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Heart Rate Variability in Patients with Bipolar Disorder: From Mania to Euthymia

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ABSTRACT

Bipolar Disorder (BD) is characterized by the occurrence of mania alternating with euthymia. The aim of the present study was to investigate the impact of BD on the autonomic nervous system, as indicated by heart rate variability (HRV). The study was registered in the Clinical Trials Registration (NCT01272518). Nineteen hospitalized, male patients (age: 34.0 ± 12.3 years) with type I BD were assessed during mania and at discharge on euthymia. HRV data were collected during 20- minutes in supine position at rest, on spontaneous breathing, using the Polar RS 800 CX frequencymeter. HRV measures included variables in time, frequency and non-linear domains. Psychiatric conditions were evaluated by the Mini International Neuropsychiatric Interview (MINI) and the Bech-Rafaelsen mania scale (BRMS). Time domain measures of RMSSD (Cohen's $d = -0.668$) and pNN50 (Cohen's $d = -0.688$) increased from first to second assessments. The high-frequency component (HFms2) also increased (Cohen's $d = -0.586$), while the LF/HF ratio decreased (Cohen's $d = 0.785$). Non-linear domain measures including the SD1 component (Cohen's $d = -0.668$), and the SD1/SD2 ratio (Cohen's $d = 1.2934$) extracted from the Poincare plot analysis increased from first to second assessment. The variables Lmean (Cohen's $d = 0.9627$), Lmax (Cohen's $d = 1.2164$), REC% (Cohen's $d = 1.0595$) and EntShannon (Cohen's $d = 1.0607$) were higher in mania. By contrast, ApEn (Cohen's $d = -0.995$) and EntSample (Cohen's $d = -1.189$) were less during mania, all reflecting ANS improvement. Findings are interpreted in the context of recently published models relating to neurovisceral integration across the continuum of time, and the implications for the future health and wellbeing of patients are considered.

Keywords: Heart Rate Variability; Bipolar Disorder; Mania; Emotion regulation; Non linear measures.

INTRODUCTION

Contemporary clinical studies report increased risks for cardiovascular morbidity and mortality in patients with bipolar disorder (BD) (Sharma & Markar, 1994; Angst et al., 2002; Laursen et al., 2007; Fiedorowicz et al., 2009) including diabetes mellitus (Kilbourne et al., 2004), hypertension (Birkenaes et al., 2007) and obesity (Simon et al., 2006). While depressive symptoms in patients with bipolar disorder are related to morbidity and mortality (Barefoot et al., 1996), few studies have specifically examined the manic phase. Critically, a study conducted on patients with BD type I demonstrated that cardiovascular risk was directly proportional to the presence of the manic phase (Fiedorowicz et al., 2009), raising questions relating to underlying pathophysiological mechanisms.

Increased heart rate (HR) observed in the acute phase of BD can be considered a risk factor for early cardiovascular mortality in bipolar disorder, perhaps due to autonomic imbalance (Tsai et al., 2017). In the present study, we report on change in heart rate variability (HRV) – a psychophysiological marker of mental and physical wellbeing (Kemp et al., 2017a) – in bipolar patients in the manic phase at admission and in the same patients during euthymia at discharge.

Heart rate variability (HRV) assesses beat-to-beat changes in the heart, and these changes reflect the outflow of the central autonomic network responsible for regulating cardioacceleratory circuits. This network includes the prefrontal cortex, cingulate cortex, insula, amygdala, and brainstem. HRV is primarily driven by parasympathetic neurons innervating the heart via the vagus nerve (Thayer et al., 2009; Reyes del Paso et al., 2013) and may be used as an index of integrity of the Autonomic Nervous System (ANS) (Task Force, 1996; Berntson et al., 1997). The ANS encompasses efferent pathways that control autonomic activity, and subsequent visceral afferent feedback that allows for this activity to be actively processed and regulated (Thayer et al., 2005; Porges et al., 2009; Kemp & Quintana, 2013; Kemp et al., 2014; Kemp et al., 2017a). Studies have demonstrated an important role for HRV in emotion regulation, potentially laying a psychophysiological foundation for better understanding the difficulty bipolar disorder patients have in regulating their emotions. For instance, a study on 172 university student participants demonstrated that resting state high frequency HRV is associated with subjective wellbeing (Geisler et al., 2010), and that this association was fully mediated by emotion regulation strategies. Another study (n=77) (Park et al., 2014) demonstrated that individuals characterized by lower resting HRV display task-driven HRV suppression, a

finding interpreted as an autonomic stress response. By contrast, individuals characterized by higher resting HRV display task-driven HRV enhancement, interpreted as greater self-regulatory effort. The relationship between HRV and emotion regulation still remains unclear in bipolar mania.

Research on the impact of mania on HRV have reported contradictory findings (Outhred et al., 2014; Faurholt-Jepsen et al., 2017a) providing the major motivation for the present study. A study on 61 unmedicated patients during bipolar mania demonstrated reductions in HRV (including reduced high frequency and a positive correlation with scores on the Young Mania Rating Scale) in comparison to sex-, age- and education-matched healthy controls (Chang et al., 2014). More recent work by the same group has proposed that while BD displays cardiac sympathetic excitation in combination with vagal impairment, patients with unipolar depression only display vagal impairment (Chang et al., 2015) and discussed by Kemp (2017). Interestingly however, other studies have reported that mania is associated with higher levels (Gruber et al., 2008; Gruber et al., 2011), rather than lower levels. For instance, a study on young adults categorized into high or low mania risk groups displayed elevated positive emotion and tonic vagal function at rest, as well as during presentation of positive, negative and neutral films (Gruber et al., 2008). While this study was conducted on non-patient population, a more recent study by these authors reported that patients with bipolar disorder (n=23) display smaller decreases in respiratory sinus arrhythmia (RSA) – as determined by the peak-valley method – during emotion-eliciting films, compared to non-clinical controls (n=24) (Gruber et al., 2011). Critically, this study further reported that “BD participants exhibited greater increases in RSA [during film stimuli] from already higher RSA levels” collected during a resting 60s baseline period relative to controls.

A recent study found a positive association between HRV and severity manic symptoms (Faurholt-Jepsen et al., 2017b). However, the patients in that study received different types, doses and combinations of medication during the study and the data were collected and analyzed from only seven patients during manic/mixed state. These contradictory findings in BD highlight the importance of continued work in this area, and emphasize the importance of within-subject designs, which provide better experimental control over confounding factors than between-subject designs.

In the current longitudinal study HRV of patients was assessed in the manic phase of bipolar disorder and after during euthymia on discharge. There are a variety of ways in which HRV may be measured and these measures are typically categorized as time-, frequency- and non-linear domains, being

the non-linear measures more sensitive to group differences (Kemp et al., 2010; Godoy, 2016). Nonlinear methods based on nonlinear systemic theory (or Chaos Theory) (Selig et al., 2011; Pivatelli et al., 2012; de Carvalho et al., 2014) may lead to greater understanding of the physiological mood swings in bipolar disorder and more interpretations of ANS activity than linear measures with less sensitive confounding variables (Woyshville et al., 1999; Yeragani et al., 2003; Sree Hari Rao et al., 2006; Bassett, 2016).

MATERIAL AND METHODS

Participants

Nineteen male patients (age: 34.0 ± 12.3 yo) in the manic phase of bipolar disorder hospitalized at the Psychiatric Hospital Adolfo Bezerra de Menezes were accompanied from the time of admission until discharge over a period of approximately 1 month. All participants underwent a diagnostic assessment based on the Mini International Neuropsychiatric Interview (MINI) Brazilian version 5.0.0 - DSM IV (Amorim, 2000) on admission, as well as the Bech-Rafaelsen Mania Scale in its Portuguese validated version (BR-MaS) (Shansis et al., 2004) both at admission (median = 19.8, range: 12 – 39) and at discharge (median = 1.10, range: 0 – 7) to assess the severity and evolution of the episode.

Participants were excluded if they: 1) fulfilled criteria for any other Axis I or II disorder; 2) presented with any associated neurological condition; 3) had already received prior electroconvulsive therapy; 4) had a prior history of cardiovascular or metabolic disease or associated medications; 5) had a prior history of drug use; 6) displayed psychomotor agitation not allowing for 20-minute resting HRV recordings. Exclusion criteria were determined during an intensive clinical interview with one of the authors (GLW).

All patients underwent a 1-week wash-out period, and soon aripiprazole in combination with lithium was introduced for the treatment of the manic phase. Patients were on no additional medications. The HRV measurement took place six days following the introduction of the drug combination, and the second measurement occurred on the day of discharge, when the same drugs were still in use. Mean dosages of lithium and aripiprazole were 900.0 ± 283.8 mg and 15.0 ± 5.8 mg, respectively. The mean serum lithium concentration was 0.85 ± 0.13 mmol/L.

The present study was approved by the Ethics Committee of the São José do Rio Preto Medical School (CEP – FAMERP/ Number 459/2010) and was also registered in Clinical Trials (protocol number: NCT01272518). All patients agreed to participate in this study and signed informed consent documentation.

HRV Analysis

Patients were instructed to fast for at least 4 hours before HRV assessment, and to refrain from consuming caffeinated beverages for at least 12 hours in preparation for the two recordings. Data was collected between the hours of 11:00 am and 01:00 pm, while participants were spontaneously breathing in a resting dorsal position for 20 minutes, with minimal movement. This assessment was preceded by a 10-minute silent period to ensure patients were sufficiently relaxed before recordings commenced.

HRV was measured by the Polar RS 800 CX (Polar, Kempele, Finland) using a heart rate chest strap monitor placed over the distal third of the sternum from which data was transmitted to a wrist sensor. This methodology has been validated in relation to Holter system and has demonstrated to produce accurate and reliable data (Gamelin et al., 2006; Vanderlei et al., 2008; Quintana et al., 2012). Two measurements were made from each participant: the first, followed six days of drug administration (before clinical response) and the second, at discharge (after clinical response).

Data analysis

Beat-to-beat heart rate (HR) was recorded and digitalized at 1000Hz and imported into the Polar Precision Performance SW software (version 4.01.029; Polar). The data were then submitted to digital filtering, carried out on the Polar software. This program is able to identify occasional ectopic beats (irregularities in heart rhythm involving extra systoles and consecutive compensatory pause) and to replace these with interpolated adjacent R–R interval values.

The data were transmitted via radiofrequency to a Polar brand wristwatch and subsequently transferred to a computer for analysis. The R-R intervals were then digitally filtered to eliminate artifacts according to a previously published protocol (Santos et al., 2013; Santos et al., 2016) known as T-RR filter. This method is equivalent to conventional filtering, however with the advantage of faster processing.

Only time series with less than 5% artifacts were included for analysis. Both linear and nonlinear measurements were extracted from the same time series and free of artifacts. HRV analysis was then

conducted using Kubios HRV Analysis Software (Biosignal Analysis and Medical Image Group, University of Eastern Finland, Kuopio, Finland) (Niskanen et al., 2004) and the following HRV measures were extracted for subsequent analyses.

HRV measures in the time domain included mean R-R (mean of normal-to-normal beat interval), mean HR, standard deviation of the average of normal R-R intervals (SDNN) representing overall variability, the root mean squared of successive differences (RMSSD), percentage of adjacent RR intervals differing by duration longer than 50 milliseconds (pNN50). Measures in the frequency domain, computed using the Fast Fourier transform (FFT), included spectral components of low-frequency (LFms²) (0.04-0.15 Hz), high-frequency (HFms²) (0.15 to 0.40 Hz), and the ratio between these components (LF/HF). Measures in the nonlinear domain included the Poincaré plot SD1 and SD2 components, DFA1 (Detrended Fluctuation Analysis; alpha1 component), Shannon's entropy (SE), Approximate Entropy (-ApEn) and Sample Entropy (EntSample) and all components of Recurrence Plot based methods including average and maximum lengths of the diagonal lines (Lmean e Lmax) and the recurrence rate (REC%), and CorrDim2.

Each of these measures provides information on associated, albeit distinct, physiological control mechanisms relating to the autonomic nervous system (Kemp et al., 2017a). In the time domain, RMSSD and PNN50 are solely related to the parasympathetic behavior, while SDNN reflects all of the cyclic components responsible for variability in a recording. In the frequency domain, commonly reported measures include high frequency oscillations (HF-HRV), which relate to parasympathetic respiratory influences, and LF oscillations (LF-HRV), which reflect mechanisms relating to blood pressure control such as the baroreflex. While researchers have interpreted the LF/HF ratio as sympathovagal balance, this view is controversial, especially under resting state conditions as reported on here (Goldstein et al., 2011; Reyes Del Paso et al., 2013). In the nonlinear domain, the elements of the Poincaré plot (SD1 and SD2) relate to the parasympathetic and sympathetic nervous systems (Vanderlei et al., 2009; Shaffer et al., 2014). The detrended fluctuation analysis (DFA) technique determines the short-term, self-similar properties of the R-R interval time series. White Gaussian noise (a totally random signal) is reflected in a value of 0.5, while a value of 1.5 indicate a Brownian noise signal (Perkiömäki et al., 2005). Alpha1 component values of approximately 1.0 are those that indicate greater proximity to normal physiological behavior. Higher values on measures extracted from the recurrence plot quantification including % REC, Lmax and Lmean variables reflect a pattern of low variability, and a compromised physiological state. Similarly, Shannon Entropy

correlates with Determinism (i.e. higher occurrence of diagonal lines); therefore, increasing values on this measure correspond to decreasing variability. Approximate (-ApEn) and Sample (EntSample) entropies are interpreted differently, lower values correspond to higher regularity or periodicity of the time series (Richman et al., 2000).

Statistical analysis

Clinical characteristics of patients are presented in Table 1. A within-subject experimental design was employed to allow each subject to be his or her own control. As most of the data displayed a non-Gaussian distribution, non-parametric Wilcoxon's signed-rank test determined within-group differences (Table 2). We also determined the correlation between measures of HRV and intensity of mania, using the Spearman's correlation coefficient (Table 3). The statistical threshold was set at $P \leq 0.05$, while p-values between 0.05 and 0.1 were labeled as trends. All effects were complemented with measures of effect size (Cohen's d : small, $d = 0.2$; medium, $d = 0.5$; large, $d = 0.8$) (correlation: small, $r = 0.1$; medium, $r = 0.3$; large, $r = 0.5$) (Vanderlei et al., 2009), consistent with recommendations emphasizing meta-analytic thinking (Perkiömäki et al., 2005; Shaffer et al., 2014).

RESULTS

Robust changes across most measures of heart rate and HRV were observed between admission and discharge. Patient's clinical characteristics during the manic phase of BD are demonstrated on Table 1.

Mean HR was higher in mania than euthymia, findings associated with a large effect size (Cohen's $d = 0.8592$). Consistent with an increased heart rate during mania, the R-R interval was also reduced in mania relative to euthymia, again findings associated with a large effect size (Cohen's $d = -0.857$). Strikingly, all significant HRV measures displayed moderate to large effect sizes, and those for the non-linear domain were generally greater than those in the time and frequency domains. Time domain measures of RMSSD (Cohen's $d = -0.668$) and pNN50 (Cohen's $d = -0.688$) increased from first to second assessments, while no significant difference was observed for the SDNN measure (Cohen's $d = -0.378$). The high-frequency component (HFms2) also increased from first to second assessment (Cohen's $d = -0.586$), while the LF/HF ratio decreased (Cohen's $d = 0.785$). Non-linear domain measures of HRV including the SD1 component (Cohen's $d = 0.70$), and the SD1/SD2 ratio (Cohen's $d = 1.2934$) extracted from the Poincare plot graph analysis

increased from first to second assessment, while no significant difference was observed for the SD2 component (Cohen's $d = -0.296$). Values of alpha1 component of DFA (Cohen's $d = 1.2747$) were greater in mania, consistent with improvements in autonomic function with successful treatment. Similarly, the Lmean (Cohen's $d = 0.9627$), Lmax (Cohen's $d = 1.2164$), REC% (Cohen's $d = 1.0595$) and EntShannon (Cohen's $d = 1.0607$) were higher in mania than those collected during euthymia. By contrast, ApEn (Cohen's $d = -0.995$) and EntSample (Cohen's $d = -1.189$) were less during mania than euthymia, a change that also reflects ANS improvement with amelioration of symptoms (Table 2).

Effect sizes were "large" and "very large", ranging between 0.8 and 1.2 in 11 of 21 variables with statistically significant difference. The effect was "medium" in the remaining 10. It is interesting to note that most of the large or very large effects arose for the nonlinear variables and medium in the linear (time) domain. This is an important finding that highlights the importance of evaluating with non-linear variables. The "r" values are derived from the "Cohen-d" formula; correlations above 0.371 are large or very large, while those from 0.243 to 0.370 are medium. A positive correlation, with borderline statistical significance, was observed for LF/HF ms^2 , indicating that the higher the clinical symptoms, the higher the LF component. (Table 3).

DISCUSSION

This study examined HRV in bipolar patients, comparing mania at admission and at discharge in the same patients. The major finding was that mania is associated with increased heart rate and decreased HRV compared to euthymia. While heart rate reflects a combination of multiple physiological factors, including sympathetic input, HRV provides a more specific measure of vagally mediated cardiac activity.

Alterations in HRV were present in the three domains, but with a special emphasis on the nonlinear domain, with several variables showing a high effect size, supporting previous observations that non-linear measures may be more robust to group differences (Kemp et al., 2010; Young & Benton, 2015). In contrast to other measures of HRV and their interpretation, it is noteworthy that the LF/HF ratio was increased in mania relative to euthymia (Cohen's $d = 0.785$), although this measure wasn't positive correlated with intensity of mania (determined using the Bech-Rafaelsen score) (Spearman's rank correlation = 0.451392; $P = 0.0533$). While the LF/HF ratio has been regarded as an independent measure of sympathetic-

parasympathetic balance, this issue is controversial (Niskanen et al., 2004; Santos et al., 2016). Nevertheless, the findings we present here are consistent with this interpretation and there was a trend between LF/HF and manic symptom severity in our sample.

Nonlinear measures including those extracted from the Poincare plot, Recurrence plot, DFA, and entropy-based analysis are all consistent with lower parasympathetic activity during mania, findings associated with a large effect size. To our knowledge, this is the first study in the literature with controlled medication (aripiprazole plus lithium) where the transition from mania to euthymia was investigated in male patients with BD type I. Prior studies (Cohen et al., 2003; Todder et al., 2005; Henry et al., 2010; Chang et al., 2014) have investigated a specific stage of the disorder relative to control patients, whereas our study was the first to examine the longitudinal autonomic dynamics across phases of the disorder within the same participants with linear and nonlinear measures. This is notable strength of our study considering the contradictory findings that have been reported in the literature for bipolar disorder (as discussed in the introduction).

In addition to the large and significant alterations in heart rate and HRV between patients at different stages of illness (mania versus euthymia), it is interesting to note that we did not observe significant associations with the clinical intensity of manic symptoms (determined using the Bech-Rafaelsen mania scale). Interestingly, a prior study also reported positive associations between more severe manic symptoms and the LF/HF ratio during rest (Henry et al., 2010). It is known that the human body works in a nonlinear manner and is considered a nonlinear dynamic complex system and, thus, it may be difficult to correlate a physiological measure of nonlinear origin with a scale based on linear methods of evaluation (Borsboom, 2017). This hinders replication and a greater understanding of the data based on the literature.

The data clearly indicate that there is a difference between euthymic state and manic state. Although we had a small sample size, the findings reported here were associated with “large” or “very large” effects across the majority of measures, especially in the nonlinear domain. Furthermore, while we do not have an independent control group, we employed a within-subject design avoiding many of the potentially confounding factors that may impact on findings characterized by between-subject designs, given that each patient is their own control.

Although participants were receiving medications, these were consistent across all participants and the first HRV assessment occurred following 6 days of treatment, so initial treatment effects would be

minimal. Moreover, aripiprazole has no appreciable affinity for cholinergic muscarinic receptors and therefore, no anticholinergic effects are expected to impact on HRV (Huang et al., 2013). While lithium has been shown to decrease depolarization of the cardiac sinoatrial node (Rosenqvist et al., 1993; Chong et al., 2001), we suggest that this is unlikely to be driving the effects we report here because first HRV assessment took place 6 days after commencing medications. The research into the effects of lithium and anticonvulsant medications (the latter used in the treatment of mood disorders) suggests absence of effect upon HRV. The findings for antipsychotic medications are more heterogeneous, and there is evidence that prolonged use of antipsychotic medications may lead to normalization of reduced HRV provoked by the relevant medications (Bassett, 2016).

Therefore, we suggest that autonomic changes in BD are state-dependent, unlike findings in major depressive disorder (MDD) (Licht et al., 2010; Kemp et al., 2016). Notably, medicated patients with MDD show chronic HRV reduction as compared to healthy controls, regardless of medication type (Licht et al., 2010; Kemp et al., 2016).

Although research on HRV has been directed toward a variety of behaviors including positive mood states, emotional regulation, cognitive function, inflammatory processes and even brain plasticity, relationships between HRV changes and the neurophysiology of bipolar disorder are still scarce in the literature, especially on the manic phase. Even so, some inferences can be made. It is well-established that vagal dysfunction indicates poor homeostatic behavior, and is related to increased morbidity and mortality (Kemp & Quintana, 2013; Kemp et al., 2017a & 2017b). Patients with BD have deficits in executive control, learning and verbal memories, working memory and sustained attention, especially during manic episodes, where neurotoxic pathophysiological changes, such as reduced brain-derived neurotrophic factor (BNDF) and increased inflammatory cytokines, are present (Martinez-Aran et al., 2017). HRV changes caused by the vagus nerve normalized function indirectly stimulate neurogenesis through the expression of BNDF, with consequent cognitive improvement (Kemp et al., 2017a & 2017b). Another intriguing mechanism is the association between vagal activity and social cognition (Kemp et al., 2017a). Thus, low HRV may indicate difficulty in maintaining social relationships and emotional processing, especially during a manic phase (Strejilevich & Martino, 2017).

In conclusion, the present study provides important new evidence on the adverse effects of bipolar mania on autonomic nervous system, reducing HRV. Findings also indicate that HRV increases from mania

to euthymia following drug treatment. Together with the existing literature, our findings may provide a useful framework to understand emotion dysregulation in patients with bipolar disorder.

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Table 1. Patient's clinical characteristics.

Characteristics	
Number of patients	19
Age (years \pm SD)	34.0 \pm 12.3
Age of BD onset (years \pm SD)	19.3 \pm 2.13
Suicide attempts	0-4
Number of previous hospitalizations	0-7
Mania episodes	0-4
Mixed episodes	0-2
Depression episodes	0-3

SD=standard deviation

Table 2. Differences in heart rate variability between affective states in bipolar disorder (mania X euthymia).

Variables	Mania	Euthymia	P-value	Cohen's d	Effect size r
<i>Time Domain</i>					
MeanRR bpm	702.3±90.0	785.8±104.3	P = 0.0034	-0.857	-0.394
MeanHR 1/min	86.8±11.1	77.6±10.3	P = 0.0049	0.8592	0.3947
SDNN ms	19.3±9.8	24.5±16.8	P = 0.1525	-0.378	-0.186
RMSSD ms	13.6±7.9	22.5±17.1	P= 0.0161	-0.668	-0.317
pNN50 %	1.32±2.6	7.10±11.6	P= 0.0276	-0.688	-0.325
<i>Frequency Domain</i>					
LF ms ²	315.3±272.1	470.6±731.3	P= 0.3296	-0.281	-0.139
HF ms ²	84.3±99.5	309.9±535.1	P= 0.0515	-0.586	-0.281
LF/HF ms ²	6.15±5.4	2.87±2.4	P= 0.024	0.785	0.3654
<i>Non-linear Domain</i>					
SD1 ms ²	9.6±5.6	15.9±12.1	P= 0.0161	-0.668	-0.317
SD2 ms ²	25.5±12.8	30.6±20.7	P= 0.2589	-0.296	-0.147
SD2/SD1	2.86±0.64	2.10±0.53	P=0.0003	1.2934	0.5431
Lmean beats	12.3±4.3	9.1±1.9	P= 0.0051	0.9627	0.4337
Lmax beats	400.5±228.4	182.9±108.8	P= 0.002	1.2164	0.5196
REC %	34.7±8.6	26.2±7.4	P= 0.0007	1.0595	0.4681
DET%	98.4±0.81	96.8±1.4	P=0.0002	1.399	0.5732
EntShannon	3.3±0.32	3.0±0.24	P= 0.0011	1.0607	0.4685
ApEn	1.42±0.11	1.52±0.09	P=0.0013	-0.995	-0.445
EntSample	1.56±0.19	1.78±0.18	P=0.0004	-1.189	-0.511
DFA alpha1	1.38±0.15	1.14±0.22	P= 0.0001	1.2747	0.5375
DFA alpha2	1.38±0.15	1.14±0.22	P= 0.0001	0.6422	0.3057
CorrDimD2	0.56±0.17	0.46±0.14	P= 0.0244	-0.652	-0.31

Data are expressed as mean ± standard deviation and absolute measures of Cohen's d effect size.

Table 3. Spearman's Rank Correlations between HRV measures and Bech-Rafaelsen scores before treatment.

Variables	Spearman's Rank Correlation	P-value
<i>Time Domain</i>		
MeanRR bmp	-0.04354	P = 0.8598
MeanHR 1/min	0.04354	P = 0.8541
SDNN ms	-0.282565	P = 0.2404
RMSSD ms	-0.34121	P= 0.1518
pNN50 %	-0.233035	P= 0.3348
<i>Frequency Domain</i>		
LF ms ²	-0.295004	P= 0.2199
HF ms ²	-0.368756	P= 0.1213
LF/HF ms ²	0.451392	P= 0.0533
<i>Non-linear Domain</i>		
SD1 ms ²	-0.34121	P= 0.1518
SD2 ms ²	-0.245245	P= 0.3094
SD2/SD1	0.348319	P= 0.1439
Lmean beats	0.319884	P= 0.18
Lmax beats	0.295893	P= 0.2171
REC %	0.31633	P= 0.185
DET%	0.279899	P= 0.2435
EntShannon	0.302113	P= 0.206
ApEn	-0.071085	P= 0.7702
EntSample	-0.110182	P= 0.6517
DFA alpha1	0.28523	P= 0.2345
DFA alpha2	0.31633	P= 0.185
CorrDimD2	-0.323136	P= 0.1775

All authors declare no conflict of interest.