A novel technique to investigate the effect of ageing on ventricular repolarization characteristics in healthy and LQTS subjects

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***Abstract*- Ventricular repolarization(VR) characteristics is affected by ageing alongside several other factors like Heart rate(HR),respiration, modulation of autonomic nervous system, different drug effects, genetical factors affecting the cardiac ion channel characteristics, gender etc. Therefore, total VR variability (i.e. QT interval variability in surface ECG) consists of two components: one dependent on HR variability (HRV) and another independent of HRV. Analysis of QT interval variability (QTV) is crucial for both healthy and pathological conditions as increase in VR variability measured by QTV increases cardiac repolarization instability, which might lead to arrhythmogenesis. Analyzing the effect of ageing using a widely used measure of QTV (i.e. QTVI) is reported inconsistently in Healthy subjects whereas the same for Long QT Syndrome (LQTS) subjects is not widely reported. In this study, we propose a novel time domain measure from beat-to-beat QT-RR distribution to analyze how ageing affects VR in both Healthy and a group of genotyped LQTS1 subjects. A total of 139 Healthy subjects and 134 LQTS1 subjects of three different age groups (i.e. Young: age 20-35, Middle-aged: 40-55 and Old: age>60) were analyzed for this study. The proposed measure is also compared with other existing widely used measures of QTV like SDQT and QTVI in differentiating different age groups. The proposed measure stands out to be more discriminatory than other existing variability measures of QT interval.**

I. Introduction

Ageing is an important cardiovascular risk factor that causes degeneration in autonomic nervous system (in both parasympathetic and sympathetic branches) regulating cardiovascular function and consequently affecting both heart rate variability (HRV) and ventricular repolarization variability (VRV) [1-3]. VRV measured as QT interval variability(i.e. QTV) in surface ECG is affected mainly by two factors: the direct effect of HRV measured by the a series of previous RR intervals (i.e. RR dependent component of QTV) and other factors independent of RR like ageing, respiration, drug effects on cardiac ion channels, autonomic nervous system modulation, genetical factors etc. [4,11]. Age related alteration of QTV is important for the prognosis of ventricular arrhythmias [4]. Decrease in HRV measured by RR interval variability is found in both healthy ageing and in aged pathological subjects [1-3]. Besides HRV, QTV is used in several studies for analyzing ventricular repolarization changes due to alteration in cardiac autonomic modulation with ageing [2,5]. However, the use of QTV parameters is not consistent in analyzing age related VRV changes as reported in recent studies [3].

Heart rate corrected QT (i.e. QTc) prolongation is found in ageing but the choice of an accurate heart rate correction formula makes this measure unreliable for VRV analysis [6, 16]. The most widely used parameter for measuring QTV is QT variability index normalized by heart rate (i.e. QTVI) proposed by Berger et al [7] and it was used for studying ageing effects on QTV in healthy subjects in various studies [2,3,8]. However, the use of QTVI in analyzing ageing gave inconsistent results in various age groups of healthy subject population [3]. Some study results showed no significant differences between QTVI of young and elderly subjects [9, 10], whereas some studies found significant differences [2, 3]. Increase in the decoupling of QT and RR intervals with ageing is reported in some studies [3,11] indicating that the influence of RR on QT interval decreases with ageing. Interestingly, a change in the RR independent component of QTV has been reported to be sensitive with ageing in both healthy and pathological subjects [12,13]. The presence of the RR independent component of QTV is also reported in LQTS subjects [6,14].

The determination of RR independent QT variability component is generally done through model based multivariate spectral analysis [12], which is a complex procedure as the correct quantification of different QTV component depends on the performance of proper model identification techniques. In this study, we propose a new time domain analysis technique to quantify the QTV components from beat-to-beat QT and RR interval distribution derived from short-term ECG segment (i.e. 10 min). This method calculates the portion of cardiac beats where QT interval changes from the previous beat without or with a very small change in RR interval within a threshold limit in a particular length of ECG segment. The number of such cardiac beats actually quantifies the amount of QTV component independent of RR (i.e. the higher the number of this type of beats the higher the RR independent component of QTV in total QTV). We hypothesize that the portion of QTV component that is not affected by HRV increases with ageing. In this study, we used the proposed measure in both Healthy and LQTS1 subjects to investigate the alteration of QTV component independent of HRV with ageing and its performance is compared in differentiating three age groups with other standard QTV measures like SDQT and QTVI.

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II. SUBJECTS AND METHODOLOGY

A. Subjects and ECG analysis

ECG signals from a set of Healthy and LQTS type 1 subjects were collected from the Telemetric and Holter ECG warehouse (THEW, www.thew-project.org) [17]. A total of 139 Healthy subject's ECGs were used for this study from the Database named E-HOL-03-203-003. 134 subjects out of 171 patients detected with genotyped LQTS 1 were used from the database named E-HOL-03-0480-013. The selection criteria of the ECG segment were clearly detectable high amplitude T waves and the absence of abnormal T wave morphology due to Long QT syndrome. In both groups, the subjects were divided into three age groups as following: Young (20-35 years), Middle-aged (40-55 years) and Old (>60 years). A five-year gap is maintained within the age groups for clear discrimination of VR characteristics due to ageing. 10 min ECG segment from the diurnal part of the recording was used for our analysis. RR intervals, QT intervals and QT variability index (i.e. QTVI) were determined from the baseline filtered 10 min ECG segment using Berger's Template matching algorithm [7]. Heart rate corrected QT interval was calculated using Bazett's equation. Total Heart rate variability (HRV) and ventricular repolarization variability (VRV) were determined from the Standard deviation of the determined RR and QT time series (i.e. SDRR and SDQT respectively). Non-parametric version of one-way ANOVA (i.e. Kruskalwallis test) with Bonferroni post hoc test was used to check the statistical difference of different QTV measures between three age group in MATLAB 2012b. The proposed methodology for quantifying QTV component independent of HRV is described in the next section.

B. Novel measures for beat-to-beat QT-RR distribution analysis

In this paper, we propose a novel time domain methodology using beat-to-beat QT and RR interval time series for quantifying the QTV component independent of RR. This is done by calculating the number of cardiac beats having beat-to-beat QT changes with insignificant or no change in corresponding RR intervals. Therefore, the higher amount of such cardiac beats contributes larger QTV component, which is independent of RR within that ECG segment. The changes of beat-to-beat RR and QT intervals were measured as the percentage of change for $(n+1)^{th}$ beat with respect to n^{th} beat. The steps involved in the calculation of the proposed measures are described below:

Step 1: Let, the beat-to-beat RR and QT interval time series is denoted as *RR(n)* and *QT(n)*, where n=1,2,3…..N and N is the total number of extracted RR and QT intervals of the corresponding time series. RR and QT intervals were extracted from a fixed length ECG signal (i.e. 10 min in this study) using the appropriate methodology for QRS wave, R wave and T wave detection [7].

Step 2: The Percentage Index (*PI*) time series for both RR and QT interval time series are determined by calculating the normalized successive beat-to-beat changes using the following equations:

$$RR_{PI}(n) = \frac{RR(n+1) - RR(n)}{RR(n)} \times 100 \qquad (1)$$

$$QT_{PI}(n) = \frac{QT(n+1) - QT(n)}{QT(n)} \times 100 \qquad (2)$$

Here n =1,2,3… to N-1 and N is the total number of samples of RR and QT time series. RR_{PI} and QT_{PI} time series contain the magnitude of both positive and negative changes of consecutive RR and QT intervals and thus calculate the total temporal variability of RR and QT interval of that ECG segment.

Step 3: RR_{PI} and QT_{PI} series derived in the previous step are used to generate a 2D (two-dimensional) scatter plot where, RR_{PI} is plotted along the horizontal axis (i.e. x axis) and QT_{PI} is along the vertical axis (i.e. y axis). Fig. 2 shows the conceptual illustration of the proposed methodology. The top panel shows the RR, RR_{PI}, QT and QT_{PI} series of an example subject and the bottom panel shows the 2D scatter diagram. Every point in the RR_{PI}-QT_{PI} plane which indicates the amplitude and polarity of changes in both RR and QT intervals from the previous beat is denoted as $P(x_i, y_i) = P(RR_{PI}, QT_{PI})$ where $x_i = i^{th}$ value of RR_{PI} time series, $y_i = i^{th}$ value of QT_{PI} time series and i=1,2,……N-1, N is the total number of samples in RR or QT time series.

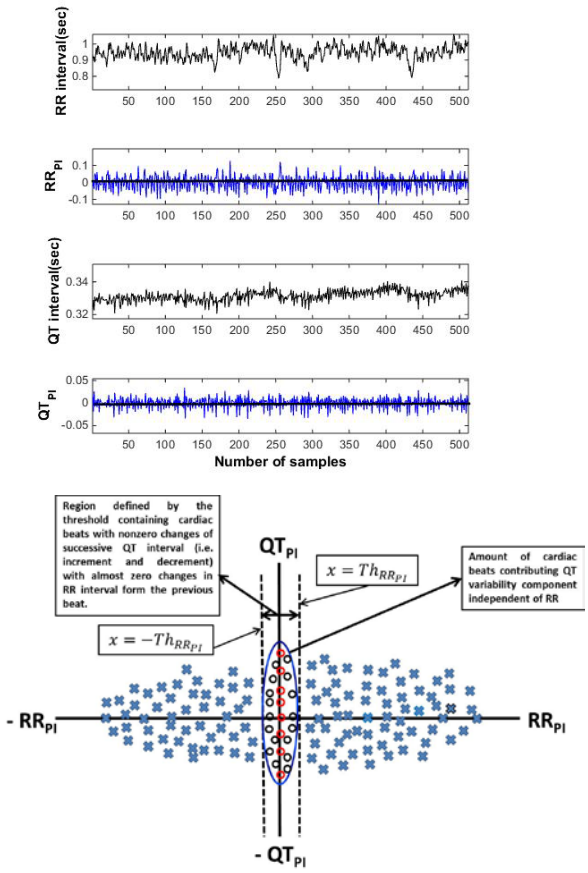

Figure 1. Generation of two dimensional (2D) scatter plot of RR_{PI} and QT_{PI} series to measure amount of cardiac beats contributing the QTV componenet independent of RR changes. Top panel shows the time series of RR, QT and percent index time series of RR (i.e. RR_{PI}) and QT time series (i.e. QT_{PI}) of an example subject. Bottom panel shows the 2D x-y palne (i.e. RR_{PI} - QT_{PI} plane) with the distribution of points plotted as stars and circles. The point density within the threshold limit (i.e. points plotted as circles) indicates the amount of cardiac beats contributing to quantify the

QT variability component independent of RR. The threshold value is defined from the RR_{PI} time series termed as $Th_{RR_{PI}}$.

Step 4: A threshold level is then defined to measure the density of cardiac beats with beat-to-beat RR changes are very small or zero. Theoretically the amount of beats contributing QTV independent of RR variation can be calculated from the points that lie on $RR_{PI} = 0$ line of RR_{PI} - QT_{PI} plane (i.e. the red colored circles along the *y* axis representing the beats where QT interval increases or decreases with no changes in RR in Figure 1). However, we think $RR_{PI} = 0$ is a very strict criteria and a sufficient number of cardiac beats is hard to found with no change in successive RR intervals in healthy populations where HRV is normally quite high. Moreover, beat-to-beat RR interval changes do not become zero except in subjects with artificial pacing arrangements (i.e. cardiac pacemaker) or severe pathological conditions, where HRV is diminished heavily. Therefore, we define a threshold level denoted as $Th_{RR_{PI}}$ from RR_{PI} time series such that for any sample of RR_{PI} series that falls within a defined limit (i.e. if $-Th_{RR_{PI}} \leq RR_{PI} \leq Th_{RR_{PI}}$) then the corresponding QT_{PI} sample is considered having $RR_{PI} = 0$. In our study, we measured the 75th percentile of RR_{PI} time series and take 1 percent of that value as the threshold using the following equation:

$$Th_{RR_{PI}} = 0.01 * (75th\ percentile(abs(RR_{PI})) \quad (3)$$

The 75th percentile or the third quartile of RR_{PI} time series indicates the dominant pattern of RR time series variation in every subject and 1% of that change is a reasonable criterion to determine the portion of cardiac beats where RR variation is quite small. The threshold region is defined from negative $Th_{RR_{PI}}$ to positive $Th_{RR_{PI}}$ value along the RR_{PI} axis (i.e. area between the two vertical lines in Figure 1) and the number of points within this region indicates the ECG beats with QT changes but RR changes are within the threshold value.

Step 5: Finally, three measures are calculated to count the number of cardiac beats within the threshold in the RR_{PI}-QT_{PI} plane. If $\boldsymbol{P_{total}}$ indicates the total number of points in the RR_{PI}-QT_{PI} plane, it can be measured as:

$$\boldsymbol{P_{total}} = |\{\boldsymbol{P}(x_i, y_i)\}: (-\mathbf{RR_{PI}} \leq x_i \leq \mathbf{RR_{PI}}), (-\mathbf{QT_{PI}} \leq y_i \leq \mathbf{QT_{PI}})| \quad (4)$$

Where, $|.|$ indicates the cardinality of the set which contains the total number of points in RR_{PI}-QT_{PI} plane.

The number of cardiac beats having the increase of QT interval from the previous QT beat (i.e. positive change in QT) within the RR_{PI} threshold termed as $\boldsymbol{P_{pe}}$ is calculated as:

$$\boldsymbol{P_{pe}} = \left|\{\boldsymbol{P}(x_i, y_i)\}: (-\boldsymbol{Th_{RR_{PI}}} \leq x_i \leq \boldsymbol{Th_{RR_{PI}}})\ \boldsymbol{and}\ y_i > 0\right| \quad (5)$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane above the *x* axis within the threshold.

The number of cardiac beats having the decrease of QT interval from the previous QT beat (i.e. negative change in QT) within the RR_{PI} threshold denoted by $\boldsymbol{P_{ne}}$ is calculated as:

$$\boldsymbol{P_{ne}} = \left|\{\boldsymbol{P}(x_i, y_i)\}: (-\boldsymbol{Th_{RR_{PI}}} \leq x_i \leq \boldsymbol{Th_{RR_{PI}}})\ \boldsymbol{and}\ y_i < 0\right| \quad (6)$$

where $|.|$ indicates the cardinality of the set which contains the total number of points in RR_{PI}-QT_{PI} plane within the threshold below the *x* axis.

Then the percentage of cardiac beats having both increment and decrement of beat-to-beat QT interval changes within the RR threshold (i.e. $\boldsymbol{QTRR_{PE}}$ and $\boldsymbol{QTRR_{NE}}$ respectively) are calculated using the following equations:

$$\boldsymbol{QTRR_{PE}} = \frac{\boldsymbol{P_{pe}}}{\boldsymbol{P_{total}}} \times \mathbf{100} \quad (7) \quad \text{and} \quad \boldsymbol{QTRR_{NE}} = \frac{\boldsymbol{P_{ne}}}{\boldsymbol{P_{total}}} \times \mathbf{100} \quad (8)$$

Finally the total amount of beats with the combination of both positive and negative changes of consecutive QT beats within the RR threshold in the ECG segment termed as $\boldsymbol{QTRR_{PNE}}$ is calculated as:

$$\boldsymbol{QTRR_{PNE}} = \boldsymbol{QTRR_{PE}} + \boldsymbol{QTRR_{NE}} \quad (9)$$

TABLE 1. COMPARISON OF DIFFERENT QT AND RR VARIABILITY MEASURES IN HEALTHY AND LQTS TYPE 1 GROUP SUBJECTS

	Healthy subject group (E-HOL-03-203-003)				LQTS type 1 subject group (E-HOL-03-0480-013)			
	Young (20-35 year)	Middle-aged (40-55 year)	Elderly (above 60 year)	*P* value	Young (20-35 year)	Middle aged (40-55 year)	Old (above 60 year)	*P* value
N	64	57	18		79	38	17	
Age	27.13 ± 4.37	46.67 ± 4.58	67.89 ± 6.23	0	28.25 ± 4.69	47.48 ± 3.75	67.21 ± 4.23	0
SDQT(ms)	14.30 ± 6.69	13.40 ± 6.58	11.80 ± 5.46	0.3683	15.30 ± 10.01	14.45 ±9.69	12.73 ± 7.01	0.505
SDRR(ms)	95.10 ± 38.30	86.95 ± 34.50^	60.70 ± 30.91*	0.0039	73.71 ± 40.30	63.82 ± 31.12	49.45 ± 18.20	0.052
QTc(ms)	375 ± 22	380 ± 23^	404 ± 19*	0.00004	484 ± 78	477 ± 70	452 ± 34	0.42
QTVI	-0.98 ± 0.26	-0.96 ± 0.31	-0.74 ± 0.41	0.074	-0.79 ± 0.45	-0.72 ± 0.46	-0.59 ± 0.47	0.196
$QTRR_{PE}(\%)$	0.90 ± 0.62	1.28 ± 0.92#	1.77 ± 1.28*	0.0008	0.89 ± 0.80	0.67 ± 0.50^	1.12 ± 0.54*	0.0037
$QTRR_{NE}(\%)$	0.92 ± 0.66	1.112 ± 0.79	1.17 ± 1.13*	0.0064	0.95 ±0.90	1.06 ± 0.57	1.15 ± 0.54*	0.022
$QTRR_{PNE}(\%)$	1.82 ± 1.19	2.47 ± 1.159#	3.46 ± 2.56*	0.0014	1.84 ± 1.07	1.75 ± 0.92^	2.231 ± 0.93*	0.0084

All values are shown as Mean ± Std. # indicates the Middle-aged group is significantly different from Young, * indicates the Old group is significantly different from Young and ^ indicates the Middle-aged group is significant different from Old group. A value of $p < 0.05$ was considered significant.

III. RESULTS

Results obtained using the proposed parameters including standard QT and RR variability measures are shown in Table 1. The HRV measure, SDRR (i.e. standard deviation of RR intervals) decreases both in Healthy and LQTS subject groups but the decrease is only significant in Healthy subject group. SDRR can significantly differentiate the old from the young group and the middle-aged subjects from the old group. The gross VRV measure SDQT decreased with ageing in both groups but cannot differentiate any age group significantly. The magnitude of SDQT is much smaller than SDRR, which indicate that decrease in HRV is more dominant than the decreases in VRV with ageing. The QTV index (i.e. QTVI) increases with ageing in both subject groups but cannot classify any age group significantly. The rate corrected QT interval (i.e. QTc using Bazett's formula) increased significantly only in healthy subject group and can

classify between old and young group and between middle-aged and old group. QTc was found to decrease with ageing in LQTS group although the values remained above 450 ms in all three age groups (table 1).

In contrast to standard QT and RR variability parameters, proposed parameters ($QTRR_{PE}$, $QTRR_{NE}$ and $QTRR_{PNE}$) were found significantly different among three age groups in both Healthy and LQTS subjects. $QTRR_{PNE}$ increased gradually with ageing in Healthy group by differentiating the Young and Middle-aged group and Young and Old group significantly. However, this index cannot differentiate significantly Middle-aged from Old group though the gradual increase is found between the groups (Table 1).

On the other hand, for LQTS group $QTRR_{PNE}$ decreased slightly from Young to Middle-aged group, but increased again from Middle-aged to Old group. Values of $QTRR_{PNE}$ were significantly (p<0.01) different between Middle-aged and Old group as well as Young and Old group (Table 1). $QTRR_{PE}$ showed the same pattern in classification as $QTRR_{PNE}$ in both the groups, whereas the other measure $QTRR_{NE}$, can only differentiate the young and old subjects in both Healthy and LQTS subject groups.

IV. Discussions and Conclusion

Both HRV and QTV studies are crucial for analyzing the cardiovascular health. In our study the gross variability measure of HRV, SDRR decreased significantly with ageing in Healthy subject groups but the decrease was not significant in LQTS1 group. The significant decrease in SDRR in Healthy subjects supports other previous findings [3,5]. The gross variability measure of VRV, SDQT decreases with ageing in both Healthy and LQTS1 subject groups but cannot significantly differentiate between the groups. QTVI was found to increase with ageing which was aligned with other previous studies [2,3], but this measure cannot classify any of the groups significantly in this study.

Our proposed method for quantifying RR independent QTV component gave a clear picture of the dynamical distribution of cardiac beats with beat-to-beat changes in both RR and QT intervals. We have used normalized beat-to-beat difference time series of RR and QT intervals to derive the measures, which reduce the problem of both intra and inter-subject variability of QT-RR distribution [16]. Beat-to-beat analysis of QTV was found more effective than the gross variability measures (i.e. QTVI, SDQT) in describing the dynamical changes in VR associated with ageing and other pathological conditions [10,11]. In our study, SDQT and QTVI cannot differentiate the three age groups in any subject group but the proposed measure ($QTRR_{PNE}$) effectively differentiated the three age groups in both Healthy and type 1 LQTS subjects. Our study findings indicate that in both healthy and LQTS subject groups ageing actually increases the density of cardiac beats having beat-to-beat QT changes with unchanged RR, which contribute to the increase in HRV independent component of QTV and might reflect the age related increase in sympathetic activation [5] which affect the ventricular repolarization [12]. Our future study includes the analysis of gender effect on VR and the sensitivity of the proposed measures with shorter ECG recording length (i.e. 5 min ECG).

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