Multiscale Cardiovascular Autonomic Modulation Following Treatment in Patients with Anorexia Nervosa

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Abstract

Eating disorders such as Anorexia Nervosa may be associated with changes in the cardiovascular system. Such changes have the potential to be identified using analysis of Heart Rate Variability (HRV). This study investigates multiscale HRV analysis in order to identify possible changes in the autonomic control of the cardiovascular system in subjects with anorexia nervosa. We investigated R-R intervals recorded during sitting position at admission and following a 6-week treatment program. HRV analysis included standard deviation and higher moments of R-R interval, as well as multiscale Renyi entropy.

Analysis using multiscale measures may prove a useful diagnostic and prognostic tool in anorexia nervosa, particularly in clinical monitoring of patients with increased risk of cardiovascular complications and sudden death.

Results showed statistically significant differences between controls and patients before intervention, suggesting changes to the cardiovascular autonomic function associated with eating disorders, which can be observed before treatment but not after. This can be observed in 20-minute recordings but not in 5-minute recordings.

1. Introduction

Sudden death can occur in patients suffering from eating disorders. This includes the unexpected demise of those who are apparently weight recovered. Cardiac arrhythmias have been implicated. Eating disorders are known to be associated with perturbations of the cardiovascular system [1]. It has been shown that patients with Anorexia Nervosa (AN) have altered autonomic cardiac control, but so far studies have found inconsistent alterations in Heart Rate Variability (HRV) in patients with anorexia nervosa prior or following treatment [2]. Reduced HRV has been demonstrated in AN using linear analysis methods but little work has been completed on the role of nonlinear methods in in eating disorders [2-4]. Such perturbations suggest a link between pathology and the autonomic regulation of the heart.

1.1. Heart Rate Variability (HRV)

HRV refers to the analysis of fluctuations in the beat-to-beat interval (R-R) or heart rate, and indicates modulation of cardiac rhythm by the autonomic nervous system. This includes the balance between sympathetic and parasympathetic effects [5]. In the case of AN, it is known that heart rate decreases and HRV increases in the acute stage of the disease, while the opposite is true for chronic AN [6,7].

HRV is commonly used in assessing the functioning of cardiac autonomic regulation [8]. The autonomic nervous system (ANS) regulates heart rate (HR) through sympathetic and parasympathetic branches. Roughly speaking, sympathetic activity increases HR and decreases HRV, whereas parasympathetic activity decreases HR and increases HRV [9]. HR is expressed as the number of beats per minute. The HR varies considerably between individuals, but a typical adult heart rate is 60-80 beats per minute.

The ECG signal is often degraded by the presence of noise, so that the most reliable feature that can be obtained from low quality recordings (and therefore the most easily obtained measurement) is the interval between successive R peaks, known as the R-R interval (inverse of heart rate). R-R intervals are obtained from the recorded ECG and the R-R variation can be subjected to further analysis through a variety of algorithms in order to yield variables with good discriminant power, based on

the difference of R-R interval variability with respect to the total recording interval.

The analysis of HRV has been the subject of extensive work using time and frequency based methods [10]. More recent analysis methods have shown an increased sensitivity for identifying risk of future morbidity and mortality in diverse patient groups. For example, an estimate of HRV using the standard deviation of R-R intervals found that this is higher in well-functioning hearts but can be decreased in coronary artery disease, congestive heart failure and diabetic neuropathy [11]. Although HRV is useful in disease detection, when only a simple derived measure is used, such as the standard deviation of R-R intervals, it is no better than the average heart rate and in fact has been shown to contain less information for risk prediction after acute myocardial infarction [12]. This indicates that more advanced measures of HRV should be explored. Some of the measures derived from the R-R interval fluctuations and used in this work are now discussed.

1.2. Multi-scale moments

Moments are measures of distribution, in this work the distribution of R-R intervals in a given recording. The familiar arithmetic mean and variance can be informally viewed as moments of order 1 and 2 respectively, where order refers to the exponent used in calculating these values. Higher order moments can be defined as:

$$m_k = E[(X-\mu)^k]$$

where *E[x]* is the expectation of *X*, and μ is the arithmetic mean of the variable *X*. Expectation is commonly interpreted as the sum of observations on *X* in a sample of size *n*, divided by *n*, so that for example the second moment or variance is defined as:

$$s^2 = \frac{1}{n}\sum_{i=1}^{n}(x_i - \bar{x})^2$$

which calculates deviation in observations x_i in the sample of size *n* from the mean. The third and fourth moments have a known interpretation, as the Skewness and Kurtosis respectively, although these are usually subject to corrections in order to address statistical bias and magnitude. Odd moments reflect the amount of asymmetry of the distribution and so can reveal whether the distribution is leaning to the left or right, and consequently whether the tails are larger on the lower or upper sides of the distribution.

Higher moments can be used to compare different groups of patients. It is usual to normalize these moments to provide a scale invariant spectrum:

$$\mu_k = \frac{m_k}{\sigma^k}$$

where μ_k is the standardized moment, and σ_k is the standard deviation raised to the power of *k*.

1.3. Multi-scale Renyi entropy

The multi-scale entropy has previously been introduced and applied to physiologic time series [13]. Renyi entropy H_α is a generalization of the Shannon entropy to include measures of different orders:

$$H_\alpha(X) = \frac{1}{1-\alpha} log_2\left(\sum_{i=1}^{n} p_i^\alpha\right)$$

where α is an exponent which determines the order. In terms of deriving a measure from a recording of R-R intervals, *X* is the vector of R-R intervals and p_i is the probability of each sub-sequence of *X*. This can be estimated by its similarity with all other sequences of the same length p_i [14]. Each sub-sequence is regarded as a point in a π-dimensional space, and its probability is estimated using a Gaussian kernel centered on each such point [15]. Then p_i is given by this density function:

$$p_i = \sum_{j=0}^{n} exp\left(\frac{-dist_{ij}^2}{2\sigma^2}\right)$$

where σ is a parameter controlling the width of the density function and *dist()* is a distance measure:

$$dist_{ij} = \sum_{k=0}^{\pi}\left(x_{i+k} - x_{j+k}\right)^2$$

Here, x_{i+k} is one R-R sample out of sequence of length π, the pattern length over which comparison occurs. Renyi entropy may be calculated for a range of α providing a spectrum of measures.

2. Methods

Participants in the study were 35 females diagnosed with Anorexia Nervosa (AN), and 35 aged matched, healthy weight stable female controls. The patient group participated in a specialised six weeks treatment program of nutritional rehabilitation and psychotherapy in which weight gain and containment of weight losing behaviors were the aim. 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 [16,17] and by use of a computerised diagnostic instrument (EEE-C) [18]. All patients had been engaging in weight losing behaviors prior to hospital admission and the majority were anxious and/or depressed. HRV was obtained from both groups, measured before and after intervention. This provided four groups or measurement conditions: controls measured before intervention, controls measured after intervention, patients measured before intervention and patients measured after intervention. R-R intervals were obtained using a standard 3-lead electrocardiogram (ECG) while subjects were seated. HRV analysis included the calculation of moments and Renyi

coefficients. Groups were compared using Mann-Whitney test, as distributions of most of these variables were observed to be far from normal. Moments were further normalized by subtracting the median value and dividing by the inter-quartile range.

Following this analysis, 5-minute recordings were extracted from the middle of the 20-minute recording for each measurement condition, and HRV analysis was carried out in a similar manner.

3. Results

Based on the 20-minute recording, a comparison of the median values of the normalized moments for each measurement condition was made using the Mann-Whitney test. This showed significant differences between patients and controls before intervention, but not for any other groups. The results with smallest p-values are shown in Table 1. The row labeled "Pre Con vs Pat" present p-values obtained comparing patients with controls at the first measurement before intervention, and contains p-values less than 0.05, showing a significant difference between these groups.

Table 1. Results of Mann-Whitney test for higher moments, showing p-values obtained. Only the difference between patients and controls before intervention was significant ($p < 0.05$).

Test	M03	M05	M07	M09	M11
Con Pre vs Post	0.38	0.41	0.48	0.55	0.54
Pat Pre vs Post	0.75	0.86	0.92	0.94	0.57
Pre Con vs Pat	**0.0095**	**0.036**	**0.034**	**0.034**	**0.039**
Post Con vs Pat	0.33	0.25	0.29	0.32	0.51

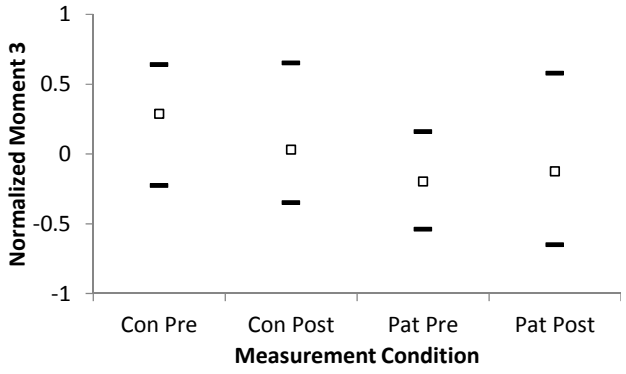

Figure 1. Median, 25 and 75 percentiles for the normalized 3rd moment, showing a lower value for the measurement collected from patients before treatment.

Figure 1 shows the median, 25 and 75th percentiles for the measurement with the smallest p-value of 0.0095 from Table 1, the 3rd moment. The 75th percentile of patients pre-intervention is lower than the median for controls pre-intervention. After treatment, this measure appears to move closer to the value observed for controls.

Analysis of data from 5-minute recordings showed no significant difference between any groups for any of the normalized moments.

Based on the 20-minute recording, a comparison of the median values of the multiscale Renyi exponents for each measurement condition was made using the Mann-Whitney test. This showed no significant differences at the ($p < 0.05$) level. However, there were some results with $p < 0.1$. The results with smallest p-values are shown in Table 2. Once again, the smallest p-values were found for the patient vs control test before intervention. The smallest p-value found was 0.069 for Renyi entropy with exponent of 4 or 5. The p-values for the negative exponents were all larger. Even though these results are not significant, they are much lower than p-values for any other groups. These results suggest that the Renyi entropy is less useful than the higher moments for distinguishing these measurement groups, but confirms that the largest difference found was between controls and patients before treatment.

Analysis of data from 5-minute recordings showed no significant difference between any groups for any of the Renyi entropy measures.

Table 2. Results of Mann-Whitney test for Renyi entropy using positive exponents, showing p-values obtained. None of these results were significant at the ($p < 0.05$) level.

Test	H(1)	H(2)	H(3)	H(4)	H(5)
Con Pre vs Post	0.22	0.17	0.16	0.16	0.16
Pat Pre vs Post	0.21	0.16	0.16	0.16	0.16
Pre Con vs Pat	0.15	0.090	0.072	0.069	0.069
Post Con vs Pat	0.36	0.32	0.33	0.33	0.34

4. Conclusions

The results show significant difference between the median values of patients and controls for some of the higher moments extracted from 20-minute recordings. This suggests that these measures might be suitable as a diagnostic tool. Differences between the median values of patients and controls were also observed for Renyi entropy, but these were not significant at the $p<0.05$ level. However, for both sets of multiscale measurements, differences were largest between controls and patients before intervention, than between any other groups.

Differences between patients and controls before

intervention suggests that Anorexia Nervosa does have an impact on cardiovascular autonomic function, and that this effect can be measured from HRV alone. It is important to note that these differences were not detected using standard deviation of R-R intervals, and that more sophisticated measures were necessary.

These results demonstrate an underlying disturbance in the cardiovascular autonomic regulating system in patients with eating disorders, which adds to the growing body of knowledge concerning the link between anorexia nervosa and cardiovascular autonomic function.

The benefit of nonlinear and multiscale analysis is that it provides a numeric scale that allows identification of the extent of cardiac dysfunction using ECG recordings, making the results easy to interpret for non-specialists such as general practitioners.

Eating disorder patients exhibited distinct alterations in HRV characterized by decreased parasympathetic modulation and sympathetic-parasympathetic imbalance with predominance of sympathetic modulation depending on whether acute or chronic AN is present. Our results of moment analysis suggest that the main differences were found with the positive moments associated with parasympathetic modulation. However the large IQR indicates that the AN group shows heterogeneity and better results may be obtained if the group is separated based on pre-treatment HRV or clinical history into an acute or chronic group.

HRV measures indicate effects of diverse physiological control mechanisms including thermoregulation, endocrine function, as well as the sympathovagal contribution to the heart rate. Our work suggests that AN patients are not a uniform group in terms of how their eating behavior affects different subsystems, which in turn affect heart rate and cardiac function.

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