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Decreased Sample Entropy to Orthostatic Challenge in Anorexia Nervosa

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Abstract

Objective: The objective was to determine changes in heart rate variability (HRV) in response to orthostatic challenge in a convenience sample of patients with anorexia nervosa compared to age-matched controls. A decrease in HRV has been shown to correlate with an increased risk of heart attack in coronary artery disease and heart failure patients.

Method: Clinical data and ECG recordings were collected from 37 patients with eating disorders of which 16 had a diagnosis of anorexia nervosa and 42 controls. HRV was analyzed using linear and nonlinear methods during rest and orthostatic challenge from sitting to standing.

Results: Significant sympathovagal changes were identified in the anorexia nervosa group, especially with nonlinear HRV parameters and orthostatic challenge. Sample entropy, a nonlinear measure provided the best discrimination between the two groups on standing (1.58 ± 0.42 vs. 1.19 ± 0.4; $p<0.0001$) and when the change in HRV was measured from sitting to standing (-0.06 ± 0.36 vs. -0.42 ± 0.34; $p<0.0001$). The anorexia nervosa group had a significantly larger response to orthostatic challenge compared to the control group suggesting sympathetic dysfunction. Discussion: Including nonlinear measures and orthostatic challenge from an ECG recording of anorexia nervosa patients at initial clinical assessment on admission to hospital provides a noninvasive, sensitive tool to determine loss of normal physiological autonomic control of heart rate that may be related to an increased risk of arrhythmic events that requires further monitoring.

Conclusion: Nonlinear HRV measures are more sensitive in identifying sympathetic and parasympathetic changes associated with orthostatic challenge in patients with anorexia nervosa.

Keywords: Arrhythmic risk; Metabolic changes; HRV; Antidepressants

Introduction

Eating disorders (ED) 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 [1,2]. People with ED have the highest mortality of any psychiatric disorder, associated with an increase in cardiovascular morbidity and sudden cardiac death [3-5]. The greatest concerns are cardiac complications related to arrhythmias and electrolyte disturbances that may be caused by factors associated with malnutrition [6]. 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 vagal overdrive as a response to low BMI [7,6,8]. However metabolic factors may also lead to sympathetic predominance and further contribute as comorbidities in anorexia nervosa [9].

Patients with a BMI below 18.5 kg/m^2 have been shown to be at risk of various cardiac arrhythmias [10] including QT-interval prolongation, T-wave and a decrease in left ventricular ejection fraction also contributes to the morbidity and mortality seen in AN patients [11,12]. Alterations in sympathetic and parasympathetic regulation of the heart as a response to oxidative stress and inflammation, electrolyte and body-water disturbances, muscular damage, renal disease and structural changes of the heart have also been observed in AN [13,14].

Sympathetic and parasympathetic control of the heart rate can be explored using heart rate variability (HRV) analysis and determined from heart rate recordings whilst in supine, sitting, or standing position using simple plethysmograph from finger or wrist straps, making the investigation less invasive and quicker. Orthostatic challenge has been advocated previously as a more sensitive measure of

the ANS contribution to heart rate in AN and is correlated with an abnormal sympathetic activation and vagal withdrawal [15,16]. Decreased vagal activity and/or increased sympathetic input to the heart's pacemaker reduce the variability and complexity of cardiac dynamics [17]. HRV analysis is divided into linear and nonlinear measures, which provide information on different aspects of the temporal variation of the heart rate signal [18]. The study of HRV in patients with ED has already provided important information on the integrity and function of the complex physiologic mechanisms controlling heart rate in this chronic condition [19,20]. However, the studies in AN patients primarily utilized linear methods to evaluate sympathovagal balance. Several of these studies have reported decreased vagal tone whilst others found an increase in parasympathetic activity [21,22,6,23-25]. Other studies report no change or altered sympathovagal balance [26,27]. Head-up tilt or HRV change following standing and investigating sympathetic and parasympathetic activity have also been reported [16,28] One study investigated influence of medication [29]. These highly controlled studies are essential in establishing physiological mechanisms and possible causes for disease development and progression but do not address the utility of HRV measures in a clinical situation at admittance to a treatment facility.

The aim of this study was to assess HRV from short-term electrocardiogram (ECG) recordings of AN patients and healthy controls using both linear and non-linear methods of analysis to understand the relationship between orthostatic HR changes in patients with AN at admittance to a treatment facility.

Methods

Study population

Thirty-seven patients referred to the inpatient Eating Disorders Unit at the Sydney Northside Clinic, who fulfilled the DSM-V criteria (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) for eating disorders [30] were recruited using convenience sampling. Subsequently sixteen patients were identified with AN and included in the study. Forty-two healthy age-matched subjects were recruited from the University of Sydney to form the control group. All participants gave fully informed consent. The study was approved by the University of Sydney Ethics Committee (Reference number 7475) and the Ramsay Sydney Psychiatric Hospital Ethics Committee (Reference number 114).

Experimental procedures

All participants completed a general health status questionnaire on admission to the clinic. Medical records were accessed to obtain additional information on clinical diagnoses, laboratory findings and medication use.

A PowerLab 2/20® 2-channel data acquisition system with 16-bit resolution (Model ML850, ADInstruments, Australia) at a sampling rate of 400 Hz was used to obtain the ECGs at time of admission to the program. Resting ECGs in a sitting position were recorded for 20 minutes after a 5-minute rest in a and for five minutes in the standing position after allowing one minute for adaptation to standing posture. Biosignal recording was undertaken in silence in an ambient temperature room during admission between 10 am and midday. Clients were requested to abstain from smoking, caffeine and alcohol from the previous day to attending the clinic.

Body mass index (BMI) was calculated from the weight and height data measured for both patients and controls at admission to the hospital. Only patients who had results for ECG and BMI were included in the study.

Software

Chart™ (Version 5.0.1, ADInstruments, Australia) was used for recording the ECG traces. Kubios HRV software (Kuopio, Finland) was used to determine time and frequency domain parameters as well as nonlinear measures. For HRV analysis, 5-minute ECG data segments and corresponding RR intervals were extracted from the end of the sitting period and from the beginning of the standing period. All RR time series were first preprocessed to remove frequencies below 0.04 Hz and ectopic beats [31] and time series 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 (150 second window and 50% overlap).

Measurement of heart rate variability

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), root mean square of successive RR interval differences (RMSSD) and percentage of successive RR intervals differing more than 50 ms (pNN50). The HRV triangular index (HRVtri) and triangular interpolation of RR interval histogram (TINN) were also computed. Frequency-domain parameters included peak frequencies at low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz) bands, powers of LF and HF bands in absolute (ms2) and normalized units (n.u.), the LF/HF ratio and total spectral power. Poincaré plot analysis quantified by standard deviations SD1 and SD2, and their ratio SD1/SD2, sample entropy (SampEn), detrended fluctuation analysis (DFA, quantified by slope coefficients α1 and α2), recurrence plot analysis (RPA, quantified by coefficients REC, DET and Lmean), and correlation dimension (D2) were the nonlinear parameters of the study (http://kubios.uef.fi/) [31].

Statistical analysis

Statistical calculations were performed using SPSS (Version 22 for Windows) and Matlab (Version R2012a for Windows). Basic clinical data are expressed as mean ± standard deviation. The normality of all variables was assessed by the Kolmogorov-Smirnov goodness-of-fit test. HRV parameters not normally distributed, are expressed as median ± interquartile range (IQR) and statistical differences between the healthy control and AN group were analyzed using the non-parametric Wilcoxon rank-sum test at $p<0.05$.

Results

All patients with AN were taking a variety of medications including antidepressants (e.g. SSRIs), antibiotics, anti-asthmatics, hormone-replacement therapy and/or contraceptive pills, multivitamins, minerals and analgesics. Control subjects had normal weight and activity levels and reported use of non-prescription analgesics, antibiotics, asthma medication and oral contraceptives. All participants were free of known cardiovascular disease, diabetes mellitus, neurological and other systemic diseases.

Clinical characteristics

The demographic, clinical and lifestyle characteristics of all 58 participants 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 (16.8 ± 1.7 kg/m^2) were significantly lower than those of the control group (21.4 ± 2.7 kg/m^2).

Lifestyle factors

The percentage of smokers in the patient group was significantly greater than in the control group ($p<0.05$). Caffeine use was also higher among patients. No significant difference was noted for any of the HRV variables with respect to caffeine or smoking use for control and patient groups ($p>0.05$).

	Controls	Patients	p-value
Sample size (n)	42	16	
Age (years)	23.4 ± 5.5	21.7 ± 10.5	NS
(Range)	(17-46)	(15-59)	NS
BMI (kg/m^2)	21.4 ± 2.7	16.8 ± 1.7*	<0.05
Smokers (%)	2	25$^\#$	<0.05
Caffeine Users (%)	47	75$^\#$	<0.05

Values are expressed as means ± SD and range for Age and BMI. Values are % for smokers and caffeine users. Significance of differences: *Groups compared with using the 2-sample independent-groups t-test. $^\#$Groups compared using Pearson's Chi-Squared test with Fisher's exact test. BMI-body mass index.

Table 1: Basic clinical and life style characteristics of patients diagnosed with eating disorders compared with control subjects.

Differences in HRV parameters in sitting position

No significant differences were found for time domain, frequency domain and non-linear parameters whilst in a sitting position in patients with AN and control participants.

HRV parameters in standing position

Table 2 and Table 3 shows the median values for HRV parameters obtained from the 5-minute standing recording of patients with AN and control.

The triangular index was significantly lower and RMSSD and pNN50, which are indicators of parasympathetic function, were reduced. Frequency domain parameters were not significantly different between the groups, although lower HF peak values in the AN group were suggestive of parasympathetic withdrawal.

SD1/SD2 and SampEn were significantly decreased in the AN group. DFAα2, the recurrence plot analysis results and the correlation dimension (D2) were all significantly higher in the AN group compared to control.

Table 4 compares the change in HRV to orthostatic challenge between the groups. Between group differences were again apparent in nonlinear HRV measures. Heart rate increased dramatically in the AN group and was the only significant outcome for time domain measures. The percentage change in heart rate variability on standing from a sitting position was significantly different between the control and ED group (9.8 ± 9.5 vs. 18.04 ± 9.2, <0.001).

Discussion

Approximately one third of deaths of anorexia nervosa patients are due to cardiac complications [32,5]. Heart rate and HRV were established as significant clinical predictors for cardiac morbidity and mortality by various groups [33,34]. Previous research has indicated that HRV whilst standing or following orthostatic challenge may give more sensitive measures of ANS functionality [35,15]. However no HRV studies including an orthostatic challenge were conducted in patients at admission to a treatment program as a sensitive indicator of risk of cardiac arrhythmia. The importance of the current paper is that although a clinical review by the admissions nurse can in many instances identify abnormal orthostatic vital signs such as syncope, available HRV can add a simple quantifiable measure and provide admission nurses with an indication of rhythm disturbance requiring further assessment not otherwise identified even with an ECG.

HRV measures	Controls (n=42)	Patients (n=16)	p-value$^\#$
Time domain			
Mean RR intervals (ms)	692.87 ± 163.10	644.23 ± 92.48	0.07
SDNN (ms)	33.50 ± 20.31	24.17 ± 20.82	0.15
RMSSD (ms)	22.21 ± 17.48	15.97 ± 16.62	0.09
pNN50 (%)	2.12 ± 11.36	0.59 ± 3.00	0.09
HRVti	9.37 ± 3.91	6.48 ± 4.47	0.03
TINN (ms)	175 ± 86	161 ± 126	0.57
Frequency domain			
LFpeak (Hz)	0.08 ± 0.04	0.07 ± 0.03	0.4
HFpeak (Hz)	0.19 ± 0.10	0.17 ± 0.04	0.09
LF power (ms^2)	577.03 ± 964.63	436.11 ± 876.57	0.27
HF power (ms^2)	243.77 ± 359.45	103.02 ± 246.44	0.12
LF/HF ratio	3.36 ± 3.82	3.76 ± 4.54	0.4
Total Power (ms^2)	1168.02 ± 1342.10	746.51 ± 1330.14	0.22

Table 2: Comparison of HRV measures evaluated from 5-minute standing ECG recordings in control subjects and patients diagnosed with anorexia nervosa.

Nonlinear HRV analysis following an orthostatic challenge may be useful as additional clinical marker for risk stratification at admission to a treatment facility and indicate a more closer monitoring the patient as well as more carefully re-nourishing the patient and restricting physical exercise is required.

Studies on the changes in HRV following orthostatic challenge in AN patients have not produced consistent findings [27,2,36,28,32]. The time and frequency domain analysis in seated subjects showed no significant differences between the control and AN group in agreement with some previous studies [26,24,37]. A decreased low frequency power was found in our study but was not significant in contrast to studies reported by [38,2,22]. However other studies report no

difference in LF power [39]. Increased low frequency activity [21,23,28,32,6,40,7] and an unaltered HRV [41] or very similar HRV results with a decrease in LF have also been observed [42,27]. ECG recording and analysis from a sitting patient is not uncommon and has been shown not to influence HRV analysis significantly but may result in a lower parasympathetic amplitude response and higher sympathetic response [43,44].

Nonlinear			
SD1 (ms)	15.72 ± 12.38	11.30 ± 11.77	0.09
SD2 (ms)	44.30 ± 26.24	33.50 ± 29.55	0.15
SD1/SD2	0.34 ± 0.99	0.28 ± 0.17	0.04
SampEn	1.58 ± 0.42	1.19 ± 0.40	0.0001
DFA α1	1.41 ± 0.34	1.39 ± 0.39	0.80
DFA α2	0.57 ± 0.16	0.72 ± 0.27	0.02
REC (%)	0.31 ± 0.09	0.38 ± 0.08	0.0006
DET(%)	0.98 ± 0.01	0.99 ± 0.01	0.0002
Lmean	9.88 ± 3.02	11.94 ± 4.60	0.003
D2	1.05 ± 2.94	0.49 ± 1.24	0.05

Values are expressed as medians ± IQR.

[#]p-values from Wilcoxon rank sum test for the difference between controls and patients. Abbreviations: RR interval- Interpeak interval from the QRS wave of the ECG; SDNN-Standard deviation of normal RR intervals; RMSSD-Root mean square of standard deviation of RR intervals; pNN50-Mean number of times change in successive normal sinus (NN) intervals exceeds 50 ms per hour; HRVti-Heart Rate Variability Triangular Index; TINN- Triangular interpolation of normal RR intervals; LF-Low frequency power derived from Fast Fourier Transform of time series; HF- High frequency power derived from Fast Fourier Transform of time series; SD1-Poincaré Plot short term correlation property; SD2-Poincaré Plot long-term correlation property; SampEn- Sample Entropy; DFA α1-Detrended Fluctuation Analysis-Short-term correlation; DFA α2-Detrended Fluctuation Analysis-Long-term correlation; REC(%)-Percent recurrence rate of RR intervals; DET (%)-Percentage determinism from recurrence plot; Lmean-Mean length of recurrence plot; D2-Correlation dimension. Extended definitions of HRV measures can be found in [31].

Table 3: Comparison of HRV measures evaluated from 5-minute standing ECG recordings in control subjects and patients diagnosed with eating disorders.

Of note in Table 4 is the significant difference in adjustment of the sympathovagal balance. During standing the levels of sympathovagal balance measured by LF/HF were similar in both groups.

However in the AN group the change was nearly 3 times greater on orthostatic challenge. Concomitant with this change in sympathovagal balance was a significant decrease in the HFpeak frequency, which indicates a greater change in breathing frequency occurring in the AN group.

Results of the nonlinear HRV parameters indicate that the HRV complexity, measured by SampEn, decreased significantly in the AN group. The ΔSD1/SD2 also differed significantly between groups. Recursive plot analysis indicated a much more extensive drop in complexity following orthostatic challenge in the AN group with a significant difference between groups as well.

HRVti, which was significantly reduced in the AN group, is a measure of parasympathetic regulation and indicates parasympathetic withdrawal [39,26].

Nonlinear measures including sample entropy were significantly decreased, whilst the recurrence mapping features and DFA α2 showed significant increases. Similarly SD1/SD2 was significantly lower in the AN group suggesting increased sympathetic activity.

Combined, these nonlinear HRV features suggest a decrease in complexity of the fundamental control of the heart rate response in AN patients whilst standing due to possible increased sympathetic activity or vagal withdrawal.

A conclusion that can be drawn from these results is that heart rate signals in AN patients whilst standing show less complex behavior and that heart rate changes are less correlated over time [45,37,46].

These results are further corroborated by the decreased fractal correlation dimension (D2) and an increased mean Lyapunov exponent (Lmean) in the AN group.

Clinical consequences and implications

Most of our patients were taking medications and had other concurrent illness such as depression, which may have affected HRV to some extent. However, recent studies have demonstrated that the therapeutic doses of SSRIs do not alter HRV measures in depressed patients and are therefore not likely to have had a strong influence on the current results [18].

Despite the limitations discussed above, the present study clearly demonstrates that AN is associated with cardiac autonomic dysfunction in a group of AN patients at admission to a treatment facility.

Further research is required to investigate whether changed HRV on orthostatic function can identify patients who subsequently go on to develop a cardiac arrhythmia or whose clinical outcome might be different.

HRV measures†	Control (n=42)	Patient (n=16)	p-value#
Time domain			
ΔMean RR intervals (ms)	-62.46 ± 67.66	-125.50 ± 6.04	0.0008
ΔSDNN (ms)	-7.18 ± 8.83	-7.95 ± 13.37	0.76
ΔRMSSD (ms)	-9.97 ± 12.40	-13.40 ± 16.87	0.3
ΔpNN50 (%)	-6.21 ± 15.64	-3.39 ± 24.89	0.96
ΔHRVti	-1.55 ± 3.56	-1.69 ± 2.47	0.37
ΔTINN (ms)	-38 ± 55	-17 ± 86	0.59
Frequency domain			
ΔLFpeak (Hz)	0.002 ± 0.028	-0.008 ± 0.055	0.25
ΔHFpeak (Hz)	-0.003 ± 0.083	-0.060 ± 0.145	0.04
ΔLF power (ms²)	-109.45 ± 597.34	-126.62 ± 524.51	0.891
ΔHF power (ms²)	-144.70 ± 264.72	-212.80 ± 661.02	0.43
ΔLF/HF ratio	0.79 ± 1.80	2.08 ± 2.56	0.04
ΔTotal Power (ms²)	-447.32 ± 806.74	-334.28 ± 753.72	0.85
Nonlinear			
ΔSD1 (ms)	-7.06 ± 8.78	-9.49 ± 11.95	0.3
ΔSD2 (ms)	-7.45 ± 11.71	-8.87 ± 19.87	0.78
ΔSD1/SD2	-0.087 ± 0.15	-0.17 ± 0.18	0.004
ΔSampEn	-0.06 ± 0.36	-0.41 ± 0.34	0.0001
Δ DFA α1	0.23 ± 0.21	0.31 ± 0.43	0.08
Δ DFA α2	0.02 ± 0.15	0.12 ± 0.21	0.09
ΔREC(%)	0.03 ± 0.11	0.11 ± 0.13	0.03
ΔDET(%)	0.01 ± 0.02	0.02 ± 0.02	0.009
ΔLmean	0.77 ± 2.57	3.24 ± 3.22	0.007
ΔD2	-0.47 ± 1.97	-0.43 ± 1.57	0.72

Values are expressed as medians ± IQR, differences from sitting to standing (Δ=standing minus sitting). ‡Wilcoxon signed rank test to test the significance between the two-paired samples (sitting vs. standing).

Table 4: Comparison of changes from sitting to standing in HRV measures in control subjects and eating disorder patients.

In conclusion, non-linear HRV analysis combined with orthostatic challenge may constitute a valuable clinical tool in assessing patients with AN to identify cardiac autonomic neuropathy to provide appropriate treatment options to reduce risk of cardiac arrhythmia.

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