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RR-QT Interval Trend Covariability for Sudden Cardiac Death Risk Stratification

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Abstract— **This paper examines the feasibility of the trend covariability between QT and RR Intervals (QTIs and RRIs) be a novel mean of the sudden cardiac death (SCD) risk stratification. Twenty four hour beat to beat QTIs and RRIs are measured from Holter ECG recordings of 25 normal control subjects (SCD-C), 14 low SCD risk patients (SCD-L) with high blood pressure or light cardiac arrhythmia and 11 SCD high risk patients (SCD-H) with heart attack history. The Kalman filtering technique has been applied to decompose 24 hour short term mean QTIs and RRIs sequences into trend components and additive random variations. The correlation coefficients (TC-QT/RR) and cross entropies (TE-QT/RR) between the QT and RR trend signals are estimated. Cross entropy TE-QT/RR achieved the best stratification of subject groups. TE-QT/RR distribution for SCD-C, -L –H subject groups were 1.697±0.058, 1.160±0.099, 0.920±0.067. The differences in entropy values are statistically significant for all classes pairs (SCD–H and –C ($p<0.00001$); –L and –C ($p<0.001$); -H and –L ($p<0.05$) The result indicates that the TE-QT/RR could be a novel index for the SCD risk stratification.**

Keywords—**sudden cardiac death, circadian rhythm, Kalman filter, QT intervals, RR intervals, risk stratification, biosignal classification**

I. Introduction

A survey of American Heart Association as of June 2011 shows that nearly 400,000 sudden cardiac death (SCD) incidents have been happening in the U.S. annually and this has been a serious social problem. Many of the incidents could be prevented by implementing cardioverter defibrillators (ICDs) to people with high SCD risk or at least by knowing one's SCD risk in advance. Some of the known indices[1]-[4] are ECG QT dispersion, late potentials observed in the signal averaging ECG (SAECG) or T wave alternans. All those indices, documented well in the literature, are derived from short term ECG recordings. Recent study[5] showed that circadian variability of RR and QT intervals could have prognostic significance of cronic heart failure. Since SCD risk indices based on such a long term ECG recordings are not fully studied, authors have explored to search for a novel index of the risk assessment based on 24 hour Holter ECG recordings. This paper examines a feasibility of the trend correlation coefficient and mutual entropy between 24 hour QT and RR short term mean interval sequences(TC-QT/RR and TE-QT/RR) being another measure of the SCD risk assessment. Beat to beat QT and RR intervals (QTIs and RRIs) are measured from cardiac outpatients with variety of SCD risks and control subjects. Kalman filtering techniques[6][7] have been applied to the short term mean RR and QT interval sequences to decompose them into trend and random variation. Then the degree of covariability between RR and QT interval trend time series are evaluated by the TC-QT/RR and TE-QT/RR as possible indices for SCD risk stratification.

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II. Methods

Data acquisition and preprocessing

Holter ECG recordings (*Cardiomemory RAC-3100: Nihon Kohden, Tokyo Japan*) were made from 25 normal subjects (SCD-C) , 14 low SCD risk patients (SCD-L) with high blood pressure or light cardiac arrhythmia and 11 SCD high risk patients (SCD-H) with heart attack history. Data were digitized with the sampling frequency set at 200 (Hz) and processed offline. Base line drift and recording noise were eliminated by band pass FIR filtering with the filter length and pass frequency band set at 1001 and 0.5-60 (Hz). These parameters were determined empirically. Then RR and QT intervals are measured automatically. Fig. 1 shows a typical example of beat to beat RR and QT intervals measured from the Holter ECG recordings of the control subject. For the subsequent data analysis, short term mean RR and QT interval series are obtained for every one minute. They are denoted as $y_R[n]$ and $y_Q[n], n = 1,..., N$. N is set to be 1441 for 24 hour Holter recordings.

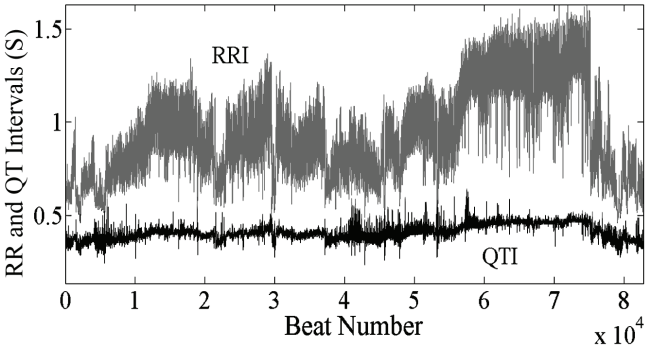

Fig. 1 A typical beat to beat RR and QT intervals (Upper trace: RRIs; Lower trace QTIs)

Data Analysis

RR and QT short term mean interval sequences are decomposed into smooth trend and random residual components.

$$y_R[n] = \bar{y}_R[n] + w_R[n];\ y_Q[n] = \bar{y}_Q[n] + w_Q[n] \quad ..(1)$$

Kalman filtering technique is applied for this decomposition [5][6]. Trend component is characterized by the variations whose second order differences $\Delta^2 \bar{y}_R[n]$ and $\Delta^2 \bar{y}_Q[n]$ are small in the sense that they are Gaussian distributed zero mean random variables with a small pre-assigned variance σ_v^2 .This trend characterization yields the following state and observation equations[6].

$$\bar{Y}_R[n] = F \cdot \bar{Y}_R[n-1] + G \cdot v_R[n] \quad \ldots(2)$$

$$y_R[n] = H \cdot \bar{Y}_R[n] + w_R[n] \quad \ldots(3)$$

$$\bar{Y}_Q[n] = F \cdot \bar{Y}_Q[n-1] + G \cdot v_Q[n] \quad \ldots(4)$$

$$y_Q[n] = H \cdot \bar{Y}_Q[n] + w_Q[n] \quad \ldots(5)$$

Here,

$$\bar{Y}_R[n] = \left[\bar{y}_R[n], \bar{y}_R[n-1]\right]^T,\ \bar{Y}_Q[n] = \left[\bar{y}_Q[n], \bar{y}_Q[n-1]\right]^T$$

$$F = \begin{bmatrix} 2 & -1 \\ 1 & 0 \end{bmatrix},\ G = \begin{bmatrix} 1 & 0 \end{bmatrix}^T,\ H = \begin{bmatrix} 1 & 0 \end{bmatrix}$$

$v_R[n]$ and $v_Q[n]$ are state noise; $w_R[n]$ and $w_Q[n]$ are observation noise. Equations (2) and (4) are called state equations. Equations (3) and (5) are called observation equations. Given observations $y_R[n]$ and $y_Q[n]$, the standard Kalman filter algorithm yields the state estimates, in this case trend components $\bar{y}_R[n]$ and $\bar{y}_Q[n]$. Residual random variations in Eq. (1) are estimated by Eq. (3) and (5) after trend estimation. Hyper parameters, variances of state and observation noise, are determined as those maximize the likelihood function of the observed data. After the signal decomposition, the degree of co-variations between trend components $\bar{y}_R[n]$ and $\bar{y}_Q[n]$, and random residual components $w_R[n]$ and $w_Q[n]$ are evaluated by the correlation coefficients and the mutual information:

$$I(\bar{y}_R, \bar{y}_Q) = \iint_{\bar{y}_R, \bar{y}_Q} f(\bar{y}_R, \bar{y}_Q) \log \frac{f(\bar{y}_R, \bar{y}_Q)}{f(\bar{y}_R) f(\bar{y}_Q)} d\bar{y}_R d\bar{y}_Q \quad \ldots(6)$$

$$I(w_R, w_Q) = \iint_{w_R, w_Q} f(w_R, w_Q) \log \frac{f(w, w_Q)}{f(w_R) f(w_Q)} dw_R dw_Q \quad \ldots(7)$$

These co-variation indices are compared among subject groups of different SCD risks.

III. RESULTS

Fig. 2-4 show typical examples of decomposed RR and QT short term mean interval sequences. Trends $\bar{y}_R[n]$ and $\bar{y}_Q[n]$ are shown in the upper traces: (a)'s. Residuals $w_R[n]$ and $w_R[n]$ are shown in the lower traces: (b)'s.

Normal control subjects generally show gradual increase in RR and QT interval trends after subjects' wakeup in the morning toward sleep in the evening. They show a sudden decrease in transition phase from sleep to awake as shown in Fig. 2(a). High degree of co-variability is obviously observed by eye inspections. It should be also noted that the periodic changes corresponding to REM cycles or ultradian rhythms are clearly observed. Residuals (Fig. 2(b)) show fairly stationary random fluctuations indicating the decompositions are reasonable.

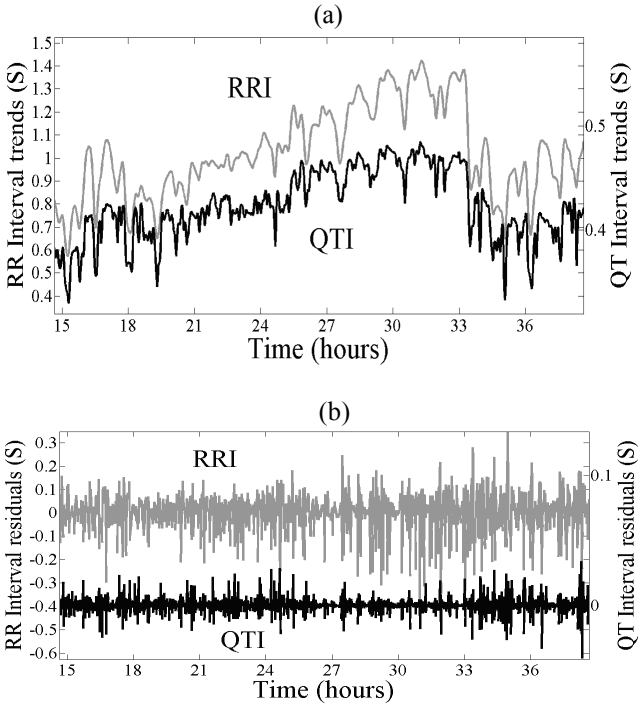

Fig. 2 Decomposed RR and QT interval sequences for control subjects (Interval trends (a) and residuals (b)).

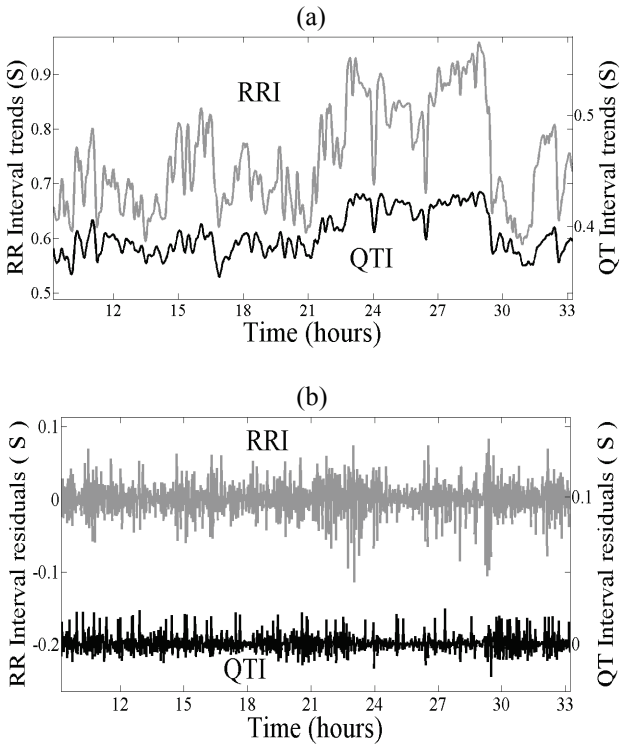

Fig. 3 Decomposed RR and QT interval sequences for low risk patients (Interval trends (a) and residuals (b)).

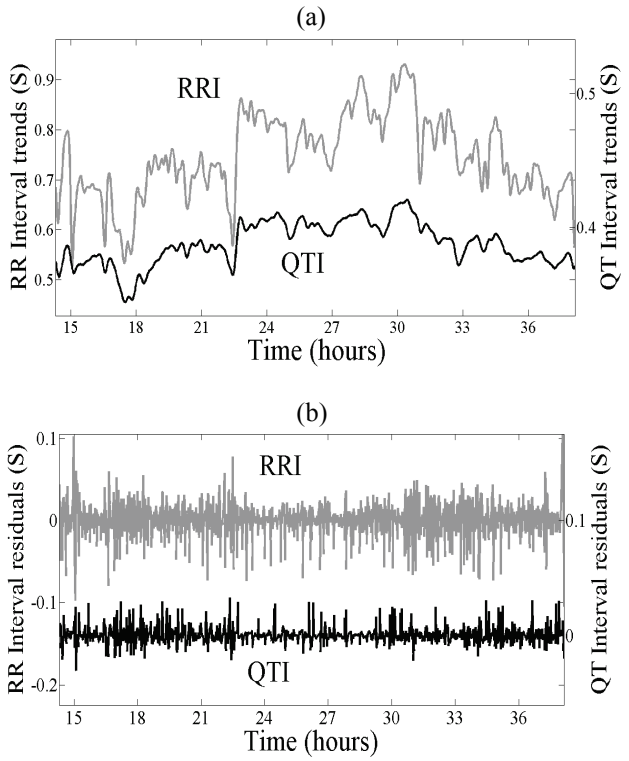

Fig. 4 Decomposed RR and QT interval sequences for high risk patients (Interval trends (a) and residuals (b)).

Fig. 3 and 4 show the same sample data from SCD low risk patients (Fig. 3) and high risk patients (Fig. 4). The co-variability of the RR and QT intervals are visible but not as prominent as that in the control subjects. REM cycles and ultradian rhythms are not clearly seen unlike control cases. Residuals show as a whole stationary random variations with some noticeable changes in variance during the course of 24 hour recordings.

Correlation coefficients of both trends and residuals between RR and QT intervals are estimated for three different SCD risk groups. TABLE I and Fig. 5 show the result. TABLE I shows the mean and standard error of the coefficients and Fig. 5 (a)(b) are their box plots. Correlation coefficient (CC) values for RR and QT interval trends were significantly larger than those for residuals and the values showed gradual changes according to the level of SCD risks. CC values for residuals showed significantly larger values compared to those for patients with SCD risks.

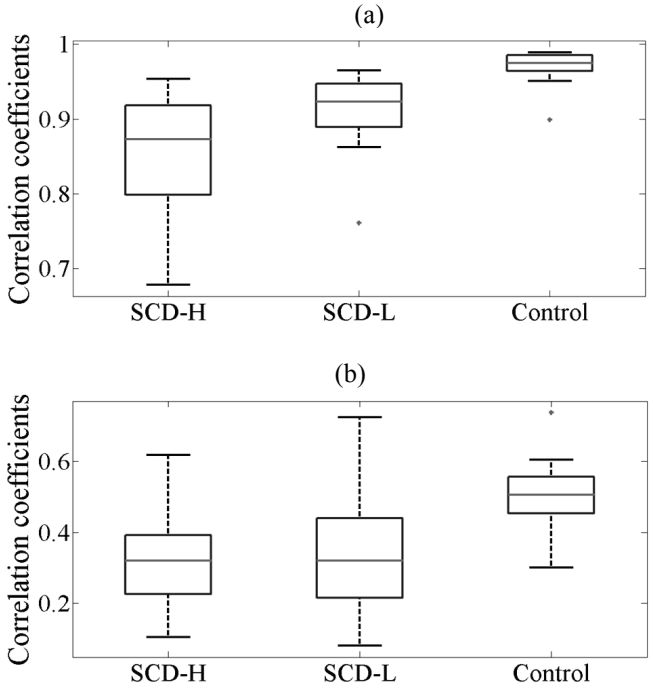

Fig. 5 Correlation coefficients between RR and QT short term mean interval sequences ((a): trends; (b): residuals).

TABLE I. COVARIABILITY OF RR AND QT INTERVALS (CORRELATION COEFFICIENTS)

	Control	SCD-L	SCD-H
Trends	0.971 ± 0.004	0.909 ± 0.015	0.854 ± 0.027
Residuals	0.509 ± 0.017	0.341 ± 0.045	0.334 ± 0.046

To see the statistical significance of index differences among subject classes, Mann-Whitney rank sum test has been applied to the data. Obtained *p*-values are listed on Table II. Table II shows that the control group can be differentiated from the patient groups of high or low SCD risks by correlation coefficient between RR and QT short term mean interval sequence. Both trend and residual interval series are effective for the risk discrimination.

TABLE II. P-VALUES OF THE MEDIAN DIFFERENCE IN CORRRELATION COEFFICIENTS

	C v.s. H	C v.s. L	H v.s. L
Trends	0.49×10^{-5}	0.65×10^{-4}	0.114
Residuals	0.0025	0.0007	0.962

C, H and L respectively denote Control, SCD-high risk and SCD-low risk subject groups.

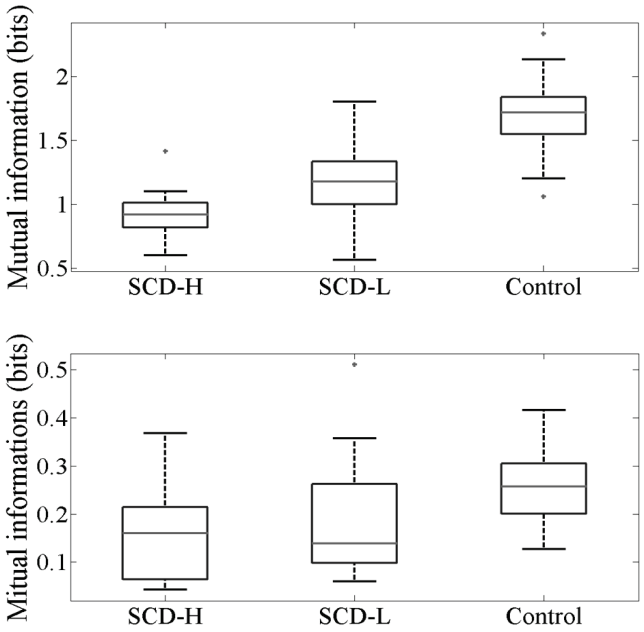

Fig. 6 Cross entropy between RR and QT shot term mean interval sequences ((a): trends; (b): residuals)

TABLE III. COVARIABILITY OF RR AND QT INTERVALS (MUTUAL INFORMATION(bits))

	Control	SCD-L	SCD-H
Trends	1.697 ± 0.058	1.160 ± 0.099	0.920 ± 0.067
Residuals	0.263 ± 0.016	0.190 ± 0.031	0.158 ± 0.030

TABLE IV. P-VALUES OF THE MEDIAN DIFFERENCE IN CROSS ENTROPY VALUES

	C v.s. H	C v.s. L	H v.s. L
Trends	0.58×10^{-5}	0.15×10^{-3}	0.0426
Residuals	0.0039	0.0085	0.537

However, SCD-high risk group cannot be differentiated from SCD-low risk patient group. Fig. 6 and TABLE III show the cross entropy values for different subject groups. General tendency of discrimination properties of the mutual entropy is the same as correlation coefficient but every pairwise comparison of entropy for RR and QT interval trends between different SCD risk groups showed statistical significance (control v.s. SCD-H: $p< 0.00001$; control v.s. SCD-L: $p<0.001$; SCD-H v.s. SCD-L: $p<0.05$).

IV. DISCUSSION and CONCLUSION

RR and QT interval covariability has been examined as a novel mean to stratify the SCD risks. Mutual entropy and correlation coefficient between RR and QT interval trend time series extracted from short term mean interval sequences have been compared. The mutual entropy showed better discrimination capability and could be a promising candidate of a novel index for the SCD risk stratification. The nonlinear dependency of QT intervals on RR intervals may justify the result that the mutual entropy better differentiate the SCD risks. The presence of REM cycles or ultradian rhythm distinctively observed in control subjects may be additional indicator of risk assessment. RR or QT interval signal decomposition into such additional rhythm components in the framework of state space analysis will realize such extended analysis. Although data analyses over larger data set are necessary to validate the findings described in this paper, it may be a promising direction of study to explore to find indices characterizing long term ECG records for SCD risk assessment.

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