Relationship between Corrected QT Intervals and QT Variability Methodologies in Subjects with and without Coronary Artery Disease

Lianke Yao*, Xiuli Qiu, Zhongwen Dou, and Dexu Zhang

School of Aeronautic Engineering, Shandong University of Aeronautics, Binzhou 256600, China

Abstract. Although alterations in QT interval variability (QTV) and the clinical utility of corrected QT (QTc) intervals for risk stratification are well-documented in cardiac patients, the association between myocardial ischemia and QTc intervals remains controversial. Moreover, the relationship between QTc intervals and QTV has not been systematically investigated. Here, using QT interval time series derived from 5-minute ECG recordings of 93 patients with coronary artery disease (CAD) and 107 non-CAD controls, QTc intervals were analyzed using both traditional and individual-specific formulas, while QTV was assessed through tools from time and frequency domains, as well as nonlinear signal analysis. Our results revealed that, compared with non-CAD controls, CAD patients exhibited significantly prolonged QTc intervals and elevated QTV. However, our results indicated that QTc prolongation and QTV elevation are not strictly parallel phenomena in either group; furthermore, no strong association was found between atherosclerotic burden and either metric. Sex differences were observed in QTc intervals but not in QTV. Only weak-to-moderate correlations between QTc and QTV were observed in both groups. Significant correlations between QTc and QTV indices were more prevalent in non-CAD subjects than in CAD patients. Finally, the QTc−QTV correlation was found to be influenced by the sex difference in QTc intervals. These findings indicate ischemic pathology fundamentally disrupts intrinsic repolarization dynamics, positioning QTV as a distinct and sex-independent biomarker for cardiovascular risk assessment.

1 Introduction

The QT interval of the electrocardiogram (ECG), which reflects the approximate durations of both ventricular depolarization and repolarization, is affected by diverse physiological, pharmacological, and pathological factors [1, 2]. Since heart rate (HR) plays a predominant role, different HR-corrected QT (QTc) interval formulas have been developed to enable more adequate interpretation of QT interval dynamics [3]. Though no single formula is universally optimal due to individual differences and the various sources of above factors [4], prolonged QTc intervals are consistently associated with increased all-cause and cardiovascular mortality [5, 6] and higher incidence of adverse events including stroke [7], torsades de pointes [8], and sudden cardiac death (SCD) [9, 10].

Meanwhile, the beat-to-beat QT interval variability (QTV), a quantitative measure of repolarization lability across consecutive heartbeats [11], has been proved as a valuable marker for the risk stratification of ventricular arrhythmias, SCD, and cardiovascular death [12-14]. Compared with healthy subjects, elevated QTV has been observed in patients with heart failure (HF) [15, 16], myocardial infarction [17-19], and coronary artery disease (CAD) without prior infarction [20]. In addition, a direct association between myocardial ischemia and QTV elevation has been documented [21].

Despite the prognostic value of QTc intervals and QTV, the association between QTc interval prolongation and myocardial ischemia remains controversial. On one hand, prolonged QTc intervals have been found during ischemia provoked by exercise stress testing [22], the infusion of adenosine or dipyridamole [23], dobutamine stress echocardiography [24], and balloon angioplasty [25]. On the other hand, other studies have reported no significant QTc interval changes between CAD patients and healthy controls [20], nor during the episodes of transient ischemia in patients with unstable angina [26].

Furthermore, although myocardial ischemia has been demonstrated to induce both QTV elevation and QTc prolongation, few studies have explored the relationship between QTc intervals and QTV in cardiac patients. Specifically, whether QTc interval prolongation are equivalent to QTV elevation has not been investigated comprehensively. In healthy subjects, QTc intervals correlate positively with the standard deviation of QT intervals (SDQT) [27], but not with other three QTV parameters including the root mean square of differences (RMSDQT) [28], the QT variability index (QTVi) [29], and short-term QT variability (STVQT) [30]. Conversely, moderate positive correlations across these indices are

* Corresponding author: 1064686304@qq.com

exhibited in patients with long QT syndrome (LQTS) [28-30]. Besides, as sex differences in QTc intervals are documented [31], their potential effect on the QTc–QTV correlation requires further investigation.

The main purpose of this study was to explore the relationship between QTc intervals and QTV among non-CAD controls and CAD patients. QTc intervals and QTV were compared between the two groups to explore the potential alterations caused by myocardial ischemia. Considering HR variability (HRV) as a major source of QTV [11] and autonomic nervous dysfunction in CAD patients [32, 33], HRV analysis was also conducted. Then, associations of atherosclerotic burden with QTc intervals and QTV were evaluated. Given the potential influence of sex differences, the relationship of QTV elevation with prolonged QTc intervals as well as the correlation of QTc intervals with QTV were assessed.

2 Methods

2.1 Study subjects

This study included 107 non-CAD controls and 93 CAD patients, both recruited at the Shandong Provincial Qianfoshan Hospital. Controls had clinically normal results of carotid ultrasonography, echocardiography (Echo), and 12-lead ECG exams, with no cardiovascular history. CAD inclusion required coronary angiography (CAG) evidence of ≥ 50% stenosis in at least one major coronary artery. General exclusions for both groups comprised age ≥ 75 years, cancer, electrolyte disturbance, cerebrovascular or mental illness, severe hepatic or renal impairments, and thyroid dysfunction. CAD-specific exclusions further included valvular disease, prior MI or HF, left ventricular ejection fraction (LVEF) ≤ 40%, and Class I/III antiarrhythmic therapy. Written informed consent was acquired from each volunteer. No attempt was made to control their medicine administration.

2.2 Measurement

2.2.1 Physical examination

Each subject completed a questionnaire on age, gender, smoking history, and prior disease history. Systolic and diastolic blood pressures (SBP and DBP) were measured after a 10-min rest using electronic sphygmomanometers (Omron, Kyoto, Japan). Height, weight, and body-mass index (BMI) were also measured. Hypertension was defined as SBP/DBP ≥ 140/90 mm Hg, anti-hypertensive treatment, or self-reported hypertension. Resting 12-lead ECG examinations were performed by technicians using an ECG-1250C machine (Nihon Kohden, Tokyo, Japan). Physical exams were conducted with the assistance of trained nurses.

2.2.2 Laboratory testing

Fasting blood samples (≥ 8h) were collected on the day of data collection. Biochemical analyses were performed at a central laboratory with an automated machine (TBA-FX8, Autobio, Zhengzhou, China) under strict quality control. Biochemical indicators included serum glucose (GLU), triglycerides (TG), low- and high-density lipoprotein cholesterol (LDL-C and HDL-C), and total cholesterol (TC). Diabetes was defined as fasting GLU ≥ 7.0 mmol/L, self-reported history, or use of antidiabetic medication. Hyperlipidemia was defined as TG ≥ 2.3 mmol/L, TC ≥ 6.2 mmol/L, LDL-C ≥ 4.1 mmol/L, or HDL-C < 1.0 mmol/L.

2.2.3 Ultrasound examination

Transthoracic Echo examinations were performed for all subjects using an EPIQ 7C ultrasound system (Philips, Best, Netherlands). Carotid artery ultrasound tests were conducted only for non-CAD controls using a LOGIQ E9 ultrasound system (GE, Boston, USA). These exams were conducted on the date of physical exams for non-CAD controls and maximum four days before the CAG exam for CAD patients.

2.2.4 Coronary angiography

CAG was conducted by experienced cardiologists for all CAD patients via the right radial or femoral arteries according to the Judkins technique [34]. Interpretation of angiogram was implemented by physicians blinded to clinical data, and the stenosis severity was estimated as the percentage of lumen diameter reduction. To evaluate the atherosclerotic burden quantitatively, the number of stenosed vessels (narrowing ≥ 50%) and the Gensini score (GS) were calculated [35]. The GS system grades the stenosis degree in each main coronary artery within a range of 1–32 separately, with larger values indicating increased stenosis lesion [35].

2.2.5 QTc and QTV measurements

The ECG data collection for measurements of QTc and QTV was conducted on the day of physical exams for non-CAD controls and within two days before CAG for CAD patients. After resting for 10 min, each volunteer underwent a 5-min ECG recording in the standard limb lead I configuration with a sampling rate of 1 kHz. Recordings were collected in a quiet and temperature-controlled (25 ± 3 °C) room during the daytime using a cardiovascular function detection device (Huiyironggong, Jinan, China).

ECG preprocessing and RR/QT interval extraction were performed as previously described [36]. Briefly, recommendations for ECG standardization were adopted for ECG preprocessing [37]. Algorithms with publicly accessible codes were applied to detect fiducial points including R-wave peaks, T-wave offsets, and QRS complex onsets [38-40]. Then, a physician blinded to participant status manually identified ectopic beats and excluded recordings with excessive noise contamination. Finally, RR and QT interval time series were derived from remaining ECGs with intervals corresponding to ectopic beats removed. To remove the influence of data

length, only the last 256 intervals in each ECG recording were utilized. The QTc intervals were calculated using four different formulas: Bazett formula: $QTc_{Baz} = QT/RR^{1/2}$; Fridericia formula: $QTc_{Frid} = QT/RR^{1/3}$; Framingham formula: $QTc_{Fram} = QT+0.154\cdot(1 - RR)$; Hodges formula: $QTc_{Hod} = QT+ 0.00175\cdot([60/RR] - 60)$. Since individual-specific formulas were recommended to address practical implications of above conventional approaches [4], the optimal individual-specific QTc interval, QTc_{Opt}, was determined by adopting the least-squares method. The QT-RR relationship was further investigated with various regression models shown in **Supplementary Table S1**. Those 17 functions were used to fit possible shapes of individual QT-RR patterns and could achieve a more precise estimation that accounts for the inherent non-linearity of cardiac electrophysiology.

To analyze HRV and QTV, nine commonly used indicators from time and frequency domains as well as nonlinear dynamics were employed. The time-domain indices included QTVi, variability ratio (VR), SD and STV of RR and QT intervals (SDRR, SDQT, STVRR, and STVQT). For frequency domain analysis, the power spectral density of RR and QT interval time series was computed using a 16th-order Burg's method to quantify components in low- (0.04–0.15 Hz, HRV_{LF} and QTV_{LF}) and high-frequency (0.15–0.4 Hz, HRV_{LF} and QTV_{LF}), along with their ratios ($HRV_{LF/HF}$ and $QTV_{LF/HF}$) [11]. Prior to frequency analysis, RR and QT interval time series were interpolated at 4 Hz and detrended using a smoothness prior approach [41]. Moreover, two entropy measures, distribution entropy (DistEn) [42] and sample entropy (SampEn) [43], were calculated as nonlinear tools to quantify the complexity of time series data.

2.3 Statistical analysis

Clinical characteristics are presented as frequencies (percentages), means ± SD, or medians with interquartile ranges. Categorical variables were compared using Chi-square or Fisher's exact tests. Continuous variables were assessed via independent Student's t-tests (after Box-Cox transformations for non-normal distributions, verified by the Shapiro–Wilk test) or Mann–Whitney U tests, with variance homogeneity tested by the Levene's test. Receiver operating characteristic (ROC) curves and the areas under the curve (AUC) were also calculated to evaluate the discriminative ability of all utilized indices. Multivariable logistic regression analysis was further performed to determine risk factors. A regression model was constructed with one index and the characteristics showing statistical significance in the above univariate analyses. The Box–Tidwell test was used to verify the assumption of linearity, and collinearity diagnostics were conducted using tolerance and variance inflation factor. Standardized odd ratios (OR) with per one-SD increase in the independent variable were calculated with the 95% confidence interval (CI).

To evaluate the association between atherosclerotic burden and QT interval measurements, all studied QTc and QTV indices were compared among three subgroups of CAD patients categorized according to the number of stenosed vessels and GS, respectively. The subgroups based on stenosed vessel numbers included patients with 1, 2, and 3 or more vessels. Based on GS, patients were divided into low- (< 20), moderate- (≥ 20 but < 40), and high-risk (≥ 40) subgroups [44]. Then, sex differences of QTc interval, QTV, and HRV indices were evaluated separately for CAD patients and non-CAD volunteers. Next, subjects in each group were individually classified into two subgroups based on QTc interval duration: normal and prolonged QTc, according to established criteria (men: ≥ 420 ms; women: ≥ 430 ms). Following this, QTV indices were compared: (i) between non-CAD controls with normal versus prolonged QTc; (ii) between CAD patients with normal versus prolonged QTc; (iii) between non-CAD controls and CAD patients both with normal QTc; and (iv) between the two groups both with prolonged QTc intervals.

Table 1. Comparisons of clinical characteristics between non-CAD controls and CAD patients.

Clinical characteristics	Non-CAD (*N* = 107)	CAD patients (*N* = 93)	*P*
Age (years)	61.0 (55.0–66.0)	63.00 (56.00–69.00)	0.11
Male (*N*; %)	67 (62.62)	56 (60.22)	0.77
Height (m)	1.68 (1.64–1.76)	1.68 (1.59–1.72)	<0.05
Weight (Kg)	72.22±11.18	71.34±10.30	0.57
BMI (Kg/m^2)	25.04±2.93	25.68±3.05	0.13
SBP (mm Hg)	123.00 (115.00–138.00)	131.00 (121.50–144.00)	$<10^{-3}$
DBP (mm Hg)	78.77±12.66	78.48±12.57	0.88
LVEF (%)	-	64 (62–67)	-
Medical history			
Smoking (*N*; %)	22 (20.56)	37 (39.78)	<0.01
Hyperlipidemia (*N*; %)	17 (15.89)	19 (20.43)	0.46
Hypertension (*N*; %)	18 (16.82)	57 (61.29)	$<10^{-9}$
Diabetes (*N*; %)	5 (4.67)	30 (32.26)	$<10^{-6}$
No. of stenosed vessels (*N*; %)			
1	-	35 (37.63)	-
2	-	28 (30.11)	-
≥ 3	-	30 (32.26)	-
Gensini score	-	22 (9–43)	-
Glucose (mmol/L)	5.13 (4.81–5.56)	5.45 (4.88–6.60)	<0.05
Triglycerides (mmol/L)	1.16 (0.88–1.75)	1.32 (1.05–1.94)	0.06
TC (mmol/L)	5.05±0.99	4.44±1.03	$<10^{-4}$
LDL-C (mmol/L)	2.84±0.82	2.64±0.86	0.09
HDL-C (mmol/L)	1.31 (1.08–1.55)	1.07 (0.91–1.27)	$<10^{-7}$

[a] Values are mean ± standard deviation, frequencies (percentages), or median (interquartile range); LVEF: left ventricular ejection fraction; LDL-C and HDL-C: low- and high-density lipoprotein cholesterol; SBP and DBP: systolic and diastolic blood pressure; TC: total cholesterol; BMI: body-mass index.

Furthermore, correlations between QTc and QTV indices were analyzed separately within CAD patients and non-CAD controls, using Pearson or Spearman correlation tests, depending on variable normality. Given the influence of sex differences, correlation analyses stratified by sex were also conducted within each group.

Table 2. Comparisons of studied QTc and QTV indices between non-CAD controls and CAD patients.

Indices	Non-CAD controls (N = 107)	CAD patients (N = 93)	P	AUC	Logistc regression	
					OR (95% CI)	P
QTc_{Baz}	403.93 ± 21.58	420.85 ± 22.96	$<10^{-6}$	0.71	1.09 (1.02–1.15)	<0.01
QTc_{Frid}	397.54 ± 19.09	414.45 ± 20.21	$<10^{-8}$	0.68	1.12 (1.06–1.16)	$<10^{-3}$
QTc_{Fram}	386.17 ± 27.81	402.81 ± 25.04	$<10^{-4}$	0.74	1.10 (1.04–1.16)	$<10^{-3}$
QTc_{Hod}	385.77 ± 27.79	402.41 ± 25.03	$<10^{-4}$	0.68	1.10 (1.04–1.16)	$<10^{-3}$
QTc_{Opt}	385.87 ± 27.79	402.51 ± 25.03	$<10^{-4}$	0.68	1.10 (1.04–1.16)	$<10^{-3}$
SDQT	2.99 ± 1.06	3.47 ± 1.27	<0.01	0.61	1.05 (0.99–1.11)	0.10
STVQT	1.39 ± 0.41	2.34 ± 1.10	$<10^{-13}$	0.81	1.20 (1.13–1.26)	$<10^{-9}$
QTVi	-1.31 ± 0.30	-0.93 ± 0.46	$<10^{-9}$	0.75	1.12 (1.06–1.19)	$<10^{-4}$
VR	0.14 ± 0.09	0.32 ± 0.29	$<10^{-11}$	0.78	1.07 (1.03–1.11)	$<10^{-3}$
QTV_{LF}	5.02 ± 0.61	5.49 ± 0.76	$<10^{-5}$	0.67	1.10 (1.04–1.16)	$<10^{-3}$
QTV_{HF}	5.40 ± 0.59	6.24 ± 0.84	$<10^{-5}$	0.79	1.15 (1.10–1.20)	$<10^{-8}$
$QTV_{LF/HF}$	0.93 ± 0.08	0.88 ± 0.06	$<10^{-7}$	0.72	0.90 (0.86–0.96)	$<10^{-3}$
$SampEn_{QT}$	1.90 ± 0.35	2.17 ± 0.41	$<10^{-5}$	0.69	1.12 (1.06–1.18)	$<10^{-4}$
$DistEn_{QT}$	0.37 ± 0.05	0.39 ± 0.05	<0.01	0.62	1.06 (1.00–1.11)	<0.05

[a] Confounding factors included age, gender, height, SBP, smoking, hypertension, diabetes, glucose, TC, and HDL-C.

Table 3. Comparisons of studied HRV indices between non-CAD controls and CAD patients.

Indices	Non-CAD controls (N = 107)	CAD patients (N = 93)	P	AUC	Logistic regression	
					OR (95% CI)	P
SD_{RR}	32.37 ± 11.90	23.99 ± 11.00	$<10^{-7}$	0.72	0.93 (0.88–0.98)	<0.01
STV_{RR}	12.78 ± 7.19	10.08 ± 5.70	<0.01	0.61	1.00 (0.94–1.06)	0.95
HRV_{LF}	9.99 ± 0.86	9.07 ± 1.00	$<10^{-9}$	0.76	0.90 (0.85–0.96)	$<10^{-3}$
HRV_{HF}	9.71 ± 1.12	9.25 ± 1.12	<0.01	0.61	0.99 (0.94–1.05)	0.83
$HRV_{LF/HF}$	1.04 ± 0.09	0.99 ± 0.10	$<10^{-4}$	0.66	0.92 (0.87–0.97)	<0.01
$SampEn_{RR}$	1.56 ± 0.27	1.57 ± 0.33	0.93	0.22	1.04 (0.98–1.10)	0.19
$DistEn_{RR}$	0.74 ± 0.06	0.69 ± 0.07	$<10^{-6}$	0.71	0.93 (0.88–0.98)	<0.05

Statistical significance was defined as a two-tailed $P < 0.05$. All analyses were executed in R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

3.1 Subject characteristics

As summarized in **Table 1**, CAD patients had shorter stature ($P < 0.05$), elevated SBP ($P < 10^{-3}$), and higher prevalence of smoking, hypertension, and diabetes, in comparison with non-CAD controls ($P < 0.01$, $P < 10^{-10}$, and $P < 10^{-6}$, respectively). CAD patients also exhibited lower TC and HDL-C and higher GLU levels, relative to non-CAD individuals ($P < 0.05$, $P < 10^{-4}$, and $P < 10^{-7}$, respectively).

3.2 QTc and QTV between non-CAD controls and CAD patients

Comparative results of QTc and QTV indices between non-CAD controls and CAD patients is detailed in **Table 2**, with corresponding ROC curves to illustrate their discriminative capacity (**Fig. 1**). Univariate analysis showed that nearly all QTc interval and QTV indices were significantly increased in CAD patients than non-CAD volunteers (at least $P < 0.01$). The highest AUC values among QTc and QTV indices were observed for QTc_{Fram} and STVQT, respectively. Multivariable logistic regression demonstrated that almost all QTc and QTV indices were associated with an increased risk of CAD, with STVQT showing the strongest association.

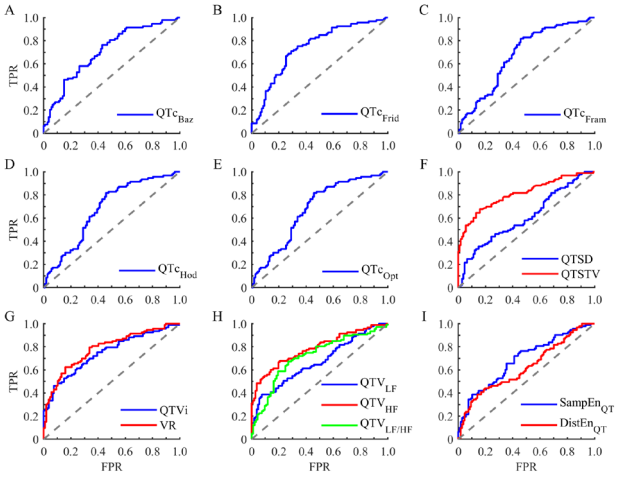

Fig. 1. ROC curves of QTc and QTV indices in differentiating CAD patients from non-CAD controls (TPR = true positive rate; FPR = false positive rate).

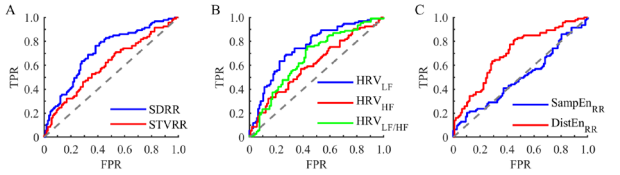

Fig. 2. ROC curves of HRV indices in differentiating CAD patients from non-CAD controls

Table 3 shows comparative results of HRV indices between the two groups, and corresponding ROC curves are portrayed in **Fig. 2**. Nearly all HRV metrics were significantly lower in CAD patients than in non-CAD

controls, indicating a decreased autonomic modulation in CAD patients. HRV_{LF} exhibited the maximum AUC score. Logistic regression results showed RRSD, HRV_{LF}, $HRV_{LF/HF}$, and $DistEn_{RR}$ were significantly associated with increased odds.

3.3 QTc, QTV, and Atherosclerotic Burden

Table 4. Comparisons of QTc and QTV indices among three subgroups of CAD patients classified based on the Gensini score (GS).

Indices	Low-risk GS < 20 (*N* = 39)	Moderate-risk 20 ≤ GS < 40 (*N* = 26)	High-risk GS ≥ 40 (*N* = 28)
QTc_{Baz}	426.30±26.02	419.14±18.35	415.85±21.17
QTc_{Frid}	419.2±21.50	412.83±18.53	409.32±18.98
QTc_{Fram}	406.37±24.72	401.28±26.93	399.26±23.91
QTc_{Hod}	405.97±24.71	400.88±26.92	398.86±23.89
QTc_{Opt}	406.08±23.72	400.99±26.92	398.97±23.89
SDQT	3.44±1.16	3.37±1.10	3.61±1.56
STVQT	2.28±0.95	2.24±0.94	2.51±1.27
QTVi	-0.93±0.46	-0.98±0.37	-0.90±0.53
VR	0.33±0.22	0.23±0.12	0.40±0.44
QTV_{LF}	5.52±0.71	5.48±0.71	5.47±0.88
QTV_{HF}	6.20±0.81	6.16±0.83	6.37±0.89
$QTV_{LF/HF}$	0.89±0.06	0.89±0.05	0.86±0.06[*,†]
$SampEn_{QT}$	2.19±0.41	2.19±0.45	2.15±0.39
$DistEn_{QT}$	0.39±0.05	0.39±0.05	0.40±0.06

[a] *: P <0.05 compared with low-risk patients; †: P <0.05 compared with moderate-risk patients.

Table 5. Comparisons of QTc and QTV indices among three subgroups of CAD patients classified according to the number of stenosed vessels.

Indices	1 vessel (*N* = 35)	2 vessels (*N* = 28)	≥ 3 vessels (*N* = 30)
QTc_{Baz}	420.78±21.21	421.55±26.79	420.28±21.79
QTc_{Frid}	416.36±17.79	413.97±23.90	412.67±19.60
QTc_{Fram}	408.37±19.11	400.21±29.65	398.75±26.10
QTc_{Hod}	407.96±19.11	399.81±29.64	398.35±26.09
QTc_{Opt}	408.07±19.11	399.92±29.64	398.46±26.09
SDQT	3.46±1.11	3.22±1.01	3.72±1.60
STVQT	2.41±0.97	2.06±0.80	2.51±1.30
QTVi	-0.94±0.40	-1.02±0.48	-0.84±0.50
VR	0.27±0.16	0.35±0.33	0.36±0.37
QTV_{LF}	5.56±0.64	5.34±0.68	5.56±0.94
QTV_{HF}	6.32±0.72	6.03±0.84	6.34±0.95
$QTV_{LF/HF}$	0.88±0.05	0.89±0.06	0.88±0.06
$SampEn_{QT}$	2.21±0.43	2.20±0.38	2.11±0.43
$DistEn_{QT}$	0.40±0.05	0.38±0.05	0.40±0.06

Table 4 and **5** exhibit the comparative results of QTc and QTV indices for three subgroups of CAD patients classified based on the GS and the number of stenosed vessels, respectively. The only remarkable difference was observed for $QTV_{LF/HF}$ when comparing high-risk patients with those in low or moderate risks (both P < 0.05). None indices showed notable differences for the three subgroups based on the number of stenosed vessels.

Table 6. Comparisons of QTV indices between non-CAD controls with normal and prolonged QTc.

QTV indices	Men with QTc < 420 (*N* = 57)	Men with QTc ≥ 420 (*N* = 10)	*P*	Women with QTc < 430 (*N* = 28)	Women with QTc ≥ 430 (*N* = 12)	*P*
SDQT	2.83 ± 0.86	3.05 ± 0.90	0.47	3.05 ± 1.28	3.57 ± 1.35	0.12
STVQT	1.38 ± 0.40	1.28 ± 0.39	0.65	1.34 ± 0.42	1.61 ± 0.34	0.06
QTVi	-1.31 ± 0.31	-1.32 ± 0.37	0.94	-1.34 ± 0.26	-1.20 ± 0.28	0.15
VR	0.15 ± 0.09	0.12 ± 0.07	0.52	0.12 ± 0.06	0.20 ± 0.14	<0.05
QTV_{LF}	4.99 ± 0.61	4.76 ± 0.55	0.28	4.98 ± 0.62	5.44 ± 0.52	<0.05
QTV_{HF}	5.43 ± 0.56	5.19 ± 0.75	0.23	5.29 ± 0.64	5.68 ± 0.40	0.06
$QTV_{LF/HF}$	0.92 ± 0.07	0.93 ± 0.09	0.78	0.95 ± 0.09	0.96 ± 0.07	0.68
$SampEn_{QT}$	1.93 ± 0.35	1.82 ± 0.32	0.44	1.85 ± 0.36	1.95 ± 0.30	0.41
$DistEn_{QT}$	0.36 ± 0.05	0.37 ± 0.05	0.61	0.37 ± 0.05	0.40 ± 0.05	0.11

Table 7. Comparisons of QTV indices between CAD patients with normal and prolonged QTc.

QTV indices	Men with QTc < 420 (*N* = 32)	Men with QTc ≥ 420 (*N* = 24)	*P*	Women with QTc < 430 (*N* = 18)	Women with QTc ≥ 430 (*N* = 19)	*P*
SDQT	3.10 ± 1.13	3.56 ± 1.05	<0.05	3.94 ± 1.72	3.42 ± 1.17	0.37
STVQT	2.14 ± 1.00	2.50 ± 0.98	0.09	2.70 ± 1.37	2.12 ± 0.78	0.13
QTVi	-1.01 ± 0.54	-0.88 ± 0.38	0.33	-0.82 ± 0.52	-0.99 ± 0.32	0.23
VR	0.31 ± 0.29	0.34 ± 0.21	0.17	0.35 ± 0.17	0.29 ± 0.16	0.52
QTV_{LF}	5.31 ± 0.69	5.60 ± 0.70	0.14	5.80 ± 0.92	5.36 ± 0.69	0.11
QTV_{HF}	6.07 ± 0.79	6.37 ± 0.84	0.10	6.42 ± 1.03	6.18 ± 0.71	0.40
$QTV_{LF/HF}$	0.88 ± 0.05	0.88 ± 0.06	0.66	0.91 ± 0.06	0.87 ± 0.07	0.10
$SampEn_{QT}$	2.08 ± 0.28	2.36 ± 0.44	<0.01	2.15 ± 0.57	2.12 ± 0.34	0.85
$DistEn_{QT}$	0.38 ± 0.06	0.40 ± 0.05	0.09	0.41 ± 0.06	0.39 ± 0.05	0.21

3.4 QTV and Prolonged QTc intervals

The comparative results of QTV indices between non-CAD subjects with normal and prolonged QTc intervals are illustrated in **Table 6**. Non-significant differences were shown by almost all QTV indices, except VR and QTV_{LF} in women (both P < 0.05). Similar situations were found in CAD patients (**Table 7**). Nearly all QTV indicators showed notable alterations among CAD patients with prolonged QTc intervals, except $SampEn_{QT}$ and SDQT in men. The prevalence of prolonged QTc intervals among CAD patients were higher than that in non-CAD controls (men: 43% vs. 15%; women: 51% vs. 30%).

Table 8 and **9** exhibit comparative results of QTV indices between non-CAD controls and CAD patients, both having normal or prolonged QTc intervals. There still existed QTV alterations characterized by certain QTV variables between non-CAD controls and CAD patients regardless of having normal or prolonged QTc intervals.

Table 8. Comparisons of QTV indices between non-CAD controls and CAD patients both with normal QTc.

QTV indices	Men with QTc < 420			Women with QTc < 430		
	Non-CAD controls (N = 57)	CAD patients (N = 32)	P	Non-CAD controls (N = 28)	CAD patients (N = 18)	P
SDQT	2.83 ± 0.86	3.10 ± 1.13	0.50	3.05 ± 1.28	3.94 ± 1.72	0.06
STVQT	1.39 ± 0.40	2.14 ± 1.00	$<10^{-4}$	1.34 ± 0.42	2.70 ± 1.37	<0.05
QTVi	-1.31 ± 0.31	-1.01 ± 0.54	<0.01	-1.34 ± 0.26	-0.82 ± 0.52	<0.05
VR	0.15 ± 0.09	0.31 ± 0.29	<0.01	0.12 ± 0.06	0.35 ± 0.27	$<10^{-4}$
QTV_{LF}	4.99 ± 0.61	5.31 ± 0.69	<0.05	4.98 ± 0.62	5.80 ± 0.92	<0.05
QTV_{HF}	5.43 ± 0.56	6.07 ± 0.79	$<10^{-4}$	5.29 ± 0.64	6.42 ± 1.03	$<10^{-4}$
$QTV_{LF/HF}$	0.92 ± 0.07	0.88 ± 0.06	<0.01	0.95 ± 0.09	0.91 ± 0.06	0.11
$SampEn_{QT}$	1.93 ± 0.35	2.08 ± 0.28	<0.05	1.85 ± 0.36	2.15 ± 0.57	0.06
$DistEn_{QT}$	0.36 ± 0.05	0.38 ± 0.06	0.10	0.37 ± 0.05	0.41 ± 0.06	<0.05

Table 9. Comparisons of QTV indices between non-CAD controls and CAD patients both with prolonged QTc.

QTV indices	Men with QTc < 420			Women with QTc < 430		
	Non-CAD controls (N = 10)	CAD patients (N = 24)	P	Non-CAD controls (N = 12)	CAD patients (N = 19)	P
SDQT	1.28 ± 0.39	2.50 ± 0.98	$<10^{-4}$	1.61 ± 0.34	2.12 ± 0.78	
STVQT	-1.32 ± 0.37	-0.88 ± 0.38	<0.05	-1.21 ± 0.28	-0.99 ± 0.32	0.09
QTVi	0.12 ± 0.07	0.34 ± 0.21	$<10^{-4}$	0.20 ± 0.14	0.29 ± 0.16	0.06
VR	4.76 ± 0.55	5.60 ± 0.70	<0.05	5.44 ± 0.52	5.36 ± 0.69	<0.05
QTV_{LF}	5.19 ± 0.75	6.37 ± 0.84	$<10^{-3}$	5.68 ± 0.40	6.18 ± 0.71	0.74
QTV_{HF}	0.93 ± 0.09	0.88 ± 0.06	0.06	0.96 ± 0.07	0.87 ± 0.07	<0.05
$QTV_{LF/HF}$	1.82 ± 0.32	2.36 ± 0.44	<0.01	1.95 ± 0.30	2.12 ± 0.34	<0.01
$SampEn_{QT}$	0.37 ± 0.05	0.40 ± 0.05	0.06	0.40 ± 0.05	0.39 ± 0.05	0.16
$DistEn_{QT}$	1.28 ± 0.39	2.50 ± 0.98	$<10^{-4}$	1.61 ± 0.34	2.12 ± 0.78	0.70

The comparative results of QTV indices between non-CAD individuals with normal and prolonged QTc intervals are displayed in Table 6. Most indices showed no significant differences, except VR and QTV_{LF} in women (both $P < 0.05$). Similar situations were found in CAD patients (**Table 7**). Nearly all QTV indices showed notable alterations among CAD patients with prolonged QTc intervals, except $SampEn_{QT}$ and SDQT in men. The prevalence of prolonged QTc intervals among CAD patients were higher than that in non-CAD controls (men: 43% vs. 15%; women: 51% vs. 30%).

Table 10. Comparisons between sex in the studied QTc and QTV indices among non-CAD controls.

Indices	Men (N = 67)	Women (N = 40)	P
QTc_{Baz}	395.63 ± 18.54	417.84 ± 19.16	$<10^{-7}$
QTc_{Frid}	390.83 ± 16.79	408.78 ± 17.52	$<10^{-6}$
QTc_{Fram}	382.57 ± 28.30	392.19 ± 26.21	<0.05
QTc_{Hod}	382.17 ± 28.28	391.79 ± 26.20	<0.05
QTc_{Opt}	382.27 ± 28.28	391.90 ± 26.20	<0.05
SDQT	2.86 ± 0.86	3.21 ± 1.30	0.37
STVQT	1.37 ± 0.40	1.42 ± 0.41	0.53
QTVi	-1.31 ± 0.31	-1.30 ± 0.27	0.89
VR	0.14 ± 0.09	0.14 ± 0.10	0.99
QTV_{LF}	4.96 ± 0.61	5.12 ± 0.62	0.19
QTV_{HF}	5.40 ± 0.59	5.41 ± 0.60	0.91
$QTV_{LF/HF}$	0.92 ± 0.07	0.95 ± 0.09	0.06
$SampEn_{QT}$	1.91 ± 0.35	1.88 ± 0.34	0.67
$DistEn_{QT}$	0.36 ± 0.05	0.37 ± 0.05	0.17

Table 8 and **9** exhibit the comparative results of QTV indices between non-CAD controls and CAD patients, both having normal or prolonged QTc intervals. There still existed QTV alterations characterized by certain QTV variables between non-CAD controls and CAD patients regardless of having normal or prolonged QTc intervals.

3.5 Correlations between QTc and QTV

Table 11. Comparisons between sex in the studied QTc and QTV indices among CAD patients.

Indices	Men (N = 56)	Women (N = 37)	P
QTc_{Baz}	413.00 ± 21.06	432.72 ± 20.70	$<10^{-4}$
QTc_{Frid}	407.52 ± 18.80	424.95 ± 17.76	$<10^{-4}$
QTc_{Fram}	397.62 ± 24.80	410.66 ± 23.61	<0.05
QTc_{Hod}	397.22 ± 24.79	410.27 ± 23.59	<0.05
QTc_{Opt}	397.32 ± 24.79	410.37 ± 23.59	<0.05
SDQT	3.34 ± 1.12	3.67 ± 1.46	0.47
STVQT	2.30 ± 1.00	2.41 ± 1.13	0.71
QTVi	-0.95 ± 0.48	-0.90 ± 0.43	0.60
VR	0.32 ± 0.26	0.32 ± 0.34	0.88
QTV_{LF}	5.43 ± 0.71	5.58 ± 0.88	0.38
QTV_{HF}	6.20 ± 0.82	6.30 ± 0.89	0.60
$QTV_{LF/HF}$	0.88 ± 0.05	0.89 ± 0.07	0.25
$SampEn_{QT}$	2.20 ± 0.38	2.13 ± 0.46	0.43
$DistEn_{QT}$	0.39 ± 0.05	0.40 ± 0.06	0.60

Tables 10 and **11** present sex differences in QTc and QTV indices. In both groups, all QTc markers were significantly higher in females (at least $P < 0.05$), while no QTV indices showed sex differences. None of HRV

indices displayed remarkable differences (**Table 12** and **13**).

Table 12. Comparisons of the studied HRV indices between male and female non-CAD controls.

HRV indices	Men (N = 67)	Women (N = 40)	P
SDRR	32.37 ± 11.95	32.38 ± 11.97	0.90
STVRR	12.86 ± 7.65	12.65 ± 6.44	0.82
HRV_{LF}	10.02 ± 0.81	9.94 ± 0.94	0.64
HRV_{HF}	9.68 ± 1.14	9.76 ± 1.11	0.70
$HRV_{LF/HF}$	1.04 ± 0.09	1.02 ± 0.09	0.41
$SampEn_{RR}$	1.57 ± 0.27	1.54 ± 0.29	0.53
$DistEn_{RR}$	0.74 ± 0.06	0.73 ± 0.06	0.89

Table 13. Comparisons of the studied HRV indices between male and female CAD patients.

HRV indices	Men (N = 56)	Women (N = 37)	P
SDRR	24.62 ± 11.41	23.04 ± 10.44	0.29
STVRR	10.11 ± 5.75	10.04 ± 5.71	0.94
HRV_{LF}	9.18 ± 1.07	8.91 ± 0.87	0.20
HRV_{HF}	9.24 ± 1.22	9.26 ± 0.96	0.95
$HRV_{LF/HF}$	1.00 ± 0.10	0.97 ± 0.09	0.14
$SampEn_{RR}$	1.55 ± 0.34	1.60 ± 0.31	0.45
$DistEn_{RR}$	0.69 ± 0.08	0.68 ± 0.06	0.38

Table 14. Correlations between studied QTc and QTV indices in non-CAD controls (N = 107).

Correlation coefficients (r)	QTc_{Baz}	QTc_{Frid}	QTc_{Fram}	QTc_{Hod}	QTc_{Opt}
SDQT	0.19*	0.23*	0.23*	0.24*	0.24*
STVQT	0.13	0.18	0.16	0.16	0.16
QTVi	0.28†	0.22*	-0.01	-0.01	-0.01
VR	0.41†	0.15	-0.32†	-0.32†	-0.32†
QTV_{LF}	0.25*	0.20*	0.03	0.03	0.03
QTV_{HF}	0.13	0.17	0.15	0.15	0.15
$QTV_{LF/HF}$	0.26†	0.13	-0.18	-0.18	-0.18
$SampEn_{QT}$	0.04	0.05	0.05	0.05	0.05
$DistEn_{QT}$	0.21*	0.23*	0.20*	0.20*	0.20*

[a] *: P <0.05; †: P <0.01.

Table 15. Correlations between studied QTc and QTV indices in CAD patients (N = 93).

Correlation coefficients (r)	QTc_{Baz}	QTc_{Frid}	QTc_{Fram}	QTc_{Hod}	QTc_{Opt}
SDQT	0.12	0.17	0.18	0.18	0.18
STVQT	0.05	0.08	0.14	0.14	0.14
QTVi	0.05	0.02	-0.01	-0.01	-0.01
VR	0.22*	0.11	-0.10	-0.10	-0.10
QTV_{LF}	0.10	0.14	0.15	0.15	0.15
QTV_{HF}	0.08	0.11	0.15	0.15	0.15
$QTV_{LF/HF}$	0.04	0.06	0.05	0.05	0.05
$SampEn_{QT}$	0.03	0.03	-0.03	-0.03	-0.03
$DistEn_{QT}$	0.09	0.12	0.12	0.12	0.12

Tables 14 and **15** present the results of Spearman's correlation analyses between QTc and QTV indices in non-CAD controls and CAD patients, respectively. In general, significant correlations were weak to moderate (r = 0.19–0.41), with more correlations in non-CAD controls than in CAD patients, suggesting different correlation relationships for the two groups. **Tables 16** and **17** present the results of Spearman's correlation analyses between QTc and QTV indices in male and female non-CAD individuals, respectively. In males, QTc_{Baz} correlated positively with QTVi and VR, while QTc_{Fram}, QTc_{Hod}, and QTc_{Opt} were remarkable negatively correlated with VR. Females exhibited more correlations. Specifically, all QTc indices correlated positively with SDQT, STVQT, QTV_{LF}, QTV_{HF}, and $DistEn_{QT}$. QTc_{Baz} and QTc_{Frid} also correlated positively with QTVi and VR. However, no QTc indices correlated with $QTV_{LF/HF}$ and $SampEn_{QT}$.

Table 16. Correlations between the studied QTc and QTV indices among male non-CAD controls (N = 69).

Correlation coefficients (r)	QTc_{Baz}	QTc_{Frid}	QTc_{Fram}	QTc_{Hod}	QTc_{Opt}
SDQT	0.06	0.08	0.05	0.05	0.05
STVQT	0.01	-0.02	-0.05	-0.05	-0.05
QTVi	0.27*	0.17	-0.06	-0.06	-0.06
VR	0.50†	0.16	-0.41†	-0.41†	-0.41†
QTV_{LF}	0.11	0.04	-0.17	-0.17	-0.17
QTV_{HF}	0.08	0.02	-0.09	-0.08	-0.08
$QTV_{LF/HF}$	0.20	0.12	-0.18	-0.18	-0.18
$SampEn_{QT}$	0.14	0.09	-0.09	-0.09	-0.09
$DistEn_{QT}$	0.07	0.08	0.01	0.01	0.01

Table 17. Correlations between the studied QTc and QTV indices among female non-CAD controls (N = 40).

Correlation coefficients (r)	QTc_{Baz}	QTc_{Frid}	QTc_{Fram}	QTc_{Hod}	QTc_{Opt}
SDQT	0.43†	0.57†	0.45†	0.45†	0.45†
STVQT	0.35†	0.50†	0.44†	0.44†	0.44†
QTVi	0.44†	0.35*	0.03	0.03	0.03
VR	0.58†	0.35*	-0.11	-0.11	-0.11
QTV_{LF}	0.51†	0.54†	0.32*	0.32*	0.32*
QTV_{HF}	0.37*	0.56†	0.50†	0.50†	0.50†
$QTV_{LF/HF}$	0.14	-0.08	-0.29	-0.29	-0.29
$SampEn_{QT}$	0.01	0.16	0.29	0.29	0.29
$DistEn_{QT}$	0.44†	0.57†	0.43†	0.43†	0.43†

Table 18. Correlations between the studied QTc and QTV indices among male CAD patients (N = 58).

Correlation coefficients (r)	QTc_{Baz}	QTc_{Frid}	QTc_{Fram}	QTc_{Hod}	QTc_{Opt}
SDQT	0.30*	0.44†	0.38†	0.38†	0.38†
STVQT	0.24	0.34†	0.31*	0.31*	0.31*
QTVi	0.17	0.16	0.11	0.11	0.11
VR	0.32*	0.19	-0.04	-0.04	-0.04
QTV_{LF}	0.31*	0.43†	0.38†	0.38†	0.38†
QTV_{HF}	0.26*	0.34†	0.30*	0.30*	0.30*
$QTV_{LF/HF}$	0.10	0.19	0.21	0.21	0.21
$SampEn_{QT}$	0.27*	0.29*	0.11	0.11	0.11
$DistEn_{QT}$	0.28*	0.38†	0.31*	0.31*	0.31*

Conversely, more significance correlations were found in male CAD patients than in female ones, as shown in **Table 18** and **19**). These indicated the influence of sex differences in QTc intervals. In detail, for males, all QTc indices correlated positively with SDQT, STVQT, QTV_{LF}, QTV_{HF}, and $DistEn_{QT}$ (at least r = 0.27, P < 0.05). Significantly positive correlation can also be observed between QTc_{Baz} and VR (r = 0.33, P < 0.05). However, for females, merely QTc_{Frid} correlated inversely with STVQT (r = -0.35, P < 0.05), further reflecting the influence of sex differences on QTc on the correlation relationship.

Table 19. Spearman's correlations between the studied QTc and QTV indices among female CAD patients ($N = 36$).

Correlation coefficiens (r)	QTc_{Baz}	QTc_{Frid}	QTc_{Fram}	QTc_{Hod}	QTc_{Opt}
SDQT	-0.19	-0.22	-0.15	-0.15	-0.15
STVQT	-0.32	-0.35*	-0.16	-0.16	-0.16
QTVi	-0.19	-0.27	-0.24	-0.24	-0.24
VR	0.19	0.02	-0.24	-0.24	-0.24
QTV_{LF}	-0.28	-0.32	-0.18	-0.18	-0.18
QTV_{HF}	-0.22	-0.25	-0.10	-0.10	-0.10
$QTV_{LF/HF}$	-0.17	-0.25	-0.23	-0.23	-0.23
$SampEn_{QT}$	-0.23	-0.23	-0.20	-0.20	-0.20
$DistEn_{QT}$	-0.22	-0.27	-0.20	-0.20	-0.20

4 Discussion

Our findings demonstrated significantly elevated QTV and prolonged QTc intervals in CAD patients, when compared with non-CAD controls. Prior studies attribute the QTV elevation in CAD to increased heterogeneity in the final phase of ventricular repolarization resulting from reduced coronary blood flow [20]. Experiments on rabbit hearts have reported temporarily prolonged action potential duration (APD) in ventricular myocytes during coronary underperfusion [45], and studies on isolated human ventricular muscles under chronic ischemia have shown ischemia-related prolongation of the final repolarization phase [46]. Similarly, transient APD prolongation at the initial phase of ischemia is deemed the dominant factor for QTc prolongation [25]. At the cellular level, ischemia-induced APD prolongation involves acidosis, sodium influx, temperature drops, impedance changes, and sodium channel activity [25]. Nevertheless, structural ventricular changes may also contribute, as prior research shows no QTV differences between ischemic and non-ischemic cardiomyopathy [47], whereas hypertrophic cardiomyopathy correlates hypertrophy with longer QTc [48]. The utility of QTc and QTV as ischemia markers warrants further research.

Moreover, our analyses revealed no significant association between worsening atherosclerotic burdens and prolonged QTc intervals or QTV elevation. Though previous QT-RR dynamic studies suggest differences across stenosis severity, certain metrics like SDQT and RMSSDQT failed to reflect this [20]. We postulate this discrepancy is driven by underlying LV impairment. Because QTV correlates strongly with LV function and stroke volume [18, 49], repolarization metrics cannot serve as direct surrogates for atherosclerotic burden without rigorously adjusting for LV status.

Our analyses further indicated QTc prolongation does not always match QTV changes in both non-CAD controls and CAD patients. In addition, the QTV alteration between CAD patients and controls persisted regardless of whether subjects had normal or prolonged QTc intervals. Studies based on large populations support the prognostic value of prolonged QTc and QTV indices for risk stratification in cardiovascular-related events [5, 6, 14]. Although the concept of repolarization reserve suggests that myocardial cells can prevent arrhythmias [50], further work is needed to see if QTV offers advantages over QTc in risk stratification.

We also found males had shorter QTc intervals than females in both groups, but QTV indicators showed no sex differences. These findings align with prior studies on diabetic complications, LQTS, drug effects, exercise, and sleep [51-55], possibly owing to shorter early repolarization in males [56].

However, the non-significant sex differences in QTV presented by this study are not completely consistent with earlier findings. In healthy adults, females showed higher short-term SDQT in most leads [57], and higher VR and QTVi in ambulatory ECGs [58, 59]. These may reflect greater autonomic modulation in females [60]. Conversely, other two studies on the ambulatory ECG showed no sex differences in SDQT [58, 59]. For infants and children, QTVi calculated from 120 heartbeats also displayed no sex differences [61]. More research is needed to clarify sex-related QTV differences.

Finally, we observed weak-to-moderate correlations between QTc and QTV indices in both groups, with more significant correlations in non-CAD controls than CAD patients. Another important finding was that the correlations were influenced by sex differences in QTc. The adaptive response of QT interval to HR changes is an intrinsic property of myocardial cells, manifesting as cellular dependency of APD on several prior cardiac cycles. Besides, as shown in **Table 3**, a remarkable alternation of autonomic modulation was found between the two groups. Prior research has proved an increase of parasympathetic tone prolongs APD in ventricular myocytes, particularly in subepicardial regions [20]. Hence, it could be postulated that the differences of correlation relations in the two groups could either be a cellular phenomenon resulting from more heterogeneous ventricular repolarization in CAD patients or an altered autonomic tone.

5.Limitations

Several limitations of this study should be acknowledged. First, the relatively small sample size may limit the statistical power and generalizability of our findings. Second, our research design precludes longitudinal follow-up, lacking a comparative prognostic evaluation of QTc versus QTV in predicting long-term mortality. Finally, although various individual-specific formulas have been applied to correct the QT interval for HR, there still exists no consensus regarding the formula optimally suitable for clinical use.

6 Conclusions

CAD patients exhibited significantly prolonged QTc intervals and higher QTV compared with non-CAD controls. QTc prolongation did not directly correspond to elevations in QTV in either group, and there appears to be no strong association between the severity of atherosclerotic burden and these indices. Sex differences were observed in QTc but not in QTV across both groups. Weak to moderate correlations between QTc and QTV were identified, with more significant relationships in non-CAD subjects. Additionally, the QTc-QTV

correlation was influenced by sex differences in QTc. These findings imply ischemic pathology fundamentally disrupts intrinsic repolarization dynamics, positioning QTV as a distinct, sex-independent biomarker for risk assessment of cardiovascular diseases.

Acknowledgments

This work was supported by the Shandong Natural Science Foundation Youth Program No. ZR2023QF108. We would also like to extend our sincere gratitude to all the nurses of the No. 45 inpatients area at Shandong Provincial Qianfoshan Hospital for their unselfish assistance with the data acquisition.

References

1. G.K. Isbister and Page C.B., Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. Br J Clin Pharmacol. **76**, 48 (2013)
2. P. G Postema and AM Wilde A., The measurement of the QT interval. Current cardiology reviews. **10**, 287 (2014)
3. B. Vandenberk, et al., Which QT correction formulae to use for QT monitoring? Journal of the American Heart Association. **5**, e003264 (2016)
4. V.N. Batchvarov, et al., QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. Am J Physiol Heart Circ Physiol. **282**, H2356 (2002)
5. A. Montanez, et al., Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. Archives of internal medicine. **164**, 943 (2004)
6. J.D. Rich, et al., QTc prolongation is associated with impaired right ventricular function and predicts mortality in pulmonary hypertension. International journal of cardiology. **167**, 669 (2013)
7. E.Z. Soliman, et al., Prolongation of QTc and risk of stroke: The REGARDS (REasons for Geographic and Racial Differences in Stroke) study. Journal of the American College of Cardiology. **59**, 1460 (2012)
8. K.P. Letsas, et al., Clinical characteristics of patients with drug-induced QT interval prolongation and torsade de pointes: identification of risk factors: KP Letsas et al. Clinical research in cardiology. **98**, 208 (2009)
9. A.J. Moss, Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. The American journal of cardiology. **72**, B23 (1993)
10. S.M. Straus, et al., Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. Journal of the American College of Cardiology. **47**, 362 (2006)
11. M. Baumert, et al., QT interval variability in body surface ECG: measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electrophysiology. Europace. **18**, 925 (2016)
12. G. Piccirillo, et al., QT variability strongly predicts sudden cardiac death in asymptomatic subjects with mild or moderate left ventricular systolic dysfunction: a prospective study. European heart journal. **28**, 1344 (2007)
13. P. Oosterhoff, et al., Short-term variability of repolarization predicts ventricular tachycardia and sudden cardiac death in patients with structural heart disease: a comparison with QT variability index. Heart Rhythm. **8**, 1584 (2011)
14. M.N. Niemeijer, et al., Short-term QT variability markers for the prediction of ventricular arrhythmias and sudden cardiac death: a systematic review. Heart. **100**, 1831 (2014)
15. G. Piccirillo, et al., Age and QT variability index during free breathing, controlled breathing and tilt in patients with chronic heart failure and healthy control subjects. Translational Research. **148**, 72 (2006)
16. P. Li, et al., in *2011 Computing in Cardiology*. (IEEE, 2011), pp. 309
17. E. Nahshoni, et al., Complexity of the dynamic QT variability and RR variability in patients with acute anterior wall myocardial infarction: a novel technique using a non-linear method. Journal of Electrocardiology. **37**, 173 (2004)
18. K. Hiromoto, et al., Correlation between beat-to-beat QT interval variability and impaired left ventricular function in patients with previous myocardial infarction. Annals of noninvasive electrocardiology. **11**, 299 (2006)
19. M. Hasan, Abbott D., and Baumert M., Beat-to-beat QT interval variability and T-wave amplitude in patients with myocardial infarction. Physiological measurement. **34**, 1075 (2013)
20. B. Vrtovec, Starc V., and Starc R., Beat-to-beat QT interval variability in coronary patients. Journal of electrocardiology. **33**, 119 (2000)
21. T. Murabayashi, et al., Beat-to-beat QT interval variability associated with acute myocardial ischemia. Journal of electrocardiology. **35**, 19 (2002)
22. D. Arab, et al., Usefulness of the QTc interval in predicting myocardial ischemia in patients undergoing exercise stress testing. Am J Cardiol. **85**, 764 (2000)
23. F. Guideri, et al., QTc interval prolongation during infusion with dipyridamole or adenosine. Int J Cardiol. **48**, 67 (1995)
24. T. Vora, et al., Prolongation of the QT-corrected interval during dobutamine stress echocardiography: A marker for ischemia. Coronary artery disease. **14**,

233 (2003)

25. D.N. Kenigsberg, et al., Prolongation of the QTc interval is seen uniformly during early transmural ischemia. Journal of the American College of Cardiology. **49**, 1299 (2007)
26. C. Kerr, Hacking A., and Henning H., Effects of transient myocardial ischemia on the QT interval in man. The Canadian Journal of Cardiology. **3**, 383 (1987)
27. B.T. Jensen, et al., Beat-to-beat QT dynamics in healthy subjects. Annals of Noninvasive Electrocardiology. **9**, 3 (2004)
28. J. Němec, et al., QT interval variability and adaptation to heart rate changes in patients with long QT syndrome. Pacing and clinical electrophysiology. **32**, 72 (2009)
29. K. Bilchick, et al., Temporal repolarization lability differences among genotyped patients with the long QT syndrome. The American journal of cardiology. **94**, 1312 (2004)
30. M. Hinterseer, et al., Relation of increased short-term variability of QT interval to congenital long-QT syndrome. Am J Cardiol. **103**, 1244 (2009)
31. J. Vicente, et al., Mechanisms of sex and age differences in ventricular repolarization in humans. American heart journal. **168**, 749 (2014)
32. V.C. Kunz, et al., The relationship between cardiac autonomic function and clinical and angiographic characteristics in patients with coronary artery disease. Brazilian Journal of Physical Therapy. **15**, 503 (2011)
33. Y. Chen, et al., Association between cardiac autonomic nervous dysfunction and the severity of coronary lesions in patients with stable coronary artery disease. Journal of International Medical Research. **46**, 3729 (2018)
34. M.P. JUDKINS, Percutaneous transfemoral selective coronary arteriography. Radiologic Clinics of North America. **6**, 467 (1968)
35. G.G. Gensini, A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol. **51**, 606 (1983)
36. L. Yao, et al., Comparison of QT interval variability of coronary patients without myocardial infarction with that of patients with old myocardial infarction. Computers in Biology and Medicine. **113**, 103396 (2019)
37. P. Kligfield, et al., Recommendations for the standardization and interpretation of the electrocardiogram: part I: the electrocardiogram and its technology: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society endorsed by the International Society for Computerized Electrocardiology. Circulation. **115**, 1306 (2007)
38. V.X. Afonso, et al., ECG beat detection using filter banks. IEEE Trans Biomed Eng. **46**, 192 (1999)
39. Q. Zhang, et al., An algorithm for robust and efficient location of T-wave ends in electrocardiograms. IEEE Transactions on Biomedical Engineering. **53**, 2544 (2006)
40. X. Hu, et al., Automatic detection of onset and offset of QRS complexes independent of isoelectric segments. Measurement. **51**, 53 (2014)
41. M.P. Tarvainen, Ranta-Aho P.O., and Karjalainen P.A., An advanced detrending method with application to HRV analysis. IEEE transactions on biomedical engineering. **49**, 172 (2002)
42. P. Li, et al., Assessing the complexity of short-term heartbeat interval series by distribution entropy. Medical & biological engineering & computing. **53**, 77 (2015)
43. J.S. Richman and Moorman J.R., Physiological time-series analysis using approximate entropy and sample entropy. American journal of physiology-heart and circulatory physiology. **278**, H2039 (2000)
44. H. Jiang, et al., High levels of HB-EGF and interleukin-18 are associated with a high risk of in-stent restenosis. Anatolian journal of cardiology. **15**, 907 (2015)
45. R. Kurz, et al., Ischaemia induced alternans of action potential duration in the intact-heart: dependence on coronary flow, preload and cycle length. European heart journal. **14**, 1410 (1993)
46. K. Mubagwa, Flameng W., and Carmeliet E., Resting and action potentials of nonischemic and chronically ischemic human ventricular muscle. Journal of cardiovascular electrophysiology. **5**, 659 (1994)
47. R.D. Berger, et al., Beat-to-beat QT interval variability: novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. Circulation. **96**, 1557 (1997)
48. A. Dritsas, et al., QT-interval abnormalities in hypertrophic cardiomyopathy. Clin Cardiol. **15**, 739 (1992)
49. M. Lewis and Short A., Relationship between electrocardiographic RR and QT interval variabilities and indices of ventricular function in healthy subjects. Physiological measurement. **29**, 1 (2008)
50. D.M. Roden, Taking the" idio" out of" idiosyncratic": predicting torsades de pointes. Pacing & Clinical Electrophysiology. **21** (1998)
51. M. Veglio, et al., The relation between QTc interval prolongation and diabetic complications. The EURODIAB IDDM Complication Study Group. Diabetologia. **42**, 68 (1999)
52. A.S. Vink, et al., Effect of age and sex on the QTc interval in children and adolescents with type 1 and 2 long-QT syndrome. Circulation: Arrhythmia and Electrophysiology. **10**, e004645 (2017)
53. M.-D. Drici and Clément N., Is gender a risk factor for adverse drug reactions? The example of drug-

induced long QT syndrome. Drug safety. **24**, 575 (2001)

54. V.S. Chauhan, et al., Sex differences in QTc interval and QT dispersion: dynamics during exercise and recovery in healthy subjects. Am Heart J. **144**, 858 (2002)
55. P.A. Lanfranchi, et al., Sex-selective QT prolongation during rapid eye movement sleep. Circulation. **106**, 1488 (2002)
56. P. Smetana, et al., Sex differences in repolarization homogeneity and its circadian pattern. American Journal of Physiology-Heart and Circulatory Physiology. **282**, H1889 (2002)
57. M.A. Hasan, Abbott D., and Baumert M., Relation between beat-to-beat qt interval variability and t-wave amplitude in healthy subjects. Annals of Noninvasive Electrocardiology. **17**, 195 (2012)
58. R. Baranowski and Zebrowski J.J., Assessment of the RR versus QT relation by a new symbolic dynamics method. Gender differences in repolarization dynamics. J Electrocardiol. **35**, 95 (2002)
59. T.T. Krauss, et al., Gender effects on novel time domain parameters of ventricular repolarization inhomogeneity. Pacing and Clinical Electrophysiology. **32**, S167 (2009)
60. M. Nakagawa, et al., Gender differences in autonomic modulation of ventricular repolarization in humans. Journal of cardiovascular electrophysiology. **16**, 278 (2005)
61. H. Kusuki, et al., Beat-to-beat QT interval variability in children: normal and physiologic data. Journal of Electrocardiology. **44**, 326 (2011)

Appendix

Supplementary Table S1. Individual-specific heart rate-corrected QT formulas

1-Parameter (a) Formulas
$QT = aRR^{1/2}$ (a = QTc; RR in sec)
$QT = aRR^{1/3}$ (a = QTc; RR in sec)
$QT = aRR$ (a = QTc; RR in sec)
$QT = a \cdot \log RR$ (a = QTc/3; RR in msec)
2-Parameter (a, b) Formulas
$QT = aRR^{1/2} + b$
$QT = aRR^{1/3} + b$
$QT = (a \cdot \ln HR) + b$
$QT = 1/(a + bHR)$
$QT = aHR + b$
$QT = aRR + b$
$QT = (a \cdot \log RR) + b$
$QT = a + (b/RR)$
$QT = aRR^{b}$
$QT = a(1-e^{bRR})$
$QT = ae^{bHR}$
3-Parameter (a, b, c) Formulas
$QT = a + be^{cHR}$
$QT = a + be^{-cRR}$