Assessment of QT Interval Dynamics Induced by Heart Rate Changes through Bivariate Phase-Rectified Signal Averaging

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Abstract

The aim of this study is to investigate the relationship between the RR and QT series through the bivariate phase-rectified signal averaging (BPRSA) computed during RR decelerations, assuming that recurrent changes in the of RR (trigger signal) cause recurrent responses in QT (target signal). Moreover, the prognostic value of new deceleration-related indices in a chronic heart failure (CHF) population are assessed. The 24-hour QT and RR series were extracted from 651 Holter recordings acquired from CHF patients. First, deceleration anchor points were identified as RR increases in the trigger signal, and segments of 2L+1 samples around them were extracted from both the trigger and the target. Finally, all segments are aligned with respect to the anchors and averaged. The deceleration capacity (DC) and new bivariate deceleration-based biomarkers were computed from the average PRSA and BPRSA signals, respectively. Patients suffering from pump failure death (PFD) had significant lower DC and QT increase after heart rate deceleration. Moreover, the proposed BPRSA indices were associated to PFD in the studied population, with hazard ratios of 2.6 and 2.2 obtained for $\Delta_{1,0}^{BPRSA}$ and $\Delta_{0,-1}^{BPRSA}$ indices, respectively. In conclusion, a large QT increase in the beats immediately after heart rate deceleration is an indicator of higher mortality risk in the studied population.

1. Introduction

Phase-rectified signal averaging (PRSA) [1] has been proposed for the evaluation of periodicities in nonstationary and noisy biological signals, such as heart rate. In particular, the PRSA-derived heart rate deceleration capacity (DC) index has been shown to be a powerful predictor of mortality in post-myocardial infarction patients, outperforming conventional heart-rate variability indices [2].

A variant of PRSA, named as bivariate phase-rectified signal averaging (BPRSA), has been later proposed for the study of periodic relationships between two synchronous signals, and successfully applied to quantify the relationship between periodic modulations of systolic blood pressure, heart rate and respiration [3].

Given the fact that impaired adaptation of QT to RR changes is associated to increased cardiac risk [4, 5], the aim of this study is to investigate the relationship between the QT and RR series through BPRSA, hypothesizing that this technique will unveil changes in QT related to recurrent heart rate decelerations. Moreover, the prognostic value of new bivariate deceleration-related indices in a chronic heart failure (CHF) population will be assessed.

2. Study population

Consecutive patients with symptomatic CHF corresponding to New York Heart Association (NYHA) classes II and III were enrolled in the multicenter MUSIC (MUerte Súbita en Insuficiencia Cardiaca) study, a prospective study designed to assess risk predictors for cardiovascular mortality in ambulatory CHF patients [6]. The 24-hour Holter ECG recordings of 651 patients in permanent sinus rhythm were available for the present study. ECG signals were acquired by using SpiderView records (ELA Medical, Sorin Group, Paris, France) and two (3.2%) or three (96.8%) orthogonal leads (X, Y, Z) sampled at 200 Hz were available for each subject. Collection of clinical data for this population was reported in previous studies [6, 7]. Main characteristics are reported in Table 1.

The study protocol was approved by institutional investigator committees and all patients gave written informed consent. Patients were followed up every 6 months for 48 months. A total of 55 patients were victims of SCD, 59 of other cardiac causes (pump failure deaths, PFD), 26 of non-cardiac deaths, and 511 survivors.

Table 1: Clinical characteristics of the study population. Data are presented as mean±standard deviation and as absolute frequencies (percentages)

Variable	Overall population (n=651)
Age (years)	62.9±11.9
Gender (males)	464 (71.3%)
LVEF $\leq$ 35%	356 (54.7%)
NYHA class III	115 (17.7%)
Diabetes	244 (37.5%)
Beta-blockers	455 (69.9%)
Amiodarone	61 (9.4%)
ARB or ACE inhibitors	576 (88.5%)
QRS $\geq$ 110 ms	322 (49.5%)

3. Methods

3.1. Preprocessing

Preprocessing of ECG recordings included heartbeat detection and labeling using the Aristotle ECG analysis software [8]. Then, a multilead strategy based on periodic component analysis (πCA) was used for the purpose of improving QT delineation. The strategy involves a linear spatial transformation designed to emphasize the T-wave periodicity by exploiting spatial and temporal information in the ECG [9]. A single-lead, wavelet-based algorithm [10] was applied for QT delineation on the transformed lead. Finally, both the beat-to-beat RR interval series, $x_{\text{RR}}(n)$, and QT interval series, $x_{\text{QT}}(n)$, were computed.

3.2. Bivariate phase-rectified signal averaging

The BPRSA technique is a bivariate version of the PRSA, originally designed for detecting periodicities in non-stationary and noisy signals [1]. In this study, we propose the use of BPRSA [3] for quantifying the relationship of periodic behavior between heart rate, directly from the RR series (trigger signal), and ventricular repolarization, extracted from the QT series (target signal), given the well-established QT/RR adaptation phenomenon.

The first step consists in the identification of anchor points in the trigger signal, according to a selection criterion. In this case, anchor points are defined by a heart rate deceleration, that is, an instantaneous prolongation in the RR interval with respect to the previous one:

$$x_{\text{RR}}(i) > x_{\text{RR}}(i-1). \tag{1}$$

Once all anchor points (i_v) are selected from the 24-hour series, signal segments of $2L+1$ samples around the anchor points are extracted and aligned with respect to the anchor for final averaging. For a segment to be included in the averaging, all beats within it need to be labelled as 'Normal' and all RR values have to be between 300 ms and 2000 ms. The final PRSA signal is computed as:

$$\bar{x}_{\text{PRSA}}(k) = \frac{1}{M}\sum_{v=1}^{M} x_{\text{RR}}(i_v + k) \tag{2}$$

where i_v is the anchor point of the v^{th} segment, $v = 1, \ldots, M$ with M the total number of selected segments, and $k = \{-L, \ldots, 0, \ldots, L\}$ the sample within the segment.

The BPRSA signal is computed in an analogous way, using the same anchor points but extracting the signal segments from the simultaneous target signal, i.e., the x_{QT} series:

$$\bar{x}_{\text{BPRSA}}(k) = \frac{1}{M}\sum_{v=1}^{M} x_{\text{QT}}(i_v + k) \tag{3}$$

Selection of anchor points, extraction of segments suitable for averaging and computation of $\bar{x}_{\text{PRSA}}$ and $\bar{x}_{\text{BPRSA}}$ signals are illustrated in Fig 1.

3.3. Heart rate deceleration-based indices

The deceleration capacity (DC), already proposed in [2], has been already associated to mortality risk. It is derived from the $\bar{x}_{\text{PRSA}}$ signal as:

$$DC = \frac{1}{4}\left(\bar{x}_{\text{PRSA}}(0) + \bar{x}_{\text{PRSA}}(1) - \bar{x}_{\text{PRSA}}(-1) - \bar{x}_{\text{PRSA}}(-2)\right) \tag{4}$$

Three new indices derived from the $\bar{x}_{\text{BPRSA}}$ are considered for risk stratification, both describing QT dynamics related to heart rate decelerations. First, the analogous bivariate DC index (BDC), defined as:

$$BDC = \frac{1}{4}(\bar{x}_{\text{BPRSA}}(0) + \bar{x}_{\text{BPRSA}}(1) - \bar{x}_{\text{BPRSA}}(-1) - \bar{x}_{\text{BPRSA}}(-2)) \tag{5}$$

In addition, we propose two indices based on the differences between consecutive samples of the BPRSA signal:

$$\Delta^{\text{BPRSA}}_{0,-1} = \bar{x}_{\text{BPRSA}}(0) - \bar{x}_{\text{BPRSA}}(-1) \tag{6}$$

$$\Delta^{\text{BPRSA}}_{1,0} = \bar{x}_{\text{BPRSA}}(1) - \bar{x}_{\text{BPRSA}}(0) \tag{7}$$

3.4. Statistical analysis

Data is presented as median (interquartile range) for continuous variables, unless otherwise specified. To evaluate differences in PRSA and BPRSA-derived indices among SCD, PFD and survivors, the non-parametric

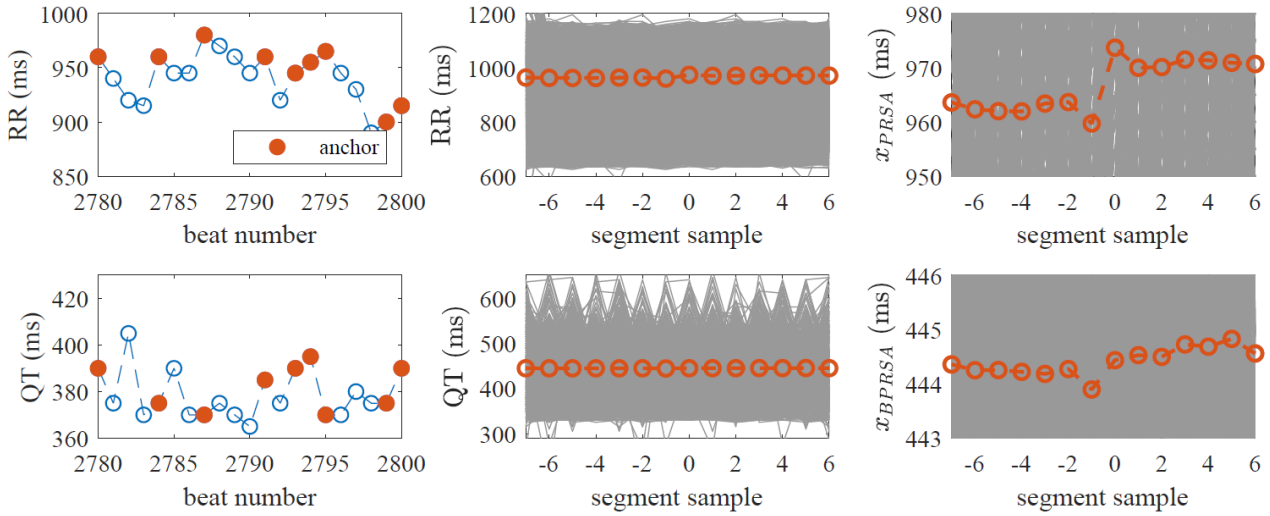

Figure 1: Illustration of BPRSA technique. Selection of deceleration-based anchor points (left column) in the trigger series, x_{RR}, (top row) and their corresponding points in the targert series, x_{QT}, (bottom row), and the final $\bar{x}_{\mathrm{PRSA}}$ and $\bar{x}_{\mathrm{BPRSA}}$ (right column), respectively obtained from averaging all selected segments (middle column).

Kruskal–Wallis test and Mann–Whitney test with Bonferroni correction were applied (M=12 multiple comparisons). Prognostic value of PRSA and BPRSA indices in predicting SCD and PFD was determined with univariate Cox proportional hazards analysis. For all tests, the null hypothesis was rejected for $p \leq 0.05$.

4. Results

Median and interquartile values of PRSA and BPRSA indices, for the SCD, PFD and survivors' groups are reported on Table 2. As expected, DC was higher in survivors than in the other two groups. However this difference was only significant with respect to the PFD group (6.36 (4.11) vs 4.46 (4.57), p=0.0013). Regarding to the BPRSA indices, no differences among patients were found for the Bivariate DC (BDC) marker, while PFD group had significant higher $\Delta^{\mathrm{BPRSA}}_{0,-1}$ values and lower $\Delta^{\mathrm{BPRSA}}_{1,0}$ than the other two groups. No significant differences between SCD and survivors were found.

The association of the indices with cardiac mortality, either due to arrhythmic or heart-failure origin, was first assessed using continuous variables. According to the results obtained in this first analysis, all indices were dicotomized by setting a risk threshold in the first or the third quartile of the total distribution of the index. That is, for each index the risk group was always defined as the 25% of the total population with the highest or lowest values, depending on the what was suggested by the continuous analysis. Results are reported on Table 3). Low deceleration capacity was associated with PFD outcome in the study population. In addition the two novel proposed indices derived from the BPRSA analysis, $\Delta^{\mathrm{BPRSA}}_{1,0}$ and $\Delta^{\mathrm{BPRSA}}_{0,-1}$ were also associated to this fatal outcome. BCD was the only marker associated with SCD risk, with hazard ratio of 1.84 for patients with BCD lower than -0.01 ms.

Table 2: Distribution of deceleration-based indices according to the patients' outcome. Data are represented as median (interquartile range).

	Survivors	**SCD**	**PFD**
DC	6.36(4.11)	5.86(5.49)	4.46(4.57)*
BDC	0.14(0.34)	0.04(0.41)	0.18(0.46)
$\Delta^{\mathrm{BPRSA}}_{1,0}$	0.01(0.98)	0.13(0.88)	-0.32(1.37)*
$\Delta^{\mathrm{BPRSA}}_{0,-1}$	0.14(1.24)	-0.09(1.62)	0.49(1.76)*†

SCD: Sudden cardiac death, PFD: Pump failure death. Significant differences *:vs Survivors; †:vs SCD

5. Discussion and conclusion

In this study the use of bivariate phase-rectified signal averaging for assessing the QT/RR dynamics phenomenon was introduced, and three novel heart-rate deceleration-based indices, describing QT dynamics related to heart rate decelerations, were proposed.

It is well know that a delayed adaptation of QT interval to heart rate changes is associated to proarrhythmic risk [11]. This is in agreement with the fact that lower $\Delta^{\mathrm{BPRSA}}_{1,0}$ values, quantifying QT changes in response to a heart rate deceleration, are associated to higher risk of heart failure

Table 3: Association of PRSA and bprsa deceleration-based indices with sudden cardiac death and pump failure death in a chronic heart failure population.

	Sudden Cardiac Death		**Pump Failure Death**	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
DC ≤ 4.31	1.38 (0.77,2.48)	0.279	**3.036 (1.82,5.06)**	**<0.001**
BDC ≤ -0.01	**1.843 (1.06,3.20)**	**0.03**	0.809 (0.43,1.53)	0.513
$\Delta^{\text{BPRSA}}_{1,0} \leq -0.473$	0.785 (0.41,1.52)	0.474	**2.619 (1.57,4.37)**	**<0.001**
$\Delta^{\text{BPRSA}}_{0,-1} \geq 0.807$	0.896 (0.47,1.70)	0.736	**2.177 (1.29,3.66)**	**0.003**

mortality. Nevertheless, the computational requirements for the assessment of QT/RR dynamics using the BPRSA technique are significantly lower than the ones required for the estimation of QT adaptation lag, avoiding the optimization problem [11]. To note, the prognostic values of the proposed indices provided better stratification than the left ventricular ejection fraction (hazard ratio of 1.79 for LVEF$\leq$35), well-established in clinical routine.

This study has been focused on QT changes restricted to heart rate deceleration capacity. However, it is known that the adaptation process id different, being faster during HR acceleration than during deceleration ("QT hysteresis"). The potential prognostic value of BPRSA indices induced by heart rate acceleration, that is, selecting anchor points as consecutive RR decrements, remains to be investigated. Another future step would be to assess the stratification performance of proposed indices in other cohorts of patients, such as atrial fibrillation, where delayed QT adaptation has already provided with prognostic value.

In conclusion, a large increase in QT synchronous to the heart rate deceleration ($\Delta^{\text{BPRSA}}_{0,-1}$) and a large enough QT decrease in the immediately following beat ($\Delta^{\text{BPRSA}}_{1,0}$) are indicators of higher mortality risk due to pumping failure in the studied population. The BPRSA technique has the advantage of characterizing QT/RR dynamics from ambulatory recordings in a computationally simple way.

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