

Tone-Entropy Analysis as a Cardiac Risk Stratification Tool

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Abstract

Improving risk assessment to provide evidence for preventative intervention has recently become more of a focus in cardiovascular medicine with atherosclerosis as an early manifestation of cardiovascular disease. The total cholesterol to high-density lipoprotein (TC/HDL) ratio is often used as an atherogenic index. High levels of the TC/HDL ratio also affect nervous system function and this study investigated the relationship between TC/HDL and heart rate variability measured by the tone-entropy algorithm. For tone there was a significant indication that cholesterol levels? influences autonomic nervous system function in control individuals with no cardiovascular disease, but not in diabetics. Entropy was not associated with TC/HDL in either the control or diabetes group. The relationship seen for tone and TC/HDL suggests that tone can be used as an initial risk indicator for further invasive cardiac function testing.

1. Introduction

Improving risk assessment to provide evidence for preventative intervention has recently become more of a focus in cardiovascular medicine with atherosclerosis as an early manifestation of cardiovascular disease. There are many cardiac risk factors including cholesterol level, gender, age, diabetes and systolic blood pressure that are implicated in atherosclerosis [1]. Coronary calcium screening and scintigraphy using SPECT, are diagnostic tools for early identification of preclinical atherosclerosis [2]. However coronary calcium screening and SPECT are not suitable for population screening purposes.

The development and progression of atherosclerosis is linked to the level of cholesterol and specifically low density lipoprotein cholesterol (LDL-C). LDL-C is susceptible to free radical damage and undergoes lipid peroxidation [3]. Lipid peroxidation and oxidative stress is more prevalent in people with diabetes due to the increased blood sugar levels (BGL). Oxidative stress due to increased BGL in people with diabetes also affects the autonomic nervous system leading to cardiac autonomic neuropathy [4]. Therefore a link between cholesterol level and autonomic nervous system function is of interest for early identification of increased risk associated with coronary artery disease and arrhythmia leading to sudden

cardiac death.

Total cholesterol/high density lipoprotein (TC/HDL) has been shown to indicate risk of future atherosclerosis and cardiovascular disease [5, 6]. Data collected from the original Framingham study was used and an appropriate cut-off for TC/HDL of 6 with the average in a healthy population being 5.2 was determined using quartiles. The Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice recommend TC/HDL <2 and for clinical testing a cut-off of 4.5 is prescribed [7]. The Australian guidelines recommend a cut-off of 5 for TC/HDL. This cut-off is higher than recommended by the World Health Organization of 4.5 mmol/L [8].

Sudden cardiac death in asymptomatic individuals and diabetes has been linked to autonomic nervous system dysfunction as a causative factor with atherosclerosis possibly augmenting arrhythmic events [9]. At least 80% of patients who experience sudden cardiac death have associated coronary artery disease. The remainder include primary arrhythmic events and a combination of atherosclerosis and arrhythmia [10]. Cardiac autonomic neuropathy has also been shown to be associated with higher cholesterol levels [11] and silent myocardial ischemia [12] in people with diabetes. The link between cholesterol level and autonomic nervous system is the level of free radicals [13].

We propose an algorithm to determine the sympatho-vagal balance of autonomic nervous system dysfunction in people with or without diabetes that allows identification of individuals at higher risk of atherosclerosis and sudden cardiac death that would benefit from coronary calcium screening and scintigraphy

2. Method

2.1. Participants

Data was selected from participants at the Charles Sturt University Diabetes Complications Screening Initiative (DiScRi). Inclusion in the analysis required a complete dataset for the patient including tone and entropy parameters as well as age, sex, BGL, blood pressure, cholesterol profile and BMI. Exclusion criteria from the study were presence of cardiovascular including peripheral vascular or cerebrovascular disease and signs

or symptoms suggestive of arrhythmia such as palpitation, hypotension, syncope or chest pain.

Cholesterol profile was determined by South West Pathology in Albury. The normal ranges are TC 3.9-3.5mmol/L, Triglycerides 0.5 – 1.7mmol/L, HDL 0.8 – 1.5mmol/L, LDL 1.7 – 3.5mmol/L and TC/HDL < 5.

2.2. ECG recording

RR intervals and QTd were determined from 12-lead ECG recordings obtained using the CardioPerfect workstation (Welsh-Allyn, Netherlands). QT interval dispersion was obtained using the Welsh-Allyn ECG recording software(Welsh-Allyn, Netherlands).

2.3. Tone-entropy (T-E) determination

RR intervals were determined from 12-lead ECG recordings obtained using the CardioPerfect workstation. The T-E algorithm was previously described [14-16]. Heart period data, RR intervals are transformed into percentage index (PI) time series:

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

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:

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

where N is a total number of PI terms. The tone, which represents the balance between accelerations (PI > 0) and inhibitions (PI < 0) of the heart, represents the sympatho-vagal balance [17]. The entropy is defined on PI probability distribution by using Shannon's formula:

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

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.

2.4. Statistical analysis

Jenks natural breaks determined a break for the TC/HDL data as part of the ARCGIS 9 software package (ESRI, UK Ltd)[18]. We combined the tone and entropy results for the diabetes group using principle component analysis (SPSS) [19]. Chi-square statistics determined whether the combined T-E using PCA in the diabetes

group with TC/HDL < 4.5 was significantly different to that of the diabetes group with TC/HDL < 4.5 (p<0.05). Kruskal Wallis statistics were used to determine the range for which TC/HDL stratified the control and the diabetes groups into two distributions for tone and entropy. The resultant p value provides the point or range of influence and was set at p<0.05. The smaller the point of influence is the greater the interaction between TC/HDL and tone and entropy.

3. Results

Data from 313 participants was analysed for a possible relationship between heart rate variability using the tone-entropy (T-E) algorithm and cholesterol level measured as TC/HDL.

The Jenks natural breaks algorithm divided the participants at TC/HDL = 4, slightly lower than the WHO cut-off of 4.5. 190 participants had TC/HDL ratios of below 4 indicating normal levels. The results for the tone and entropy analysis were combined using principle component analysis. There was no significant difference between the low and high TC/HDL groups with respect to the T-E results (mean±SE: 1.34±0.9 and 1.16±0.8 respectively, p=0.877). Taking the TC/HDL cut-off at 4.5 resulted in the mean±SE in the low TC/HDL group versus high TC/HDL group being 3.514±0.047 and 5.809±0.11 respectively. The results for the combined tone and entropy analysis for the low and high TC/HDL groups were 1.433±0.712 and 0.189±0.236 respectively (mean±SE; 95% CI -2.303, 4.791; p<0.05).

Dividing the participants into control (no diabetes mellitus type 2) and type 2 diabetes mellitus indicated that the diabetes group had a higher risk profile for atherosclerosis with significantly higher waist circumference, BMI, BGL and HbA1c results (Table 1)

Table 1. Demographics of participants.

	No DM*	DM	p
Participants	226	87	-
Age (yrs)	64.7±11	66.5±9	ns
DM (yrs)	-	9.2±8	-
Sex (F/M)	133/93	43/44	ns
WC (cm)	94.2±13	105.2±18	<0.0001
BMI	27.2±5	29.9±6	0.0003
SBP (mmHg)	130.1±19	134±18	ns
DBP (mmHg)	76.4±10	75.5±12	ns
BGL (mmol/L)	5.1±0.6	7.3±2	0.0001
HbA1c	5.8±0.3	7.6±7.5	0.0004

DM – diabetes mellitus; WC – waist circumference, BMI – body mass index; SBP – systolic blood pressure, DBP – diastolic blood pressure; BGL – blood glucose level; HbA1c – glycosylated haemoglobin, ns – non-significant.

The cholesterol profile for participants divided into

nondiabetes and diabetes is shown in Table 2. Only HDL and LDL are significantly different. In all cases the diabetes group had lower levels.

Table 2. Cholesterol profile.

	No DM*	DM	p
TC (mmol/L)	5.2±1	4.4±1	<0.0001
Trigs (mmol/L)	2±10	2.7±10	ns
HDL-C (mmol/L)	1.4±0.4	1.3±0.4	0.008
LDL-C (mmol/L)	3.2±0.9	2.4±1	<0.0001
TC/HDL	3.9±1	3.7±1	ns

DM – diabetes mellitus, TC – total cholesterol, Trigs – triglycerides, HDL-C – high density lipoprotein cholesterol, LDL-C – low density lipoprotein cholesterol, TC/HDL – total cholesterol: High density lipoprotein cholesterol ratio, ns – non-significant.

In this paper we define the parameter ‘points of influence’ as the cut-off where points or a range of TC/HDL values are significantly associated with tone and entropy. Tone was shown to be significantly associated with TC/HDL for the control participants for TC/HDL between 3.8 to 4.9 ($p < 0.05$) with an optimum at TC/HDL of 4.5 and $p = 0.0167$. No significant association between tone and TC/HDL could be found for the diabetes participants with an optimum between a TC/HDL of 4.8 to 4.9 at p between 0.07 and 0.09 (Figure 1).

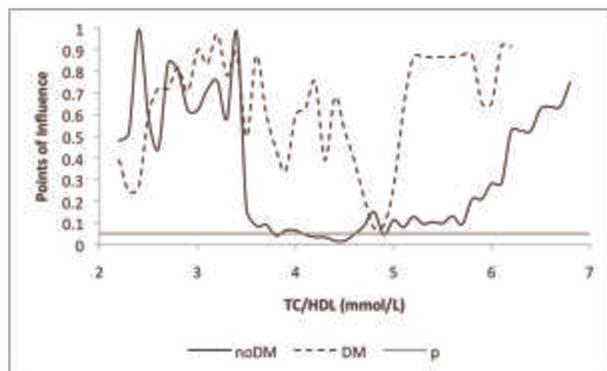


Figure 1. Relationship between TC/HDL and tone for controls and diabetics. p – cut-off for significant association between tone and TC/HDL.

For the control and diabetes groups no significant points of influence between entropy and TC/HDL were identified (Figure 2). For the control group the optimum association was at TC/HDL of 6.5 and $p = 0.0824$. For the diabetes group the best association to TC/HDL was for TC/HDL of 5 at $p = 0.183$.

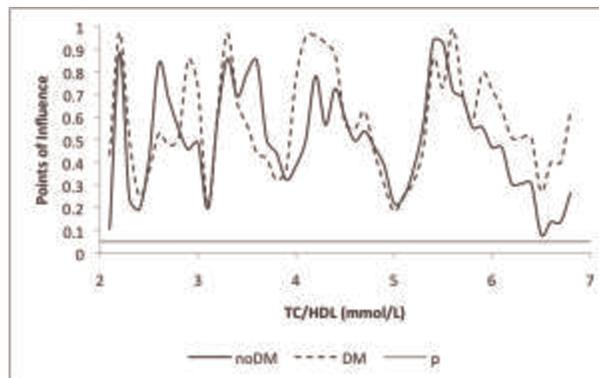


Figure 2. Relationship between entropy and TC/HDL for control and people with diabetes. p – cut-off for significant association between entropy and TC/HDL.

4. Discussion

Preventive strategies for primary health requires sensitive and accurate markers that incorporate measures that reflect the multifactorial nature of cardiovascular disease progression and identifies high-risk patients for intensive treatment. Whether a relationship between the atherosclerosis and autonomic nervous system dysfunction exists has not been clarified. This study utilized the tone-entropy algorithm to assess whether a relationship between tone or entropy and TC/HDL exists.

Our results suggest that tone is related to TC/HDL. In previous studies tone has been shown to be related to cardiac autonomic neuropathy, which increases the risk of arrhythmias [16]. The effect of TC/HDL has a hermetic relation to tone with normal inter-beat variation occurring between 3.8 to 4.9 [20]. Outside of this range TC/HDL showed no influence on tone. That is, between a certain range of TC/HDL values, the inter-beat variation measured by tone and indicating the average of the accelerating and inhibiting influences on heart rate may be related to the degree of risk of atherosclerosis with plaque formation possibly already present in the coronary arteries. Whereas at lesser and greater TC/HDL values this influence dissipates and is not as evident. The imbalance is due to damage of the autonomic nervous system by free radicals that also damage blood vessel lining. The combined effect is an increase risk of arrhythmia and sudden cardiac death. The results for the diabetes group showed a small possible relationship between tone and TC/HDL but overall the data is not interpretable at this stage and a larger data set is required.

Entropy represents the total autonomic nervous system activity. This may be the reason why no direct relationship between the level of TC/HDL and entropy could be identified for both the control and diabetes groups. A sawtooth distribution is seen for entropy in both the control and diabetes groups suggesting over the total time interval of the ECG recording and the

associated accelerating and slowing of the heart rate no direct influence of TC/HDL on the entropy was observed.

T-E does not require multiple tests to determine risk and can be used for patient stratification for coronary calcium screening to identify atherosclerotic plaques and lead to more timely intervention and better treatment outcomes.

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