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# Increased beat-to-beat T-wave variability in myocardial infarction patients

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**Abstract:** The purpose of this study was to investigate the beat-to-beat variability of T-waves (TWV) and to assess the diagnostic capabilities of T-wave-based features for myocardial infarction (MI). A total of 148 recordings of standard 12-lead electrocardiograms (ECGs) from 79 MI patients (22 females, mean age  $63 \pm 12$  years; 57 males, mean age  $57 \pm 10$  years) and 69 recordings from healthy subjects (HS) (17 females,  $42 \pm 18$  years; 52 males,  $40 \pm 13$  years) were studied. For the quantification of beat-to-beat QT intervals in ECG signal, a template-matching algorithm was applied. To study the T-waves beat-to-beat, we measured the angle between T-wave max and T-wave end with respect to Q-wave ( $\angle\alpha$ ) and T-wave amplitudes. We computed the standard deviation (SD) of beat-to-beat T-wave features and QT intervals as markers of variability in T-waves and QT intervals, respectively, for both patients and HS. Moreover, we investigated the differences in the studied features based on gender and age for both groups. Significantly increased TWV and QT interval variability (QTV) were found in MI patients compared to HS ( $p < 0.05$ ). No significant differences were observed based on gender or age. TWV may have some diagnostic attributes that may facilitate identifying patients with MI. In addition, the proposed beat-to-beat angle variability was found to be independent of heart rate variations. Moreover, the proposed feature seems to have higher sensitivity than previously reported feature (QT interval and T-wave amplitude) variability for identifying patients with MI.

**Keywords:** electrocardiogram (ECG); QT interval; repolarization; T-wave alternans; T-wave.

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## Introduction

The QT interval reflects the global electrical depolarization and repolarization of the ventricles, whereas the T-wave signifies the last remnants of ventricular repolarization. Generally, ventricular repolarization is longer in duration than depolarization. Indeed, the ventricular repolarization is reflected by the T-wave and is believed to be a predictor for the risk of ventricular arrhythmias [12, 14, 22, 23]. In addition, increased heterogeneity of ventricular repolarization is thought to be coupled with the high risk of sudden cardiac death [30, 45]. Moreover, it is found to be an independent predictor in risk stratification studies [42], useful for identifying patients with myocardial infarction (MI) [17]. Gender differences in healthy subjects (HS) have been observed through vectorcardiographic approaches in repolarization [39] and a detailed review can be found in the recent article [16].

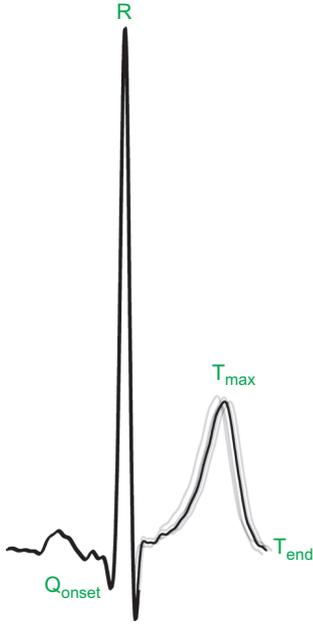
MI is one of the major causes of mortality in the world [41]. As ventricular repolarization of the myocardial cells is altered after MI [15, 46], variability in ventricular repolarization (see Figure 1 as an example) on a beat-by-beat basis has attracted significant clinical interest. However, the beat-to-beat variability of T-waves (TWV) in patients with MI has been insufficiently investigated. In addition, the relationships of existing repolarization variability indexes were incompletely explored. In particular, the performance of the repolarization variability parameters has not been compared in the earlier studies. Moreover, the effect of age and gender on TWV has not been fully elucidated.

Therefore, the purpose of this research was to study TWV along with its relationship between existing and proposed markers to assess the diagnostic capabilities for identifying MI patients.

## Methods

### Subjects

We have obtained the publicly available data from (<http://www.physionet.org>) Physikalisch-Technische Bundesanstalt (PTB) diagnostic database and used the data set [resting 12-lead electrocardiograms (ECGs)] as published previously [19]. In brief, a total of 148 recordings



**Figure 1:** Example of beat-to-beat variations of T-waves (gray) in ECG of a healthy subject. The averaged ECG is shown in black.

were included in our analysis, where 79 were from MI patients and 69 recordings were from HS. Details are given in Table 1. Note that the recordings of MI patients were acquired between 7 and 14 days after the infarction date. All the recordings were on average of 2-min duration. The sampling frequency of the ECG data was 1 kHz with a 16-bit resolution over a range of  $\pm 16.384$  mV. In this study, we have analyzed limb lead II, because this lead is found to be relatively unaffected with respect to noise and displays high T-wave amplitudes.

### T-wave variability analysis

In this study, we have used the T-wave template-matching approach, which was originally introduced by Berger and his co-workers [5] for computing beat-to-beat QT interval in ECG signal. An updated ECG pre-processing stage was incorporated in the present T-wave template-matching algorithm to increase the accuracy of finding the interval between Q-wave onset and T-wave offset [21]. In short, we have replaced the R-peak detection algorithm in T-wave template-matching approach that was proposed by Pan and Tompkins [31] by our updated R-peak detection algorithm [21]. Moreover, to handle

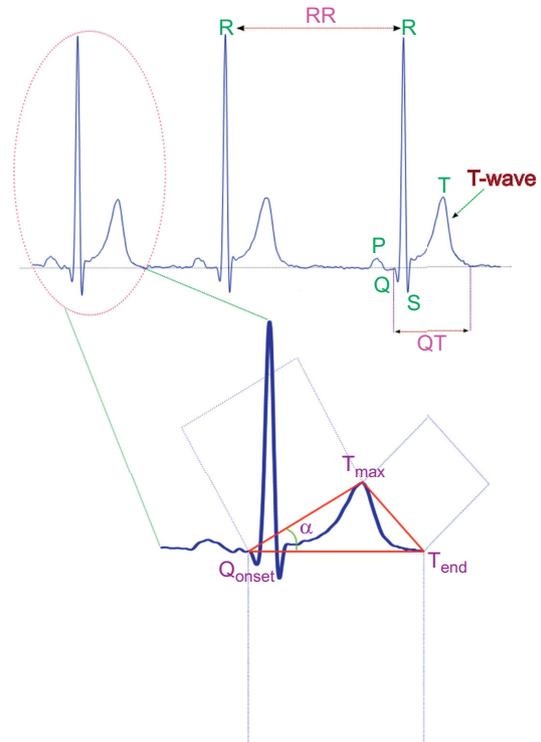
**Table 1:** Study population information.

Variable	Healthy subjects (n = 69)	MI patients (n = 79)	p-Value
Age, years	40.59 $\pm$ 14.76	58.67 $\pm$ 10.82	< 0.05
Sex, male/female	52/17	57/22	> 0.05
Hypertension, n (%)	0 (0)	27 (34.18)	< 0.05
Diabetes, n (%)	0 (0)	8 (10.13)	< 0.05
Obesity, n (%)	0 (0)	12 (15.9)	< 0.05
QRS width $\geq$ 120 ms	None	None	

the baseline wander in ECG, our pre-processing stage incorporated cubic spline interpolation for suppressing baseline wander [21]. After detecting the R-peak, the operator chooses a template of QT interval by selecting the onset of Q-wave and the offset of T-wave for one beat in the ECG signal [5]. The template-matching algorithm then determines the duration of QT interval in all other ECG beats by finding the extent to which each T-wave must be stretched or compressed in terms of time for best matching with the template beat [5]. Note that the quantification of QT intervals in all ECG beats can be biased due to the selection of longer/shorter QT template defined by the operator. Thus, comparatively, a robust estimation of beat-to-beat QT interval is achieved by considering the whole T-wave [5]. After that, we quantified the amplitude of T-wave by using the MATLAB (The Mathworks Inc., Natick, MA, USA) custom-designed software to detect the peak voltage deflection within the ST segment. In addition, we computed the standard deviation (SD) of the beat-to-beat T-wave amplitude in each recording. The Euclidean distance between Q-wave onsets and T-wave max, T-wave max and T-wave end, and Q-wave onset and T-wave end (see Figure 2) was computed as follows:

$$d(x_a, x_b) = |x_a - x_b| = \sqrt{(x_{a_1} - x_{b_1})^2 + (x_{a_2} - x_{b_2})^2}. \quad (1)$$

Here,  $d$  denotes the Euclidean distance between two points  $x_a$  and  $x_b$  on the Cartesian plane, where the points correspond to the time and voltage of 2-dimensional ECG signal, and these distances can be derived from the Pythagorean theorem. After that, the cosine angle (see Figure 2) between  $T_{max}$  and  $T_{end}$  with respect to Q-wave onset ( $\angle\alpha$ ) was computed for each beat. Finally, the SD of the beat-to-beat angles ( $\angle\alpha$ ) was computed for both groups.



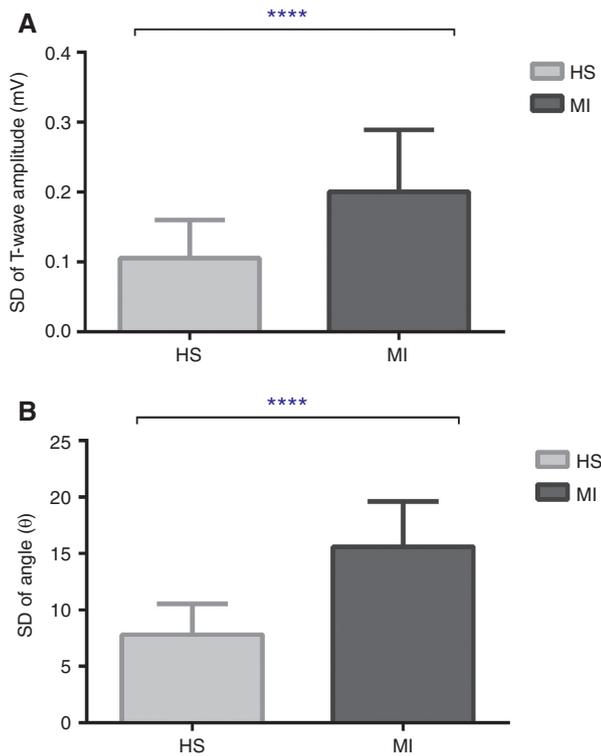
**Figure 2:** Example of beat-to-beat ECG with basic information of ECG waves. The computation of T-wave features: T-wave amplitude, angle between  $T_{max}$  and  $T_{end}$  with respect to Q-wave onset ( $\angle\alpha$ ).

## Statistical analysis

For statistical analysis, we have used GraphPad Prism 6® (GraphPad Software, Inc., La Jolla, CA, USA) and Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA). All quantitative data were expressed as mean  $\pm$  SD unless stated otherwise. Beat-to-beat TWV features and QT intervals were computed as the SD of those parameters. Student's t-test was applied to compare the T-wave features and QT characteristics between patients and HS. In addition, two-way analysis of variance (ANOVA) was applied to test the gender and age with group differences in T-wave features for both studied subjects. Moreover, Pearson's linear correlation coefficient was computed to assess the relationship between extracted T-wave-based features, heart rate variability (SD of normal RR intervals) and QT interval in MI patients in their log-transformed values. Finally, analysis of receiver-operating characteristic (ROC) curve was generated for distinguishing patients from HS. Statistical tests were considered significant if  $p < 0.05$ .

## Results

Mean and SD of the TWV are shown in Figure 3A. Higher beat-to-beat TWV amplitudes were found in MI patients compared to HS ( $0.20 \pm 0.08$  mV vs.  $0.10 \pm 0.05$  mV,



**Figure 3:** Mean and standard deviation of beat-to-beat T-wave amplitude variability (A). Mean and standard deviation of beat-to-beat angle variability in MI patients and healthy subjects (B). Here,  $p < 0.0001$ –\*\*\*\*.

$p < 0.0001$ ). The variability of angle ( $\angle\alpha$ ) was higher in MI patients compared to HS ( $15.57^\circ \pm 4.03^\circ$  vs.  $7.81^\circ \pm 2.71^\circ$ ,  $p < 0.0001$ ) and is shown in Figure 3B.

## Age comparison on beat-to-beat T-wave features

Two-way ANOVA confirmed significant group (HS: young, 17–35 years and old, 36–81 years; MI: young, 36–58 years and old, 59–81 years) differences in T-wave amplitude variability ( $p < 0.0001$ ), but did not show an age effect ( $p > 0.05$ ) as shown in Figure 4. Beat-to-beat TWV amplitudes were comparable between younger and older age populations for both MI patients ( $0.20 \pm 0.08$  mV vs.  $0.19 \pm 0.09$  mV) and HS ( $0.09 \pm 0.03$  mV vs.  $0.11 \pm 0.06$  mV). Similarly, the beat-to-beat variability of angles ( $\angle\alpha$ ) was not significantly different between younger and older subjects.

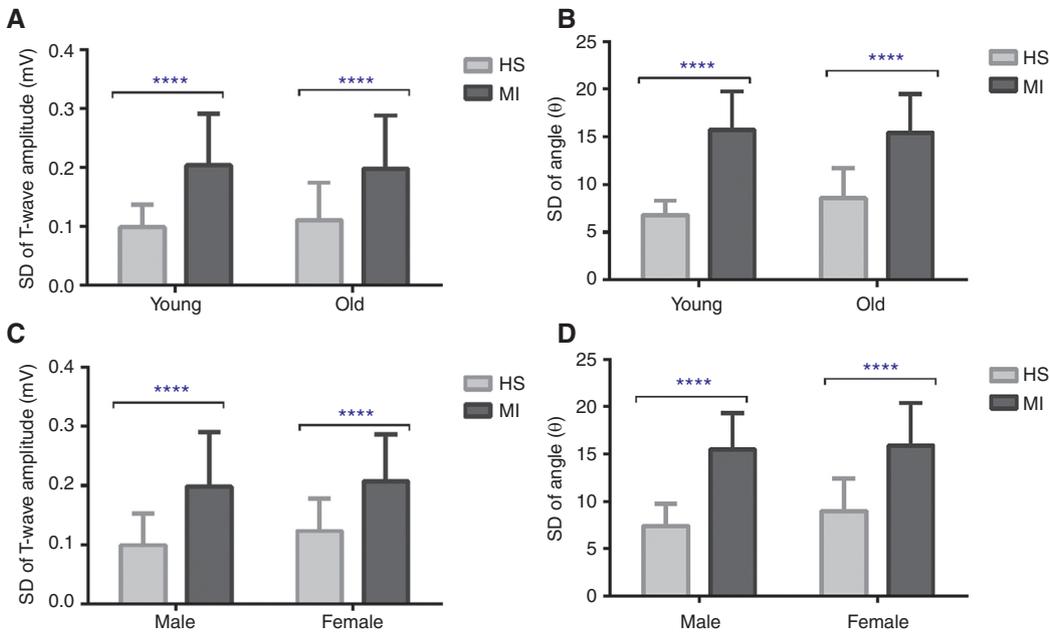
## Gender comparison on beat-to-beat T-waves features

Two-way ANOVA confirmed significant group differences ( $p < 0.0001$ ) between patients and HS in all studied T-wave based features, but no significant differences of beat-to-beat TWV amplitudes were detected between male and female in both patients ( $0.19 \pm 0.09$  mV vs.  $0.20 \pm 0.07$  mV) and HS ( $0.09 \pm 0.05$  mV vs.  $0.12 \pm 0.05$  mV) in our study (Figure 4). A similar scenario was observed in other extracted T-wave features.

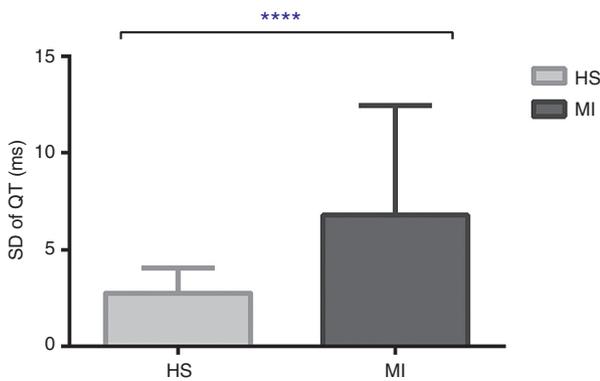
Comparing beat-to-beat QT interval variability (QTV) between MI patients and HS as shown in Figure 5, significantly higher QTV values were observed in MI patients ( $6.79 \pm 5.66$  ms vs.  $2.74 \pm 1.30$  ms;  $p < 0.0001$ ).

A significant positive correlation ( $r = 0.60$ ,  $p < 0.0001$ ) was found between beat-to-beat TWV amplitude and beat-to-beat variability of angle ( $\angle\alpha$ ) in MI patients as shown in Figure 6A. However, there was no significant relationship found between beat-to-beat QTV and variability of angle ( $r = 0.19$ ,  $p > 0.05$ ) as well as between beat-to-beat QTV and T-wave amplitude ( $r = -0.2$ ,  $p > 0.05$ ) as shown in Figure 6B and C, respectively. Moreover, the beat-to-beat angle variability was found not to be correlated ( $r = 0.14$ ,  $p > 0.05$ ) with the heart rate variations in patients with MI.

Finally, ROC curves for the classification of MI patients using beat-to-beat QTV, T-wave amplitude and angle are as shown in Figure 7. Our study shows that beat-to-beat angle variability provides better diagnostic



**Figure 4:** Mean and SD of beat-to-beat T-wave amplitude variability for younger and older subjects (A). Beat-to-beat angle variability for younger and older subjects (B). Beat-to-beat T-wave amplitude variability for male and female (C). Beat-to-beat angle variability for male and female (D). Here,  $p < 0.0001$ –\*\*\*\*.

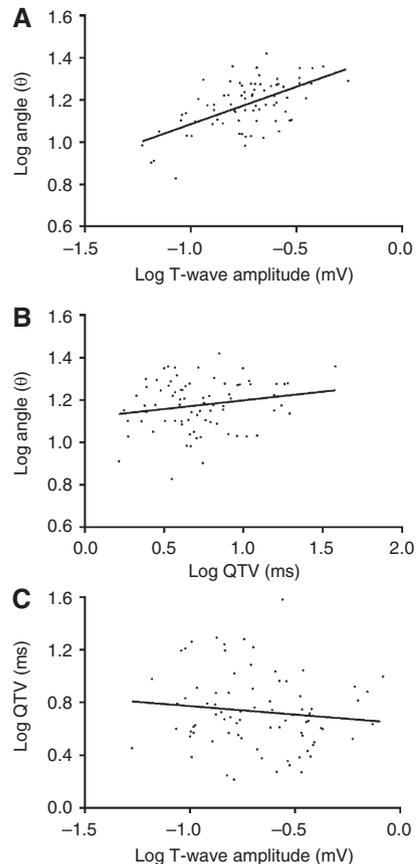


**Figure 5:** Mean and SD of beat-to-beat QT interval variability in healthy subjects and MI patients. Here,  $p < 0.0001$ –\*\*\*\*.

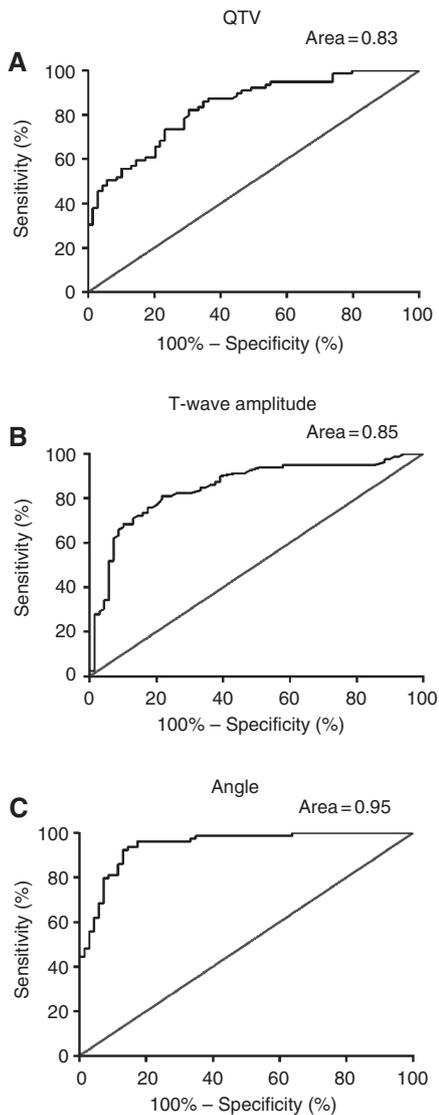
capabilities for classifying MI patients and HS (area under the curve (AUC)=0.95,  $p < 0.0001$ ) compared to beat-to-beat QTV (AUC=0.85,  $p < 0.0001$ ) and beat-to-beat TWV amplitude (AUC=0.83,  $p < 0.0001$ ).

## Discussion

The main finding of our study is an elevated beat-to-beat TWV in patients with MI compared to HS. Moreover, there was no significant effect of age and gender on extracted beat-to-beat TWV features in both studied groups. In



**Figure 6:** Relation between beat-to-beat variability of T-wave amplitude and angle (A), beat-to-beat variability of QT and angle (B) and beat-to-beat variability of QT and T-wave amplitude (C).



**Figure 7:** Receiver-operator characteristic curves for beat-to-beat QTV (A), T-wave amplitude (B) and measured angle (C) for distinguishing MI patients from healthy subjects.

addition, the proposed beat-to-beat angle variability may have the diagnostic power for identifying patient group. Furthermore, the proposed beat-to-beat angle variability is found not be influenced by heart rate variations in MI patients.

Our study confirms that beat-to-beat TWV amplitude is higher in patients with MI compared to HS, which indicates that ventricular repolarization is dispersed in MI patients [32, 43, 44]. Increased TWV has also been reported in multicenter automatic defibrillator implantation trial II (MADIT II) patients [10], in Chagas disease patients [34] and in dilated cardiomyopathy patients [40]. Periodic TWV amplitude was also observed in several studies through studying T-wave alternans [7, 8, 20, 26, 29, 37]. Although

our study did not aim for detecting T-wave alternans in MI patients due to the technical challenges associated with it [1, 24, 25], it appears that TWV may be employed in future studies as a more general marker of ventricular repolarization liability and potentially as a predictor for pro-arrhythmic risk.

Similarly, our study demonstrates that the beat-to-beat angle variability is higher in patients with MI compared to HS. These findings demonstrate increased TWV in MI patients. Indeed, the quantification of the TWV and T-wave morphology might be influenced to some degree because of the restriction of appropriate delimitation of repolarization waves in ECG [3, 11].

### Age comparison

In this study, we did not find significant difference in extracted T-wave features between younger and older age groups in patients with MI as well as in HS. This finding is somewhat in contrast with the observation of one study on patients with chronic heart failure (CHF), where elevated temporal repolarization variability was reported only in an elderly (age  $\geq 65$  years) patient group than age-matched healthy controls [33]. Note that in that study, the repolarization variability was investigated through the  $T_{\text{peak}} - T_{\text{end}}$  interval and found significant differences in the mean value of  $T_{\text{peak}} - T_{\text{end}}$ . Nevertheless, no significant differences were observed between younger and middle-age subjects in CHF and healthy controls [33], which shows partial agreement with our finding. Moreover, our study demonstrates that there is a significant difference in TWV between MI patients and HS individually in younger and older groups, which is in line with the previous study on patients with ventricular tachyarrhythmia compared to control subjects [38].

### Gender comparison

We have observed no effect of gender on TWV. Our observations are in keeping with previously reported repolarization variability findings [19]. In addition, our study demonstrates that there are no significant differences in T-wave features found between male and female for MI patients and HS. But, three earlier studies reported that T-wave amplitude is somewhat higher in men compared to women in normal population [6, 13, 35]. However, our study shows the significant group (MI patients and HS) differences of beat-to-beat extracted T-waves between male and female populations.

## QT interval variability

In our study, we have observed elevated beat-to-beat QTV in patients with MI compared to HS, which is in full agreement with several earlier studies [9, 19, 27, 36]. However, the underlying mechanisms of higher QTV in MI patients are not completely understood. Increased sympathetic outflow to the ventricles following MI may be partly responsible for increased QTV [4, 28]. Small T-waves may contribute to low signal-to-noise ratios and artificially increased QTV [18, 19].

## Relation between the variability of QT, T-wave amplitude and angle

Studying beat-to-beat QTV, T-wave amplitude and angle, we have observed that beat-to-beat angle variability has a significant positive correlation with beat-to-beat TWV amplitude. This relation indicates that the angle can fluctuate due to the variation of T-wave amplitude. Moreover, the variation of beat-to-beat angle can also be influenced to some extent due to the limited methodological accuracy of T-wave end-point detection [11]. Because, the T-wave end point is not always perfectly laid on the iso-electric line of the ECG signal, which may add variations for the measurement of beat-to-beat angle. However, no significant positive correlation between beat-to-beat QTV and beat-to-beat angle variability was noticed. This observation suggests that the beat-to-beat angle variability may not associate completely with the beat-to-beat QTV in patients with MI. Similarly, no significant inverse correlation was reported between beat-to-beat QTV and T-wave amplitude; nevertheless, the correlation value was observed in the negative trend, which is somewhat in agreement with our previous findings [19]. However, our study shows that the beat-to-beat angle variability may have higher diagnostic power than QT and T-wave amplitude variabilities for distinguishing MI patients from HS.

## Relation between the variability in heart rate and angle

Considering the relationship between heart rate variability and angle variability, we have observed that the proposed angle variability was not affected by heart rate variations in patients with MI. Therefore, this study suggests that the proposed angle variability may be independent of heart rate variations, which is in agreement with one of the previous studies [2].

## Limitations of the study

Among several limitations, one of the main limitations of our study was found to be significantly higher average age of patients with MI compared to HS, which may have some effect on our results, requiring further study. In addition, the younger and older age ranges were different between MI patients and HS in the available data, which might influence the age comparison results. Moreover, the comparison of age and gender effect between the HS and MI patients was made in a small cohort of subset patients, where the large subset size of data may enhance the statistical results. Secondly, in our data set, several MI patients had some comorbidities (such as diabetes, obesity and hypertension), which may have an impact on our results. Thirdly, we have used relatively short ECG recordings from PTB database, whereas the data with long duration might increase the statistical power of extracted T-wave features between patients and HS. Finally, the body mass index (BMI) values were absent in the PTB database for both MI patients and HS.

## Conclusion

This study demonstrates that the beat-to-beat TWV in ECG may provide markers for identifying repolarization abnormalities in MI patients. In addition, the study shows that beat-to-beat angle variability may be independent of heart rate variations in MI patients. Further, it appears that the proposed beat-to-beat angle variability may be an alternative indicator for analyzing T-wave variability and can be utilized to identify high-risk patients through future studies. Finally, an open question for future research is to investigate all the repolarization and depolarization related parameters in the ECG signal and their relationship with performance for diagnosing MI patients.

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