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Comparison of QT interval variability of coronary patients without myocardial infarction with that of patients with old myocardial infarction

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ABSTRACT

Background: The significant association of myocardial ischemia with elevated QT interval variability (QTV) has been reported in myocardial infarction (MI) patients. However, the influence of the time course of MI on QTV has not been investigated systematically.

Method: Short-term QT and RR interval time series were constructed from the 5 min electrocardiograms of 49 coronary patients without MI and 26 patients with old MI (OMI). The QTV, heart rate variability (HRV), and QT–RR coupling of the two groups were analyzed using various time series analysis tools in the time- and frequency-domains, as well as nonlinear dynamics.

Results: Nearly all of the tested QTV indices for coronary patients with OMI were higher than those for patients without MI. However, no significant differences were found between the two groups in any of the variables employed to assess the HRV and QT–RR coupling. All of the markers that showed statistical significances in univariate analyses still possessed the capabilities of distinguishing between the two groups even after adjusting for studied baseline characteristics, including the coronary atherosclerotic burden.

Conclusions: The results suggested that the QTV increased in coronary patients with OMI compared to those without MI, which might reflect the influence of post-MI remodeling on the beat-to-beat temporal variability of ventricular repolarization. The non-significant differences in the HRV and QT–RR couplings could indicate that there were no differences in the modulation of the autonomic nervous system and interaction of QT with the RR intervals between the two groups.

1. Introduction

Survivors of myocardial infarction (MI), particularly those with adverse left ventricular (LV) remodeling or dysfunction, have elevated risks of all-cause mortality and cardiovascular death, as well as some other manifestations of further serious events, e.g., stroke, malignant ventricular arrhythmias (VAs), and heart failure (HF) [1–3]. To improve clinical interventions and overall outcomes, a variety of non-invasive methods based on the measurement of the cardiac electrical substrate have shown promise as risk stratifiers for post-MI patients [4–7], including QT interval variability (QTV), QT dispersion (QTD), T-wave alternans (TWA), and Tpeak-Tend interval methods. Among these techniques, the prognostic value of the QTV, which quantifies the temporal fluctuation in ventricular repolarization on a body surface electrocardiogram (ECG), has been recognized in prior research [7,8]. Additionally, the methodology to assess QTV has allowed investigators to explore the underlying mechanism regulating the repolarization process, as well as its lability under various cardiac and psychiatric conditions [9].

Previous studies have reported a higher degree of QTV in MI patients [10,11] and coronary patients without MI [12], as well as during an episode of acute myocardial ischemia [13], which indicate the existence of a significant association between increased repolarization lability and myocardial ischemia. However, the influence of the time

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course after MI on QTV has not been investigated systematically. It has been increasingly demonstrated that, except for acute ischemia, MI can lead to progressive LV remodeling involving complex alterations in the ventricular architecture and contractile function deterioration [14–16]. Using the T-wave spectral variance (TSV), which is an index to assess the beat-to-beat variability of a T-wave morphology, Pedro et al. found a variation pattern that first increased and then decreased from healthy subjects to patients within the first 7 days after MI and then to those 60 days after MI [17]. An animal experiment also showed significantly higher values of TWA and short-term variability (STV) of the QT interval in patients on the 21st day after MI than in those 1 day after MI, which suggested that these two markers could reflect different phases of post-MI remodeling [18]. At the cellular level, different alterations of the action potential duration (APD) in the myocytes from different regions of the infarct zone have been observed for a period from 5 min to 60 days after MI [19]. In addition, though various QTV variables have been described in the previously mentioned research, no direct comparison has been made to determine the differences in their discriminating power values [20]. Hence, in the present study, the QTV of coronary patients without MI was compared with that of those with old MI (OMI) who experienced MI over 4 weeks prior to entering the study, using various techniques for time series analyses in the time- and frequency-domains, as well as nonlinear dynamics. Because the oscillation of the heart rate variability (HRV) is one of the major sources of QTV [9], the HRV and its coupling with the QTV (the interaction between one QT interval and one preceding RR interval) for these two groups were also analyzed. Moreover, the discriminating capabilities of the studied variables for these two groups were compared by analyzing the receiver operating characteristic (ROC) curves.

2. Subjects and methods

2.1. Subjects

Forty-nine coronary patients without MI and 26 with OMI were selected from 282 subjects who were recruited consecutively in Shandong Provincial Qianfoshan Hospital between November 2017 and September 2018. Each participant was scheduled to undergo a coronary angiogram within 2 days when they agreed to join the experiment. All of the subjects provided written informed consent prior to participation in this study. No attempt was made to control their medicine administration. The research protocol was approved by the Clinical Ethics Committee of the aforementioned hospital and complied with the Declaration of Helsinki. The inclusion criteria were coronary artery disease with angiographic evidence of having at least one major coronary artery narrowed ≥50% and a diagnosis of OMI with acute MI that occurred more than 4 weeks prior to this study and no re-infarction incident recorded before enrollment. The exclusion criteria included cancer, an HF history, mental disease, hepatic or renal dysfunction, valve disease, cerebrovascular disease, class I or III antiarrhythmic drug use, an electrolyte disturbance, an LV ejection fraction (LVEF) < 40%, and advanced age (> 75 years).

2.2. Data acquisition

For each patient, a 5 min ECG recording with the standard lead I configuration sampled at 4 kHz was acquired continuously in the supine position after a 10 min rest. The ECG data were acquired in a quiet, temperature-controlled room (25 ± 3 °C) between 2 p.m. and 6 p.m. using a cardiovascular function detection device (CVFD-II, Huiyironggong Technology Co., Ltd, Ji'nan, China).

Moreover, demographic data (age, body mass index (BMI), and sex) and some other risk factor profiles (smoking history, hypertension, hyperlipidemia, and type 2 diabetes) were noted. Any administration of medication related to ventricular repolarization (beta-blockers, Ca^{2+} channel blocker, angiotensin receptor blocker, and angiotensin-converting enzyme inhibitor) and the results of physical exams (systolic and diastolic blood pressures (SBP and DBP) and LV ejection fraction (LVEF)) were also recorded.

The atherosclerotic burden in the coronary arteries was evaluated via the number of stenosed vessels (narrowing ≥ 50%) and the Friesinger score (FS) [21]. The FS varies between 0 and 15, with higher values indicating an increased degree of stenosis and higher number of stenosed vessels. It is computed by separately grading the stenosis severity of each of three major coronary arteries within a range 0–5 (the stenosis in the left main stem is scored for both the anterior descending and the circumflex) [22]. In this study, the number of stenosed vessels and FS were independently estimated from the angiography report by a physician (C. Du) blinded to the circumstances of the individual patients.

2.3. ECG preprocessing and variability series construction

The raw ECG recordings were preprocessed using the following steps: (i) the power-line interference at 50 Hz was removed using an IIR notch filter, (ii) the baseline wander was minimized using a polynomial order 3 Savitzky–Golay filter [23], (iii) redundant frequency components were eliminated using a 0.05–150 Hz FIR band-pass filter [24], and (iv) denoising was implemented using a stationary wavelet transform with the Symmlet 8 mother wavelet, level 4 decomposition, and hard thresholding method [25,26].

Then, fiducial points related to the construction of the QT and RR interval series were automatically detected. In each ECG, the R-wave peak was primarily located with a heartbeat detector comprising a filter bank [27,28]. The QRS complex onset was located using a decision tactic method [29], and the T-wave terminus was found via an approach based on seeking an indicator correlated with the area under the T-wave curve [30]. A physician (C. Du) blinded to the subject's circumstances visually inspected the fiducial point delineation and annotated ectopic beats. We rejected ECGs containing excessive noise that interfered with the delineation and those where the number of ectopic beats exceeded 5% of the total beat amount [31]. Finally, the QT and RR interval series were extracted from the remaining ECGs, in which anomalous intervals resulting from ectopic heartbeats were removed. Specifically, in the location where an ectopic beat was identified, the adjacent RR intervals (preceding and subsequent intervals) and corresponding QT intervals were excluded.

2.4. Variability analysis

2.4.1. Time-domain indices

The QT interval mean ($Mean_{QT}$) and standard deviation (SD_{QT}), as well as the RR interval mean ($Mean_{RR}$) and standard deviation (SD_{RR}), were computed as time-domain indices. The STV (STV_{QT} and STV_{RR}) and root mean square of the successive differences ($RMSSD_{QT}$ and $RMSSD_{RR}$) were employed to evaluate the short-term fluctuations in the QTV and HRV, respectively. If D_i is the duration of the i-th interval and N is the total duration amount, the RMSSD quantifies the magnitude of incremental alterations of a time series in the temporal ordering as follows [32,33]:

$$RMSSD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(D_{i+1} - D_i)^2} \tag{1}$$

STV refers to the average distance to the line of identity for all the intervals in a Poincaré plot [34,35], which is given by

$$STV = \sum_{i=1}^{N-1} |D_{i+1} - D_i|/(N \times \sqrt{2}) \tag{2}$$

Furthermore, two HRV-normalized QTV time-domain metrics, the variability ratio (VR) and QT variability index (QTVi), were utilized. The VR was calculated as the ratio of STV_{QT} to STV_{RR} [36]. The QTVi is

defined as the logarithm of the ratio of the QT interval variance to RR interval variance, each normalized by the squared mean of the corresponding interval series [37].

2.4.2. Frequency-domain indices

Prior to the power spectrum analyses, the QT and RR interval series were resampled at 4 Hz with a poly-phase filter and detrended using a smoothness priors approach [38]. The power spectral density (PSD) values of both variability series were estimated using Burg's method with an order of 16 [39], and then integrated into low-frequency (0.04–0.15 Hz, QT_{LF} and RR_{LF}) and high-frequency bands (0.15–0.4 Hz, QT_{HF} and RR_{HF}) [9,40]. The LF to HF ratios for the QT and RR interval series ($QT_{LF/HF}$ and $RR_{LF/HF}$) were also analyzed.

In addition, squared coherence (SC) was adopted to assess the group difference in the strength of the QT–RR linear coupling between the current QT interval and one preceding RR interval, which can be defined as follows:

$$K^2_{\mathrm{QT-RR}}(f) = \frac{[C_{QT-RR}(f)]^2}{S_{QT}(f)S_{RR}(f)} \tag{3}$$

where $S_{QT}(f)$ and $S_{RR}(f)$ represent the corresponding PSD estimates of the QT and RR interval series, respectively, and $C_{QT-RR}(f)$ is the cross-PSD between the two variability series. The SC was computed using a parametric method based on an autoregressive model with an order of 10 [41]. The average and maximum SC values in the low-frequency (ASC_{LF} and MSC_{LF}) and high-frequency (ASC_{HF} and MSC_{HF}) bands were evaluated for further comparison [41].

2.4.3. Nonlinear indices

In order to assess the nonlinear dynamics of the QT and RR interval series, the sample entropy ($SampEn_{QT}$ and $SampEn_{RR}$) [42] and distribution entropy ($DistEn_{QT}$ and $DistEn_{RR}$) [43] were computed. SampEn was proposed as a statistical measure to quantify the regularity of a time series [42]. It is approximately the negative natural logarithm of the conditional probability that two vectors remain similar at $m + 1$ points given that they are similar at m points [42]. Two vectors are considered similar if their distance (maximum norm) is within a preset tolerance r. In the current study, we set $m = 2$ and $r = 0.2 \times SD$, as suggested by previous publications [44,45]. DistEn is a recently developed measure for analyzing the complexity of a short-length variability series. It directly characterizes the frequency distribution of the inter-vector distance with a histogram of M bins and is defined by the classical formula of Shannon entropy based on the distribution. The DistEn values were computed with for the purpose of comparison, and with $M = 500$ as recommended in Refs. [43,46].

Furthermore, the cross-sample entropy (XSampEn) [42] and joint distribution entropy (JDistEn) [47] were obtained to assess the strength of the nonlinear QT–RR coupling. The XSampEn measure was developed to evaluate the degree of synchronization between two related time series. Its definition is similar to that of SampEn, with the only difference being that XSampEn compares vectors of one series with those of another. JDistEn measures the nonlinear coupling of bivariate time series by combining the concepts of DistEn and a joint distance matrix. Briefly, the joint distance matrix is utilized to quantify the difference among the distances of corresponding pairs of vectors from different data channels. The input parameter values for XSampEn and JDistEn were set the same as those of their corresponding univariate counterparts [42,47].

2.5. Statistical analysis

A chi-square test was employed to evaluate the group differences in categorical variables. With regard to continuous parameters, the normality of the distribution was assessed using the Shapiro–Wilk test, and those with non-normal distributions were transformed via the Box–Cox method. An independent-sample T test was performed if a normal distribution was verified (homogeneity was evaluated using Levene's test); otherwise, the Mann–Whitney U test was utilized. Moreover, the ROC curve was analyzed to assess the efficiency of the studied indices as features to distinguish the two groups. The values of the area under the curve (AUC), corresponding standard error (SE), and 95% confidence interval (CI) were computed.

In addition, a multivariable logistic regression analysis was used for evaluating the predictive capability of each studied index, while controlling the influence of other confounders. A regression model initially consisted of 1 studied variable and 12 baseline characteristics with theoretical relevance irrespective of their statistical significance. The baseline characteristics included age, sex, BMI, smoking history, type 2 diabetes, hypertension, hyperlipidemia, SBP, DBP, LVEF, the number of stenosed vessels (1, 2, and 3 or more), and the FS. The purpose of including only 1 studied index in each model was to avoid collinearity among different indices. A collinearity diagnosis was also conducted on the 12 baseline characteristics. Considering the sample size in the present study, a model building process with backward stepwise regression was performed to estimate the coefficients more accurately. A value of $p < 0.05$ was considered significant in all of the statistical analyses. The statistical software R (version 3.6.0) for Windows was used for all of the analyses.

3. Results

Table 1 summarizes the baseline characteristics of the enrolled coronary patients without MI and those with OMI. At the baseline, the two groups did not differ significantly in almost all of the characteristics, except in LVEF. The coronary patients without MI had significantly higher LVEF values than those with OMI ($p < 10^{-3}$).

Fig. 1 shows the results for the studied time-domain indices used to assess the alterations in QTV and HRV between the two groups. The SD_{QT}, $RMSSD_{QT}$, and STV_{QT} values were significantly higher in coronary patients with OMI than in those without MI ($p < 10^{-6}$, 10^{-4}, and

Table 1
Baseline characteristics of coronary patients without myocardial infarction (MI) and those with old MI (OMI).

Variables	Coronary patients without MI	Coronary patients with OMI	p-value
	$n = 49$	$n = 26$	
Age, years	62.08 ± 7.06	63.12 ± 8.74	0.58
Male sex	34 (69)	19 (73)	0.74
BMI, kg/m^2	25.54 ± 2.95	25.78 ± 2.82	0.74
Smoking history	22 (45)	17 (65)	0.14
Type 2 diabetes	17 (35)	12 (46)	0.29
Hypertension	30 (61)	17 (65)	0.72
Hyperlipidemia	11 (22)	6 (23)	0.95
Systolic BP, mm Hg	132.51 ± 23.70	135.42 ± 21.93	0.83
Diastolic BP, mm Hg	78.55 ± 11.92	76.96 ± 12.30	0.58
LVEF, %	65.10 ± 4.30	56.62 ± 9.64	$< 10^{-3}$
Medications			
Beta-blockers	42 (86)	21 (81)	0.74
Ca^{2+} channel blocker	15 (31)	10 (38)	0.49
ACE-inhibitor/ARB	17 (35)	10 (38)	0.75
No. of stenosed vessels			0.79
1	15 (31)	6 (23)	
2	16 (33)	10 (38)	
3 or more	18 (37)	10 (38)	
Friesinger score	5.81 ± 2.36	6.81 ± 3.20	0.25

‡ BMI = Body mass index; BP = blood pressure; LVEF = left ventricular ejection fraction; ARB = angiotensin receptor blocker; ACE = angiotensin-converting enzyme.
† Categorical variables are presented as number (%) of patients, and continuous ones are expressed as mean ± standard deviation.

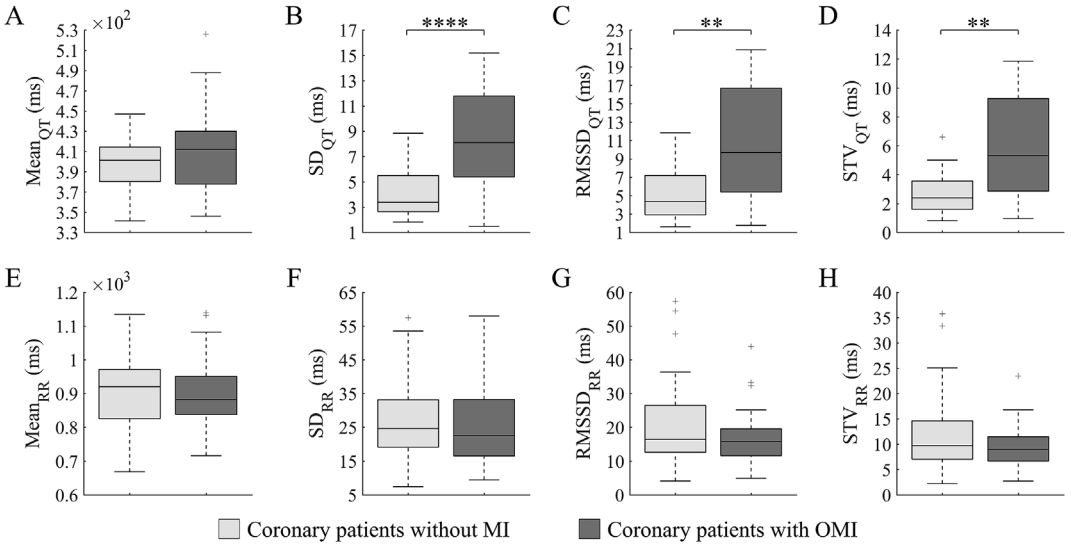

Fig. 1. Group distributions of studied time-domain indices in variability analysis of QT (A–D) and RR (E–H) interval time series between coronary patients without myocardial infarction (MI) and those with old MI (OMI).
† SD = standard deviation; RMSSD = root mean square of the successive differences; STV = short-term variability; **: $p < 10^{-4}$; ****: $p < 10^{-6}$.
‡ In these and later boxplots, the central line represents the median; the box extends from 25 to 75 percentile points, and the error bar spans from 10 to 90 percentile points.

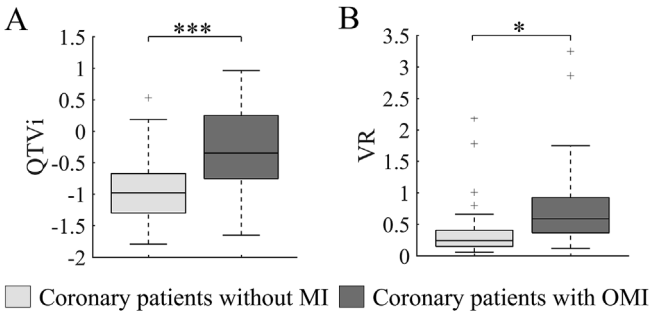

Fig. 2. Group differences in QT variability index (QTVi) and variability ratio (VR) between coronary patients without myocardial infarction (MI) and those with old MI (OMI).
† *: $p < 10^{-3}$; ***: $p < 10^{-5}$.

10^{-4}, respectively), suggesting that both the total and short-term cycle components responsible for QTV exhibit notable changes. Nevertheless, the $Mean_{QT}$ distributions showed no difference between the two groups. In the HRV assessments, though the $RMSSD_{RR}$ and STV_{RR} values were slightly lower in coronary patients with OMI than in those without MI, no statistical difference was observed in them or the other tested HRV indices. Moreover, as shown in Fig. 2, the *QTVi* and *VR* values were significantly higher among coronary patients with OMI compared to those without MI ($p < 10^{-5}$ and 10^{-3}, respectively). For coronary patients with OMI, the higher *VR* was due to a higher STV_{QT}, and the higher *QTVi* resulted from a higher SD_{QT}.

Fig. 3 depicts the results for the studied frequency-domain metrics used to assess the alterations in QTV and HRV between the two groups. In the HRV analyses, no differences were observed in any of the employed frequency-domain parameters. In contrast, all of the utilized QTV variables in the frequency-domain significantly separated the two groups. Specifically, coronary patients with OMI had higher values of QT_{LF}, QT_{HF}, and $QT_{LF/HF}$ than those without MI (at least $p < 10^{-4}$). This was attributable to a greater increase in QT_{LF} compared to the magnitude of the rise in QT_{HF}, suggesting that the dominant alteration in the spectra of the QT interval time series existed in the LF range.

Comparative results of the QT–HR linear coherence assessments are shown in Fig. 4. There were no differences in any of the utilized linear coherence indices between the two groups. Moreover, the distributions of ASC_{LF} and ASC_{HF} for both groups were below 0.5, indicating weak QT–HR linear couplings. Although the distribution range of MSC_{HF} was relatively higher than those of the other coherence indices, the MSC_{HF} values were distributed in a broader region.

Representative PSDs and coherence spectra for QT and RR interval series are presented in Fig. 5. Compared to a coronary patient without MI, virtually every coronary patient with OMI had higher PSD values for the QT interval series (Fig. 5A), as well as a similar waveform for the RR interval series (Fig. 5B). Moreover, all of the power spectra exhibited peaks centering around the respiratory frequency of 0.1 Hz, which reflected the influence of the respiration rhythm. As shown in Fig. 5C, the coherence estimates had values of less than 0.5 over the entire frequency band tested. These results are consistent with the ASC

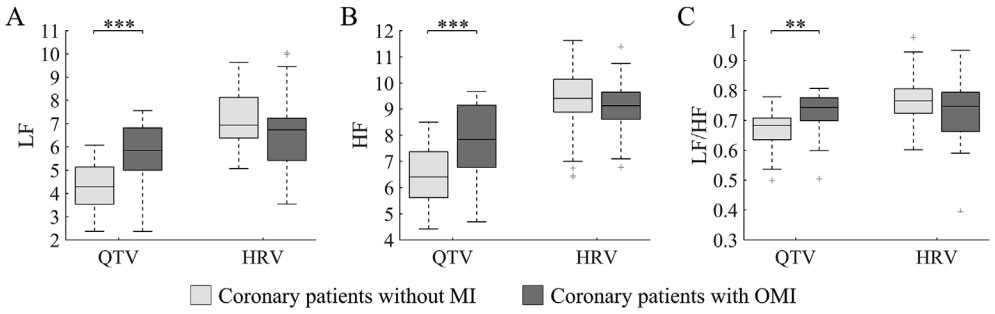

Fig. 3. Group differences in studied frequency-domain indices in variability analysis of QT and RR interval time series between coronary patients without myocardial infarction (MI) and those with old MI (OMI).
† QTV = QT interval variability; HRV = heart rate variability; LF = low frequency; HF = high frequency; LF/HF = ratio of LF to HF; **: $p < 10^{-4}$; ***: $p < 10^{-5}$.

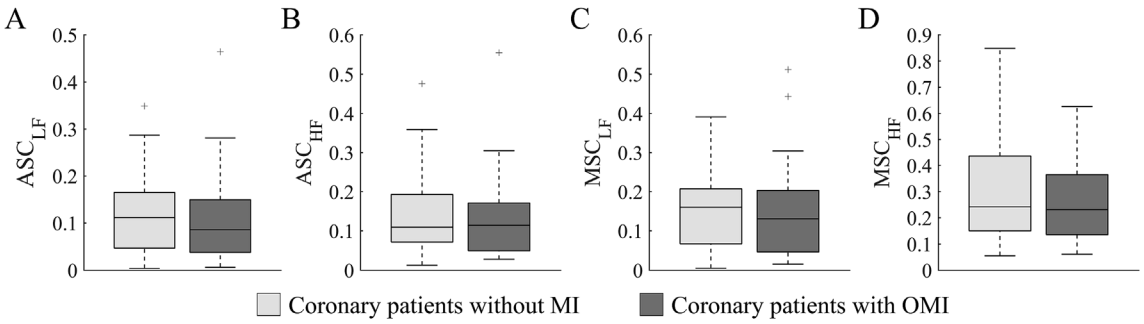

Fig. 4. Group differences in studied linear coherence indices between coronary patients without myocardial infarction (MI) and those with old MI (OMI).
† ASC = average squared coherence; MSC = maximum squared coherence; LF = low frequency; HF = high frequency.

distributions for the QT and RR interval series (Fig. 4). The two interval time series showed different coherences in the HF range, in accord with the broader distribution of MSC_{HF} (Fig. 4D).

Fig. 6 presents the results of the nonlinear indices for coronary patients without MI and those with OMI. Significantly higher $DistEn_{QT}$ values were observed in coronary patients with OMI compared to those without MI ($p < 10^{-6}$), whereas no significant difference was found in the $SampEn_{QT}$ values. The HRV assessments showed that there were no statistical differences in the $SampEn_{RR}$ and $DistEn_{RR}$ values for these two groups. Similarly, no significant differences were observed in any of the nonlinear parameters utilized for assessing the QT–RR nonlinear coupling.

Fig. 7 presents the ROC curves of certain studied variables that showed statistical significance in the previously mentioned univariate comparison. The results of the ROC curve analyses are presented in Table 2. Of these parameters, $DistEn_{QT}$ had the largest AUC (0.837, 95% CI: 0.729–0.944), whereas the least AUC was observed for *VR* (0.761, 95% CI: 0.643–0.878).

The results of multivariate binomial logistic regression analyses are tabulated in Table 3 (detailed results are presented in Table S1). There was no collinearity among the included baseline characteristics (Table S2). In general, those variables that showed statistical significances in univariate analyses still presented moderate discriminating capabilities after adjustment (at least $p < 0.05$). As shown in Table S1, except for the tested index, LVEF showed significant differences between the two groups in all of the constructed regression models (at least $p < 0.05$).

4. Discussion

The major finding of this study was that, compared to coronary patients without MI, patients with OMI were found to exhibit elevated QTV values, using various time series analysis techniques in the time- and frequency-domains, as well as nonlinear dynamics. Similar observations have been reported in previous studies that investigated the effect of the time course after MI on certain markers (STV, TWA, and TSV) used for assessing the beat-to-beat variability of ventricular repolarization, suggesting that these variables could reflect different processes of post-MI remodeling [17–19]. Nevertheless, an experimental study showed non-significant alteration in the QTV between mice with post-MI scarring and those that had sham surgeries performed on them [48]. Actually, except for the scar tissue formation, the acute loss of myocardium and the subsequent increase in ventricular volume caused a series of biochemical intracellular signaling processes that first initiated compensatory changes but later became detrimental, including ventricular dilatation and myocardial hypertrophy [15,16]. In addition, it has been demonstrated that, in the late phase of remodeling, the abnormal augmentation of the wall stress induced by MI can result in the impairment of the ventricular pump function [14,15]. These LV architectural changes that resulted from post-MI remodeling and the subsequent LV dysfunction may account for the QTV alteration by directly impacting the ventricular repolarization. With regard to the current study, we speculate that the significant LVEF deterioration in coronary patients with OMI may reflect the presence of post-MI remodeling. At the cellular level, the heterogeneity of the APD amid the wall of the heart during remodeling could also be responsible for the increased QTV. An animal experiment showed prolonged APD with notable repolarization heterogeneity in a rat's post-MI remodeled myocytes [49]. In the infarcted border zone, a peculiar region prone to the incidence of malignant VAs, remodeling increases the connective tissue and edema, which produce non-uniform anisotropy [17]. Remodeling can further extend to the remote non-infarcted myocardium, leading to marked heterogeneity of repolarization over time [9,17].

Furthermore, considering the influence of the preceding RR interval and respiratory-related artifacts [50,51], the significant alteration in the QTV, and particularly the results of spectral analyses, may be biased by some components independent of the genuine QTV. The non-significant difference in $SampEn_{QT}$ may be due to the insufficient utility of the distribution of the inter-vector distances in SampEn, in contrast to $DistEn_{QT}$, which takes full advantage of the distribution property [46]. Moreover, because template matching algorithms for QT interval delineation have been demonstrated to be more robust than other conventional methods [52], the measurement error-induced noise in the

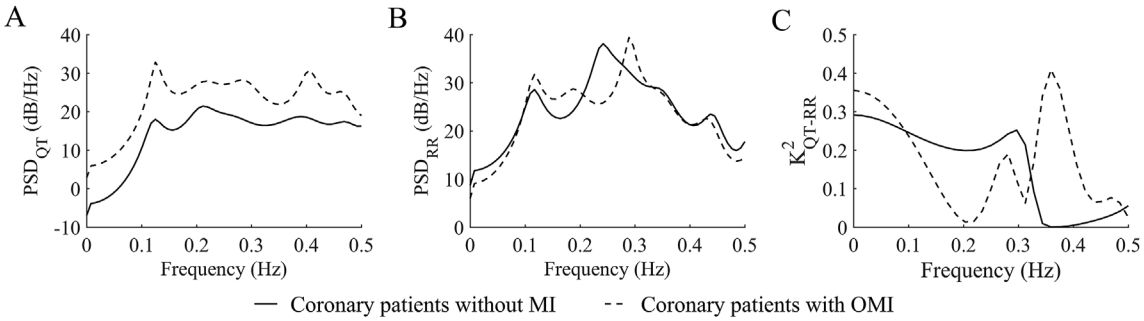

Fig. 5. Representative power spectral density (PSD) values of QT and RR interval series (A and B), as well as their squared coherence (C) values in coronary patients without myocardial infarction (MI) and those with old MI (OMI).

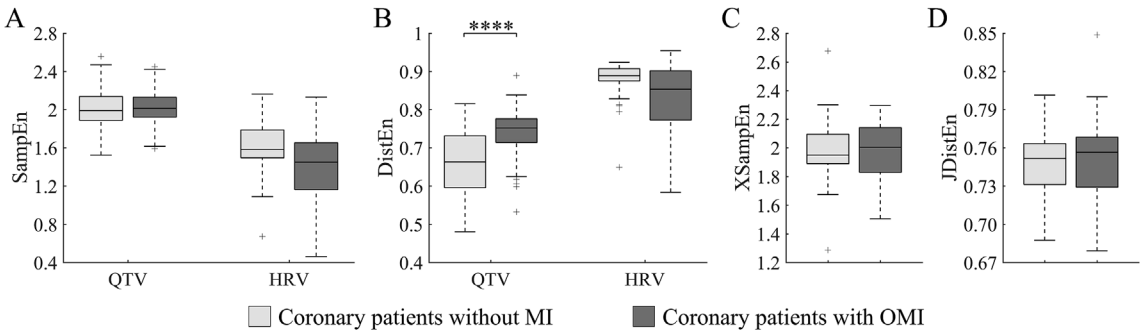

Fig. 6. Group differences in studied nonlinear indices in variability analysis of QT and RR interval time series (A and B) as well as their nonlinear coupling (C and D) between coronary patients without myocardial infarction (MI) and those with old MI (OMI).
† SampEn = sample entropy; DistEn = distribution entropy; XSampEn = cross-sample entropy; JDistEn = joint distribution entropy; QTV = QT interval variability; HRV = heart rate variability; ****: p < 10-6.

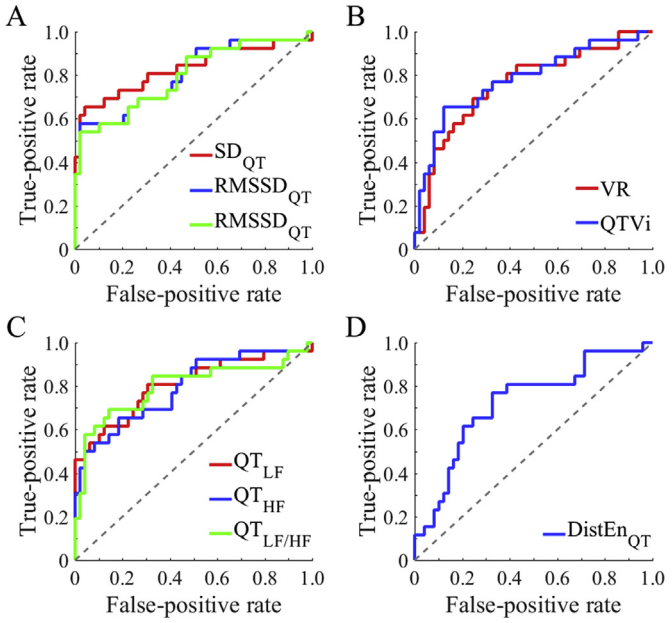

Fig. 7. Receiver operating characteristic (ROC) curves illustrating performances of studied indices to distinguish between coronary patients without myocardial infarction (MI) and those with old MI (OMI).
† Only the performances of the studied indices with significant differences are shown.

QT interval time series can artificially inflate the values of QTV indices and further blur the statistical results.

In contrast to the significant alterations in the QTV, none of the studied HRV markers exhibited significant differences between the two groups, which indicated the unchanged modulation of the autonomic nervous system (ANS). Although the correlation between *QTVi* and ANS activity has repeatedly been reported under different conditions, the significant *QTVi* difference in the current study was due to the notable alteration in SD_{QT} (Figs. 1B and 2A). Similarly, the marked change in STV_{QT} caused a significant increase in *VR* (Figs. 1D and 2B). Nevertheless, whether certain QTV markers could represent the ANS modulation is still a controversial issue. Previous research has suggested that in healthy subjects, *QTVi* is inversely correlated to increased vagal tone [53], whereas *QTVi* is positively correlated to sympathetic activity in patients with hypertension [54]or HF [53]. Sympathetic activation has also been found to be correlated with a QT_{LF} increase during exercise and mental stress tests [9], as well as in patients with hypertension [54] or diabetes [55]. Additionally, a positive correlation of the sympathetic activity with STV_{QT} has been found in dogs with pacing-induced HF [56].

Table 2
Results of receiver operating characteristic (ROC) analyses of studied variables to distinguish between coronary patients without myocardial infarction (MI) and those with old MI (OMI).

Variables	AUC	SE	95% confidence interval	
SD_{QT}	0.830	0.057	0.718	0.942
$RMSSD_{QT}$	0.802	0.057	0.691	0.913
STV_{QT}	0.794	0.058	0.681	0.907
QTVi	0.781	0.059	0.666	0.896
VR	0.761	0.060	0.643	0.878
QT_{LF}	0.807	0.058	0.694	0.920
QT_{HF}	0.793	0.057	0.681	0.805
$QT_{LF/HF}$	0.797	0.062	0.676	0.919
$DistEn_{QT}$	0.837	0.055	0.729	0.944

† Only the performances of the studied indices with significant differences are shown.
‡ AUC = area under the curve; SE = standard error; SD = standard deviation; STV = short-term variability; RMSSD = root mean squared standard deviation; QTVi = QT interval variability index; VR = variability ratio; LF = low frequency; HF = high frequency; SampEn = sample entropy; DistEn = distribution entropy.

Table 3
Results of logistic regression analysis adjusted for baseline characteristics compared with those of unadjusted analysis.

Variables	Unadjusted analysis	Binomial logistic regression		
	p-value	*p*-value	OR	95% CI for OR
SD_{QT}	$< 10^{-6}$	< 0.005	1.562	1.243–2.150
$RMSSD_{QT}$	$< 10^{-4}$	< 0.005	1.305	1.130–1.588
STV_{QT}	$< 10^{-4}$	< 0.005	1.600	1.240–2.274
QTVi	$< 10^{-5}$	< 0.05	1.172[a]	1.060–1.320[a]
VR	$< 10^{-3}$	< 0.005	1.127[a]	1.021–1.293[a]
QT_{LF}	$< 10^{-5}$	< 0.005	1.093[a]	1.031–1.166[a]
QT_{HF}	$< 10^{-5}$	< 0.005	1.090[a]	1.034–1.161[a]
$QT_{LF/HF}$	$< 10^{-4}$	< 0.05	1.163[c]	1.044–1.324[c]
$DistEn_{QT}$	$< 10^{-6}$	< 0.005	1.161[b]	1.070–1.287[b]

† Only the performances of the studied indices with significant differences are shown.
‡ OR = odds ratio; CI = confidence interval.
[a, b, c] For 0.1-, 0.01-, or 0.001-unit increase in the corresponding index, respectively.

In addition, the assessments of both the linear and nonlinear QT–RR couplings showed no differences between the two groups. This may have been because only the interaction between one current QT interval and one preceding RR interval was evaluated in this research. Several previous studies related to the corrected QT interval have demonstrated improvements when taking into account a range of previous RR intervals, indicating an interaction between the QT interval and a series of

preceding RR intervals [57,58]. Moreover, a strong asymmetry in the mutual information flows of the QT interval and history of the RR intervals has been found in healthy subjects using the transfer entropy method [59]. Hence, another explanation of the inability of the studied coupling indices to distinguish the two groups might be their mixtures when quantifying the interactions in two different directions (from RR to QT, and from QT to RR).

Based on the current findings, the QTV measurement might be an effective means of reflecting the time elapsed after MI. Our study might aid in understanding the influence of post-MI remodeling on the beat-to-beat variability of ventricular repolarization. A direct comparison of the discriminating capabilities of the studied QTV markers would help clinicians and epidemiologists research the utility of ECG-derived markers for arrhythmias and mortality.

5. Limitations

A larger sample population would certainly improve the statistical power of the results. The present study did not investigate the underlying mechanism of ventricular repolarization, and the analyses simply pointed to the comparison. Only the QT and RR interval series derived from the lead I ECG recording were used for the analyses. Moreover, the use of template matching algorithms would diminish the measurement error in the QT interval detection and further decrease the noise in the interval series. Although a physician identified and excluded abnormal QT intervals manually, the determination of the T-wave end is still difficult, particularly in the presence of a flat T-wave or T–U fusion [9]. The exclusion of the ectopic beat was based on a qualitative visual inspection rather than a quantitative assessment. In addition, we did not consider the effect of the T-wave amplitude on the QTV analyses, which may have introduced additional bias [9,11].

Because post-MI remodeling involves complex alterations in the ventricular structure and function [14–16], the influence of different stages of remodeling on the QTV still need to be further investigated. Apart from myocardial ischemia, the location, size, and transmurality of the infarction also play important roles in the process of remodeling [14–16]. In the present study, the influences of the above three factors were not considered, even though the evaluations of the atherosclerotic burdens based on FS and the number of stenosed vessels were comparable between the two groups and logistic regression was performed to eliminate the effect of the baseline characteristics. The correlations between the QTV indices and the results of some direct examinations to determine remodeling, including the LV mass and LV end systolic diameter, need to be further studied.

6. Conclusions

This study demonstrated the elevated QTV in coronary patients with OMI compared to the QTV in patients without MI. This might reflect the influence of post-MI remodeling on the beat-to-beat temporal variability of ventricular repolarization. None of the studied HRV indices showed significant differences between the two groups, suggesting unchanged ANS modulation. Moreover, there was no difference in the QT–HR linear and nonlinear couplings between the two groups.

Conflicts of interest

There is no conflict of interest declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2019.103396.

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