A Novel Technique for Analysing Beat-to-beat Dynamical Changes of QT-RR Distribution for Arrhythmia Prediction

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Abstract

Ventricular tachycardia (VT) leading to ventricular fibrillation (VF) is the major cause of sudden cardiac death (SCD) with subjects with or without any history of cardiac disease. Prediction of the initiation of ventricular fibrillation is crucial for both successful preventive measure and effective defibrillation therapy. A lot of studies have been done based on electrocardiogram (ECG) waveform analysis for VF detection but this field still needs more perfection. Both HRV and QTV related parameters were reported to be analysed for VT/VF detection and prediction with inconsistent results in different populations. In this study, we propose a novel time domain measurement tool to detect the pattern of dynamical changes of both RR and QT intervals in subjects having sustained VT/VF episodes form VFDB and AHA database (www.physionet.org). We also analyse the same pattern in some healthy subjects from Fantasia database and compare the distribution of patterns between healthy and VT/VF subjects. Our findings showed that the distribution of QT-RR dynamics are statistically significantly different ($p<0.05$) in healthy subjects from VT/VF in particular before the start of VF episode. Therefore, distribution of change in QT-RR dynamics may provide insight of the underlying instability before VF events and can be used for better prediction of arhythmogenesis.

1. Introduction

Ventricular arrhythmias (VA) (i.e. Ventricular flutter, ventricular tachycardia and ventricular fibrillation) are the main causes of Sudden Cardiac Death (SCD) in both subjects having a history of cardiac disease or without any history of structural heart disease [1]. A lot of research has been done in the field of devising methodology of predicting the initiation of arrhythmia and the detection of different types of ventricular arrhythmias for efficient defibrillation therapy [2-4]. Different electrocardiogram (ECG) signal waveform analysis methods were analysed for the detection for Ventricular tachycardia (VT) and ventricular fibrillation (VF) but the performance still need to be improved [4, 5]. Cardiac electrical instability due to ventricular repolarization variability (QTV) was analysed as a predictor of VT/VF using QT–RR modelling techniques [6]. However, similar instability was also found in healthy subjects with no history of arrhythmia [7], which reduced the reliability of that technique in prediction of VA. Heart rate variability (HRV) and QTV are also used for the investigation of risk prediction of VF and VT [8-10]. But the trend of changes in HRV and QTV parameters are not consistent before the initiation of VT [9]. Some studies have reported the increase of QT interval whereas some reported the decrease in QT interval before the initiation of VT/VF [11]. Therefore, we hypothesize that the analysis of beat-to-beat change in QT and RR interval might provide useful information for the prediction of ventricular arrhythmias.

In this paper, we propose a novel two dimensional time domain measurement tool that can examine how beat-to-beat QT and RR intervals increase or decrease from the previous cardiac beat within the recorded ECG signal segment. The main objective of this study is to measure the variation in distribution of changes in beat-to-beat QT and RR intervals, in particular before the initiation of ventricular arrhythmias (i.e. VT/VF). In this study, we compare the QT-RR beat distribution of two databases (i.e. VFDB and AHA database) having ECG recordings with sustained ventricular tachycardia or fibrillation episodes with healthy subject groups of two different ages (i.e. Fantasia database).

2. Subjects and ECG processing

Two annotated public domain ECG databases were used for ECGS with sustained VT and VF episodes. 10 min ECG segments just before the start of VT/VF of nine subjects from the MIT-BIH Malignant Ventricular Arrhythmia Database (VFDB) [12], and 10 records(8001-8010)the American Heart Association Database

(AHADB) were analysed. 20 young and 20 old Healthy subject 's ECG from Fantasia database were used as controls for comparing with ECGs with VT/VF episodes [12]. Baseline filtered ECG signal segments were used to determine RR intervals using the algorithm of Pan et al [13] and QT intervals were detected as Q wave to T wave end interval using slope intercept method [14]. Ectopic beats were removed from the derived RR and QT interval time series using the methodology described in [15] and ectopic free QT and RR intervals were used to determine the proposed measures.

2.1. Novel measures for dynamic beat-to-beat QT-RR analysis

In this paper, we propose a novel time domain methodology using QT and RR interval time series for analysing their beat-to-beat variation patterns. This is done by calculating the number of cardiac beats having specific patterns of beat-to-beat QT and RR variation. In this study, considered four different parameters based on four different patterns: i) $QTRR_{PP,}$ which quantifies the cardiac beats where both QT and RR increases from the previous beat showing positive changes in QT and RR intervals; ii) $QTRR_{NN,}$ which quantifies the beats where both QT and RR interval decreases form the previous beat; iii) $QTRR_{PN,}$ indicates the amount of beats having QT interval increase and decrease in RR interval from the previous beat (i.e. positive change in QT and negative change in RR); and iv) $QTRR_{NP,}$ which measure the beat-to-beat decrease in QT and increase in RR interval. Beats with no change in RR or QT interval compared to previous interval was not considered for these measurements. The steps involved in the calculation of the proposed measures are described below:

Step 1: 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 using Percentage Index (*PI*) time series . 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. The *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. The normalization with the previous beat value reduces the intra and inter subject variability of QT-RR distribution[16].

Step 2: 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. 1 shows the conceptual illustration of the proposed methodology. 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 $P(x_i, y_i)$ 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.

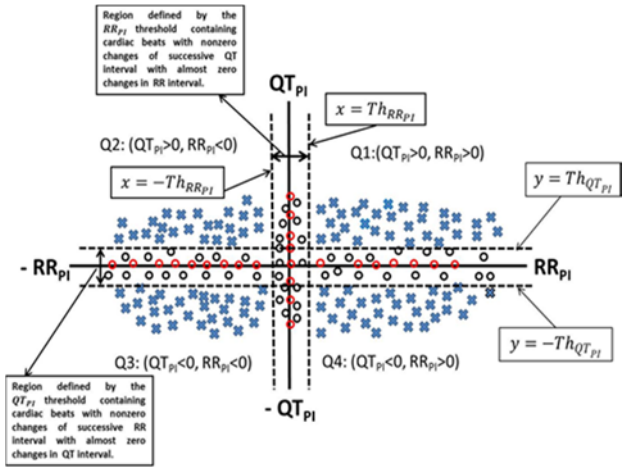

Figure 1: Two dimensional (2D) scatter plot of RR_{PI} and QT_{PI} series to measure cardiac beats showing the different patterns of beat-to-beat QT and RR changes. It shows the 2D x-y plane (i.e. RR_{PI} - QT_{PI} plane) with the distribution of points plotted as stars and circles. The point density within the threshold limit (i.e. points plotted as circles) indicates the amount of cardiac beats having either QT or RR changes with RR or QT unchanged or with a very small change from the previous beat within the threshold. The four quadrants (i.e. Q1:Q4) indicates the pattern of beat-to-beat changes of QT and RR.

Step 3: A threshold level is then defined to define the positive and negative changes of RR and QT. Theoretically the beats that lie on $RR_{PI} = 0$ line (i.e. the red colored circles along the y axis) of RR_{PI} - QT_{PI} plane representing the beats where QT interval increases or decreases with no changes in RR (Figure 1). However, we think $RR_{PI} = 0$ is a very strict criteria and very small variation due to sampling or measurement noise can affect heavily. Therefore, we define a threshold level denoted as $Th_{RR_{PI}}$ for 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 (Figure 1). Similarly a threshold was defined for QT_{PI} series as:

$$Th_{QT_{PI}} = 0.01 * (75th\ percentile(abs(QT_{PI})) \quad (4)$$

The points within the defined thresholds were discarded, since they do not represent simultaneous beat-to-beat changes in QT and RR intervals.

Step 4: Finally, the four measures are calculated to count the number of cardiac beats that are outside the threshold regions 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:

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

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 in both QT and RR interval from the previous beat (i.e. positive change in QT and RR) is calculated as:

$$\boldsymbol{P_{pp}} |\{\boldsymbol{P}(\boldsymbol{x_i}, \boldsymbol{y_i})\}: (\boldsymbol{x_i} > \boldsymbol{Th_{RR_{PI}}}\ \boldsymbol{and}\ \boldsymbol{y_i} > \boldsymbol{Th_{QT_{PI}}})|$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane in Q1 quadrant (Figure 1). Similarly

$$\boldsymbol{P_{pn}} = |\{\boldsymbol{P}(\boldsymbol{x_i}, \boldsymbol{y_i})\}: (\boldsymbol{x_i} < -\boldsymbol{Th_{RR_{PI}}}\ \boldsymbol{and}\ \boldsymbol{y_i} > \boldsymbol{Th_{QT_{PI}}})|$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane in Q2 quadrant (Figure 1)

$$\boldsymbol{P_{nn}} = |\{\boldsymbol{P}(\boldsymbol{x_i}, \boldsymbol{y_i})\}: (\boldsymbol{x_i} < -\boldsymbol{Th_{RR_{PI}}}\ \boldsymbol{and}\ \boldsymbol{y_i} < -\boldsymbol{Th_{QT_{PI}}})|$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane in Q3 quadrant (Figure 1) and

$$\boldsymbol{P_{np}} = |\{\boldsymbol{P}(\boldsymbol{x_i}, \boldsymbol{y_i})\}: (\boldsymbol{x_i} > \boldsymbol{Th_{RR_{PI}}}\ \boldsymbol{and}\ \boldsymbol{y_i} < -\boldsymbol{Th_{QT_{PI}}})|$$

where $|.|$ indicates the cardinality of the set which contains the total number of points RR_{PI}-QT_{PI} plane in Q4 quadrant (Figure 1).

Finally the percentage of cardiac beats having the above mentioned patterns of changes defined as the four measures were calculated using the following ratios:

$$\boldsymbol{QTRR_{PP}}(\%) = \frac{\boldsymbol{P_{pp}}}{\boldsymbol{P_{total}}} \times \mathbf{100}$$

$$\boldsymbol{QTRR_{PN}}(\%) = \frac{\boldsymbol{P_{pn}}}{\boldsymbol{P_{total}}} \times \mathbf{100}$$

$$\boldsymbol{QTRR_{NN}}(\%) = \frac{\boldsymbol{P_{nn}}}{\boldsymbol{P_{total}}} \times \mathbf{100}$$

$$\boldsymbol{QTRR_{NP}}(\%) = \frac{\boldsymbol{P_{np}}}{\boldsymbol{P_{total}}} \times \mathbf{100}$$

Statistical comparison between groups was performed using non-parameteric Mann-Whitney U-test in Matlab 2014b. Since, number of subjects were small non-parametric tests were more suitable than parametric one and $p<0.05$ was considered significantly different.

3. Results and discussion

In this study we compared the four proposed measures to identify the pattern of changes in beat-to-beat QT and RR intervals between VT/VF and healthy subjects. We also used two different age groups for healthy subjects to compare the changes with subjects having VT/VF episodes and investigate if ageing affects the pattern of changes as ageing is known to affect both HRV and QTV [17, 18].

Table 1: Comparison of dynamic QT-RR distribution measures between Fantasia and VFDB database

Features	$QTRR_{PP}$	$QTRR_{NN}$	$QTRR_{PN}$	$QTRR_{NP}$
VFDB	24.84±3.78	24.70 ± 5.08	18.64±5.51	18.29 ± 4.06
FY	17.42±3.05	16.96 ± 3.58	15.28 ± 2.99	16.23 ± 3.60
FO	16.14±3.31	15.49 ± 3.76	17.08 ± 4.16	16.66 ± 4.27
p1	<0.001	<0.001	0.041	0.185
p2	<0.001	<0.001	0.412	0.345

FY – Fantasia Young
FO – Fantasia Old
p1 – *p* values between VFDB and FY
p2 – *p* values between VFDB and FO

Table 1 shows the changes of the measures in both young and old healthy subjects with VFDB subjects. Both $QTRR_{PP}$ and $QTRR_{NN}$ changes significantly between the groups indicating the amount of cardiac beats having both positive and negative changes QT and RR intervals increases in VFDB ECGs in comparison to healthy group subjects. This finding support the increase of temporal instability of RR and QT intervals before VT/VF starts [6, 9]. $QTRR_{PN}$ was also found significantly different between healthy young and VFDB subjects but not found in aged subjects.

Table 2: Comparison of dynamic QT-RR distribution parameters between Fantasia and AHADB database

Features	$QTRR_{PP}$	$QTRR_{NN}$	$QTRR_{PN}$	$QTRR_{NP}$
AHADB	18.70±6.08	20.64± 5.98	22.35 ± 4.80	21.30 ± 4.29
FY	17.42±3.05	16.96± 3.58	15.28 ± 2.99	16.23 ± 3.60
FO	16.14±3.31	15.49± 3.76	17.08 ± 4.16	16.66 ± 4.27
p1	0.471	0.025	<0.001	0.004
p2	0.137	0.006	0.003	0.006

FY – Fantasia Young
FO – Fantasia Old
p1 – p values between AHADB and FY
p2 – p values between AHADB and FO

Table 2 showed the comparison of the measures between healthy and AHADB subjects. In this subject groups $QTRR_{NN}$, $QTRR_{PN}$ and $QTRR_{NP}$ were found significantly different between both young and old with subjects with VT/VF. The significant increase of $QTRR_{NN}$ and $QTRR_{PN}$ in AHADB subjects in the segments before VF starts indicates the rapid increase in heart rate (i.e. decrees in RR intervals) and both increase and decrease in beat-to-beat QT intervals as found in previous studies[8, 9, 11]. The increase in $QTRR_{NP}$ indicates the decrease in QT interval with increase in RR intervals (i.e. increase in heart rate) which was also reported in a previous study[11].

The different findings of the pattern of changes in both QT and RR changes before VT/VF starts in two databases (i.e. VFDB and AHADB) indicates the subjective variation of the initiation pattern of VA. The common pattern found in two groups was the change in $QTRR_{NN}$ and $QTRR_{PN}$ in both subject groups which might indicate that electrical instability that initiates VT/VF can be determined form the change of these two patterns of dynamic changes in QT and RR intervals. These patterns are also found similar irrespective of ageing in healthy subjects.

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