Cardiac Autonomic Neuropathy Associated Alteration of Sympatho-Vagal Balance through the Tone Entropy Analysis of Heart Periods

AH Khandoker[1], HF Jelinek[2], M Palaniswami[1]

[1]The University of Melbourne, Parkville, Australia
[2]Charles Sturt University, Albury, Australia

Abstract

This study presents the usefulness of tone-entropy (T-E) analysis of heart rate variability (HRV) using short term ECG recordings (~20 minutes) for screening the degree of severity (mild, definite and severe) of cardiac autonomic neuropathy (CAN). Tone reflects sympatho-vagal balance whose validity has been already examined on typical physiological cases. Entropy which is the autonomic regularity activity was evaluated though Shannon entropy of HRV. Both indexes were defined on a distribution of successive variations of heart periods. The results showed that the tone was high and the entropy was low in the definite group compared with the early and normal group. When the result was plotted in two-dimensional T-E space, it revealed a curve-linear relation between the tone and entropy. The findings could form the basis of a cheap and non-invasive test for screening CAN in patients with or without diabetes.

1. Introduction

Early sub clinical assessment of severity of cardiac autonomic neuropathy (CAN) and intervention are of prime importance for risk stratification and early treatment in preventing sudden death due to silent myocardial infarction. A non-invasive Ewing test battery [1] was specifically designed for identifying CAN consists of five tests. Combining the five test results allows classification into mild (early), moderate or severe (definite) CAN. The Ewing battery however requires patient cooperation. It is also less sensitive to changes associated with cardiac autonomic neuropathy compared to spectral methods [2]. More importantly the Ewing battery is often not able to be performed due to co-morbidities in the patients that would benefit most These co-morbidities include existing heart or respiratory disease, which is a counter indication for the Valsalva manoeuvre. Use of antihypertensive medication influences the outcome of the lying to standing test that measures blood pressure changes on standing and identifies orthostatic hypotension. The hand grip test is hindered by lack of strength in the elderly and more often by arthritis in the hands. The lying to standing heart rate (HR) test is the easiest test to perform, although it may be difficult for some with a lack of mobility as is often found in the elderly [3].

It was shown that the vago-sympathetic balance could be detected even in time domain through the tone-entropy (T-E) analysis in a previous study [4]. Tone was verified to reflect the vago-sympathetic balance by a pharmacological experiment where tone changed in value consistently in a heart rate recovery experiment after exercise where parasympathetic division became predominant [4]. 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 further advantage is that there is no need to control respiration rate in the T-E method: data could be obtained in a natural process [5].

Therefore, the aim of this study iw to elucidate any alterations of cardiac autonomic functions in patients in relation to severity (early and definite) of CAN by T-E analysis. Results are examined in T-E space and compared with the standard T-E values obtained in an experiment of standard perturbations of autonomic function in healthy subjects.

2. Methods

After standard exclusion criteria were applied to ensure that any changes in HRV detected were due to the severity of the CAN, thirty four participants of a health screening clinic at Charles Sturt University were included in the study. Twenty one participants were CAN+ (13 early CAN+ and 8 definite CAN+), whilst the remaining thirteen were CAN-, being without clinical signs and symptoms of CAN. The research protocol was approved by Charles Sturt University Ethics in Human Research Committee (03/164). Five cardiac autonomic nervous system function tests as described by Ewing were recorded. These measured change in heart rate during lying to standing, deep breathing and Valsalva manoeuvre. Change in blood pressure was measured for lying to standing and hand-grip test. The criterion for no autonomic neuropathy was that all five cardiac autonomic nervous system function tests had to be within the normal range. For early signs of CAN one heart rate test had to be abnormal or two borderline. Definite CAN was defined as two or more heart rate tests had to be abnormal plus one or more of the blood pressure tests. ECGs were recorded over 20 minutes using a lead II configuration (Maclab ADInstruments, Australia) and recorded on Macintosh Chart version 5 with a sampling rate set at 400 Hz and a notch filter at 50 Hz. Intervals between successive R waves of the QRS complex (i.e. R-R intervals in seconds) were calculated using the algorithm developed by Pan and Tomkin [6]. The HRV analysis described in the following sections was performed on 1000 RR intervals.

2.1. Tone-entropy method

The methodology was described in detail in previous reports [4,5]. In brief, acquired heart periods (RR intervals) are transformed into percentage index (PI) time series:

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

where $H(n)$ is a heart period 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:

$$\sum_n PI(n) / N \quad \text{(non-dimensional)} \qquad (2)$$

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 [4,5]. The entropy is defined on PI probability distribution by using Shannon's formula [7]:

$$-\sum_n p(i) \log_2 p(i) \quad \text{(bit)} \qquad (3)$$

where $[p(i)]$ is a probability that PI(n) has a value in the range, $i < \mathrm{PI}(n) < i + 1$, 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. The tone has an origin in the investigations in the last century where autonomic control of heart rate was studied as an antagonistic interactive operation between acceleration and inhibition. On the contrary, the entropy evaluates HRV almost the same way as conventional second-order moments, for example, as standard deviation.

3. Results

Figure 1 illustrates typical examples of heart periods (RR intervals), PI time series and their histograms selected from normal and definite CAN+ groups. Alteration of the distributions is clearly discernible. Figure 2 illustrates individual and averaged data of tone and entropy in normal(N), early(e) CAN+ and definite(d) CAN+ groups. A clear tendency was noticed corresponding with the severity of CAN. Tone increased significantly ($p<0.05$) with severity of CAN [-0.02454±0.0182 (dCAN+), -0.0561±0.0366 (eCAN+)], whereas entropy decreased significantly ($p<0.05$) with the severity of CAN [1.9285±0.353 (dCAN+), -2.344±0.422 (eCAN+)]. Averaged data of the three groups are shown by rectangles (mean ± SE). Three rectangles were arranged on the curvi-linear relation.

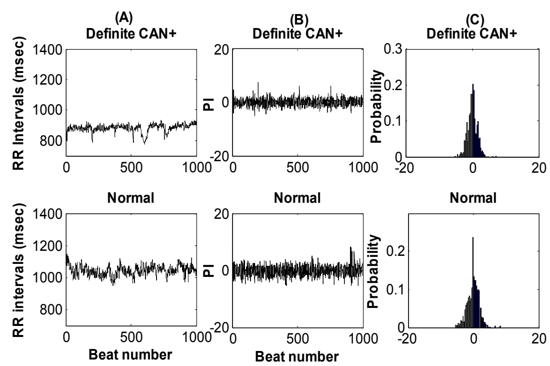

Figure 1. Typical heart period (RR intervals) time series (A), PI time series deduced from left (B), and its probability distributions in histogram (C) selected in each group (Normal and definite CAN+).

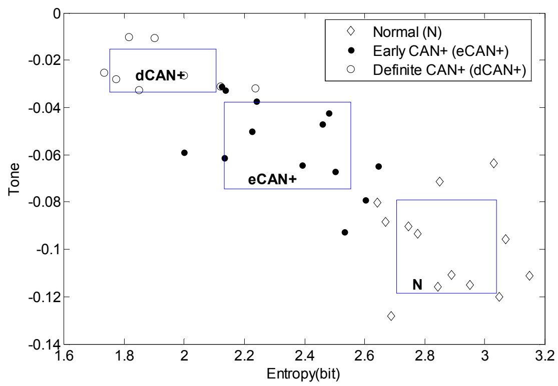

Figure 2. Evaluated tone and entropy in T-E space, ensemble averages by open rectangles (averages ± SE), and individuals, by symbols. N, eCAN+ and dCAN+ are significantly ($p<0.01$) different among each other.

4. Discussion and conclusions

Clinically the autonomic nervous system function test battery suggested by Ewing is widely used either in its complete form consisting of five tests or utilizing one or more tests chosen from the battery with different clinicians having a preference for different tests [8] The battery consists of three tests that measure heart rate variability when standing from a supine position, deep breathing over a set interval and the valsalva manoeuvre. These three tests are deemed to indicate parasympathetic regulation. The remaining two tests measure blood pressure changes following standing from a supine position and retaining a hand grip at a steady force for a certain period of time. These latter two tests are seen as indicating more a sympathovagal interaction, with emphasis on the sympathetic component.

In this study, CAN associated alteration of autonomic function was studied on 34 subjects through T-E analyses. T-E analysis showed that the severity of CAN traced a curvi-linear relation from right-bottom (without CAN) to left-top (definite CAN+) in 2-D T-E space. Tone increased and entropy decreased significantly with severity of CAN.

The high entropy values, concomitant with lower (negative) values of tone, observed for normal subjects without CAN (Figure 2) suggests that the two cardiac autonomic pathways are always active and that vagal activity predominates in the vago-sympathetic balance for a healthy population at rest. The scheme is completely consistent with the statement of Oida [4].

Our participants drawn from the health screening clinic completed the Ewing battery satisfactorily and the results were able to be used for classification of CAN into normal, early and definite CAN. In conclusion, we propose that our research could be an alternative test to the Ewing battery that both indicates the pathophysiological changes in heart function regulation and correlates with the clinical findings of the Ewing battery.

Acknowledgements

This work was partially supported by an early career grant awarded to AH Khandoker by University of Melbourne.

References

[1] Ewing DJ, Martyn CM, Young RJ, Clarke BF: The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care 1985; 8: 491-493.

[2] Pagani M: Heart rate variability and autonomic diabetic neuropathy. Diabetes, Nutrition and Metabolism 2000; 13(6): 341-346

[3] Ewing DJ, Campbell IW, Murray A, Neilson JM, Clarke BF: Immediate heart-rate response to standing: simple test for autonomic neuropathy in diabetes. British Medical Journal 1978; 1:145-147.

[4] Oida E, Moritani T, Yamori Y. Tone-entropy analysis on cardiac recovery after dynamic exercise. J Appl Physiol 1997;82:1794-1801.

[5] Oida E, Kannagi T, Moritani T, Yamori Y. Aging alteration of cardiac vagosympathetic balance assessed through the Tone-entropy analysis. J Gerontology 1999;54A:219-224.

[6] Pan J, Tompkins WJ. Real time QRS detector algorithm. IEEE Trans Biomed Eng 1985; 32: 230-323.

[7] Shannon CE. A mathematical theory of communication. Bell Sys Tech J 1948;27:379-423.

[8] Vinik AI, Maser RE, Mitchell BD and Freeman R: Diabetic autonomic neuropathy. Diabetes Care 2003; 26:1553-1562.

Address for correspondence

Dr Ahsan Khandoker
Dept. of Electrical & Electronic Engg.
The University of Melbourne, Parkville, VIC -3010, Australia.
E-mail:ahsank@unimelb.edu.au