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Heart Rate Variability and QT Dispersion in a Cohort of Diabetes Patients

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Abstract

Heart rate is dependent on a cycle of depolarization and repolarization of the atria and ventricles that is regulated by intrinsic and extrinsic factors. Inhomogeneity in ventricular repolarization, measured as QT interval dispersion (QTd) is likely to lead to arrhythmia. The role of the autonomic nervous system in the development of this inhomogeneity is still uncertain. Autonomic regulation can be measured using the tone-entropy algorithm, which indicates inter-beat interval variation. When a sliding cut-off for QTd was used only the control group had a significant association between QTd and both tone and entropy. This finding suggests that for certain levels of ventricular inhomogeneity, autonomic control becomes more dissociated from intra-beat variation measured by QTd. This may be an early sign of potentially fatal arrhythmia.

1. Introduction

Cardiovascular disease (CVD) accounts for the majority of morbidity and mortality world-wide. Both are exacerbated by increases in associated risk factors such as obesity, diabetes and hypertension [1]. Causes of cardiac mortality can be divided into two categories: 1) cardiac, which includes both structural components such as heart failure and 2) functional components such as arrhythmogenic (neurologic) causes [2]. A significant proportion of morbidity and mortality is associated with asymptomatic cardiac disease and sudden cardiac death is due to the latter [3].

To reduce the risk of sudden cardiac death, non-invasive testing for the risk and presence of cardiovascular disease is an important area of research and clinical innovation. Traditional ECG markers such as ST segment, QRS, and P-wave changes have been well documented and used clinically [4]. Ventricular repolarization is reflected by QT interval dispersion (QTd) on the surface ECG. QTd changes have been shown in people with diabetes without arterial hypertension, ECG abnormalities or chronic degenerative complication [5]. QTd is usually between 20 and 50 msec in normal subjects and between 60 and 80 msec for cardiac patients. The threshold for a value of QTd, which predicts arrhythmia and sudden cardiac death also varies

with the population under study and disease presence from 58msec to 140msec [6, 7].

Apart from changes in the ECG morphology measured as QTd, the ECG also indicates the contribution of the autonomic nervous system in regulation of heart rhythm. Evidence that QTd is in part due to autonomic regulation has been reported [8]. Autonomic control of heart rhythm can be assessed by analysing heart rate variability (HRV)[9]. The prognostic value of HRV in predicting cardiac death in post-infarction patients has been described, but there is less evidence for their association with arrhythmic events [10, 11].

HRV can also be determined as a function of tone and entropy [12]. The advantage of the tone-entropy (T-E) algorithm is that it describes the involvement of the individual components of the autonomic nervous system as an increase or decrease in beat interval length on a beat-to-beat basis. The T-E algorithm has also been shown to distinguish between diabetics with and without cardiac autonomic neuropathy [13]. However, contradictory results associated with electrical rhythm disturbances have been reported and require further investigation in people with diabetes [14, 15]. This study examines the relationship between QTd and autonomic sympatho-vagal balance as measured by the Tone-Entropy (T-E) algorithm.

2. Method

People with and without diabetes were selected from participants at the Charles Sturt University Diabetes Complications Screening Initiative (DiScRi). Inclusion in the analysis required a complete patient dataset including QTd, heart rate variability as well as age, sex, blood pressure, BMI and blood chemistry. Exclusion criteria from the study were presence of cardiovascular disease including peripheral vascular or cerebrovascular disease and signs or symptoms suggestive of arrhythmia such as palpitation, hypotension, syncope or chest pain.

2.1. 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.

2.2. Tone-Entropy Determination

The methodology was previously described [16, 17]. 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 the 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 [18]. The entropy is defined on the 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 the 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 as described by [19], where autonomic control of heart rate was studied as an antagonistic interactive operation between acceleration and inhibition.

2.3. Statistical Analysis

We used Jenks natural breaks to determine a break for the QTd data using the ARCGIS 9 software package (ESRI, UK Ltd) [20]. Kruskal Wallis statistics were used to determine the range for which QTd stratified the control and the diabetes groups into two distributions for tone and entropy. The resultant p value provides the point of influence and was set at $p < 0.05$. Finally we combined the tone and entropy results for the diabetes group using principle component analysis (SPSS) [21]. Chi-square statistics determined whether the number of people with diabetes above and below a cut-off for QTd of 77msec, which corresponds to a clinical indicator for ventricular repolarization inhomogeneity as significant ($p < 0.05$).

3. Results

Baseline characteristics of all participants is shown in

Table 1.

Table 1. Demographics of participants.

Parameter	No DM*	DM	P value
Diabetes	131	36	-
Years of diabetes	-	10.3 ± 9	-
Sex (F/M)	74/57	19/17	ns
Age (yrs)	63.6 ± 10	67.7 ± 9	ns
Smoking	0	0	ns
Waist Circ. (cm)	93.6 ± 12	106.3 ± 14	< 0.001
BMI*	26.5 ± 5	31.2 ± 6	< 0.001
SBP (mmHg)	130 ± 18	132 ± 16	ns
DBP (mmHg)	70 ± 9	73 ± 11	ns
BGL (mmol/L)	5 ± 0.6	7.4 ± 3	< 0.001
HbA1c	5.7 ± 0.3	6.9 ± 1	< 0.001

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

The Jenks natural breaks algorithm identified QTd = 77msec as an appropriate divider for a two group paradigm (lesser and greater QTd). The results for the tone and entropy analysis were then combined using principle component analysis. 21.9% of participants with diabetes fell into the lesser QTd and 25% into the greater QTd group, ($X_{33,2}=8.83$, $p < 0.05$). Tone was also greater in the greater QTd group (1.989±1) compared to the lesser QTd group (-0.041±1.6) with $p < 0.000$.

In this paper we define the parameter 'points of influence' as the point or range of QTd values where tone and entropy values can be divided into two significantly different distributions. Significance was assessed by applying the Kruskal Wallis test for each QTd in the control and diabetes groups and setting $p < 0.05$. QTd values from the control participants between 37msec to 83msec tone can be divided into two distribution ($p < 0.05$). No significant association between tone and QTd could be found for the diabetes participants. The optimum association in tone for the diabetes group was between 111msec to 117msec at $p = 0.086$, (Figure 1). However the distribution for tone in the diabetes group is sigmoidal with a weaker point of influence at QTd 68-69msec and tone ($p=0.22$).

For entropy, significant points of influence were found between QTd 88 msec to 184 msec with the best fit between 134 and 184 msec and $p=0.054$ (Figure 2). For the diabetes group the best association to QTd was between 118-122msec at $p = 0.93$.

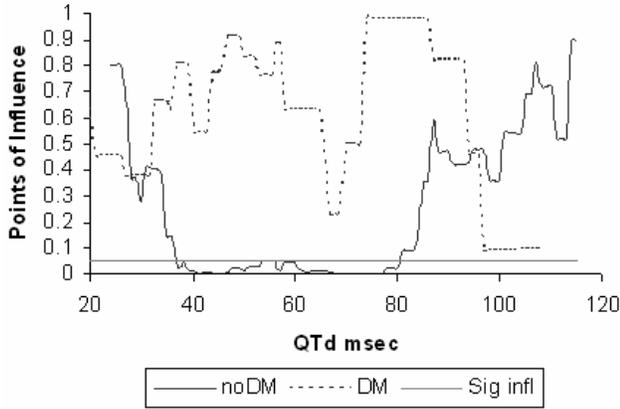


Figure 1. Relationship between QTd and tone for control and people with diabetes. Sig infl – significant association between tone and QTd.

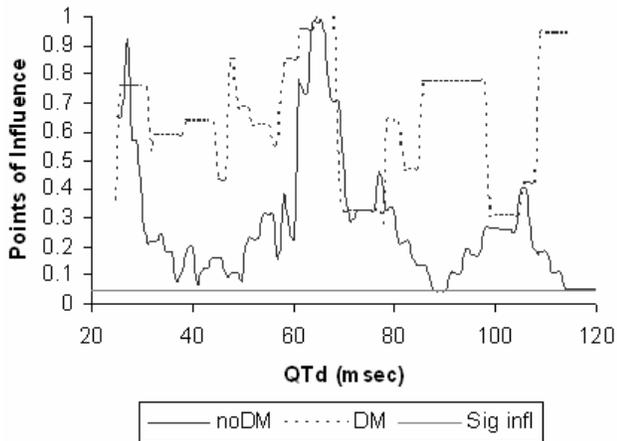


Figure 2. Relationship between entropy and QTd for control and people with diabetes. Sig infl – significant association between entropy and QTd.

The range of influence for entropy based on classified QTd, was again considerably weaker for the diabetes cohort with ($p = 0.3$) between QTd of 101msec and 107msec. For entropy both the control and diabetes group exhibited a bimodal distribution

4. Discussion

QTd reflects the variation that occurs in the duration of electrical events in a single heart beat (ventricular repolarization heterogeneity) being the intra-beat variation. Entropy and tone reflect the variation that occurs in the interval between consecutive heart beats (inter-beat variation). The variation in both is influenced by inputs from the sympathetic and parasympathetic nervous systems. QTd and HRV have been investigated as tools for predicting cardiac arrhythmias and sudden

cardiac death [22, 23]. Increased QT dispersion calculated from sinus beats identifies patients at risk of sustained arrhythmia and sudden cardiac death. However, predictive accuracy is limited with substantial variation [24]. For clinical diagnosis no set QTd has been established but is usually taken to be lower in healthy compared to patients with pathology. Similarly the threshold for a positive predictive value of QTd varies with the population under study and disease presence.

We have investigated QTd and its relationship to tone and entropy in control and diabetic subjects. In particular we investigated whether segregating subjects using QTd was reflected in differences when tone and entropy were combined using PCA. At a QTd cut-off of 77msec a significantly larger number of people with diabetes and greater QT dispersion presented with increased tone that indicates a worsening of autonomic balance. Similarly a decrease in entropy indicates a reduction of total autonomic nervous system activity.

A closer investigation of QTd and its relation to tone and entropy (Fig.1 and 2) indicates that a complex relationship exists, which differs between control and diabetes groups.

Tone in the control group indicates hormesis as an optimal range of influence for the autonomic nervous system on QTd [25]. That is QTd values less than 40msec and greater than 80msec are associated with lesser autonomic influence. The withdrawal of this autonomic influence suggests that the balance between sympathetic and parasympathetic input (inter-beat variability) does not correspond to QTd (intra-beat variability) leading to abnormal ventricular repolarization events. The bimodal distribution seen for tone in the diabetes group may indicate the presence and absence of cardiac autonomic neuropathy but this will have to be further investigated [13]. A similar bimodal distribution is seen for entropy however it is present in both control and diabetes groups. That is, between a certain range of QTd, the intra-beat variation is optimally influenced by the autonomic nervous system, whereas at lesser and greater QTd this influence dissipates and is not as evident in diabetes.

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