Assessing Sympatho-Vagal Balance in Schizophrenia through Tone-Entropy Analysis

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Abstract

Although schizophrenia patients more likely commit suicide, however, more than two thirds of patients with schizophrenia, compared with approximately one-half in the general population, die of coronary heart disease (CHD). The aim of this study, therefore, is to determine whether Tone-Entropy (T-E) analysis method can determine how and to what extend the symaptho-vagal balance is altered with the severity of psychiatric disorders as determined by Global Assessment of Functioning (GAF) scale. Tone represents sympatho-vagal balance and entropy, the autonomic regularity activity. This study included 32 high-GAF, 32 low-GAF and 118 healthy control subjects. Evaluated tones and are significantly (p<0.01) different among three groups. The significantly higher tone and lower entropy in the low-GAF group might suggest altered sympatho-vagal balance which could predict increasing risks of cardiovascular death.

1. Introduction

Schizophrenia is a complex brain disorder, which affects about one in a 100 or around 190,000 Australians [http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Schizophrenia]. The illness is characterised by a breakdown of thinking and emotions, and a loss of contact with reality. Symptoms of schizophrenia vary widely but may include hallucinations, delusions, thought disorders, social withdrawal, lack of motivation and impaired thinking and memory. It usually begins in late adolescence or early adulthood and does not spare any race, culture, class or sex.

Although the major symptoms are due to cognitive dysfunction, there have been an increasing number of studies reporting autonomic nervous system (ANS) abnormalities and heart diseases in patients with this disorder. Ruschena et al. reported that patients with schizophrenia are threefold more likely to experience sudden unexpected death than individuals from the general population [1]. Increased mortality in patients with schizophrenia, compared to the general population, has been consistently reported worldwide [2]. Furthermore, individuals with schizophrenia have more major coronary heart disease events, such as acute myocardial infarction [3]. A few studies investigated heart rate variability (HRV) to assess the ANS in schizophrenia [4-6], but the measures of HRV differ among investigations. Rechlin reported based on spectral analysis and statistical measures of HRV, that there were no significant differences in the ANS between schizophrenic patients and control subjects [5].

A previous study has shown that sympatho-vagal balance can be detected even in the time domain through the tone-entropy (T-E) [7,8]. Tone was verified to reflect the sympatho-vagal balance by a pharmacological experiment where tone changed in value consistently in a heart rate recovery experiment after exercise where the parasympathetic division became predominant [7]. The T-E evaluation process is not influenced by the time period of data acquisition, nor the baseline heart rate. In addition, the T-E data processing has no signal deformation process such as filtering, window, or limiting process. A very important advantage is that there is no need to control respiration rate in the T-E method, allowing data to be obtained in a natural process [8].

Therefore, the aim of this study was to elucidate any alterations of cardiac autonomic functions in patients in relation to severity of schizophrenia patients and healthy well-matched controls by T-E analysis.

2. Methods

2.1. Subjects

The present study involved 64 schizophrenia patients (56.2 ± 1.7 years) hospitalized in the psychiatric clinic at Seishinkai Fujisawa Hospital in Japan. They met diagnostic criteria for schizophrenia according to the DSM-IV.13 Patient data were compared with those obtained from 118 healthy control subjects (52.2±1.2

years). None of the controls had any history of physical and/or psychiatric disorders, and none was taking any medication. The Global Assessment of Functioning (GAF) Scale in DSM-IV was used to evaluate psychiatric assessment [9]. Scale values range from 1 (sickest individual) to 100 (healthiest individual). To investigate the association between the severity of schizophrenia and ANS activity, we further divided the 64 patients without major cardiovascular risks into two groups (32 patients in each group) based on the median values of the GAF scores: low-GAF (<30), and high-GAF (>30).

The details of ECG signals acquisition are described in an earlier study [6]. Intervals between successive R waves of the QRS complex (i.e. instantaneous heart rate (IHR) in beats per min (bpm)=60/R-R intervals in seconds) were calculated and HRV analysis described in the following sections was performed on IHR of 250 beats.

2.2. Spectral and Tone-Entropy analysis

Spectral analysis was performed on linearly resampled (1 Hz) time series using Welch's method. The 256-point fast Fourier transform was repeatedly computed with 50% overlap between adjacent segments. Then the spectral power of each segment was computed and averaged. Hanning window was applied to avoid spectral leakage. Subsequently, spectral powers in the low frequency (LF) band (0.04–0.15 Hz) and high frequency (HF) band (0.15–0.40 Hz) were obtained by integration [10]. Finally LF/HF was estimated.

Tone-Entropy analysis methodology was described in detail in previous reports [7,8]. In brief, acquired heart periods (RR intervals) are transformed into percentage index (PI) time series:

$$PI(n) = [IHR(n) - IHR(n+1)] \times 100 / IHR(n)$$

where *IHR(n)* is a instantaneous heart rate time series, and *n* a serial number of heart beats. The tone is defined as a first order moment (arithmetic average) of this PI time series as:

$$\sum_n PI(n)/N \quad \text{(non-dimensional)}$$

where N is a total number of PI terms. The tone, balance between accelerations (PI > 0) and inhibitions (PI < 0) of the heart, represents the sympatho-vagal balance faithfully as appreciated in all the previous studies [7,8]. The entropy is defined on PI probability distribution by using Shannon's formula:

$$-\sum_n p(i)\log_2 p(i) \quad \text{(bit)}$$

where [*p(i)*] is a probability that PI(n) has a value in the range, *i*<PI(*n*) < *i* + 1, *i* an integer. The entropy evaluates total acceleration–inhibition activities, or total heart period variations, in a familiar unit of bit. It is to be remarked that the tone has no corresponding parameters in conventional methods.

3. Results

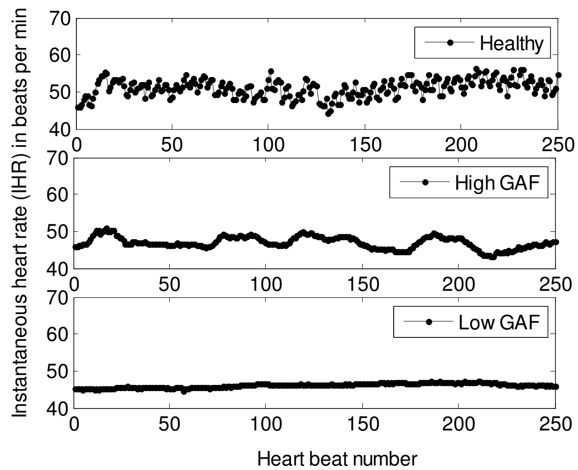

Figure 1. Examples of IHR data of three groups (healthy, high GAF and low GAF subjects).

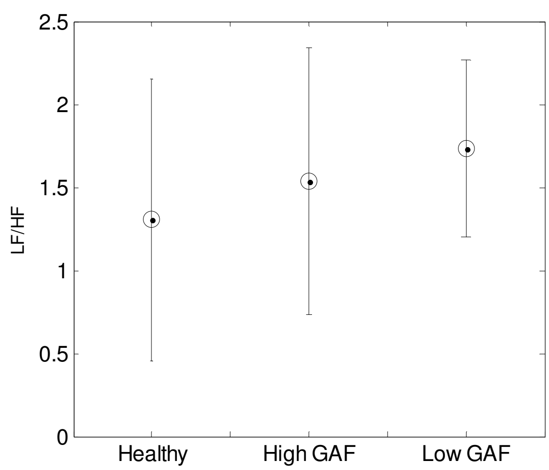

Figure 2. Errorbar of the ratio of LF and HF powers of IHR data of all subjects in three groups.

Task Force [10] on Heart rate variability of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology proposed a low value of LF/HF ratio of HRV spectra as a practical sign of predominant vagal modulation activity. An increase of LF/HF with Schizophrenia severity progression seems to be very obvious in Figure 2. The results are however statistically non-significant.

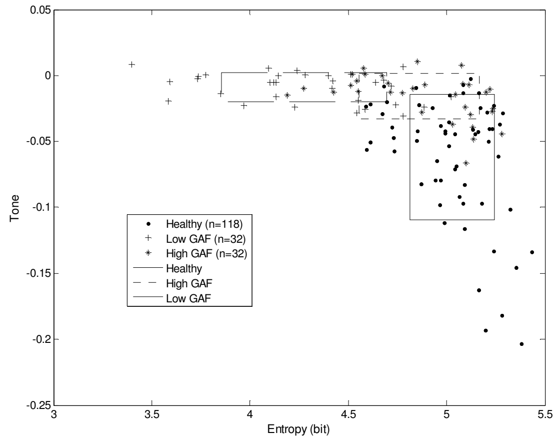

Figure 3. Tone-Entropy plot of all subjects in three groups. Rectangles show the mean and standard errors of Tone and Entropy values of each group.

Figure 3 illustrates individual and averaged data of tone and entropy in healthy controls, high GAF and low GAF groups. A clear tendency was noticed corresponding with the severity of Schizophrenia. Tone increased significantly ($p<0.05$) with severity of Schizophrenia [Table 1 and 2], whereas entropy decreased significantly ($p<0.01$) with the severity of Schizophrenia [Table 1 and 2]. Averaged data of the three groups are shown by rectangles (mean ± SE). Three rectangles were arranged on the curvi-linear relation.

Table 1. Mean and SE values of Tone (T), Entropy and LF/HF of three groups of subjects.

		Mean	SE
Healthy	T	-0.06	0.05
	E	5.03	0.21
	LF/HF	1.30	0.84
HGAF	T	-0.02	0.02
	E	4.86	0.31
	LF/HF	1.54	0.80
LGAF	T	-0.01	0.01
	E	4.27	0.42
	LF/HF	1.73	0.53

Table 2. Statistical analysis results (p values) among T, E and LF/HF values of three groups

	T	E	LF/HF
Healthy v HGAF	0.250	0.003	0.205
Healthy v LGAF	0.000	0.00	0.010
LGAF v HGAF	0.070	0.00	0.250

4. Discussion

LF and HF powers in schizophrenia are reduced as reported in previous studies [6,11,12]. There is a possibility that psychotic states might act as a mental stressor, causing the suppression of HRV in low GAF Schizophrenia patients. The apparent increase of LF/HF ratio could be interpreted as an indirect evidence of shift of sympatho-vagal balance toward diminished vagal modulatory activity.

The present study supports these previous findings and suggests that schizophrenia patients possessed markedly depressed ANS activity, which was further associated with the degree of psychiatric severity on schizophrenia. We speculate that physiological functions in both branches of the ANS might deteriorate more as the schizophrenia becomes more severe. We suggest that the present results of decreasing entropy are an alternate expression of this reduction of HRV because entropy represents the total acceleration-inhibition activity of the cardiac autonomic nervous system function and outcome.

The high entropy values, concomitant with lower (negative) values of tone, observed for healthy subjects (Figure 3) indicates that the two cardiac autonomic pathways are always active and that vagal activity predominates in the sympatho-vagal balance for a healthy population. This results are with previous reports discussing sympatho-vagal balance [7,8].

It is of interest that the high GAF group was found midway between the healthy and high GAF groups. It suggests that parallel to the severity of CAN, parasympathetic efferent pathways are progressively withdrawing their activity. Thus our results suggest that Schizophrenia deterioration causes an alteration in the T-E balance that correlates with the progressive denervation of parasympathetic activity.

Acknowledgements

This study was supported by an Australian Research Council (ARC) research network on Intelligent sensing, sensor networks and information processing (ISSNIP) at the University of Melbourne.

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