Sudden Cardiac Arrest Risk Stratification based on 24-hour Holter ECG Statistics *

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Abstract— **This study examined the feasibility of using indices obtained from a long term Holter ECG record for sudden cardiac arrest (SCA) risk stratification. The ndices tested were the QT-RR interval co-variability and the alternans ratio percentile (ARP(θ)) which is defined as the θ^{th} percentile of alternans ratios over a 24 hour period. The QT-RR interval co-variabilities are evaluated by the serial correlation coefficient between QT and RR trend sequences (QTRC). Previously reported Kalman filter technique and a simple smoothing spline method for the trend estimation are compared. Parameter θ in the alternans ratio percentile index was optimized to achieve the best classification accuracy. These indices were estimated from 26 cardiovascular outpatients for Holter ECG record. Patients were classified into high and low risk groups according to their clinical diagnosis, and the obtained indices were compared with those of 25 control subjects. A risk stratification using the two indices QTRC and ARP(θ) yielded an average sensitivity of 0.812 and a specificity of 0.925. The sensitivities and specificities of all three categories exceeded 0.8 except for the sensitivity to detect the high-risk patient group. Other short-term ECG parameters may need to be incorporated in order to improve the sensitivity.**

Keywords— **Sudden Cardiac Arrest Stratification, T-Wave Alternans Ratio, QT-RR covariability, Holter ECG**

I. INTRODUCTION

The risk assessment of Sudden Cardiac Arrest (SCA) is a serious healthcare research objective since SCA is one of the major causes of deaths worldwide [1]. A number of ECG based indices for its risk assessment are known, *e.g.* QRS widening [2], QTc prolongation [3], Short QT syndrome[4], ST elevation[5] or T-wave alternans [6]. These are based on standard 12-lead short term ECG recordings. Recently there are some studies to utilize Holter long term ECG recordings for the risk assessment[7]-[10]. Palaniappan *et al.* discusses the possibility of abnormal HRV, observed in 24-hour RR intervals, to be a SCA risk indicator for dialysis patients[7]. Some attempts were made to detect T-wave alternans from Holter ECG recordings [8][9]. In this case, the authors proposed to use singular value decomposition (SVD) for reliable T-wave morphology characterization as well as a new index named Alternans Ratio Percentile (ARP(θ)) defined as θ^{th} percentile of alternans ratios estimated for every 2 minute record[9]. SVD essentially decomposes segmented T-waves into a set of orthogonal signals to eliminate irregular noise. This is useful for cleansing of noisy Holter data. In this report, the parameter θ in ARP(θ) is optimized to obtain the optimal classification result. The authors also proposed to utilize QT-RR co-variability as a SCA risk indicator[10] where Kalman filtering technique is introduced to decompose QT and RR interval sequences into trend and residual components. The QT-RR co-variability is shown to be useful to assess the SCA risk. To simplify the method, spline smoothed QT-RR median intervals are introduced and compared. Finally, this study investigates whether or not combining the two indices obtained from the Holter ECG signals improves the SCA risk stratification. The proposed methods have been applied to Holter ECG recordings from 51 subjects for validation.

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II. METHODS

A. Data acquisition and preprocessing

ECG Holter recordings were made from 26 cardiovascular outpatients and 25 normal healthy subjects. The group of outpatients are divided into two categories: SCD High Risk (HR) and Low Risk (LR). Patients in HR group experienced life threatening incidents or severe arrhythmia. They are diagnosed as *e.g.* myocardial infarction, angina pectoris, ventricular tachycardia or cardio-pulmonary arrest. The LR group patients have less serious symptoms such as high blood pressure without arrhythmia or supraventricular tachycardia. Data were digitized at 200 (Hz) and beat to beat RR and QT intervals are measured. They are denoted as $x_R[m]$ and $x_Q[m]$, $m=1,\cdots,M$. Examples of extracted RR and QT intervals are shown in Fig.1(a)(b). Here, M is the number of beats in the record. It is clearly observed that co-variabilities of QT-RR intervals is small for the high risk patient. QT and RR intervals are for the co-variability analysis. Then for T-wave alternans analysis, beat to beat T-wave segments are extracted as T-wave peak times ± 150 (msec). T-wave signals of the m-th beat are denoted as:

$$x_T[n,m], \quad n=1,\cdots,N; \quad m=1,\cdots,M. \qquad (1)$$

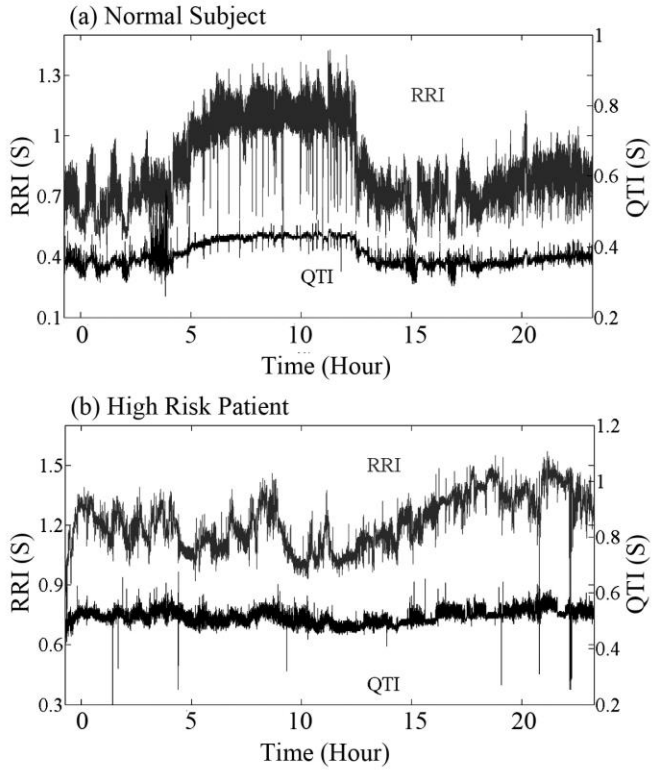

Fig. 1. Diurnal variation of RR and QT intervals

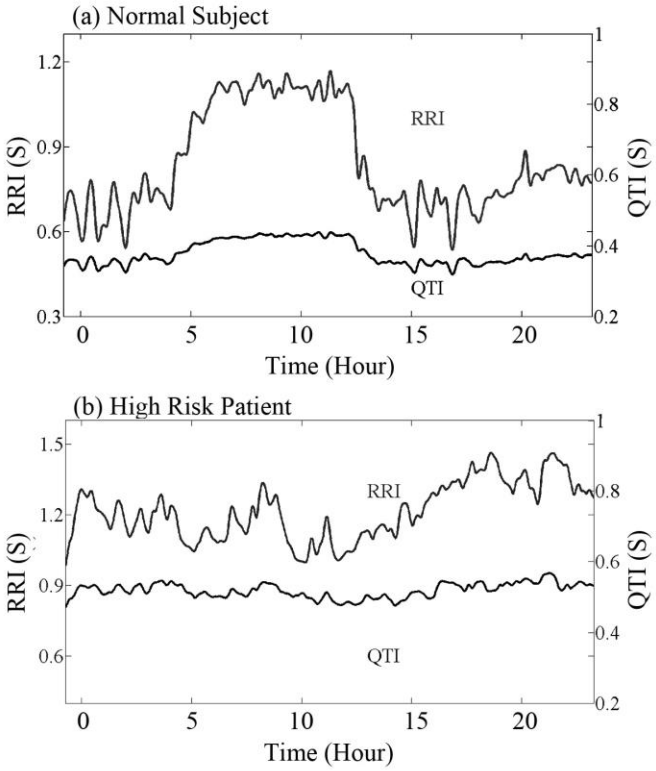

Fig. 2. QT-RR median sequences

B. Co-variability of QT and RR intervals

In our previous study[10], Kalman Filtering technique is applied to decompose the original RR and QT interval sequences into trend and residuals. Then, QT-RR co-variabilities of trend components are shown to be effective for the classification of subject groups. Here we utilize an alternative method of signal decomposition. RR and QT median interval sequence measured in every 1 minute intervals $\bar{x}_R[l]$ and $\bar{x}_Q[l]$, $l = 1, \cdots, L$ are to be spline smoothed to minimize the following evaluation function.

$$\alpha \sum_l (\tilde{x}_\bullet(t_l) - \bar{x}_\bullet[l])^2 + (1-\alpha) \int \left(\frac{d^2 \tilde{x}_\bullet(t)}{dt^2} \right)^2 dt \qquad (2)$$

In Eq. [2], $\bullet$ denotes either R or Q depending on the sequence of concern is RR or QT intervals. $\tilde{x}_\bullet(t)$ is a third order piece wise continuous spline polynomial function. The parameter α to balance the accuracy and smoothness is set to 0.999 empirically. The sequences $\tilde{x}_\bullet(t_l)$ are utilized to evaluate the QT-RR co-variability. The first step to take median intervals eliminates sporadic extremely large measurement errors for the effective smoothing by the following spline function. Examples of spline smoothed QT-RR sequences $\tilde{x}_\bullet(t_l)$ are shown in Fig 2(a)(b). Serial correlation coefficient between these RR and QT spline smoothed sequences are estimated as an index to evaluate their co-variabilities.

C. Alternans ratio percentile

T-wave alternate morphology changes are measured by the phase signal changes. Singular value decomposition is applied first to each segmented T-waves $x_T[n,m]$ defined in Eq. (1) to obtain underlying orthogonal signals. Two major orthogonal signals

$$s_i[n,m], \quad i = 1,2; \quad n = 1, \cdots, N; \quad m = 1, \cdots, M \qquad (3)$$

are utilized to obtain the phase plot of each T-waves. An example of the plot and corresponding T-wave is shown in Fig. 3. The phase plot is named T-wave loop.

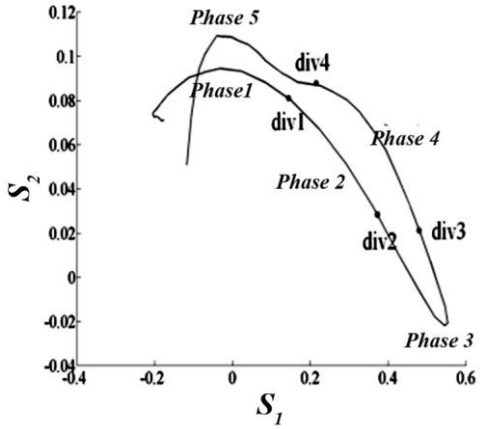

Fig. 3. An example of the phase plot of a T-wave

The T-wave loop is evenly divided into 5 phases. Then successive square differences E of adjacent and one after adjacent T-wave loop are calculated for each phase.

$$E = \{e[m, m+1], e[m, m+2]\}, m = 1, M-2 \qquad (4)$$

In Eq. (4),

$$e[m, m+k] = \sqrt{\sum_i \sum_n \left(\frac{(s_i[n,m] - s_i[n,m+k])}{s_i[n,m]} \right)^2} \quad (5).$$

Data are segmented in every 2 minutes and Periodogram of the sequence E is calculated to obtain alternans ratios of each segment. An example of the periodogram is shown in Fig. 4 in which prominent alternans is detected by excessive power at the Nyquist frequency. The alternans ratio is defined as the periodogram power at Nyquest frequency relative to surrounding background average power in the normalized frequency range 0.4-0.47. In this report average periodogram over 5 T-wave phases are utilized for the subsequent data analysis. The alternans ratios over 24 hours are ordered and θ percentile values of the alternans ratio is obtained as a risk indicator of SCA. Fig. 5 schematically shows the idea.

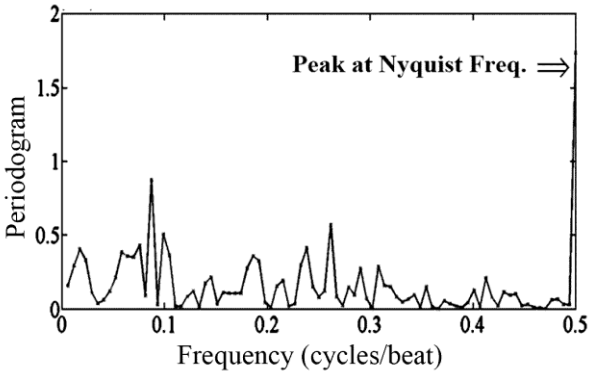

Fig.4. An example of a periodogram of the sequence E

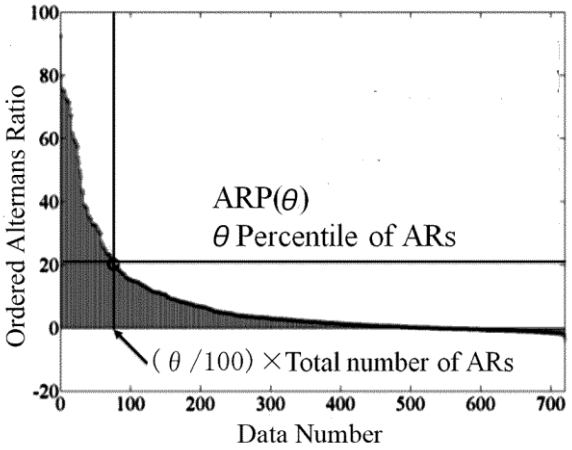

Fig. 5. Alternans ratio percentile

III RESULTS

A. Co-variability of QT and RR intervals

Table 1 and Fig. 6 show the result. In table 1, the mean value and standard error of serial correlation coefficients for each subject group are shown. The values are compared with ones in previous report[10] utilizing Kalman filter technique for the trend extraction. The proposed method simplifies the signal decomposition, yet it works equally well as the table shows. Fig. 6 shows the box plot of the coefficients. HR and LR groups as well as HR and Control groups showed statistically significant differences ($p<0.01$).

Table 1. Serial correlation coefficient of QT-RR intervals

	High Risk	*Low Risk*	*Control*
Spline	0.884±0.028	0.928±0.028	0.980±0.002
Kalman[10]	0.854±0.027	0.909±0.015	0.971±0.004

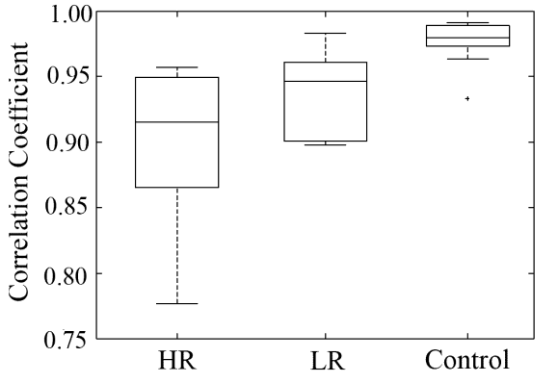

Fig. 6. Correlation coefficients for QT-RR intervals

B. Alternans ratio percentile ARP(θ)

Table 2 shows the mean and standard error of the alternans ratio percentile values when percentile values θ are changed. Table 3 shows p values for the comparison of the median values when designated two groups are compared. Table 3 shows the best θ values is 0.05 as far as the class separation power is concerned. Here again the statistically significant differences are noted except for comparison between LR and control cases.

Table 2. Alternans ratio percentile *ARP(θ)*

θ	*High Risk*	*Low Risk*	*Control*
0.01	119.7±41.9	33.8±5.27	26.9±3.19
0.05	38.2±5.90	16.1±2.76	13.1±1.22
0.1	23.3±3.79	10.4±1.85	8.86±0.89
0.15	15.3±2.45	7.67±1.40	6.70±0.74

Table 3. p Values for pairwise group comparison

θ	*HR vs. LR*	*HR vs. C*	*LR vs. C*
0.01	0.01	0.002	0.955
0.05	0.07×10^{-3}	0.08×10^{-5}	0.729
0.1	0.04×10^{-2}	0.01×10^{-3}	0.835
0.15	0.003	0.02×10^{-2}	0.861

Fig. 7 shows the box plot of ARP(θ) for each subject group using the optimal parameter θ=0.05.

C. Risk Stratification by QTRC and ARP(θ)

To explore the feasibility of SCA risk stratification using two indices QTRC and ARP(θ), scatter diagram of two parameters is plotted (Fig. 8). For the best cutoff lines shown in the figure, average sensitivity 0.812 and specificity 0.925 are achieved. Classification results are summarized in Table 4. The table shows two risk indicators give better stratification when combined.

Table 4. Risk stratification by QTRC and ARP(θ)

		HR	*LR*	*C*
ARP(0.05)	Sensitivity	0.545	0.333	0.800
	Specificity	0.973	0.778	0.609
QTRC	Sensitivity	0.364	0.833	0.920
	Specificity	0.973	0.750	0.957
QTRC and ARP(0.05)	Sensitivity	0.545	0.833	0.920
	Specificity	0.973	0.806	0.957

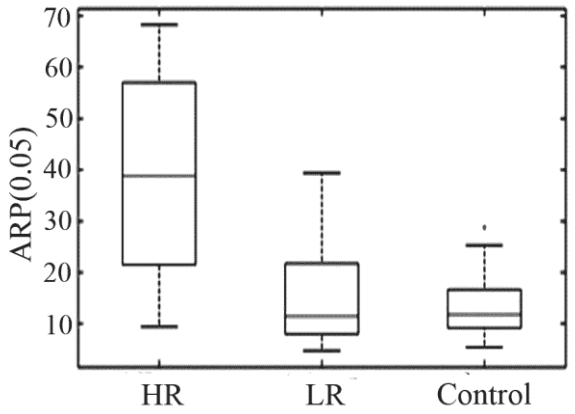

Fig. 7. Alternans ratio percentile values

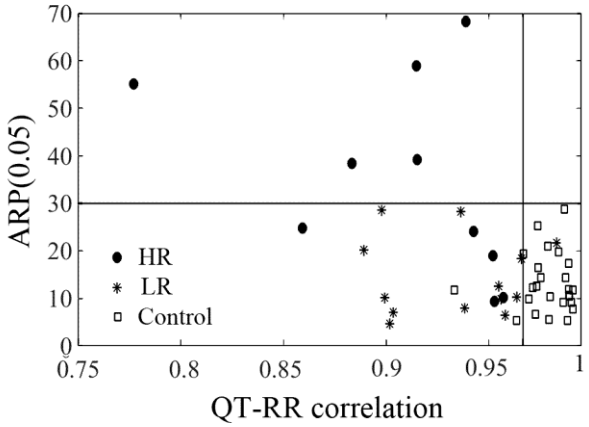

Fig. 8. Risk stratification by QTRC and ARP(θ)

IV Discussion and Conclusion

Risk assessment for sudden cardiac arrest based on Holter ECG is an emerging direction of study, that facilitates the assessment and makes it more accessible in daily. Activities. This study explored the possibility of using two indicators QTRC and ARP(θ). For the QTRC evaluation, a new method of using a simple median filter followed by spline smoothing has been introduced for extracting trend components instead of using the Kalman filtering proposed in the previous study [10]. It has been shown that the new simple signal decomposition method works just as well, and it is recommended for extensive clinical data analysis. However, Kalman filtering technique would be useful for more advanced analysis taking additional signal component such as REM is to be considered. For the alternans analysis ARP(θ) may be useful to get a consistent index value from Holter ECG since there are statistically some chances to get high alternans ratios for even control cases in a long run. Obtaining the theoretical probability distribution will become an important research topic. Finally, the two indices combined yielded a promising SCA risk stratification scheme. Sensitivities and specificities for all subject classes exceeded 0.8 except for the sensitivity of the HR group. To improve the sensitivity, other indices and subject attributes may need to be taken in to account.

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