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A 6-weeks Treatment Program Improves HRV in Eating Disorder Patients

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Abstract

Background: Eating disorders such as anorexia nervosa present with a significant cardiovascular associated risk of sudden cardiac death. Bradycardia is a serious complication of eating disorders.

Methods: Eating Disorder (ED) patients were admitted to a 6-week treatment program and assessed for of heart rate variability (HRV) at entrance to the program and at discharge from hospital. Linear heart rate variability measures were determined using Kubios software from Lead 3 ECG recordings following a 5-minute rest period. Nonparametric statistics were applied and significance set at $p < 0.05$.

Results: No significant differences in HRV parameters were noted for the control group following the 6-week treatment program. For the ED group, mean RR interval length decreased significantly following treatment (median ± IQR; -64 ± 76; $p = 0.002$). Sympathovagal function was abnormal in the ED group on admission but improved following treatment, showing a decrease in RMSSD (median ± IQR; -9 ± 18; $p = 0.048$) and SD1 (median ± IQR; -6 ± 13; $p = 0.048$). Sample entropy, a, measure of heart rate complexity did not change significantly.

Conclusion: At admission to hospital the ED group was more parasympathetic during rest compared to controls, but they became more sympathetic after the intervention and approached the HRV measures of the controls.

Keywords: Eating disorders; Heart rate variability; Treatment program; Complexity

Introduction

Eating disorders (EDs) play a significant role in health care world-wide. EDs are characterized by abnormal eating patterns and perceptual distortions related to food and weight, which in turn results in a significant impairment of physical health and psychosocial functioning [1-3]. Cardiac complications are major concerns in ED progression brought about by malnutrition [4-6] and often manifest as arrhythmias including long QT in ED patients, which can lead to changes in heart rate and sudden cardiac death. Bradycardia in particular is a strong diagnostic indicator for undiagnosed anorexia nervosa in females [7,8].

Heart rate is controlled by the autonomic nervous system (ANS), which in turn is modulated by the peripheral baroreflex and metabolic factors. Impaired ANS control of heart rate may be a consequence of an adaptation to oxidative stress and inflammation; both present in EDs [9,10] and can be explored using heart rate variability (HRV) analysis. Linear and nonlinear HRV features describe different characteristics of ANS influence on the heart [11,12]. The study of HRV in patients with ED has provided clinically important information on the integrity and function of the complex physiologic mechanisms controlling heart rate [13,14]. However the majority of studies of ED and ANS modulation have concentrated on anorexia nervosa that did not include age-matched controls and only utilized linear HRV methods. The current study explores the effect of a 6-weeks rehabilitation program in patients with ED independent of BMI.

Methods

Thirty-seven patients underwent treatment at the Eating Disorders Unit of Sydney's Northside Clinic and fulfilled the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria for eating disorders. Forty-three healthy age-matched subjects were recruited from the University of Sydney. The study was approved by the University of Sydney and the Ramsay Sydney Psychiatric Hospital Ethics Committees. All participants provided written consent. Clinical and anthropometric data was obtained at the commencement of the study form all participants.

ECG recording and HRV analysis

A PowerLab data acquisition system and Chart™ (ADInstruments, Australia) set at a sampling rate of 400 Hz was used to obtain and record the ECGs. Resting ECGs were recorded for 20 minutes after a 5-minute resting period in a relaxed sitting position. (Version 5.0.1, ADInstruments, Australia). HRV parameters were calculated with Kubios HRV software (http://kubios.uef.fi/ Kuopio, Finland) [15]. All RR time series were first pre-processed to remove very low frequency trends (< 0.04 Hz) and ectopic beats [16] and interpolated with 4 Hz cubic spline to have equidistantly sampled data for spectral analysis.

Power spectral density estimates were computed using Welch's averaged periodogram method (150s window and 50% overlap).

HRV measures

Time-domain measures of HRV included mean value of beat-to-beat RR intervals (Mean RR), standard deviation of all normal-to-normal RR intervals (SDNN), and root mean square of successive RR interval differences (RMSSD). In addition, the triangular interpolation of RR interval histogram (TINN), which is a geometric measure reflecting the range of RR intervals excluding outliers. Frequency-domain parameters evaluated from the power spectrum of RR time series included peak frequency at high frequency (HF, 0.15-0.4 Hz) band (indicating respiratory frequency), powers of LF and HF bands in absolute units (ms^2), and power ratio between LF and HF bands (LF/HF ratio). Nonlinear HRV measures included in the study were Poincaré plot analysis (quantified by standard deviations SD1 and SD2, and their ratio SD1/SD2), and sample entropy (SampEn).

Statistical analysis

Statistical calculations were performed using Matlab (Version R2012a). Basic clinical data are expressed as mean ± standard deviation. The normality of all variables was verified by the Kolmogorov-Smirnov goodness-of-fit test. Not normally distributed HRV data are expressed as median ± interquartile range (IQR) and analyzed using the non-parametric Wilcoxon rank-sum test (for independent samples) or the Wilcoxon signed rank test (for paired samples, both at $p < 0.05$).

Results

All participants were free of cardiovascular disease, diabetes mellitus, neurological and other systemic diseases. Some participants did not finish the treatment program or biosignals were not usable due to artifact. The demographic, clinical and lifestyle characteristics of all 80 subjects are presented in Table 1. There was no significant age difference between the patients and the control group ($p > 0.05$). The BMIs of the patients (19.7 ± 3.3 kg/m^2, $p < 0.05$) were significantly lower than those of the control group (21.4 ± 2.7 kg/m^2).

	Control	Patient
Sample size	43	37
Age (years)	23.4 ± 5.5	22.9 ± 9.6
BMI (kg/m^2)	21.4 ± 2.7	19.7 ± 3.3*
SBP (mmHg)	102.3 ± 8.5	98.2 ± 13.0
DBP (mmHg)	72.5 ± 7.7	64.3 ± 8.4*

Table 1: Basic clinical characteristics of patients diagnosed with eating disorders compared to control subjects. Values are expressed as Mean ± SD. a2-sample independent-groups t-test for the difference between controls and patients (*$p < 0.05$).

HRV results at baseline indicated an abnormal sympathovagal balance in the patient group with LF/HF and SD1/SD2 ratios being significantly lower when measured in the sitting position ($p < 0.05$) (Table 2). To obtain a better response under sympathovagal challenge, patients also had their heart rate recorded and analyzed whilst standing. The results indicated a change in the nonlinear parameters with a lower SD1/SD2 ratio ($p = 0.022$) and a lower HRV complexity measured by SampEn ($p < 0.001$).

At Admission	Control	Patient	p
Sitting	(N = 41)	(N = 36)	
Mean RR (ms)	793 (169)	813 (171)	ns
RMSSD (ms)	35 (23)	32 (27)	ns
TINN (ms)	211 (100)	197 (145)	ns
HF peak (Hz)	0.21 (0.13)	0.27 (0.11)	ns
LF power (ms^2)	750 (692)	605 (1014)	ns
HF power (ms^2)	389 (620)	413 (595)	ns
LF/HF ratio	1.94 (1.84)	1.29 (1.75)	0.042
SD1 (ms)	25 (16)	23 (19)	ns
SD2 (ms)	52 (21)	47 (31)	ns
SD1/SD2	0.46 (0.20)	0.48 (0.30)	ns
SampEn	1.61 (0.34)	1.61 (0.35)	ns
Standing	(N = 41)	(N = 35)	ns
Mean RR (ms)	693 (163)	670 (154)	ns
RMSSD (ms)	22 (17)	22 (16)	ns
TINN (ms)	174 (89)	203 (146)	ns
HF peak (Hz)	0.19 (0.10)	0.17 (0.08)	ns
LF power (ms^2)	577 (964)	676 (824)	ns
HF power (ms^2)	244 (359)	165 (349)	ns
LF/HF ratio	3.36 (3.82)	3.67 (2.77)	ns
SD1 (ms)	16 (12)	16 (12)	ns
SD2 (ms)	44 (26)	49 (30)	ns
SD1/SD2	0.34 (0.10)	0.29 (0.15)	0.022
SampEn	1.58 (0.42)	1.27 (0.44)	<0.001

Table 2: HRV parameter values for controls and patients at admission.

Significant differences in HRV following the 6-week treatment between the control and patient group were observed. We did not observe any change in the control group as expected, which received no treatment and were free of ED, cardiorespiratory and kidney disease (Table 3). The ED group showed a significant decrease in mean RR intervals suggesting an overall increase in heart rate ($p = 0.002$). This increase in heart rate whilst sitting is reflected by the significant decrease in RMSSD ($p = 0.048$) and TINN ($p = 0.033$). The HF peak also increased significantly for HRV measured during sitting ($p = 0.016$), which may be associated with respiration frequency in this group of patients. Measures of HRV whilst standing only indicated a significant increase in the SD1/SD2 ratio ($p = 0.007$) with sample entropy showing a slight decrease in the patient group, which was not significant.

Treatment effect	Control	Patient	p
Sitting	(N = 31)	(N = 18)	
Mean RR (ms)	7 (131)	-64 (76)	0.002
RMSSD (ms)	2 (16)	-9 (18)	0.048
TINN (ms)	22 (68)	-17 (138)	0.033
HF peak (Hz)	0.00 (0.06)	0.04 (0.07)	0.016
LF power (ms^2)	197 (744)	-101 (1250)	ns
HF power (ms^2)	96 (485)	-76 (575)	ns
LF/HF ratio	-0.01 (1.95)	0.01 (0.87)	ns
SD1 (ms)	1 (11)	-6 (13)	0.048
SD2 (ms)	4 (16)	-3 (46)	ns
SD1/SD2	0.04 (0.25)	0.01 (0.27)	ns
SampEn	0.03 (0.30)	0.05 (0.27)	ns
Standing	(N = 32)	(N = 15)	ns
Mean RR (ms)	-9 (99)	-46 (119)	ns
RMSSD (ms)	0 (17)	5 (18)	ns
TINN (ms)	12 (120)	-8 (122)	ns
HF peak (Hz)	0.01 (0.07)	0.01 (0.11)	ns
LF power (ms^2)	85 (476)	36 (893)	ns
HF power (ms^2)	-13 (211)	-29 (511)	ns
LF/HF ratio	0.71 (2.03)	-0.07 (5.43)	ns
SD1 (ms)	0 (12)	-3 (13)	ns
SD2 (ms)	5 (27)	-7 (37)	ns
SD1/SD2	-0.03 (0.07)	0.02 (0.09)	0.007
SampEn	-0.11 (0.23)	-0.05 (0.40)	ns

Table 3: Change in HRV parameter values for controls and patients following 6-weeks treatment. Values are in Median (IQR); ns-non-significant. Wilcoxon signed rank test for the difference between admission and discharge for patient group.

Discussion

Our patient group was characterized by a lower heart rate with a significantly depressed sympathovagal balance both whilst sitting and also whilst standing. We included standing as a factor following work by Kiviniemi et al. [17] who suggested that HRV should be measured whilst standing in cohorts with increased parasympathetic input due to HRV being sensitive to saturation effects.

This paper addresses a nexus between psychophysiology and clinical research in cardiology. The latter, HRV changes in heart disease [18]. However the clinical picture of ED has aspects that belong to both the pathophysiological and psychophysiological domains, which remains to be thoroughly investigated. HRV may therefore represent a means to quantify this interaction and indicate risk of cardiac complications, not only in ED but also noted in depression and other psychosis [19,20].

A lowered body mass index (BMI) is often cited as the main factor for the increased risk of cardiac morbidity and mortality due to arrhythmia and related to vagal overdrive as a response to low BMI [4,21,22]. The present finding is consistent with previous results that eating disorder patients have symptoms of vagal hyperactivity [23-26]. This sympathovagal imbalance may contribute in part to cardiac autonomic dysfunction. A non significant decreased mean RR interval and HF power in patients compared to control were observed in the standing position, reflecting withdrawal of parasympathetic autonomic modulation in the standing position. Decreased parasympathetic modulation as well as sympathetic stimulation occurs in response to standing [27]. However, eating disorder patients may experience a greater reduction of parasympathetic activity, which could lead to autonomic imbalance, indirectly and/or directly if not treated. This may account for symptoms such as dizziness or fainting that are frequently reported by eating disorder patients. Our findings are in agreement with Kreipe et al. [28] that AN patients are characterised with an inappropriate retention of both sympathetic and parasympathetic modulations of the HR in response to postural change.

Approximately one third of deaths of anorexia nervosa patients are due to cardiac complications but pronounced hypotension, bradycardia or also tachycardia are often not considered [29-31]. However eating orders in general lead to changes in electrolyte content and associated whole-body organ dysfunction including the heart. Hypotension and sinus bradycardia is common in AN [9]. This probably results from elevated parasympathetic tone, which occur to compensate for the starvation activity along with reduced metabolic expenditure. Moreover, repolarisation abnormalities and prolongation of ECG Q-T interval are thought to be associated with ventricular arrhythmia and severe weight loss [26,32]. However, a number of studies of HRV have confirmed that these structural and functional abnormalities of the cardiovascular system provoked by AN are reversible after weight restoration [9,25,28,29,33]. This study indicated that HRV in ED patients is lower than control, especially HRV complexity measured by Sample Entropy. The 6-weeks in house treatment program led to an improvement in BMI and psychological behavior, which was reflected by changes in HRV to a level that is closer to control values for the HRV features measured.

Heart rate and heart rate variability are useful as an independent predictor for cardiac morbidity and mortality [34-36]. Very few HRV studies have been conducted in eating disorder patients under the conditions that we used: at admission to a hospital treatment program, followed up at the end of treatment and using a full HRV test battery.

The majority of previous studies investigating eating disorders report findings in the time and frequency domain for describing heart rate dynamics and possible causes of arrhythmias. These studies often reported vagal predominance with only a few discussing nonlinear HRV measures. The current study reports on both linear and nonlinear measures and highlight the response to treatment. Nonlinear HRV provides additional and more sensitive indicators of HRV describing the qualitative features of the heart rate dynamics and its complexity. In our cohort sympathovagal balance improved in the patient group but the change in complexity measured by SampEn was negligible. This is an important finding and needs to be further investigated in future studies.

The present study is the largest study of cardiac autonomic dysfunction in ED that applied a battery of linear and nonlinear HRV tests and investigated the impact of a 6-weeks treatment program on an eating disorder patient group.

Limitations

The findings of several studies suggested that psychological disease such as anxiety, major depression, phobias, panic disorders and schizophrenia are associated with altered HRV and increased risk of cardiovascular disease [37-40]. In addition various cardiovascular drugs have effects on HRV [12]. The effect of antidepressants and antipsychotic drugs on HRV depends on their receptor target profile and remains controversial. Tricyclic antidepressants decrease HRV, whereas selective serotonin receptor inhibitors (SSRIs) elevate HRV and exert beneficial effects on cardiac function by stimulating the parasympathetic activity [41]. Most of our patients were taking medications and had other concurrent illness including depression, which may affect HRV to some extent. This is in agreement with studies that have shown that therapeutic doses of SSRIs having been shown not to alter HRV measures in depressed patients [41].

Conclusion

The present study clearly demonstrates that eating disorders are associated with cardiac autonomic dysfunction. Our results confirm vagal predominance and significant sympathovagal difference in the group with eating disorders compared to control. Further follow-up studies are needed to clarify and substantiate the importance of HRV in relation to physiology and disease progression and the role of BMI and comorbidities such as anxiety and depression.

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