Cardiovascular complications and sudden death associated with eating disorders

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Abstract

Sudden death in eating disordered patients has been attributed to cardiac arrhythmias and susceptibility might be identified by using heart rate variability (HRV) as a marker of impaired cardiac autonomic regulation. The aim of the study was to examine this parameter in female eating disorder patients and the effect of a short rehabilitation programme. HRV was investigated by linear and nonlinear analysis of ECG recordings from hospitalised female patients with diverse eating disorders. Twenty minute ECG recordings were made at admission, one week and six weeks later. HRV was significantly lower and of reduced complexity across eating disorder groups compared to control. Autonomic dysregulation was shown and differences between the groups persisted after six weeks of specialised hospital treatment. Heart rate variability can be measured simply and has potential as a marker of cardiac risk and an indication for high level care across the spectrum of eating disorders.

Work was carried out at the Northside Clinic Eating Disorders Program, Greenwich, Australia.

INTRODUCTION

Cardiovascular perturbations associated with eating disorders suggest that autonomic regulation of the heart is affected in these conditions. Sudden death has been reported in anorexia nervosa.(1) This could be a consequence of low body weight, weight losing behaviours, associated mood states or medications.(1-4) Heart rate variability (HRV), the moment to moment fluctuations in heart rate over time and frequency domains, reflects the underlying stability of autonomic function, the integration of sympathetic and parasympathetic modulation and susceptibility to potentially fatal cardiac arrhythmic events.(5) Previous results on heart rate variability (HRV) analysis in anorexia nervosa (AN) include some apparently conflicting data that is resolved if acute and chronic AN are considered separately. Acute AN is characterized by decreased heart rate (HR) and increased HRV. In chronic AN, HR is increased but HRV reduced.(6, 7)

Reduced HRV has been demonstrated in AN using linear analysis methods but little has been published concerning HRV in other eating disorders.(3, 4, 8) These include the syndromes of bulimia nervosa, characterised by normal body weight, binge eating and weight losing behaviours of a specified frequency, and EDNOS. In EDNOS diagnostic criteria for anorexia nervosa (emaciation as defined by a body mass index of 17.5 or less) and bulimia nervosa have not been met despite similarly eating disordered behaviours and attitudes. A risk of premature death similar to that seen in anorexia nervosa has been reported in EDNOS.(9)

METHODS

Participants in the study were females diagnosed with anorexia nervosa (N=17), eating disorders otherwise not specified (EDNOS) (N=9) and bulimia nervosa (N=3). All were participating in a specialised hospital treatment program. Subjects gave their informed consent and the study protocol was approved by the Charles Sturt University Committee on Human Research. Diagnosis was reached by clinical consensus based on DSMIV and ICD10 criteria(10, 11) and by use of a computerised diagnostic instrument (EEE-C).(12) All patients had been engaging in weight losing behaviours prior to hospital admission and the majority were anxious and/or depressed. The proportion of smokers in both patient and control groups was similar. All patients were ostensibly medically stable when first assessed and no major ECG or biochemical abnormalities were detected. HRV was analysed soon after admission, one week later and prior to discharge (mean interval 6 weeks). ECG recordings were made at least 30 minutes after main meals and smoking. During their hospital stay, patients were started on various regular medications including nutritional

supplements, hormone replacement, antidepressants and novel antipsychotic agents, depending on clinical need. When weight gain was indicated, this was achieved at a mean rate of 0.7kg per week.

Thirty five age-matched, healthy, weight stable female controls were also studied on 3 occasions over a six week period. Similar time intervals between meals and smoking were observed. Eating disorder diagnoses were excluded by use of a semi-structured interview and by assessment of BMI, the mean of which was in the normal range at 21.3[3.0] Kg/m2.

HRV was measured for 20-minute epochs using a 3-lead ECG, digitised using PowerLab® and recorded with Chart® software with which linear parameters of time and frequency domains were determined. Fast Fourier Transformation was used to calculate frequency parameters of variability.(3, 4) Parameters associated with non-linear (chaotic) properties of HRV ie approximate entropy and detrended fluctuation analysis were determined using Soft ECG (Version 1.3.8.17, copyright H Jelinek).

Statistical analysis was performed using SPSS. HRV variables which were not normally distributed were logarithmically transformed to achieve normal distribution. Student's t-tests and repeated measures ANOVA were used where appropriate to examine demographic variables, HRV changes over time and between controls and patient sub-groups, effects of medication, weight and smoking. Data from the bulimia nervosa group was not analysed separately but combined with data from the EDNOS group. All probability values were derived from 2-tailed tests and $p < 0.05$ considered significant. Means and standard deviations are shown.

RESULTS

The mean±sd body mass index (BMI) of anorexia nervosa patients at 16.2±2.2 Kg/m2 was significantly different from that of controls, in contrast to the mean BMI of the bulimia nervosa and EDNOS patients which did not differ significantly. Mean age of patient group at 23.2±10.4 years did not differ significantly from that of controls. Demographic data are shown in Table 1.

Figure 1

Table 1. Baseline characteristics of female patients with eating disorders (anorexia nervosa, bulimia nervosa and EDNOS) compared with female control patients

Parameter	Controls	Patients (overall)	Anorexia Nervosa	Bulimia nervosa	EDNOS
Sample size (n)	35	29	17	3	9
(years)	22.9±5.0	23.2±10.4	23.6±10.6	20.7±4.0	23.3±12.1
(Range)	(18-45)	(14-59)	(15-59)	(18-25)	(14-53)
BMI (kg/m2)	21.3±3.0	18.9±4.3*	16.2±2.2**	23.6±4.4	22.3±3.6
(Range)	18.7-34.2	(11.4-28.7)	(11.4-19.8)	(20.4-28.7)	(18.0-28.2)
No. smokers	9	21	6	33	44#
No. caffeine users	66	45	41	67	44

Values are mean±SD and range for age and BMI. Values are % for smokers and caffeine users. Significance of difference *p<0.05, **p<0.005 compared to the control group using the 2-sample independent groups t-test. # p<0.05 compared with control group using Pearson's Chi-Squared test and Fisher's exact test.

HRV parameters were stable and reproducible over time in control subjects. Significant differences were seen between patients (EDNOS/bulimia nervosa and anorexia nervosa sub-groups and patient group as a whole) and controls on both linear and non-linear measures of variability. These are summarised in Table 2.

Figure 2

Table 2. Comparisons of heart rate variability measures evaluated from 20-min recordings in controls and patients with eating disorders at admission and discharge.

HRV parameter	Controls (n=35)	Patients at admission (n=29)	Patients at discharge (n=29)	AN at admission (n=35)	EDNOS/BN at admission (n=12)
Time domain					
SDNN (ms)	63±14	59±23	51±22	63.1±6-3	53.8±5.0
Ln(RMSSD)	48±16	38±26*	33±21	3.6±6.3	3.3±0.3†
Ln(PNN50)	3.0±15	1.9±1.4**	1.5±1.8	2.1±0.4†	1.7±0.3†
Ln(SD1)	3.5±0.3	3.1±0.6*	3.0±0.6	3.2±0.1	3.0±0.1†
SD1/SD2	0.4±0.1	0.3±0.1*	0.3±0.1	0.37±0.04	0.3±0.02†
Frequency domain					
LF (nu)	60±13	69±13*	66±15	66.1±3.6	74.1±2.3†
HF (nu)	34±13	26±12*	27±13	29.7±3.5	21.2±1.9†
LF/HF	2.2±1	3.5±2*	3.3±2	3.2±0.6	4.1±0.7†
Ln(HF)	6.6±0.6	5.8±1.1**	5.6±1.2	6.0±1.3	5.9±0.7†
Non-linear analysis					
ApEn	1.42±0.12	1.23±0.22**	1.17±0.28	1.24±0.07a	1.22±0.03†
α_1 (beats 4 to 11)	1.15±0.19	1.26±0.27	1.25±0.27	1.19±0.07	1.38±0.05*,††
α_2 (beats 12 to 64)	0.79±0.14	0.88±0.13*	0.89±0.15	0.88±0.03	0.86±0.03

**(p<0.005), *(p<0.05) between controls and patient group (as a whole) on admission (t-test). No significant differences were seen between patients on admission and discharge (mean interval 6 weeks).

† significantly different (p<0.05) from the control group, †† significantly different from the AN group using Tukey's HSD post-hoc comparisons following one-way ANOVA (DF+ 2.61).

Abbreviations:

SDNN = standard deviation of the time between adjacent R-R peaks of normal ECG complexes (ie interbeat interval).

Ln(RMSSD) = $\log_n$ transformed square root of successive differences in interbeat interval.

Ln(PNN50) = $\log_n$ transformed number of adjacent R-R intervals differing by more than 50ms expressed as a percentage.

SD1/SD2 = ratio of time domain parameters calculated using a Poincaré plot.

LF(nu) = low frequency variability of HRV expressed as a standardised percentage index of the presence of low frequencies in the whole spectrum.

HF(nu) = high frequency variability of HRV expressed as a standardised percentage index of the presence of high frequencies in the whole spectrums (sometimes termed medium frequency (1,2).

nu = normalised unit, a standardised percentage index of the presence of high or low frequencies in the whole spectrum (as calculated by the software)

ApEn= approximate entropy a measure quantifying regularity and complexity of the time domain by algorithm (4).

α_1, α_2 = fractal scaling components using detrended fluctuation analysis.

A consistent pattern of difference was apparent with diminished parasympathetic modulation in the eating disordered groups. Linear HRV parameters (RMSSD, PNN50, SD1/SD2 or LF/HF; see Table 2 legend for abbreviations) and non-linear measures (approximate entropy (ApEn) or detrended fluctuation analysis (α_1, α_2 exponents) were reduced as shown in Figure 1. Non-linear measures also suggested differences in HRV between EDNOS and anorexia nervosa sub-groups. No association was found between HRV and weight or between HRV and use of any medication or smoking.

Figure 3

Figure 1. Representative samples of heart rate variability (HRV) of an anorexia nervosa (AN) patient, a patient with EDNOS and a control subject. Each tachogram recording shows the RR interval (ms) over 1200 consecutive beats (20 min trace). Corresponding heart rates for AN, EDNOS and controls were 71, 76, and 74 beats per minute and the approximate entropy (ApEn) was 1.2, 1.2 and 1.4, respectively. Note similarity of the reduced complexity for the two patients compared to the control tracing

AN

EDNOS

CONTROL
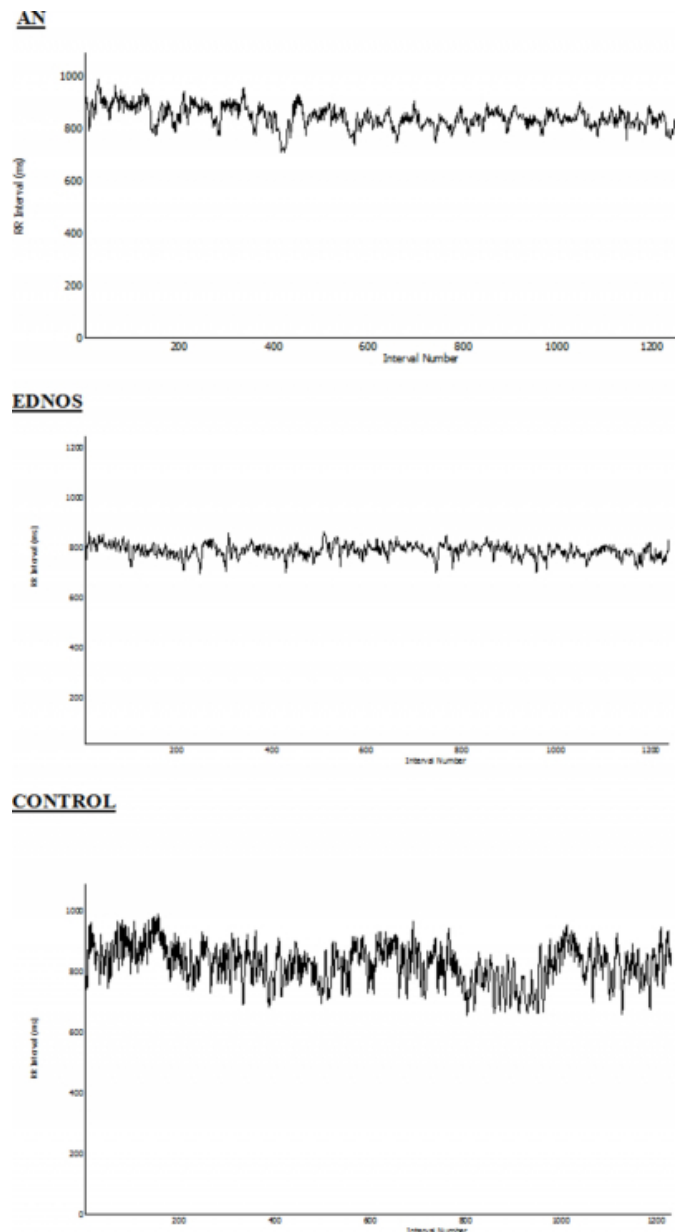
DISCUSSION

These data demonstrate lower HRV in both anorexia nervosa, and combined bulimia nervosa and EDNOS patients with no significant change after short-term clinical improvement ie weight gain, abstinence from weight losing behaviours and improved mood. Eating disorders, even those

considered to be subclinical or atypical can have pervasive cardiac autonomic consequences and despite doubt as to the utility of risk stratification in preventing sudden cardiac death in other forms of heart disease, HRV may predict prolonged susceptibility to arrhythmic events and the degree of medical risk. Sudden death in these usually young patients should be largely preventable.(13)

HRV was measured using fairly simple and portable equipment and when normal ranges can be established, it should be possible to refine the output so as to indicate whether a patient's heart rate variability indicates significant risk and thus an immediate need for high level care. With further refinement, diagnostic differentiation may be aided by this technique in conditions where patients may not always disclose the full extent of their disordered behaviours.

Emaciation should not be the sole determinant of a patient's need for high level ie specialised or tertiary care. The latter is multidisciplinary and entails nutritional rehabilitation and containment of weight losing behaviours for a prolonged period of time usually in an inpatient or intensive day program setting with appropriate support at home. Family and partners need to be assisted in helping the patient to continue with these behavioural changes when treatment is continued as an outpatient. Psychological treatments and psychoactive medications are often required to secure recovery. Techniques such as that described here to determine HRV, would seem to have promise in matching patients to appropriate treatment. It could be used to gauge progress in outpatient eating disorder clinics, in general practice or in non eating disorder specialist settings. Although general practitioner and physician training in the use of HRV assessment would not be expected to present a major problem, accessibility of high level treatment for eating disorders is becoming increasingly restricted in both public and private health sectors.(14)

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