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Evaluating Cardiovascular Risk Using the Tone-Entropy algorithm

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***Abstract*—Currently the Framingham equation is the most often used cardiovascular risk calculator in health care. The equation requires data for age, gender, cholesterol status, blood pressure, diabetes status and smoking. A large proportion of the morbidity and mortality associated with cardiovascular disease is due to arrhythmic events that are multifactorial including dysregulation by the autonomic nervous system. In this study we applied the tone-entropy algorithm for analysis of heart rate variability obtained from20 minute ECG recordings and compared the outcome with the Framingham risk stratification. Our results indicate a good agreement between the T-E algorithm and the Framingham risk equation suggesting that this algorithm may be of use for initial screening of cardiovascular risk as it is noninvasive, economical and easy to use in clinical practice.**

I. Introduction

CARDIOVASCULAR risk is an important attribute of preventative health care. Assessing cardiac risk over five years is traditionally calculated using the Framingham risk equation. Current health practice guidelines recommend that patients be treated with respect to their underlying coronary heart disease risk [1]. Accurate estimates can provide information on treatment strategies and commencement. The Framingham risk equation has been validated in general populations and includes based on age, sex, blood pressure, cholesterol (total and HDL), and smoking with diabetes status being a categorical variable [2] The Framingham risk equation has also been modified by various countries such as the Australian and New Zealand Cardiovascular Society [3] as well as alternative risk equations proposed including the Coronary Risk Evaluation (SCORE) for fatal CHD or cardiovascular disease (CVD) and the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) which incorporates glucose tolerance status and fasting plasma glucose [4], [5]. History of cardiovascular disease, physical inactivity, obesity, and left ventricular hypertrophy diagnosed by echocardiography are not included in current models of cardiovascular risk assessment [3] as their individual predictive value is unclear. However there are suggestions that additional parameters may be of benefit such as biomarkers including CRP or D-dimer [6], [7], [8].

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Heart rate variability (HRV) is an important physiological factor that is regulated by the endocrine and autonomic nervous system. Changes in have been shown to predict future heart attack and presence of asymptomatic disease progression in diabetes [9], [10]. Standards of measurement and interpretation have been recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [11].

The tone-entropy (TE) algorithm has been recently validated as a tool for analyzing HRV and shown to correlate with experimentally induced heart rate variability changes by either blocking the parasympathetic component or increasing the sympathetic influence on heart rate [12]. A clinical study analyzing HRV in a cohort of people with diabetes and classified into groups with increasing abnormal HRV activity has also shown a good correlation with the TE measure [10].

This study investigates the association of the TE score with the cardiac risk score using the Framingham risk equation.

II. Methods

A. Framingham Risk Assessment

Data for the study was obtained from the Diabetes Screening Complications Initiative (DiScRi) clinic at Charles Sturt University. The study was approved by the Charles Sturt University Human Ethics Committee and undertaken between 2004 and 2008. Patient data was only included if it was complete for demographic as well as experimental variables. Under these criteria, 319 records and ECG traces were available. The Framingham cardiac risk score was determined using the protocol outlined by Jackson [3] and determined automatically from data entered into the DiScRi ACCESS database [13]. The variables used for determination of the cardiac risk score were age, sex, blood pressure, cholesterol (total and HDL), and smoking with diabetes status being a categorical variable. Cardiac risk over a five year period was divided into very high (>20%), high (15-20%), moderate (10-15%) and mild (less than 10%) in accordance with the Australian and New Zealand Guidelines (Fig.1).

B. Tone-Entropy Determination

The methodology was described in detail in previous reports [14], [12]. In brief, acquired heart periods (RR intervals) are transformed into percentage index (PI) time series:

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

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 [11,16]. The entropy is defined on PI probability distribution by using Shannon's formula [17]:

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

where $[p(i)]$ is a probability that PI(n) has a value in the range, i<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 of Rosenbluth and Simeone [15], where autonomic control of heart rate was studied as an antagonistic interactive operation between acceleration and inhibition. Entropy evaluates HRV almost the same way as conventional second-order moments, for example, as standard deviation.

C. Statistical Analysis

Results were expressed as means (±SD). One-way ANOVA and Tukey-Kramer post hoc examination were carried out for comparisons among the four groups (mild, moderate, high and very high) to evaluate whether statistically significant differences exist among four groups. A value of $p < 0.05$ was considered significant for all examinations.

III. RESULTS

319 patients were recruited into the study with complete results form the DiScRi clinic. After exclusion of results due to noises in ECG signals, 170 patients were included in the final analysis. Of these 85 were identified with mild (50%), 37 with moderate (22%), 25 with high (14.5%), and 23 (13.4) cardiovascular risk. Demographic and cardiac risk factors according to the Framingham model are shown in table 1.

	Mean±SD	Reference Range
Sex (F/M)	96/76	
Age (yrs)	62.9±12.4	
DMT2*	53 (31%)	
Smoking	6 (3.5%)	
SBP (mmHg)	130±17	< 140
TC/HDL	3.6±1.1	< 5

DMT2 – diabetes mellitus type 2; SBP – systolic blood pressure; TC/HDL – total cholesterol:High Density Lipoprotein ratio;

Fig. 2 shows the tone and entropy mean values for each of the four groups.

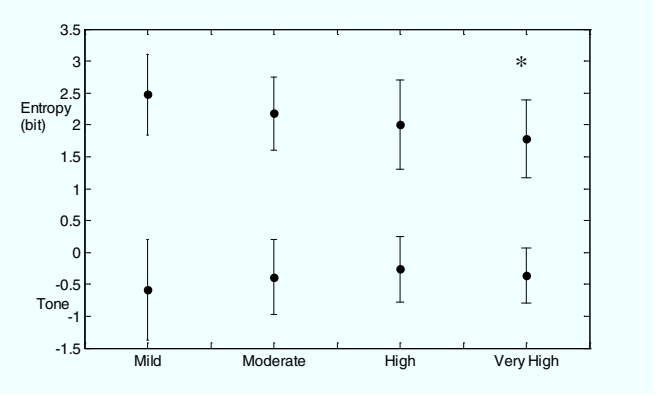

Fig.1. Errorbar plot of mean and SD of all four groups' Tone and Entropy. * means significant ($p<0.05$) difference between mild and very high groups.

The results of the TE analysis were then transformed into 2D space shown in Fig 2.

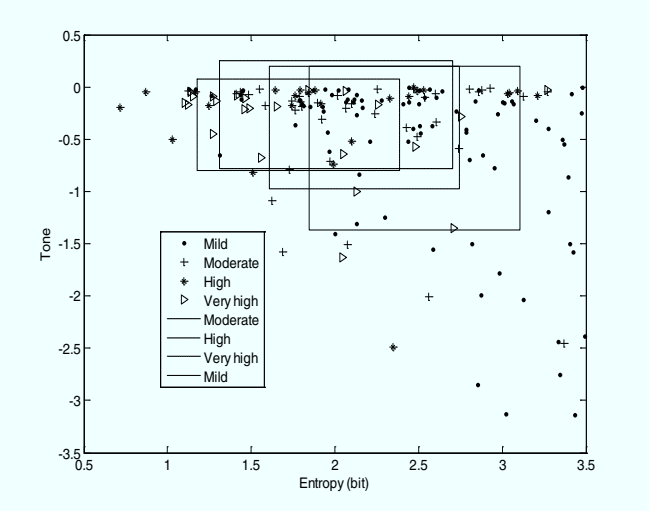

Fig.2 Tone-Entropy plot of all subjects in four groups. Rectangles show the mean and standard errors of Tone and Entropy values of each group.

Tones of subjects analyzed in this study are in the range of 0.5~ -3.5 and entropies are 0.5~3.5 [10].

IV. Discussion

T-E has two major advantages over the conventional methods of HRV analysis in that it is robust against non-stationarity and not sensitive to differences in length of recordings. This latter point makes it especially useful for clinical investigation where short time recordings are more likely to be used.

Previous autonomic perturbations experiments revealed a specific relevance of the TE measure to autonomic mechanisms where head up tilt increased sympathetic and decreased parasympathetic nervous system activity [16] and atropine decreased parasympathetic activity [17]. The T-E analysis results quantified parasympathetic nervous system activity during these perturbations as part of the sympatho-vagal control mechanism of heart function. Of physiological and clinical significance is that the mild group has higher tone and lower entropy values whereas for the very high cardiovascular risk group the TE space shows lower tone and higher entropy suggesting that some parasympathetic dysfunctions are present. The a curvi-linear relation in T-E space shown in Fig. 2, indicates that cardiac autonomic activity was reduced in correspondence with the increase in cardiovascular risk and suggests a significant impairment of vagal predominance associated with disease progression. T-E analysis is therefore corresponds to the cardiovascular risk classification and suggests a non-invasive, possibly more sensitive method of stratifying 5 year cardiovascular risk.

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