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Beat-to-beat QT interval variability and T-wave amplitude in patients with myocardial infarction

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Abstract

The purpose of this study was to investigate the effects of T-wave amplitude and ECG lead on beat-to-beat QT interval variability (QTV) in patients with myocardial infarction (MI) compared to healthy subjects. Standard resting 12-lead ECGs of 79 MI patients and 69 healthy subjects were investigated. Beat-to-beat QT intervals were measured separately for each lead using a template matching algorithm. In addition, we extracted the beat-to-beat T-wave amplitude in each lead. We computed the standard deviation of beat-to-beat QT intervals as a marker of QTV for both healthy subjects and MI patients. Significant QTV differences were observed between the 12 ECG leads as well as between the groups of healthy subjects and MI patients. Beat-to-beat QTV was significantly higher in MI patients than in healthy subjects for half of the leads. Furthermore, significant T-wave amplitude differences across leads and between groups were observed. A significant inverse relation between beat-to-beat QTV and T-wave amplitude was demonstrated. The group differences in QTV remained significant after co-varying for the T-wave amplitude. In conclusion, the increase in beat-to-beat QTV that has been repeatedly reported in patients with MI is partly due to the lower T-wave amplitudes. However, QTV remains significantly increased in MI patients after covarying for this effect.

Keywords: ECG, QT interval variability, repolarization, myocardial infarction

(Some figures may appear in colour only in the online journal)

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1. Introduction

The sum of total depolarization and repolarization durations in a cardiac cycle of a surface ECG is called QT interval and is measured from the beginning of the QRS complex (onset of QRS) to the end of the T-wave (offset of T-wave). Prolonged as well as shortened QT intervals are risk factors for ventricular tachyarrhythmia and sudden death (Couderc and Lopes 2010). Dynamic changes of QT interval duration, namely beat-to-beat QT interval variability (QTV), have also experienced significant clinical interest.

Elevated beat-to-beat QTV is thought to be indicative of cardiac repolarization lability and excessive sympathetic outflow (Baumert *et al* 2011a, 2011b, Tereshchenko *et al* 2012, Das *et al* 2012). More recently, the analysis of beat-to-beat repolarization variability has been extended through vectorcardiographic approaches for identifying cardiac repolarization instability (Hasan *et al* 2012a, Tereshchenko *et al* 2010, Hnatkova *et al* 2010).

A number of studies have demonstrated the prognostic power of increased QTV in patients with myocardial infarction (MI) (Furukawa *et al* 2006, Jensen *et al* 2005, Chen *et al* 2011). However, the underlying mechanisms of elevated beat-to-beat QTV in patients with MI are currently incompletely understood. In addition to that, little is known about the factors related to the QTV measurement procedure that may cause higher beat-to-beat variability in MI patients.

Therefore, in this study we sought to investigate waveform-dependent factors contributing to elevated beat-to-beat QTV in patients with MI compared to healthy subjects.

2. Methods

2.1. Subjects

Seventy-nine MI patients (22 female, mean age 63 $\pm$ 12 years; 57 male, mean age 57 $\pm$ 10 years) and 69 healthy subjects (17 female, 42 $\pm$ 18 years; 52 male, 40 $\pm$ 13 years) were investigated in this study. Eight patients had diabetes mellitus, 12 were obese and 27 had hypertension. Standard resting 12-lead ECGs that were recorded between one and two weeks after the infarction date were considered for this study. The duration of recording was on average 2 min. All data were obtained from the Physikalisch-Technische Bundesanstalt (PTB) diagnostic database (http://www.physionet.org), which was collected between 1990 and 1997 at the Department of Cardiology of University Clinic Benjamin Franklin in Berlin, Germany. The sampling frequency of the ECG data was 1000 Hz with a 16-bit resolution over a range of $\pm$16.384 mV.

2.2. QT variability analysis

To study beat-to-beat QTV, the accurate R-peak detection along with the correct identification of the QRS onset and T-wave offset are crucial, especially in the presence of noise and artefacts, which all ECG recordings typically contain to some degree. In this study, we used the template-matching approach that was originally introduced by Berger and his co-workers (Berger *et al* 1997) with an improved ECG pre-processing stage (Hasan *et al* 2013). The details of the updated approach have been described in our earlier article (Hasan *et al* 2013). In brief, we have implemented a robust R-peak detection algorithm replacing the original algorithm, which was proposed by Pan and Tompkins (1985). Furthermore, baseline removal based on cubic spline interpolation has been incorporated.

After detecting the R-peak, the operator defines a template of the QT interval by selecting the Q-wave onset and T-wave offset for one beat in a particular lead (Berger *et al* 1997). Then,

the beat-to-beat QT interval was determined for each of the 12 ECG leads by adopting the approach that has been previously described (Hasan *et al* 2012b). In addition, we measured the amplitude of the T-wave for each beat in all leads by following a procedure that has been published earlier (Hasan *et al* 2012b). The median of absolute values of the T-wave amplitudes of each lead was determined and used in the subsequent analysis. The signal-to-noise ratio (SNR) was determined as the ratio of the median T-wave amplitude (signal) power to the iso-electric line (noise) power ($N_{\text{iso-elec}}$) for each individual lead in each recording. We measured the iso-electric line noise starting from the end of the T-wave over a period of 70 ms for each beat in each lead. The noise in each lead was quantified as the trimmed mean value (based on 10% rejection) of the variance in the iso-electric segment of all beats. The SNR is expressed using the logarithmic decibel scale. The equation for the SNR is given below:

$$\text{SNR} = 10 \log_{10} \frac{T^2_{\text{amplitude}}}{N_{\text{iso-elec}}}. \tag{1}$$

In addition, we computed the standard deviation of normal RR intervals (sdNN) as a marker of heart rate variability (HRV) for each recording using lead II.

2.3. Statistics

We used GraphPad Prism 6® (GraphPad Software, Inc., La Jolla, CA, USA), IBM SPSS Statistics 19® (IBM Inc., Armonk, NY, USA) and Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA). Beat-to-beat QTV was computed for each lead as a standard deviation of QT intervals and compared between patients and healthy subjects using two-way ANOVA. We also performed receiver operating characteristic (ROC) curve analysis and calculated the area under the curve (AUC) for each lead. In addition, two-way ANOVA was applied to test for gender differences in QTV. Furthermore, two-way ANOVA was used to test for lead and group differences in the T-wave magnitude and SNR. Post-hoc tests across the leads were performed using Sidak's multiple comparison tests. To explore the relation between QTV and T-wave amplitude, Pearson's linear correlation coefficient was computed separately for MI patients and healthy subjects. Prior to correlation analysis, QTV and T-wave amplitude values were log-transformed. Moreover, ANCOVA was applied to co-vary for the effect of the T-wave amplitude on QTV. The Student's *t*-test was used to compare HRV between healthy subjects and MI patients. All values were expressed as mean $\pm$ standard deviation and test results were considered statistically significant if $p < 0.05$.

3. Results

Significant QTV differences were observed between leads ($p < 0.0001$) and between healthy subjects and MI patients ($p < 0.0001$) as shown in figure 1(a). The highest QTV value in healthy subjects was observed in lead III (6.87 $\pm$ 6.71 ms) and for MI patients in lead aVF (7.42 $\pm$ 7.30 ms). In MI patients, QTV appears to be higher in six of the leads (I, II, aVR, aVF, V5 and V6) compared to healthy subjects (Sidak's multiple comparison tests across the leads, $p < 0.0001$), but was not significantly different in leads III, aVL, V1, V2, V3 and V4.

Similarly, ROC curve analysis demonstrated significant beat-to-beat QTV differences in ECG leads I, II, aVR, aVF, V3, V4, V5, V6 as shown in figure 2. The highest AUC was measured in lead II and the lowest in lead V1. Table 1 ranks the AUC values of all 12 standard leads.

Significant T-wave amplitude differences were observed across leads ($p < 0.0001$) and between healthy subjects and MI patients ($p < 0.0001$) as shown in figure 1(b).

The highest T-wave amplitude in healthy subjects and patients with MI was measured in lead V3 (0.55 $\pm$ 0.22 mV versus 0.42 $\pm$ 0.24 mV). The T-wave amplitude in six leads was

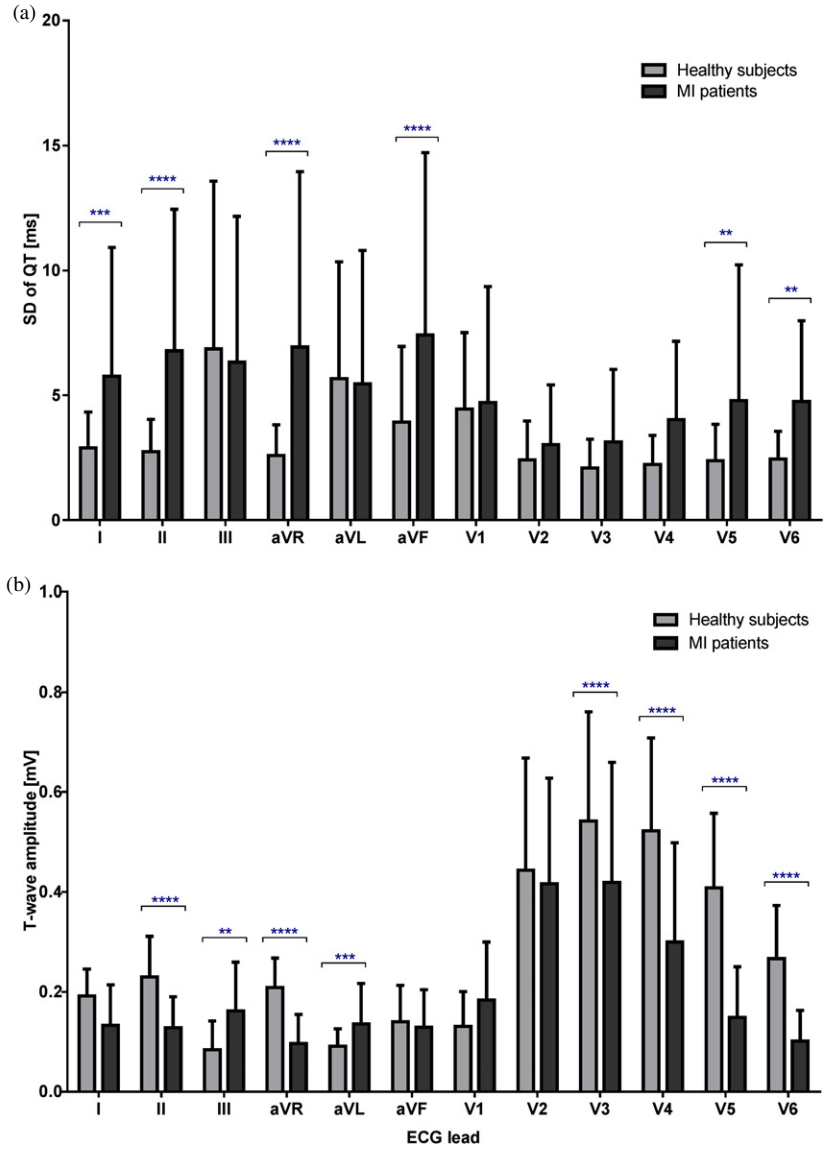

Figure 1. Mean and standard deviation of beat-to-beat QT interval variability (a) and average T-wave amplitude (b) in healthy subjects and MI patients. Here, $p < 0.0001$—****, $p < 0.001$—***, $p < 0.005$—**.

significantly lower in MI patients than the healthy subjects (Sidak's multiple comparison test across the leads, $p < 0.0001$), but was not significantly different in leads I, aVF and V2. On the other hand, the T-wave amplitude in leads III and aVL was higher in MI patients than in healthy subjects.

Significant SNR differences were found between study groups (two-way ANOVA, $p < 0.0001$) and leads as shown in figure 3. The highest SNR in the recordings of healthy subjects was observed in lead V3 (37.20 ± 4.90 dB) and the lowest was found in lead III (23.79 ± 5.15 dB) in healthy subjects. On the other hand, the highest SNR in MI recordings was measured in lead V3 (30.79 ± 6.86 dB) and the lowest was measured in lead aVR (21.58 ± 5.17 dB).

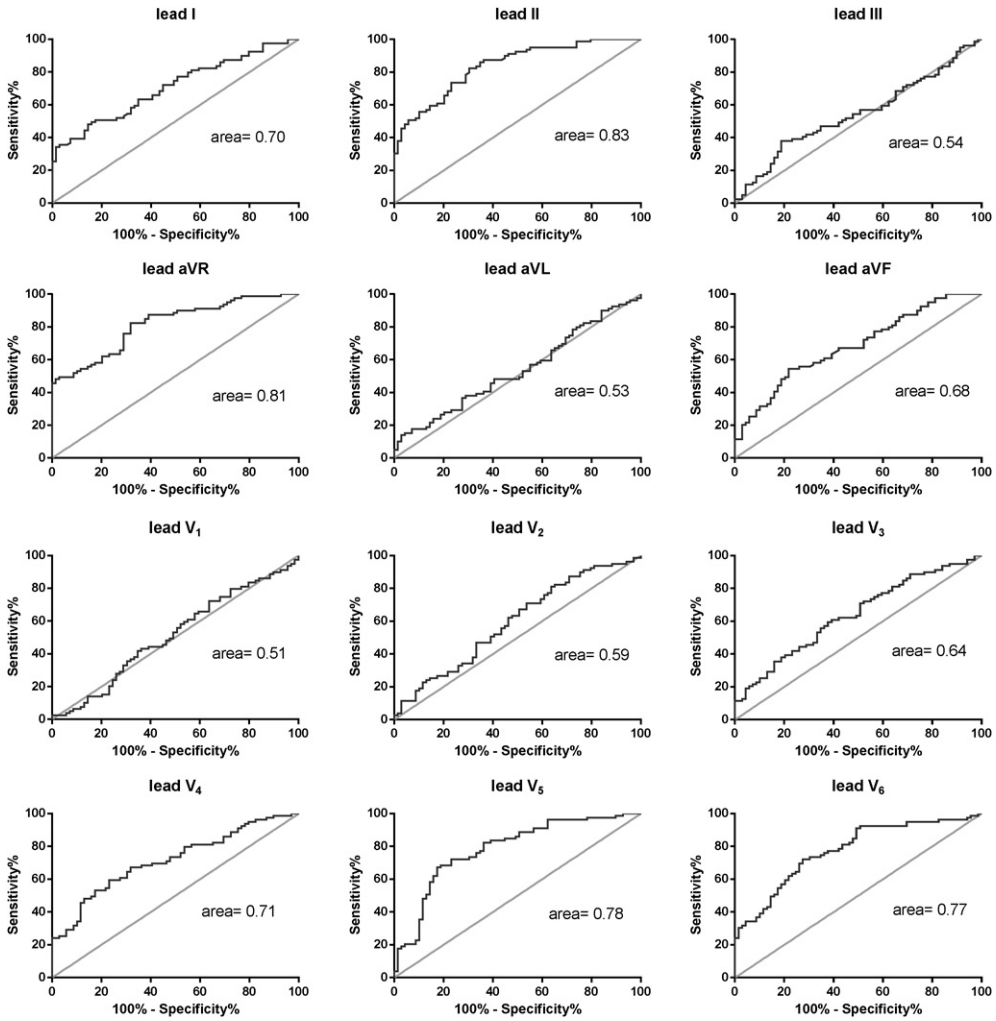

Figure 2. Receiver–operator characteristic curves for beat-to-beat QTV in the 12-lead ECG, distinguishing MI patients from healthy subjects.

A significant inverse relation between log-transformed QTV and T-wave amplitude in 12-lead ECG was observed in healthy subjects ($r^2 = 0.37$, $p < 0.0001$) and MI patients ($r^2 = 0.22$, $p < 0.0001$), see figures 4(a) and (b), respectively.

After co-varying for the T-wave amplitude, significant between-group differences in QTV were still present ($p < 0.05$; ANCOVA). However, in several leads, QTV was no longer significantly different between healthy subjects and MI patients as indicated in figure 5.

Gender-specific comparison of QTV between healthy subjects and MI patients showed significant gender differences only in lead aVL and V2, which were not significantly different between MI patients and healthy subjects. Elevated QTV values were observed in females, primarily in the group of healthy subjects (data not shown).

Comparing HRV between healthy subjects and MI patients, significantly lower sdNN values were found in MI patients (34 ± 39 ms versus 48 ± 24 ms; $p < 0.05$) as shown in figure 6.

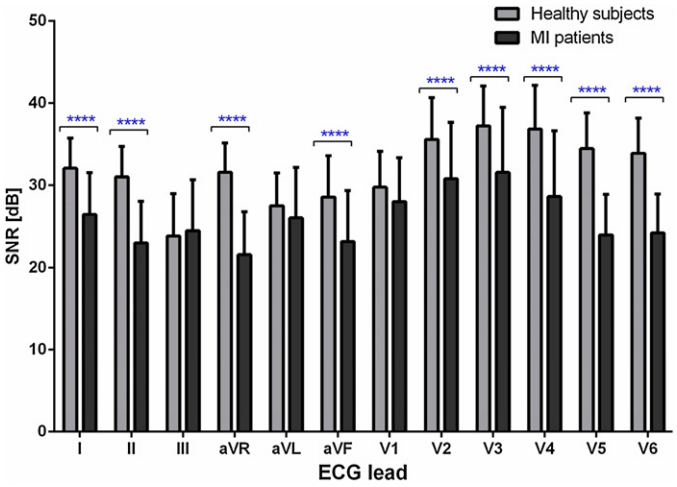

Figure 3. SNR (mean and standard deviation) in 12-lead ECG of healthy subjects and MI patients. Here, $p < 0.0001$—****.

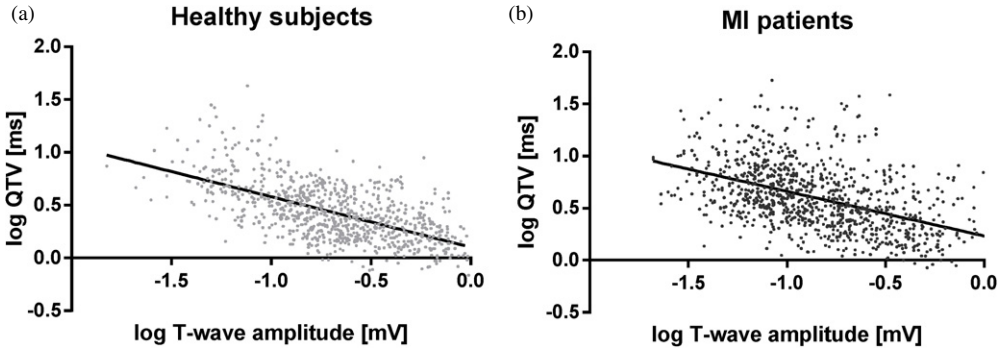

Figure 4. Relation between beat-to-beat QTV and T-wave amplitude in healthy subjects (a) and MI patients (b).

Table 1. Ranking of the 12 standard ECG leads for distinguishing MI patients from healthy subjects using QTV, based on the AUC of the ROC function.

Rank of leads	AUC	*P*-value
II	0.83	<0.0001
aVR	0.81	<0.0001
V5	0.78	<0.0001
V6	0.77	<0.0001
V4	0.71	<0.0001
I	0.70	<0.0001
aVF	0.68	<0.001
V3	0.64	<0.005
V2	0.59	>0.05
III	0.54	>0.05
aVL	0.53	>0.05
V1	0.51	>0.05

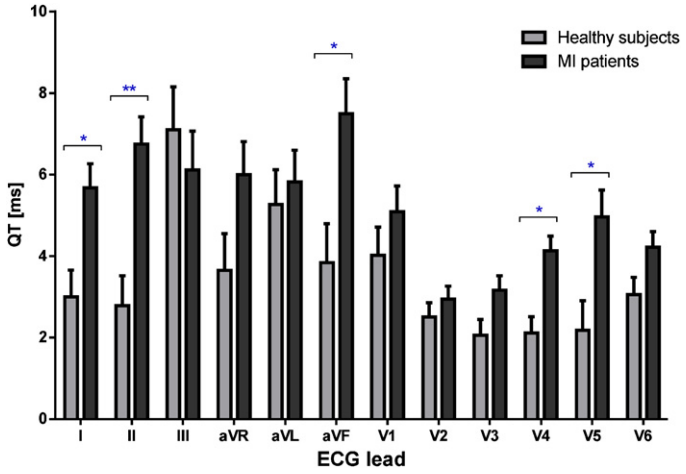

Figure 5. QT interval variability (estimated mean and standard error of the mean) in 12-lead ECG after covarying for T-wave amplitude. Here, $p < 0.001$—** and $p < 0.05$—*.

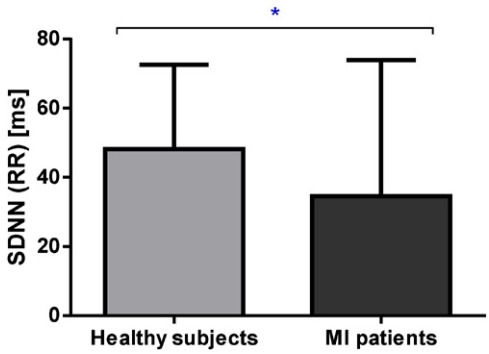

Figure 6. Heart rate variability (sdNN) between healthy subjects and MI patients expressed as mean and standard deviation. Here, $p < 0.05$—*.

4. Discussion

The main finding of our study was an increase in QTV in the 12-lead ECG of patients with MI compared to healthy subjects, which was partly independent of differences in the T-wave amplitude.

Increased QTV in MI patients has been repeatedly reported in earlier studies and was proposed as a marker of cardiac mortality (Murabayashi *et al* 2002, Vrtovec *et al* 2000, Berger *et al* 1997). Most of these studies, however, were limited to one/two lead measurements. With this study, we were able to confirm that MI patients have higher beat-to-beat QTV than healthy subjects and this was observed in half of the 12 standard ECG leads. A reason for non-significant differences in QTV in some of the leads may be the low SNR and consequently, the increase in the measurement error.

Importantly, our study clearly demonstrates the inverse relation between beat-to-beat QTV and T-wave amplitude (figure 4). This is of significance as repolarization heterogeneity may result in smaller T-wave amplitudes and increased QTV may merely be a by-product of flatter T-waves and the associated increases in measurement inaccuracies of the T-wave end,

as we have speculated previously (Hasan *et al* 2012b, Baumert *et al* 2012). Indeed, our MI patients had significantly smaller T-waves than healthy subjects (figure 1(b)) and consequently, a reduced SNR (figure 3) in most of the ECG leads. We attempted to exclude the effect of T-wave amplitude differences from our analysis. By means of analysis of covariance we were able to demonstrate a T-wave amplitude independent association between MI and QTV. Although a large part of QTV increase in MI patients could be explained by flatter T-waves, QTV was still significantly increased in leads I, II, aVF, V4 and V5. Thus, our study suggests that higher QTV in MI patients compared to healthy subjects may not be completely explained by the T-wave amplitude. Increased complexity of T-wave morphology may have contributed to QTV, but we were not able to quantify T-wave morphology in our study.

Apart from this, we have also investigated the relation between beat-to-beat QTV, location of infarction and T-wave amplitude in individual leads, but did not observe a clear association between QTV across leads and infarct location (data not shown). In addition to T-wave amplitude, rate adaptation of the QT interval is a significant contributor to QTV and may account for the group differences observed between MI patients and healthy subjects. We found significantly lower HRV in MI patients compared to the healthy subjects, which is in full agreement with many previous studies (Malik *et al* 2000, Carney *et al* 2001, Cripps *et al* 1991, Kleiger *et al* 1987). Given that HRV was reduced in MI patients, an increase in QTV through rate adaptation is implausible. On the other hand, increased sympathetic nervous system activity may have contributed to the increased QTV (Sacre *et al* 2012, Baumert *et al* 2011b) by reducing the repolarization reserve or increasing the effects of transmural dispersion in repolarization due to the arborization of sympathetic nerves, in addition to repolarization heterogeneity directly caused by tissue damage.

Our study has several limitations. The analysis was based on MI patients in comparison to healthy subjects and, therefore, our findings may not be extrapolated to post-MI risk stratification for sudden cardiac death. The average age of MI patients was significantly higher than that of healthy subjects and might have affected our results. Comorbidities (e.g. diabetes mellitus) were present in some of the patients and may have influenced our results. Similarly, we cannot exclude the possibility of medication effects on QTV. Furthermore, the ECG recordings from the PTB database were relatively short. Longer recordings might increase the consistency of the QTV measurement and thereby increase the statistical power. Moreover, there was limited patient information available in the PTB database; for example, it did not contain BMI values.

In conclusion, beat-to-beat QTV varies between leads and is inversely related to T-wave amplitude, both of which were reduced in MI patients. However, elevated beat-to-beat QTV cannot be solely attributed to flatter T-waves and thus may provide independent prognostic information.

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