responders 4 months after treatment	Non-responders 4 months after treatment			
	Mean SD B	Mean SD I	Mean SD II	*F*	*P*	Significant contrasts*
CGI*	5.54±1.1	1.24±1.1	4.8±0.94	19.79	0.000	B ≠ I
IES Total score	2.9±1.25	2.84±0.9	2.6±1.2	1.73	0.185	NS
IES intrusion	2.76±1.2	2.6±0.1	2.55±0.8	0.53	0.665	NS
IES avoidance	2.8±1.4	1.02±0.9	2.77±1.2	3.35	0.033	B ≠ I
SCL-90 Total score	3.2±0.94	1.1±0.82	3.4±1.1	1.187	0.333	NS
Depression	3.75±0.94	1.4±0.82	3.5±1.3	1.93	0.148	B ≠ I
Anxiety	3.6±0.93	1.3±0.73	3.0±0.86	4.69	0.009	B ≠ I
Interpersonal sensitivity	1.53±1.0	1.72±0.74	1.68±1.3	0.3	0.82	NS
Somatization	2.3±0.9	1.9±0.78	2.0±1.1	3.22	0.038	NS

*Significant contrasts [b]: Post-hoc tests: Tukey's HSD, alpha = 0.05, B = baseline.
CGI = Clinical Global Impression, IES = Impact of Event Scale, SCL = Symptom Check List

Table 3. Mean and SE of the PSD energy in treated PTSD, untreated PTSD and normal control populations

	PTSD patients before treatment: baseline	Treated PTSD patients: responders	Treated PTSD patients: non-responders	Normal matched controls	Post hoc Sheffe test
	(n=16) B	(n=7) I	(n=9) II	(n=16) III	
LF (%)	89.4±1.1	56.1±3.14	88.6±1.04	48.6±1.1	B ≠ I,III I ≠ II, III II ≠ III
HF (%)	10.6±1.1	43.9 ±3.14	11.4±1.04	51.4±1.1	B ≠ I,III I ≠ II, III II ≠ III
LF/HF (mean of individual ratios)	10.025±1.5	1.4±0.23	8.2±0.9	0.95±0.044	B ≠ I,III I ≠ II II ≠ III
Heart rate	82.4±1.7	76.3±1.7	84.3±3.2	62±3.25	III ≠ B, I, II
HRV	0.0732±0.016	0.78±0.017	0.072±0.028	0.95±0.04	III ≠ B, I, II

Results are expressed in normalized unit (nu) and standard error.
[1] F=165.3, P=0.0000; [2] F= 165.3, P =0.0000; [3] F= 16.6, P=0.0000; [4] F= 16.9, P=0.0000;
[5] F= 15.03, P=0.0000.

difference in HF can be attributed mainly to changes in parasympathetic tone.

Discussion

Power spectrum analysis of ECG recordings demonstrates a significant reduction of HRV, vagal tone activity and augmented sympathetic activity in untreated PTSD patients compared to normal controls. This is taken to reflect a basal autonomic state of hyperactivation characterized by increased sympathetic and decreased parasympathetic tone. Clinical observations in PTSD patients have documented symptoms of autonomic dysregulation [16], suggesting that PTSD is characterized by increased autonomic nervous system activity.

Our results show that the HRV parameters indicating autonomic dysregulation, which characterize untreated PTSD patients, are normalized by the use of SSRIs, i.e., the total sympathetic component of HRV is decreased and the parasympathetic component is increased after SSRI treatment. Several open trials have suggested the clinical efficacy of SSRIs for PTSD [11,12]. Nagy et al. [12] reported that 10 weeks of fluoxetine treatment were effective in reducing re-experiencing, avoidance and hyperarousal symptoms of PTSD. A similar improvement was also shown in depression and anxiety symptoms [12]. Van der Kolk's team [17] showed that by the fifth week of fluoxetine treatment PTSD patients demonstrated significantly reduced overall symptomatology, as assessed by the Clinician-Administrated PTSD Scale.

SCL-90 = Symptom Check List

Improvements were most marked in the arousal and numbing symptom subcategories.

Improvements in HRV parameters after SSRI therapy have been reported in panic patients taking paroxetine [18]. After 4 weeks on paroxetine, panic disorder patients showed a normalization of their autonomic dysregulation. In Rechlin's study of the effects of SSRIs compared with tricyclic antidepressants on HRV in depressed subjects [19], treatment for 14 days with amitriptyline (150 mg/day) and doxepin (150 mg/day) led to decreased coefficients of variation. However, treatment for 14 days with fluvoxamine (150 mg/day) and paroxetine (20 mg/day) showed no significant changes in HRV, using time domain analysis. Coplan et al. [20] reported that effective SSRI treatment in patients with panic disorder was paralleled by normalization of dysregulated noradrenergic function, as measured by the metabolite 3-methoxy-4-hydroxyphenylglycol. The results show that patients with panic disorder, compared with healthy volunteers, have markedly elevated plasma MHPG volatility during clonidine challenge. A greater degree of clinical global improvement was predicted by a greater magnitude of basal MHPG reduction with fluoxetine treatment.

Several possible explanations may account for these effects. First, serotonin may have a direct central effect on HRV, independent of its reduction of anxiety. In support of this, serotonin is one of several neurotransmitters (including dopamine and other catecholamines and acetylcholine) influencing heart rate via the central nervous system [21]. Secondly, these effects may be accounted for by the interactions between the serotonergic and noradrenergic systems, as reflected by their influences on the cardiovascular system [21,22]. The serotonergic (5-HT) system and noradrenergic system interact and exert mutual influences through well-defined pathways between the midbrain raphe and locus ceruleus. Moreover, the central noradrenergic system operates in close association with the peripheral sympathetic nervous system. Thirdly, an SSRI might influence sympathetic tone indirectly through the reduction in anticipatory anxiety. Alternatively, the patients may simply have become habituated to the procedure of heart rate sampling. To counteract this possibility, efforts were made to acclimate all subjects to the equipment before baseline measures. In addition, desensitization may, in general, require more than two exposures separated by a 4 month period. To thoroughly exclude the possibility that habituation confounded the results, the control subjects would need to be retested after 4 months to demonstrate stability of measures. However, no HRV studies in psychiatric patients over time were identified in which control subjects were retested, suggesting that the consensus is that habituation effects do not require separate manipulations other than desensitizing patients to equipment at the first visit.

Given the association between enhanced sympathetic tone, parasympathetic withdrawal and increased risk of mortality [23], it might be expected that agents decreasing sympathetic activity might have a crucial role in the pharmacotherapy of chronic PTSD. Future studies explaining the prolonged effects of such agents on HRV in PTSD patients are called for.

The above preliminary findings, although interesting, must be tempered by the limitations of the study. One is the smallness of the study group; the investigation should be reproduced in larger patient populations to reduce the chances for a type I error. The second limitation is that PTSD may represent a heterogeneous syndrome. Since patients with PTSD have a high rate of co-morbid panic disorder, major depression and anxiety, it could thus be argued that these co-morbid disorders, rather than PTSD, accounted for the observed result. Future research aimed at understanding co-morbidity and heterogeneity should help to illuminate the psychobiology of PTSD and eventually guide both medication and psychosocial treatments.

At present, our preliminary results demonstrate a significant difference between the cumulative baseline data for PTSD patients assessed by power spectrum analysis of HRV, and the data for SSRI-treated PTSD patients. Our finding is that PTSD patients have significant autonomic dysregulation at rest, which is corrected by SSRI treatment. Power spectrum analysis of heart rate variability thus appears to be a useful tool to assess response to medications (at the physiological level) in PTSD patients, although it is obvious that more extensive study, focusing mainly on the correlation between improvement in HRV parameters and clinical response to SSRI in PTSD, is required,

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MHPG = 3-methoxy-4-hydroxyphenylglycol

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Correspondence: Dr. H. Cohen, Beer Sheva Mental Health Center, P.O. Box 4600, Beer Sheva, Israel. Tel: (972-7) 640 1743; Fax: (972-7) 640 1742; email: hagitc@bgumail.bgu.ac.il.