34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Identifying increased risk of post-infarct people with diabetes using multi-lag Tone-Entropy analysis

Chandan Karmakar, *Member, IEEE,* Herbert Jelinek, *Member, IEEE*, Ahsan Khandoker, *Member, IEEE*, Mikko Tulppo, Timo Mäkikallio, Antti Kiviniemi, Heikki Huikuri, Marimuthu Palaniswami, *Fellow, IEEE*

Abstract— **Diabetes mellitus is associated with multi-organ system dysfunction. One of the key causative factors is the increased blood sugar level that leads to an increase in free radical activity and organ damage including the cardiovascular and nervous system. Heart rhythm is extrinsically modulated by the autonomic nervous system and cardiac autonomic neuropathy or dysautonomia has been shown to lead to sudden cardiac death in people with diabetes due to the decrease in heart rate variability (HRV). Current algorithms for determining HRV describe only beat-to-beat variation and therefore do not consider the ability of a heart beat to influence a train of succeeding beats. Therefore mortality risk analysis based on HRV has often not been able to discern the presence of an increased risk. This study used a novel innovation of the tone-entropy algorithm by incorporating increased lag intervals and found that both the sympatho-vagal balance and total activity changed at larger lag intervals. Tone-Entropy was found to be better risk identifier of cardiac mortality in people with diabetes at lags higher than one and best at lag seven.**

I. Introduction

Patients with diabetes compared to nondiabetics have up to a 4 times greater risk of cardiovascular disease and increased risk of all cause and cardiac mortality including sudden cardiac death [1]. The autonomic nervous system (ANS) is intricately linked to modulating the diverse organ systems of the body. The ANS affects basic physiological functions such as heart rate, respiratory rate, body temperature and blood pressure. The sino-atrial (SA) node in the right atrium of the heart is considered a natural pacemaker that generates electrical impulses, giving rise to the intrinsic heartbeat. These impulses generated by the SA node are controlled by parasympathetic and sympathetic nerves, which are part of the ANS. Autonomic innervation is the primary extrinsic control mechanism regulating heart rate variability and cardiac performance [2]. Autonomic dysfunction is thought to result from damage to these autonomic nerve fibres and leads to abnormal heart rate control and vascular dynamics [3]. One pathophysiological mechanism that leads to arrhythmias and heart attack is cardiac autonomic neuropathy (CAN), which is due to an increased blood sugar level, which leads to an increased production of free radicals and a subsequent destruction of parasympathetic and sympathetic postganglionic nerve terminals [2].

The conventional Tone-Entropy (T-E) method of quantifying HRV uses successive R-R interval lengths of the recorded ECG with the implicit assumption that the current beat is influenced by the immediately preceding beat. However, it has been reported that a heart beat influences not only the beat immediately following it, but also up to 6–10 beats downstream [4], possibly as a consequence of respiratory sinus arrhythmia and baroreflex activity. Thus, successive R-R interval duplets will likely underestimate the ability of a heart beat to influence a train of succeeding beats determined as the autocovariance function of R-R intervals. Moreover, the autocovariance function of the R-R intervals captures additional aspects of HRV (e.g. non-linearity) that are otherwise masked by the strong correlation between successive beats if T-E with lag equal to 1 (n vs n+1 beats) is used. Therefore, we hypothesized that multi-lag T-E analysis can overcome the limitations of the present practice of single lag T-E analysis in HRV studies.

The aims of this study was to study the benefit of using multi-lag T-E analysis to quantify autonomic nervous system activity to identify the risk of cardiac mortality in people with diabetes that presented to the hospital with a heart attack (acute myocardial infarction; AMI) but had no previous history of cardiovascular disease.

II. Subjects & Methods

A. Subjects and ECGs

Data from 1996-2001, including medical history and ECG recordings were obtained from the Division of Cardiology, University of Oulu, Finland. The participant group consisted of post-MI (myocardial infarction) patients whose medical treatment had been optimized according to contemporary guidelines. The study protocol has been reported previously in detail [5-8].

In the present study we selected patients with type 2 diabetes mellitus that had no history of cardiovascular disease and admitted to the hospital with an acute myocardial infarct. This group was subsequently divided into two groups (G1 and G2) based on following criteria:

C. Karmakar and M. Palaniswami are with the Electrical & Electronic Engineering Department, University of Melbourne, Parkville, Melbourne, VIC 3010, Australia (Phone: +61-3-8344-3077; email: karmakar@unimelb.edu.au, palani@unimelb.edu.au).

H. Jelinek is with the Centre for research In Complex Systems, Charles Stuart University, NSW 2640, Australia (email: hjelinek@csu.edu.au).

A. Khandoker Dept of Biomedical Engineering, Khalifa University, Abu Dhabi, UAE, on leave from the Electrical & Electronic Engineering Department, University of Melbourne, Parkville, Melbourne, VIC 3010, Australia.

M. Tulppo and A. Kiviniemi are with the Department of Exercise and Medical Physiology, Verve, Oulu, Finland (e-mail: miko.tulppo@verve.fi, antti.kiviniemi@verve.fi).

T. Mäkikallio and H. Huikuri are with the Division of Cardiology, Department of Medicine, University of Oulu, Oulu, Finland (e-mail: timo.makikallio@oulu.fi, heikki.huikuri@oulu.fi).

G1: Subjects alive after 8 years of study.

G2: Cardiac related mortality.

Patients with non-cardiac related mortality were excluded from this study. The demographic information of the two groups is shown in Table I. The Northern Ostrobothnia Hospital District Ethics Committee, Oulu, Finland, approved the protocol, and all patients gave written informed consent.

TABLE I. AGE, GENDER AND BMI OF THE POPULATION OF THE TWO STUDY GROUPS USED IN THIS STUDY.

	Age (years)	Gender (number)	BMI ($kg.m^{-2}$)
G1 (n=55)	60.15± 11.47	M 37, F 18	29.19± 5.34
G2 (n=18)	69.67± 5.42	M 9, F 9	28.13± 5.44

Values are expressed as mean±SD or number of subjects.

M = Male, F = Female.

A 24 h ECG recording was carried out after AMI using an Oxford Holter system (Oxford Instruments, Abingdon, UK) or a Pathfinder 700 system (Reynolds Medical, Hertford, UK). Ectopic beats were visually identified and replaced by interpolation.

B. Multi-lag Tone-Entropy (T-E)

A RR interval or period is defined as the time difference between two consecutive R peaks of the electrocardiogram (ECG) signal. Let the RR intervals time series **RR** be defined as:

$$RR \equiv (RR_1, RR_2, \ldots, RR_N)$$

where, N is the number RR intervals. Heart rate acceleration and inhibition can be determined from the difference of consecutive RR intervals. If RR_{i+1} become shorter than RR_i then it is an acceleration of heart rate. Therefore, acceleration of the heart is expressed as a plus difference and inhibition as a minus difference of RR intervals. However, to reduce the impact of heart rate variation over a wide range of time and different subjects, The RR interval data was normalized to monitor the heart rate variability. In conventional T-E analysis, the RR-intervals are normalized by taking the percentile change of the successive RR intervals with respect to the first RR interval and expressing this as the percentage index (*PI*) and defined as:

$$PI(i) = \frac{RR_i - RR_{i+1}}{RR_i} \times 100 \qquad (1)$$

The *Tone* is then defined as a first order moment (arithmetic average) of this **PI** time series as:

$$Tone = \frac{1}{N-1} \sum_{i=1}^{N-1} PI(i) \qquad (2)$$

Tone is the balance between accelerations ($PI > 0$) and inhibitions ($PI < 0$) of the heart rate and represents the sympatho-vagal balance [9-10]. *Entropy* is defined from the probability distribution of **PI** by using Shannon's formula [11]:

$$Entropy = -\sum_{i=1}^{n} p(i) \log_2 p(i) \qquad (3)$$

where, *p(i)* is a probability that *PI(n)* has a value in the range, $i < PI(n) < i+1$, i is an integer. The entropy evaluates total acceleration–inhibition activities, or total heart period variations.

For multi-lag T-E analysis, we have introduced lag (m) in to equation (1), used to derive the **PI** time series from the **RR** time series signal. Hence, in the multi-lag T-E analysis *PI* is expressed as the percentile change of the i-th and $i+m$-th RR intervals with respect to the i-th RR interval and is defined as:

$$PI(i) = \frac{RR_i - RR_{i+m}}{RR_i} \times 100 \qquad (4)$$

where, m is an integer and m=1 represents the conventional T-E analysis. The detailed methodology of conventional T-E analysis has been described in previous reports [2-3].

C. ROC analysis and Statistical methods

In order to retain the relative importance of features, receiver-operating curve (ROC) analysis was used [12], with the area under the curve for each feature represented by the ROC area. A ROC area value of 0.5 indicates that the distributions of the features are similar in the two groups with no discriminatory power. Conversely, a ROC area value of 1.0 would mean that the distribution of the features of the two groups do not overlap at all. The area under the ROC curve was approximated numerically using the trapezoidal rules [12] where the larger the ROC area is, the better the discriminatory performance.

The difference between the groups was analyzed using the nonparametric Wilcoxon-Rank Sum test. A p value of <0.05 was considered significant. MATLAB Statistics toolbox was used to perform all statistical operations.

III. RESULTS & DISCUSSIONS

The median and IQR (inter quartile range) of *Tone* and *Entropy* values for both groups (G1 and G2) and lags ($1 \leq m \leq 8$) are shown in Table II. Median *Tone* values were lower in the G1 group than G2 group except for lag 1, where the median *Tone* values were the same. In addition median *Tone* values in the G1 and G2 group decreased with increasing lag. The difference in *Tone* values between G1 and G2 was found to be significant ($p<0.05$) only for higher lag intervals m={3, 5, 6, 7, 8} (depicted in the top panel of Figure I).

Our results clearly indicate that the sympatho-vagal balance of the heart rhythm and measured by the variation of successive R-R intervals at lag greater than 3 plays an important role in cardiac related mortality. Correlations between successive beats further downstream from the initial beat diminish in the survivors (G1) group more rapidly than in the G2 group. This more rapid decrease in *Tone* in the G1 group indicates that the baroreflex mechanism constitutes a fast physiological response tool that is mainly driven by the vagal component. Conversely the smaller change in *Tone* with increasing lag in the cardiac mortality group (G2) indicates vagal withdrawal and an association with an

increased likelihood of ectopic, pathological beats gaining more influence over the intrinsic electrical conduction system of the heart and over-riding the normal rhythm, leading to a greater risk of an arrhythmic event and heart attack.

TABLE II. MEDIAN ± IQR VALUE OF TONE AND ENTROPY PARAMETERS OF G1, G2 AND G3 FOR LAGS 1~8. ROC AREA REPRESENTS THE DISTINGUISHING CAPABILITY OF TONE AND ENTROY PARAMETER AT DIFFERENT LAGS.

	Lag	G1	G2	ROC Area
Tone	1	-0.02± 0.03	-0.02± 0.03	0.53
	2	-0.03± 0.03	-0.02± 0.04	0.63
	3	-0.04± 0.03	-0.02± 0.03†	0.67
	4	-0.05± 0.04	-0.02± 0.04	0.64
	5	-0.06± 0.05	-0.03± 0.05†	0.67
	6	-0.07± 0.06	-0.03± 0.05†	0.68
	7	-0.07± 0.07	-0.03± 0.06†	0.69
	8	-0.08± 0.09	-0.04± 0.07†	0.68
Entropy	1	3.08± 0.79	3.10± 0.93	0.51
	2	3.24± 0.64	3.03± 1.09	0.61
	3	3.38± 0.67	3.07± 0.80	0.64
	4	3.55± 0.62	3.16± 0.93	0.63
	5	3.66± 0.65	3.31± 1.04†	0.66
	6	3.77± 0.64	3.34± 0.97†	0.66
	7	3.88± 0.67	3.46± 1.06†	0.67
	8	3.92± 0.70	3.46± 0.94†	0.66

† $p<0.05$ between G1 and G2

The ROC area for G1 and G2 is highest at lag 7 for *Tone* (Table II). This suggests that the use of multi-lag T-E analysis provides a better discrimination than conventional T-E analysis. The ROC curve for *Tone* at lag 1 and 7 is shown in the top panel of Figure II. From a pathophysiological perspective it indicates that the interaction between beats further apart are affected more so than interactions between beats closer together as *Tone* becomes increasingly higher with increasing lag in the mortality group (G2) compared to the survivors (G1) and is most pronounced at lag 7.

Median *Entropy* values are consistently higher in the G1 than G2 group for all lag intervals except lag 1, where the median *Entropy* value of G2 is higher than G1 but not statistically significant (Table II). The median *Entropy* values increased with increasing lag for both the G1 and G2 groups. and the difference in *Entropy* between the G1 and G2 group was significantly different ($p<0.05$) for lag intervals between 5 and 8 (depicted in the bottom panel of Figure I).

The total activity of autonomic regulation is lower in the cardiac mortality group (G2) compared to the survivor (G1) group, since *Entropy* is a function of the total activity of the system. This suggests that in the cardiac mortality group (G2) the overall cardiac activity is less with respect to accelerations and inhibitions as the lag interval is increased and therefore the change in overall rhythm of the heart over time is is less. Moreover, the significant difference at lag intervals between 5~8 indicates that the activity of the heart rhythm follows behind the faster changes associated with the sympatho-vagal balance, which shows a difference between G1 and G2 already at a lag interval of 3.

Similarly to *Tone* the highest ROC area between the two groups was found at lag 7 (Table II). The ROC curve for Entropy at lag 1 and 7 is shown in the bottom panel of Figure II.

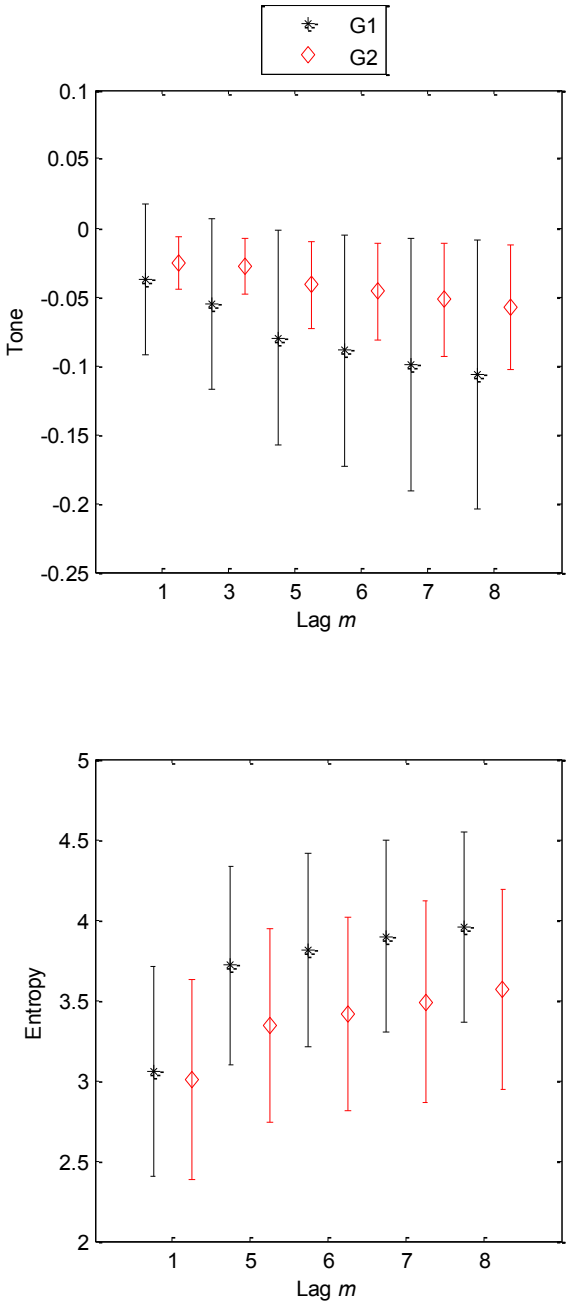

Figure 1. Errorbar (Median and IQR) of Tone and Entropy of G1 and G2 at lag *m*, where values are significantly ($p<0.05$) different.

Our results clearly indicate that the lag at which HRV is measured is an important physiological parameter that needs

to be considered in clinical decision making with the association between the survivor and mortality group becoming significant at lag greater than 3, whereas for *Entropy* significant differences between the two groups became only apparent at a lag of 5 or greater.

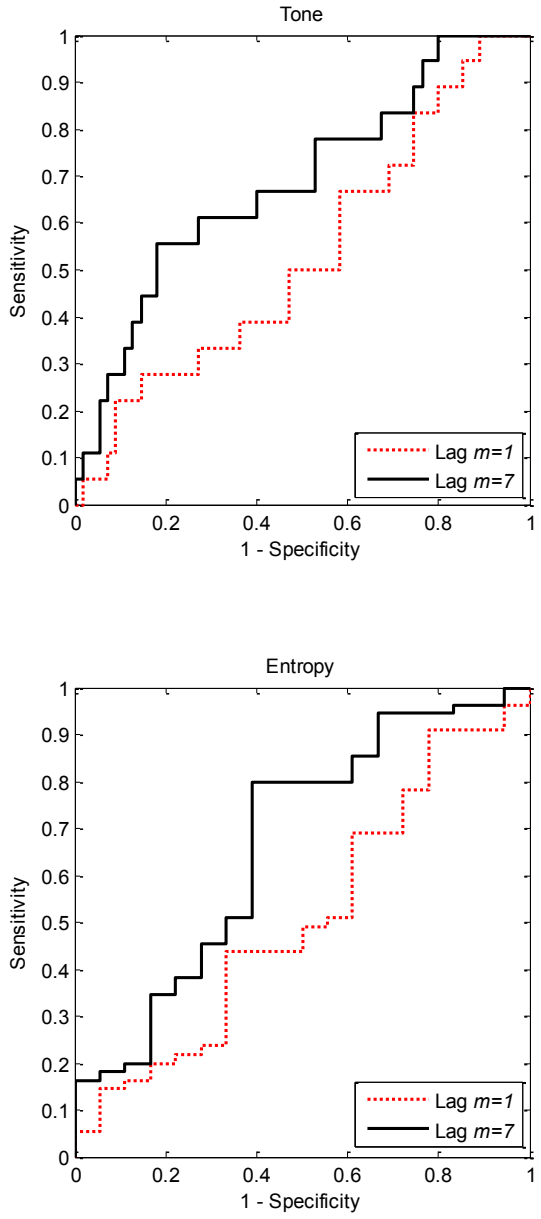

Figure 2. ROC curve for Tone and Entropy at lag 1 and 7.

IV. Conclusion

In this paper, we studied the benefit of using multi-lag T-E analysis in identifying the cardiac mortality in people with diabetes and asymptomatic cardiovascular disease. The conventional single lag T-E could not identify cardiac mortality, whereas multi-lag T-E has shown a significant difference between the survivors and the mortality group.

Acknowledgment

The authors wish to acknowledge Ian Spence for a critical review and comments on the manuscript. This study was partly funded by the Finnish Technology Development Centre (TEKES, Helsinki, Finland).

References

[1] L. N. McEwen, C. Kim, A. J. Karter, M. N. Haan, D. Ghosh, P. M. Lantz, C. M. Mangione, T. J. Thompson, and W. H. Herman, "Risk Factors for Mortality Among Patients With Diabetes: The Translating Research Into Action for Diabetes (TRIAD) Study," *Diabetes Care,* vol. 30, pp. 1736-1741, July 1, 2007.

[2] R. Pop-Busui, G. W. Evans, H. C. Gerstein, V. Fonseca, J. L. Fleg, B. J. Hoogwerf, S. Genuth, R. H. Grimm, M. A. Corson, R. Prineas, and T. A. S. Group, "Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial," *Diabetes Care,* vol. 33, pp. 1578-1584, July 1, 2010.

[3] R. E. Maser, B. D. Mitchell, A. I. Vinik and R. Freeman, "The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes," *Diabetes Care*, vol. 26(6), pp. 1895-901, 2003.

[4] C. Lerma, O. Infante, H. Perez-Grovas and M. V. Jose, "Poincare plot indexes of heart rate variability capture dynamic adaptations after haemodialysis in chronic renal failure patients," *Clin Physiol Funct Imaging*, vol. 23(2), pp. 72-80, 2003.

[5] H. V. Huikuri, J. M. Tapanainen, K. Lindgren, P. Raatikainen, T. H. Makikallio, K. E. Juhani Airaksinen and R. J. Myerburg, "Prediction of sudden cardiac death after myocardial infarction in the beta blocking era," *J Am Coll Cardiol.,* vol. 42, pp. 652 – 658, 2003.

[6] J. M. Tapanainen, P. E. Thomsen, L. Kober, C. Torp-Pedersen, T. H. Makikallio, A. M. Still, K. S. Lindgren and H. K. Huikuri, "Fractal analysis of heart rate variability and mortality after an acute myocardial infarction," *Am J Cardiol.* , vol. 90, pp. 347 – 352, 2002.

[7] A. M. Kiviniemi, M. P. Tulppo, D. Wichterle, A. J. Hautala, S. Tiinanen, T. Seppanen, T. H. Makikallio and H. K. Huikuri, "Novel spectral indexes of heart rate variability as predictors of sudden and non-sudden cardiac death after an acute myocardial infarction," *Ann Med.*, vol. 39, pp.54 – 62, 2007.

[8] T. H. Makikallio, P. Barthel, R. Schneider, A. Bauer, J. M. Tapanainen, M. P. Tulppo, G. Schmidt and H. V. Huikuri, "Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era," *Eur Heart J.*, vol. 26, pp. 762 – 769, 2005.

[9] E. Oida, T. Moritani and Y. Yamori, "Tone–entropy analysis on cardiac recovery after dynamic exercise," *J Appl Physiol*, vol. 82, pp. 1794–1801, 1997.

[10] M. Amano, E. Oida and T. Moritani, "Age-associated alteration of sympatho-vagal balance in a female population assessed through the tone–entropy analysis," *Eur J Appl Physiol*, vol. 94. pp. 602–610, 2005.

[11] C. E. Shannon, "A mathematical theory of communication," *Bell Syst Tech J*, vol. 27, pp. 379–423, 1948.

[12] J. A. Hanley and B. J. McNeil, "The meaning and use of the area under a Receiver Operating Characteristic (ROC) curve," *Radiology*, vol. 143, pp. 29-36, 1982.