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ORIGINAL ARTICLE

Short-term QT interval variability in patients with coronary artery disease and congestive heart failure: a comparison with healthy control subjects

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Abstract
This study aimed to test how different QT interval variability (QTV) indices change in patients with coronary artery disease (CAD) and congestive heart failure (CHF). Twenty-nine healthy volunteers, 29 age-matched CAD patients, and 20 age-matched CHF patients were studied. QT time series were derived from 5-min resting lead-II electrocardiogram (ECG). Time domain indices [mean, SD, and QT variability index (QTVI)], frequency-domain indices (LF and HF), and nonlinear indices [sample entropy (SampEn), permutation entropy (PE), and dynamical patterns] were calculated. In order to account for possible influence of heart rate (HR) on QTV, all the calculations except QTVI were repeated on HR-corrected QT time series (QTc) using three correction methods (i.e., Bazett, Fridericia, and Framingham method). Results showed that CHF patients exhibited increased mean, increased SD, increased LF and HF, decreased T-wave amplitude, increased QTVI, and decreased PE, while showed no significant changes in SampEn. Interestingly, CHF patients also showed significantly changed distribution of the dynamical patterns with less monotonously changing patterns while more fluctuated patterns. In CAD group, only QTVI was found significantly increased as compared with healthy controls. Results after HR correction were in common with those before HR correction except for QTc based on Bazett correction.

Keywords QT interval variability · QT variability index · Sample entropy · Permutation entropy · Dynamical patterns

1 Introduction

QT interval in body surface electrocardiogram (ECG) is a global measure representing ventricular depolarization and repolarization activities. Beat-to-beat QT intervals display temporal variability due to the fluctuations of ventricular repolarization, i.e., QT interval variability (QTV) [12]. Increased QTV, an indicator of instable myocardial recovery that can be a consequence of many cardiac abnormalities, has been related to an increased risk of ventricular arrhythmias, a leading cause of sudden cardiac death [4, 28, 29, 31].

Time-domain measures including mean, standard deviation (SD), and the normalized QT interval variance relative to the normalized heart rate variance (which is known as QT variability index, QTVI) [10] have been used to analyze QTV. Based on the spectral characteristics of heart rate variability (HRV), frequency-domain indices of QTV have also been introduced, such as the power of QTV in lower frequency band (i.e., 0.04–0.15 Hz) and the power in higher frequency band (i.e., 0.15–0.5 Hz) [7]. Nonlinear methods have also been frequently used as QTV is intrinsically nonlinear due to an adaptive, feedback control mechanism that involves both the heart and the autonomic nervous system (ANS) [2, 5, 6].

In the current study, we aimed to explore whether different QTV indices change in patients with coronary artery disease (CAD) and congestive heart failure (CHF) as compared to healthy control subjects. The two patients groups were studied because these patients usually have been experiencing ventricular repolarization lability for a long time and have increased

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risks for developing ventricular arrhythmias and sudden cardiac death [1, 15, 16, 30, 35]. The abovementioned time- and frequency-domain measures were used. As for nonlinear analyses, two information-domain measures—sample entropy (SampEn) [33] and permutation entropy (PE) [3]—were applied since many previous studies have witnessed their suitability especially for analyzing short-term physiological time series [21, 32]. In addition, PE will also allow us to explore how different dynamical patterns, the elements that PE uses for evaluating the complexity of time series but are integrated in PE, change in different groups, which may possibly provide additional references for describing the dynamics of QT time series [26, 39]. Considering the dependence of QT on heart rate (HR), all above analyses except QTVI were repeated on the HR-corrected QT time series (QTc) based on three previously established correction criteria, i.e., the Bazett method, the Fridericia method, and the Framingham method [25].

2 Methods

2.1 Subjects

Twenty-nine healthy volunteers (16 men and 13 women, aged between 42 and 72 years), 29 age-matched CAD patients (22 men and 7 women, aged between 42 and 72 years), and 20 age-matched CHF patients (9 men and 11 women, aged between 40 and 74 years) were enrolled in this study. Medical history and current medication uses were acquired from questionnaire that needed to be done during the laboratory visits. CAD patients were from those who were hospitalized for coronary angiography and only the 29 age-matched patients whose angiogram results indicated at least 50% stenosis in ≥ one major branches of coronary arteries were included in this study. Patients were considered not illegible and were excluded prior to participation if they had received treatments such as coronary artery bypass surgery and percutaneous coronary intervention. Subjects in CHF group were in class II or III based on the New York Heart Association (NYHA) functional classification. Demographical and clinical characteristics of all subjects were summarized in Table 1. Informed consents were obtained from all subjects. The study was approved by the Clinical Ethics Committee of Shandong Provincial Qianfoshan Hospital.

2.2 Protocol

All measurements were performed in a quiet room with relatively constant temperature (25 ± 3 °C) at Shandong Provincial Qianfoshan Hospital. The Cardiovascular Function Detection device (CV FD–I, Huiyironggong Tech. Co. Ltd., Jinan, P. R. China) was used for ECG collection. Before the formal collection, subjects were asked to lie down for at least 10 min on a measurement bed. A standard limb lead-II configuration was used and the sampling frequency was set 1000 Hz. ECGs were continuously recorded for 5 min, during which the subjects were asked to keep quiet and relax, and breathe regularly.

2.3 RR and QT time series construction

Prior to signal processing, a visual inspection for signal quality was performed on each ECG recording. ECG episodes with poor quality were marked. For a single ECG recording, if the percentage of marked episodes with poor quality went beyond 10%, the recording would be considered invalid and the corresponding subject would be excluded. After the quality screening, R-wave peaks were extracted from ECGs with good quality by a template-matching algorithm [23]. The raw RR interval time series were formed by the intervals of adjacent R-wave peaks and then anomalous intervals owing to ectopic heart beats were removed [24]. QRS onset as well as the apex (T-apex) and offset (T-end) of T-wave corresponding to each R-wave were identified manually. The interval between QRS onset and T-end was defined as QT interval. Similarly, QTa interval was defined as the interval between QRS onset and T-apex. Using the final RR interval time series as reference, QT and QTa time series was constructed so that each QT interval corresponds to the RR interval of the same cardiac cycle. Finally, T-wave amplitude was measured from the T-apex to T-end for each beat. Figure 1 shows an example of the construction of RR and QT interval time series.

The left panels of Fig. 2 shows three illustrative QT interval time series from: (a) a healthy subject, (b) a CAD patient, and (c) a CHF patient. The corresponding scatter plots are also shown on the right panels. For better visualization, only the first 200 cardiac cycles in each time series were shown.

2.4 Correction of QT interval by heart rate

The following three correction criteria were used [25].

1) Bazett method:

$$QTcBa = QT/RR^{1/2} \tag{1}$$

2) Fridericia method:

$$QTcFri = QT/RR^{1/3} \tag{2}$$

3) Framingham method:

$$QTcFra = QT + 154(1-RR) \tag{3}$$

Table 1 Demographical and clinical characteristics of all subjects

Variables	Healthy group	CAD group	CHF group
N	29 (16/13)	29 (22/7)**	20 (9/11)
Age (year)	56 ± 8	58 ± 8	59 ± 9
Body mass index (BMI) (kg/m^2)	24 ± 8	26 ± 3	25 ± 4
Systolic blood pressure (SBP) (mmHg)	114 ± 13	117 ± 14	118 ± 14
Diastolic blood pressure (DBP) (mmHg)	72 ± 9	74 ± 9	75 ± 9
Left ventricular ejection fraction (LVEF) (%)	65 ± 4	60 ± 6	39 ± 7*

Data are expressed as number (male/female) or mean ± SD.

*$p < 0.05$ vs. healthy group as revealed by t test

**$p < 0.01$ vs. healthy group as revealed by chi-squared test

In all three equations, QT interval is in milliseconds and the RR interval is in seconds.

2.5 QTV indices

2.5.1 Time domain indices

Time domain indices include mean and standard deviation (SD) of QT, QTc, as well as QTa time series, mean of T amplitudes and QTVI, a metric that incorporates HRV in QTV using the following formula [10]:

$$QTVI = \log_{10}\frac{QT_v/QT_m^2}{HR_v/HR_m^2}. \quad (4)$$

Here, QT_v and QT_m are the variance and mean of QT intervals, respectively. HR_v and HR_m are the variance and mean of heart rate series, respectively. QTVI was calculated only for the raw QT time series.

2.5.2 Frequency-domain indices

Before the power spectral analysis, QT and QTa time series were evenly resampled to 4 Hz by spline interpolation. Power spectral density (PSD) was estimated by autoregressive (AR) model based parametric method. In this study, the Burg's method was used to estimate the model coefficients with an order of 16 [17]. Based on the frequency-domain characteristics of HRV, two frequency bands were defined: (1) a low-frequency band from 0.04 to 0.15 Hz and (2) a high-frequency band from 0.15 to 0.40 Hz. The frequency-domain indices for QT and QTa time series include the power of low frequency bands (LF) and high frequency bands (HF).

2.5.3 Sample entropy

For the time series $\{\mathbf{u}_i = u(i), 1 \le i \le N\}$, form $N-m+1$ vectors $\{\mathbf{X}_i^m = u(i), u(i+1), \ldots, u(i+m-1), 1 \le i \le N-m\}$. Define the distance between all possible pair of vectors $\mathbf{X}_i^m$ and $\mathbf{X}_j^m$ by $d_{i,\,jm} = \max\{|u(i+k) - u(j+k)|, 0 \le k \le m-1\}$. Denote the average number of j that meets $d_{i,\,jm} \le r$ for all $1 \le j \le N-m$, $j \ne i$ by $B_i^m(\mathrm{r})$. Then increase the dimension m to $m+1$ and repeat the above-described procedures to calculate $B_i^{m+1}(\mathrm{r})$. The SampEn for $\mathbf{u}_i$ can be defined by [16]:

$$SampEn(m, r, N) = -\ln\left(\sum_{t=1}^{N-m} B_i^{m+1}(r) / \sum_{t=1}^{N-m} B_i^m(r)\right). \quad (5)$$

The threshold r value has been recommended to choose between 0.1 × SD and 0.25 × SD [27]. In this study, the threshold was set at $r = 0.2 \times SD$in order to minimize the possibility of getting invalid SampEn. The dimension was set at $m = 2$ in accordance with the previous study [40].

2.5.4 Permutation entropy and dynamical patterns

For a time series $\{\mathbf{u_i} = u(i), 1 \le i \le N\}$, form $N-m+1$ vectors $\{\mathbf{X}_i^m = u(i), u(i+1), \ldots, u(i+m-1), 1 \le i \le N-m+1\}$. A symbolic counterpart is then obtained by coarse-graining the time series using a given resolution Δ, i.e.,:

$$\varphi(i) = floor\left(\frac{u(i) - \min(\mathbf{X}_i^m)}{\Delta}\right). \quad (6)$$

The $N-m+1$ vectors can thus be represented by $\boldsymbol{\varphi}_i^m = (\varphi(i), \varphi(i+1), \ldots, \varphi(i+m-1))$. The ordinal pattern corresponding to $\boldsymbol{\varphi}_i^m$ can be defined by the index vector when rearranging $\boldsymbol{\varphi}_i^m$ in ascending order. For instance, if $\boldsymbol{\varphi}_i^m = [10, 30, 20]$, the index vector when rearranging it in ascending order should be (132) which is defined as the ordinal pattern for $\boldsymbol{\varphi}_i^m$.

Five dynamical patterns were defined by categorizing the ordinal patterns into five different groups. The five dynamical patterns for $m = 3$ were illustrated in Table 2.

The probability (frequency) of each dynamical pattern was counted and denoted by $\{p(D_i), 1 \le i \le 5\}$. PE is then calculated by:

$$PE(m, \Delta) = -\sum_i p(D^i) \ln p(D^i). \quad (7)$$

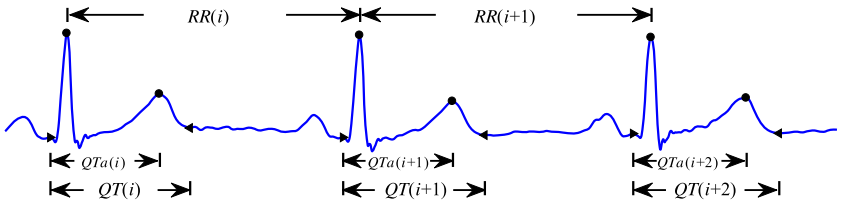

Fig. 1 Construction of RR and QT interval time series. The detected peaks of R-wave and T-wave are marked by "·". The onset of QRS complex and end of T-wave are marked by "▸" and "◂", respectively

In this study, the dimension and resolution parameters were set at $m = 3$ and $\Delta = 4$, respectively, based on a previous study [39].

2.6 Statistical analysis

Pearson correlation was performed to examine the correlations of QT time series, as well as HR-corrected QT time series, with RR time series. Normality of each QTV index in the three groups was confirmed by the Kolmogorov–Smirnov test. One-way ANOVA was performed to examine the group differences in the studied QTV indices followed by post hoc analysis to examine the difference between each two groups if ANOVA showed statistical significance, i.e., $p < 0.05$. Bonferroni criterion was used to correct for multiple comparisons. Effect size was reported by Cohen's d static. Smaller effect size was considered if $d < 0.5$ [13, 36]. All statistical analyses were performed using the SPSS software (Version 20.0, IBM, USA).

3 Results

After visual inspection, we confirmed that no subject had more than 10% anomalous intervals. Thus the results from all the 78 subjects (29 healthy volunteers, 29 CAD patients, and 20 CHF patients) were used for analyses.

3.1 Correlations of QT time series with RR time series

The correlations of QT time series, as well as HR-corrected QT time series, with RR were summarized in Fig. 3 in each studied group. QT showed a significant, positive correlation with RR interval in all three groups (healthy control group:

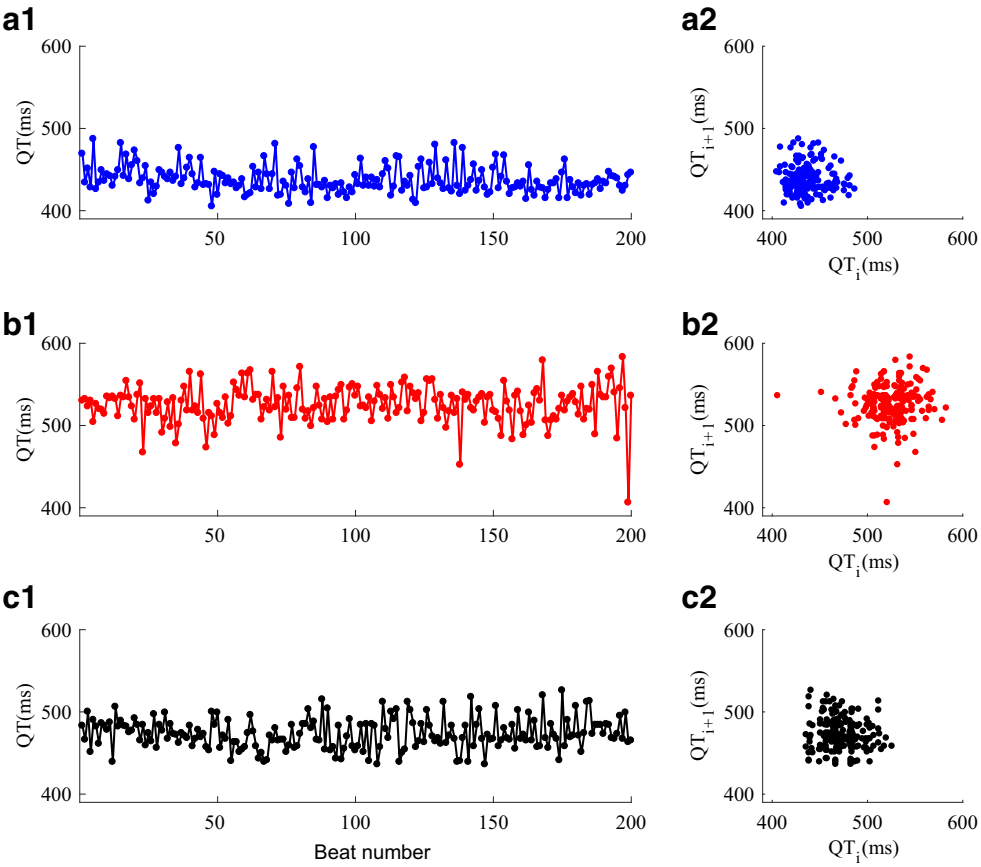

Fig. 2 Examples of the QT time series from (a1) a healthy subject, (b1) a CAD patient, and (c1) a CHF patient. (a2–c2) show the corresponding scatter plots for the three QT time series in (a1–c1), respectively

Pearson $R = 0.76$, $p < 0.01$; CAD group $R = 0.42$, $p < 0.05$; CHF group $R = 0.73$, $p < 0.01$). After corrected by the Bazett method, QTc became not correlated with RR in healthy control group and CHF group whereas was negatively correlated with RR in CAD group ($R = -0.38$, $p < 0.05$). After the Fridericia correction or Framingham correction, QTc became not correlated with RR in healthy control group and CAD group whereas was still positively correlated with RR in CHF group (Fridericia method $R = 0.47$; Framingham method $R = 0.53$; both $p < 0.05$).

3.2 Time- and frequency-domain indices

The time- and frequency-domain indices of QT, QTc, and QTa, were summarized in Figs. 4 and 5 for each studied group. One-way ANOVA demonstrated statistically significant group differences in all the time- and frequency-domain indices (all $p < 0.05$) of QT, QTc, and QTa. Post hoc analysis showed significantly increased mean, SD, LF, and HF of QT in CHF group compared to healthy control group (all $d > 0.50$, $p < 0.01$). The results persisted for QTa and the three QTc time series (all $p < 0.01$, $d > 0.90$). No differences in these time- and frequency-domain indices of QT were observed between CAD group and healthy control group (all $p > 0.05$, $d < 0.50$). For the QTa and the three QTc time series, no differences were suggested by post hoc analysis, either, except for the mean of QTc based on Bazett method (i.e., decreased in CAD group compared with healthy control group; $p < 0.05$, $d = 0.60$). In addition, the post hoc analysis also suggested significantly increased mean, SD, LF, and HF in QT, QTa and all three QTc time series in CHF group compared with CAD group (all $p < 0.01$, $d > 0.90$).

As shown in Fig. 5, one-way ANOVA demonstrated statistically significant group differences in T-wave amplitude and QTVI (both $p < 0.05$) of QT. Post hoc analysis showed significantly decreased mean T-wave amplitude ($p < 0.01$, $d = 1.54$) in CHF group compared to healthy control group while no difference was observed between CAD group and healthy control group ($p > 0.05$, $d < 0.50$). Both CHF group and CAD group showed significantly reduced absolute QTVI (CHF $d = 2.45$, CAD $d = 0.73$; both $p < 0.01$) compared with the healthy control group as suggested by post hoc analysis. In addition, the post hoc analysis also suggested significantly lower mean of T-wave amplitude and the absolute QTVI level in CHF group compared with CAD group (both $p < 0.01$, $d > 2.00$).

3.3 Results of SampEn, PE, and dynamical patterns

The SampEn and PE of QT and QTc were summarized in Fig. 6 for each studied group. One-way ANOVA revealed that there was no statistically significant group differences in SampEn (all $p > 0.05$) of QT and QTc except for the QTc based on Framingham method ($p < 0.01$). Post hoc analysis showed significantly decreased SampEn of QTc based on Framingham method in CHF group compared to healthy control group ($p < 0.01$, $d = 0.60$). In addition, one-way ANOVA demonstrated statistically significant group differences in PE (all $p < 0.05$) of QT and QTc. Post hoc analysis showed significantly decreased PE of QT in CHF group compared to healthy control group ($p < 0.01$, $d > 0.90$). The results persisted for the three QTc time series (all $p < 0.01$, $d > 0.90$). No differences in PE of QT were observed between CAD group and healthy control group (all $p > 0.05$, $d < 0.50$). For the three QTc time series, no differences were suggested by post hoc analysis, either, except for the QTc based on Bazett method (i.e., increased in CAD group compared with healthy control group; $p < 0.05$, $d = 0.58$). In addition, the post hoc analysis also suggested significantly decreased PE in QT, and all three QTc time series in CHF group compared with CAD group (all $p < 0.01$, $d > 0.90$).

The distribution of the dynamical patterns of QT and QTc were summarized in Fig. 7 for each studied group. One-way ANOVA demonstrated statistically significant group differences in all the dynamical patterns (all $p < 0.05$) of QT and QTc. Post hoc analysis showed significantly increased percentages of dynamical patterns ↘↗P and ↗↘P and decreased -P, ↘P, and ↗P in of QT in CHF group compared with healthy controls (all $p < 0.01$, $d > 0.8$). The results persisted for the three QTc time series (all $p < 0.01$, $d > 0.80$). Post hoc analysis showed a significantly reduced percentage of ↗↘P ($p < 0.01$, $d = 0.71$) while no differences in other four patterns (all $p > 0.05$, $d < 0.50$) of QT in CAD group compared with healthy control group. For the three QTc time series, no differences were suggested by post hoc analysis, either, except for dynamical pattern -P based on Bazett method (i.e., increased in CAD group compared with healthy control group; $p < 0.05$, $d = 0.58$). In addition, the post hoc analysis also suggested significantly increased percentages of ↘↗P and ↗↘P and decreased percentages of-P, ↘P, and ↗P in QT and all three QTc time series in CHF group compared with CAD group (all $p < 0.01$, $d > 0.80$).

4 Discussion and conclusion

In this study, time- and frequency-domain indices and nonlinear dynamical measures were used to assess QTV, a marker for ventricular repolarization lability. Comparisons among healthy control subjects, CAD, and CHF patients were performed, as those patients were more vulnerable to labile ventricular repolarization [15, 16]. Results suggest that not all the measures applied in this study can identify the changes in QTV, that is, be sensitive to the labile ventricular repolarization in the two patients groups. Specifically,

Table 2 Dynamical patterns and corresponding ordinal patterns

Symbols of dynamical patterns	Interpretation	Ordinal patterns
—P	Constant pattern	(111)
↘P	Non-increasing patterns	(321), (211), (221)
↗P	Non-decreasing patterns	(123), (112), (122)
↘↗P	Convex patterns	(213), (312), (212)
↗↘P	Concave patterns	(132), (231), (121)

- CHF patients exhibited increased mean QT level, increased QT variations (i.e., SD), increased powers at LF and HF bands, decreased mean T amplitude, increased QTVI, decreased PE and changed distribution of fluctuation patterns, while showed no significant changes in SampEn.
- In CAD group, only QTVI was found significantly increased as compared with healthy controls.

Changes in QTV might be a mixed effect of "intrinsic" QTV alterations combined with the altered HRV [20], which motivated us to examine the changes after performing HR correction. We repeated all the calculations except QTVI on HR-corrected QT—QTc—based on three previously established methods (i.e., the Bazett method, the Fridericia method, and the Framingham method) [25]. Results are quite consistent with those before HR correction except that for QTc based on Bazett correction. Specifically,

- In CHF patients, the mean, SD, LF, HF, and PE of QTc using all three correction methods significantly increased, and the distribution of QTc fluctuation patterns changed which are in keeping with those before HR correction. Besides, similar to the results observed before HR correction, SampEn of QTc still showed no significant changes in CHF patients.
- In CAD patients, mean level of QTc decreased significantly after Bazett correction.

We note that in the present study, results of time- and frequency- domain indices for QTa time series were in keeping with those for QT time series, which is in keeping with previous studies that suggested the use of QTa (i.e., QT intervals without the exclusion of the interval between T-apex and T-end) [7, 14].

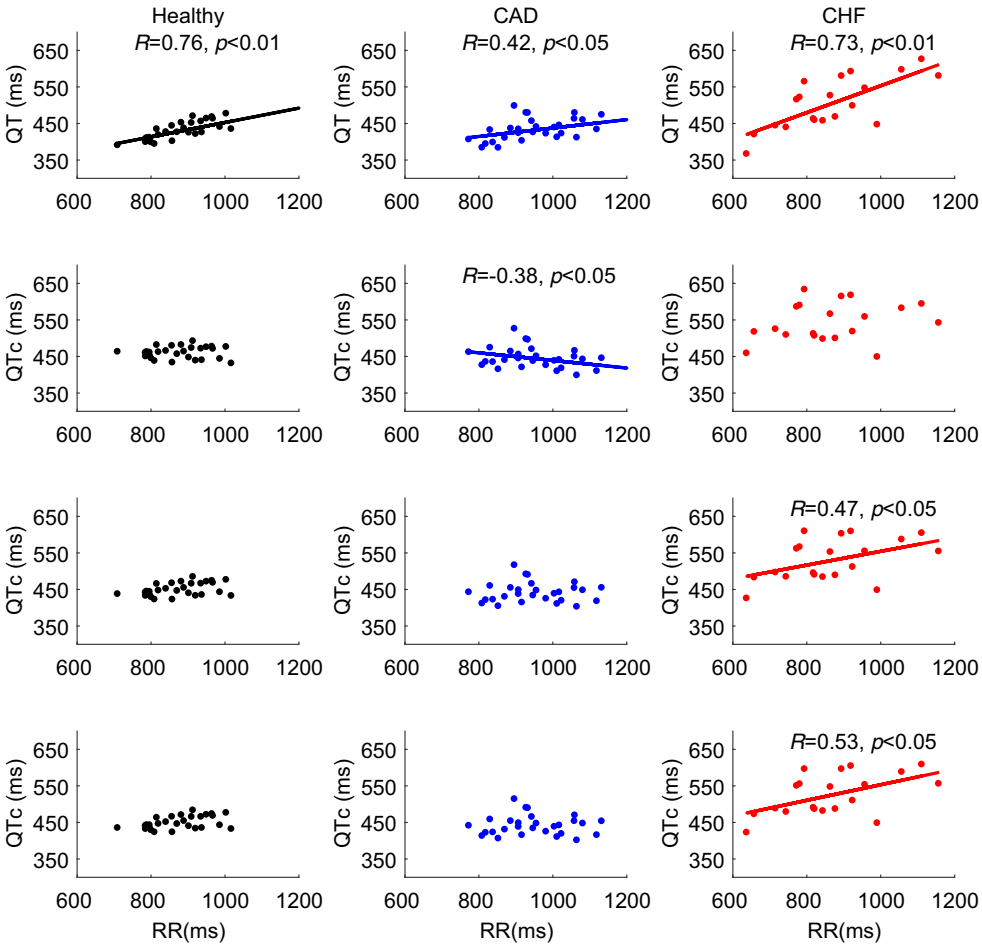

Fig. 3 Correlation of QT-RR from (a) raw QT, (b–d) QT corrected by Bazett, Fridericia, and Framingham method in different groups. The fitting lines with *p* values and *R* values are shown for statistically significant observations

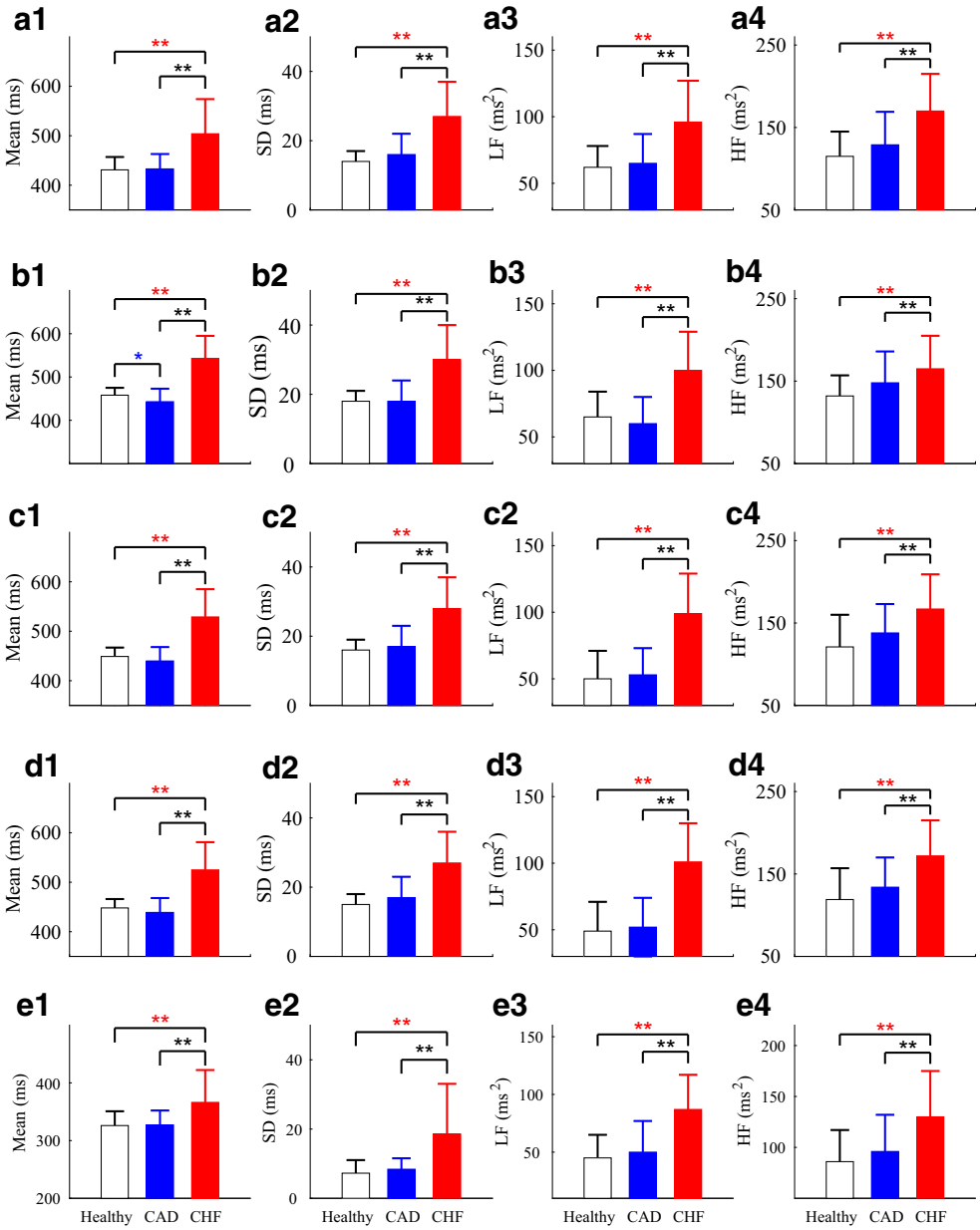

Fig. 4 Results of time- and frequency-domain QTV indices from (a) raw QT, (b–d) QT corrected by Bazett, Fridericia, and Framingham method, respectively and (e) QTa. Bar and error bar represent the mean and standard deviation (SD) of the corresponding index. *$p < 0.05$; **$p < 0.01$; one-way ANOVA followed by t test

The correlations between RR and QTc were largely not significant and differed across the three correction methods and three groups. Based on those results, it might be difficult to tell which correction method may work better than others—QT intrinsically may, or may not, be correlated to HR and the correlation may vary under different conditions. But at least the changed correlations indicate that these methods could, to some extent, attenuate the masking effect of HRV. One

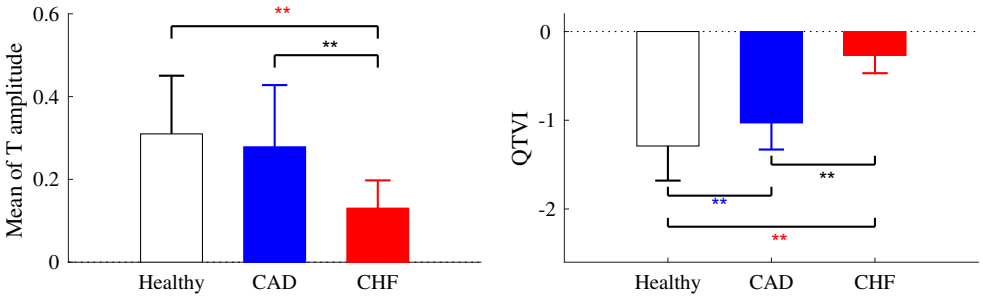

Fig. 5 Results of **a** mean of T amplitude and **b** QTVI calculated from raw QT interval time series in the three groups. Bar and error bar represent the mean and SD. *$p < 0.05$; **$p < 0.01$; one-way ANOVA followed by t test

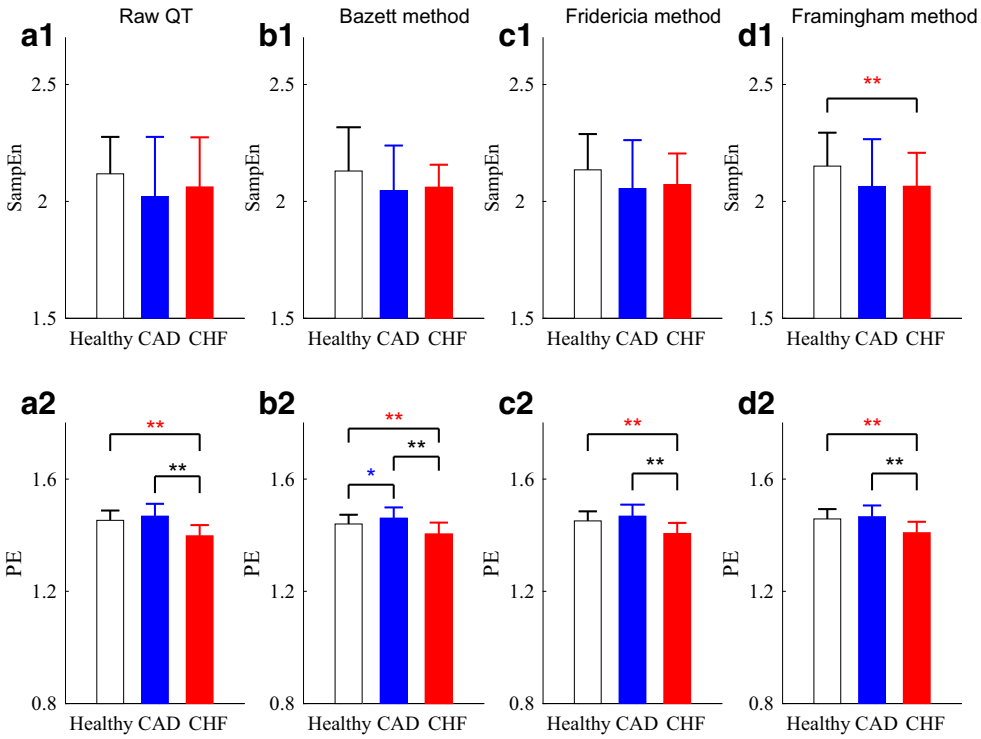

Fig. 6 SampEn and PE results. Bar and error bar represent the mean and SD. *$p < 0.05$; **$p < 0.01$; one-way ANOVA followed by *t* test

possible limitation of those methods is that they are all performed on a beat-by-beat basis. There are studies showing a hysteresis that exists in the effect of HRV on QT variations [20]. This makes the relationship between QT and HR more complex and possibly nonlinear that restricts the performance of the methods that are based on a beat-to-beat (local) mapping. On this scenario, QTVI can be understood as another correction method that considers the overall variations of both QT and RR—a global mapping approach that possibly teases different effects out. This may be a reason that only QTVI showed significant differences in both patients groups as compared with the healthy control group, as well as between the two patients groups.

We note that our results which read mean QT interval does not change significantly in CAD patients group compared with healthy controls are not in line with some previous findings that show a prolong QT interval in CAD patients [12]. Besides, we observed increased mean QTc after correcting by Bazett method in CAD group which also differs from previous studies that observed no significant changes in QTc in CAD patients [38]. Given that in the those studies both an increased mean QT and mean RR was observed, the unchanged QTc may be a consequence of the linear correction of QT by square root of RR in that study. Following the same logic, our observed QTc increase in CAD patients could come from the same correction effect—the mean QT does not change while mean RR increases in CAD patients. But this leaves us a follow-up question regarding why our results do not display significant mean QT changes in CAD patients. The algorithms that are used for identifying QT intervals may partially account for those discrepancies. In our study, in order to assure the accuracy as high as possible, we implemented a manual detection procedure. Since the Q and T wave do not usually appear as obvious spikes, this manual detection process may introduce slight offsets in each cycle which are supposed to be random and counteract each other's influence when taking the mean. Yet there is another possibility that if the offsets in all cycles drift to the same direction, a significant effect on the mean level can thus be expected which finally causes the actual difference between groups not to be able to be detected. A template compressing-stretching procedure has been applied to define QT interval in many other studies [7, 10, 18, 38]. This method requires a manually defined QT template that is used to match all other cycles by compressing or stretching [10]. In other words, QT intervals in other cycles are defined by the template interval times a compressing-stretching coefficient. In the same scenario, one can expect the overall QT interval to be drifted to the same direction if the initial template is improperly defined. Thus further examinations should be warranted to check those different methodological influences and to possibly determine a better way to define the interval of ventricular repolarization.

The significantly increased mean, SD, decreased mean T amplitude and QTVI observed in CHF patients was in keeping with previous findings [11, 19, 30]. It is hypothesized that prolonged HR-corrected QT interval is a strong, independent predictor of adverse outcome in patients with CHF [37]. The results that CHF patients have increased mean QT may thus

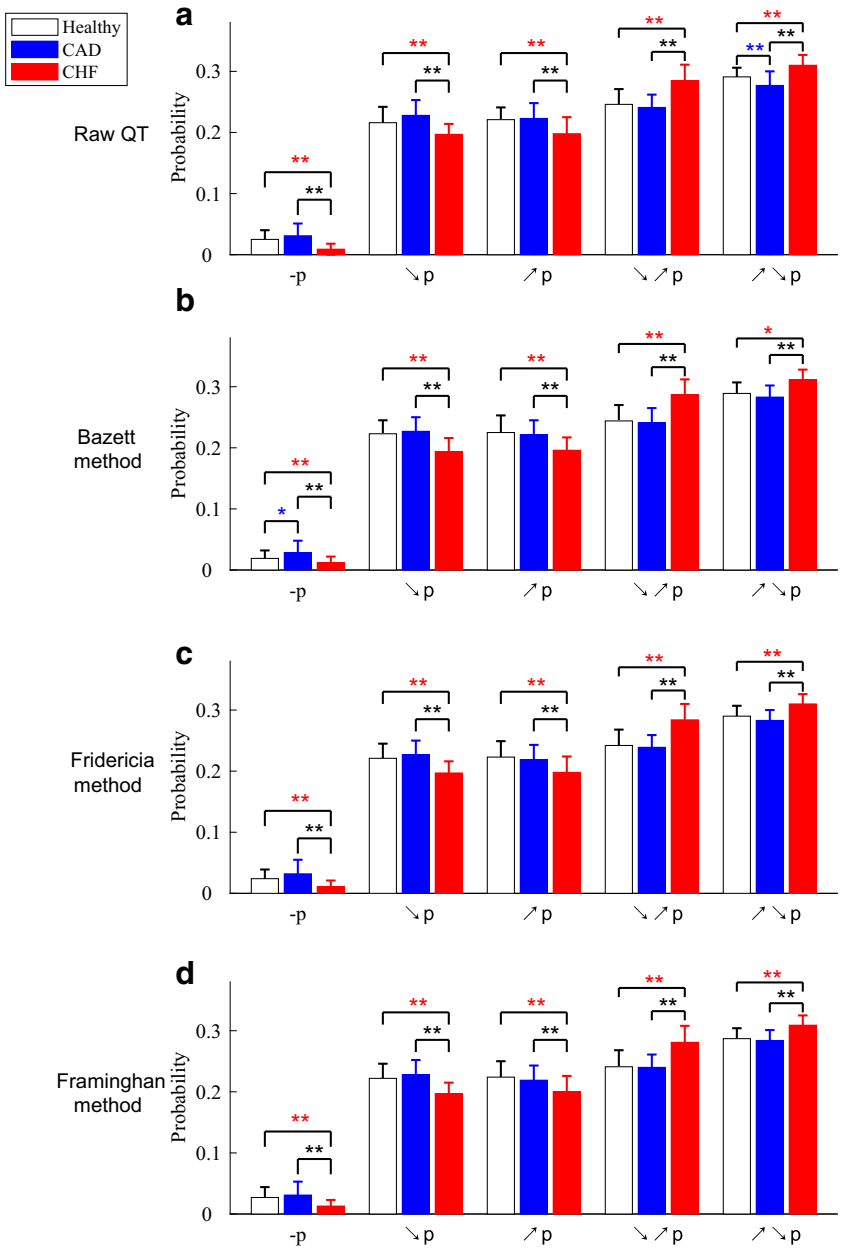

Fig. 7 Percentages of dynamic patterns. Bar and error bar represent the mean and SD, respectively. *$p < 0.05$; **$p < 0.01$; one-way ANOVA followed by t test

suggest an elevated risk for adverse cardiac events. Furthermore, CHF group demonstrated significantly increased LF and HF, which could reflect the sympathetic and parasympathetic modulation. Researches have witnessed the recognition of a significant relationship between QT interval and autonomic nervous activities [8, 9]. Although the underlying mechanisms are currently unknown, the powers of LF and HF changes suggest altered ventricular repolarization and cardiac sympathetic activity in CHF patients. Moreover, the increased QTV might be partly owing to the decreased T-wave amplitude [19], and previous study demonstrated a significant inverse relationship between T-wave amplitude and QTV [34]. The influence of the T-wave amplitude on QTV and the correction formula to account for the influence will be considered in our future work.

Regarding the two nonlinear indices—SampEn and PE, the only consistent finding is that PE values of QT and QTcs using all three correction methods decrease in CHF patients. SampEn showed significantly decreased QTc in CHF patients after Framingham method correction. Neither SampEn nor PE indicates consistent changes in CAD patients even though statistical significant changes are observed occasionally (i.e., PE of QTc after Bazett method correction). The lack of discriminatory power in SampEn may come from its parameter- and length-dependence which have more influences for short-term data [22]. By examining the distribution of different fluctuation patterns in QT and QTc time series, we found that the changes of PE in CHF patients came from (1) increased amounts of convex (↘↗P) and concave (↗↘P) patterns and

(2) decreased amounts of all other patterns including the constant (-P) pattern and two monotonously changing patterns (↗P and ↘P). The different weight of the five categories can partially be explained by the different frequency components of QTV [32]. For example, constant and monotonously changing patterns may indicate slow waves (e.g., low-frequency oscillations) while convex and concave patterns can reflect faster changing components (e.g., high frequency oscillations). The observations of dynamical patterns in CHF patients were consist after correcting by HR using all three methods. These results provide another clue that the frequency indices we applied might not be perfect for QTV analysis. However, similar to PE results, we did not observe any consistent changes in those dynamical patterns in CAD patients across QT and QTcs. To the best of our knowledge, it is the first study to analyze QT time series by means of patterns analysis. Our results suggested that the dynamical patterns analysis might provide valuable additional information on the changes of the ventricular repolarization duration and the underlying mechanisms in the cardiovascular system. In order to fully understand its possible clinical usage, a comprehensive examination with more participants is required in future studies.

Our study has several limitations. First, the specific medication profiles of CHF and CAD patients were not included in the clinical characteristics and we could not exclude the possibility that the observed results were confounded by pharmacological effects. Second, the relationship between QT interval time series and RR interval time series was only studied by linear Pearson correlation. Nonlinear correlations based on Granger causality [4], cross-sample entropy [33], and joint symbolic dynamics analysis [5], etc., are also warranted. Despite these limitations, there are still implications from the current study that are potentially helpful for future studies: (1) The coupling between QT and RR intervals needs attention in QTV analysis; (2) Nonlinear methods might be able to capture additional valuable information hidden in the time series; and (3) The methods that are appropriate for different diseases potentially vary a lot and caution should be paid when interpreting results based on results of a single method.

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Compliance with ethical standards

Informed consents were obtained from all subjects. The study was approved by the Clinical Ethics Committee of Shandong Provincial Qianfoshan Hospital.

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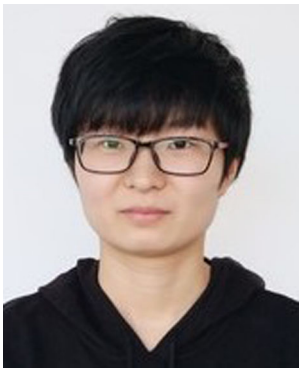

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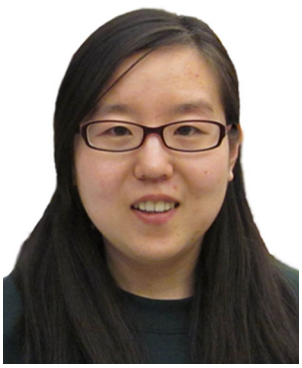

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