Quantification of Ventricular Repolarization Fluctuations in Patients with Myocardial Infarction

Martin Schmidt[1], Robin Dunker[1], Hagen Malberg[1], Sebastian Zaunseder[2]

[1] Institute of Biomedical Engineering, TU Dresden, Dresden, Germany
[2] Faculty of Information Technology, University of Applied Science and Arts Dortmund, Dortmund, Germany

Abstract

The objective of this study was to quantify ventricular repolarization fluctuations in patients with myocardial infarction (MI) by a novel ECG waveform morphology based QT interval variability (QTV) measure. We analyzed recordings of 79 MI patients and 69 healthy control subjects included in the Physikalisch-Technische Bundesanstalt diagnostic ECG database. To characterize the QT interval waveform, we employed two-dimensional signal warping (2DSW). Based on the two-dimensional template adaptation to every beat, a novel parameter QTfluc has been developed to take into account complex QT interval's waveform fluctuations in time and amplitude. To demonstrate the power of QTfluc we (1) compared MI patients and healthy subjects and (2) examined the stability of various QTV measures including QTfluc in relation to QT interval boundary shifts. A comparison of QTfluc with standard QTV measures showed a significant improvement (effect size increased up to 60 %) in discriminating between MI patients and healthy subjects. QT interval boundary shifts showed significant less impact (by factor 10) on the stability of QTfluc in comparison to standard QTV measures. The proposed measure showed significant improved characterization of ventricular repolarization lability in MI patients. Moreover, QTfluc showed more stable characteristics and is less dependent on QT interval boarders. Further investigations will focus on the evaluation of additional datasets and the application to other quasiperiodic biosignals.

1. Introduction

QT interval variations of the surface electrocardiogram (ECG) reflect beat-to-beat fluctuations of the ventricular repolarization. Several studies have shown that temporal repolarization lability as indicated by an increased QT interval variability (QTV) is associated with cardiac mortality [1, 2]. However, measuring subtle beat-to-beat changes in QT interval remains challenging. Although novel QTV techniques have improved sensitivity and robustness [3, 4], conventional QTV measures still lack in insightful QTV description [1].

Alongside the improved QTV measurement, new techniques are able to capture the entire QT interval waveform morphology [4, 5] and thus, in contrast to standard parameters based on QT interval time and its variability, offer a new feature set for the characterization of the ventricular repolarization. However, standard QTV parameter are predominantly used in most QTV studies [1].

In this study we propose a novel ECG waveform morphology based QTV measure for the characterization of the ventricular repolarization lability and employ it in patients with myocardial infarction (MI). Based on the two-dimensional waveform characterization of every beat, a novel fluctuation parameter denoted as QTfluc has been developed. QTfluc takes into account complex QT interval's waveform fluctuations instead of its length only. To demonstrate the power of QTfluc we (1) compared MI patients and healthy subjects and (2) examined the stability of QTV measures in relation to QT interval boundary shifts, i.e. we varied the interval length over which morphological changes were expected to affect QTfluc.

2. Material and Methods

2.1. Data Material

We used data originating from the Physikalisch-Technische Bundesanstalt (PTB) diagnostic ECG database [6] to measure pathophysiological variations in QT interval. The PTB database consists of 79 patients with myocardial infarction (MI) (22 female, age: 63 ± 12 years; 57 males, age: 57 ± 10 years) and 69 healthy control subjects (17 females, age: 42 ± 18 years; 52 males, age: 40 ± 13 years). Standard 12-lead ECGs were recorded at 1000 Hz during rest for about 2 min. Previous studies reported higher QTV in MI patients compared to

healthy subjects [1, 4, 7]. We performed our analysis in lead I because of the highest T wave amplitude and thus maximized signal-to-noise ratio [8].

2.2. Feature Extraction

To capture beat-to-beat waveform fluctuations in ECG, we used iterative two-dimensional signal warping (i2DSW) [4, 9]. The method is capable to account for subtle inhomogeneous shape variations of the ECG waveform in time and amplitude. i2DSW automatically generates a template beat with common features of interest (e.g. the PQ, QRS or QT intervals or amplitude related information) based on ensemble averaging of appropriate beats. To adapt the template, a 2D mesh of warping points is superimposed. By shifting warping points in time- and amplitude-direction and minimizing the Euclidean distance between template and the beat under consideration, the optimal template adaptation is calculated. From the adapted template, changes of annotated points can be tracked from beat to beat in time and amplitude. Next to the adapted template we used QT intervals and T wave amplitudes for further analysis.

We applied automatic beat rejection [4] to exclude noisy heart beats. To quantify QTV and to compare the novel QTfluc against standard parameters, we calculated standard deviations of QT intervals (SDQT) and to characterize T wave amplitude variations we calculated T wave alternans (TWA) by the approach of Nearing et al. [10].

2.3. Quantification of QT Fluctuations

In order to characterize the fluctuations of the QT interval waveform in time x and amplitude y, we developed the parameter QTfluc based on the template adapted to every beat by i2DSW. Representing every M adopted templates of length N, the Matrix $\mathbf{B_x}$ was constructed as follows:

$$\mathbf{B_x} = \begin{bmatrix} x_{1,1} - \widetilde{x}_1 & x_{1,2} - \widetilde{x}_2 & \ldots & x_{1,N} - \widetilde{x}_N \\ x_{2,1} - \widetilde{x}_1 & x_{2,2} - \widetilde{x}_2 & \ldots & x_{2,N} - \widetilde{x}_N \\ \vdots & \vdots & \vdots & \vdots \\ x_{M,1} - \widetilde{x}_1 & x_{M,2} - \widetilde{x}_2 & \ldots & x_{M,N} - \widetilde{x}_N \end{bmatrix} \tag{1}$$

$$= \begin{bmatrix} X_{1,1} & X_{1,2} & \ldots & X_{1,N} \\ X_{2,1} & X_{2,2} & \ldots & X_{2,N} \\ \vdots & \vdots & \vdots & \vdots \\ X_{M,1} & X_{M,2} & \ldots & X_{M,N} \end{bmatrix} \tag{2}$$

with

$$\widetilde{x}_n = \begin{cases} x_{\frac{N+1}{2}} & \text{for odd } N \\ \frac{1}{2}(x_{\frac{N}{2}} + x_{\frac{N}{2}+1}) & \text{for even } N \end{cases} \tag{3}$$

where $x_{m,1} \ldots x_{m,N}$ are the x coordinates for the adopted Template with $m = [1 \ldots M]$, $\widetilde{x}_n$ is the median for x coordinate with $n = [1 \ldots N]$, and $X_{m,n}$ is the median corrected x coordinate. Based on $\mathbf{B_x}$ we calculated the fluctuation matrix

$$\mathbf{F_x} = \begin{bmatrix} \sigma_{x,1} & \sigma_{x,2} & \ldots & \sigma_{x,N} \end{bmatrix} \tag{4}$$

where $\sigma_{x,n}$ represents the fluctuation of coordinate n in x calculated by

$$\sigma_{x,n} = \sqrt{\frac{1}{M-1} \sum_{i=1}^{M} (X_{i,n} - \overline{X}_n)^2} \tag{5}$$

with

$$\overline{X}_n = \frac{\sum_{i=1}^{M} X_{i,n}}{M}. \tag{6}$$

The so-called parameter QTfluc$_X$ is the median fluctuation $\sigma_{x,n}$ of the matrix $\mathbf{F_x}$ calculated as follows:

$$\text{QTfluc}_X = \widetilde{\mathbf{F_x}} = \begin{cases} \sigma_{x,\frac{N+1}{2}} & \text{for odd } N \\ \frac{1}{2}(\sigma_{x,\frac{N}{2}} + \sigma_{x,\frac{N}{2}+1}) & \text{for even } N \end{cases} \tag{7}$$

QTfluc$_X$ normalized by the mean QT interval QT_{mean} and scaled by scaling factor ω is calculated as

$$\text{QTfluc}_{X,\text{norm}} = \frac{1}{QT_{mean}} \cdot \text{QTfluc}_X \tag{8}$$

Thus, QTfluc$_X$, is a complex measure that captures the temporal beat-to-beat variability of a set of points. Analogously to the calculation of the QT fluctuations in time x by QTfluc$_X$, the calculation of the fluctuations in amplitude is done resulting in QTfluc$_Y$ and

$$\text{QTfluc}_{Y,\text{norm}} = \frac{1}{\overline{T}_{amp}} \cdot \text{QTfluc}_Y \tag{9}$$

where $\overline{T}_{amp}$ is the median T wave amplitude.

QTfluc represents the QT interval waveform fluctuations in time and amplitude and is based on the combination of QTfluc$_X$ and QTfluc$_Y$ defined as follows:

$$\text{QTfluc} = \sqrt{\text{QTfluc}_{X,\text{norm}}^2 + \text{QTfluc}_{Y,\text{norm}}^2} \tag{10}$$

We scaled the normalized QTfluc parameters by a factor of 1000 to achieve a comparable domain to non-normalized and standard parameters and thus a better visualization.

Table 1. Comparison of healthy controls and patients with myocardial infarction (MI) of the PTB diagnostic ECG database by QT interval variability and T wave alternans versus QT fluctuation in time and amplitude (median±interquartile range). Statistical evaluations were performed with a Wilcoxon rank sum test (P value) and effect size r.

	healthy	MI	P	r
SDQT, ms	2.77±2.10	3.87±4.46	<0.001	0.28
$QTfluc_X$, ms	1.38±0.87	2.46±5.86	<0.001	0.39
$QTfluc_{X,norm}$, 1	3.63±2.58	6.17±13.35	<0.001	0.37
TWA, μV	11.21±22.78	10.44±15.92	0.207	0.11
$QTfluc_Y$, μV	8.71±7.27	11.48±9.57	<0.050	0.21
$QTfluc_{Y,norm}$, 1	4.96±3.72	11.94±16.88	<0.001	0.41
QTfluc, 1	6.37±4.40	16.58±34.80	<0.001	0.45

X, time domain; Y, amplitude domain; SDQT, standard deviation of QT intervals; $QTfluc_X$, QT fluctuation in time; $QTfluc_{X,norm}$, normalized QT fluctuation in time; TWA, T wave alternans; $QTfluc_Y$, QT fluctuation in amplitude; $QTfluc_{Y,norm}$, normalized QT fluctuation in amplitude; QTfluc, normalized QT fluctuation in time and amplitude.

2.4. Statistical Analysis

SDQT, TWA, and non-normalized and normalized QTfluc parameters have been tested for standard normal distribution using the Kolmogorov-Smirnov test. Group comparisions between healthy control subjects and MI patients have been done with the Wilcoxon rank sum test and quantified by the Wilcoxon effect size r. We compared the effect sizes for fluctuations in time and amplitude with the corresponding standard measures to demonstrated the improvements in group discrimination. To analyze the stability of QTfluc and standard measures in relation to QT interval boundary shifts, we varied the end of the QT interval boarder (QTend) by ±10 ms to its original annotation. For each QTend shift we calculated the considered measures and quantified the stability by the median range and the coefficient of variation.

3. Results and Discussion

Kolmogorov-Smirnov test showed non-standard normal distribution for all analyzed parameters ($P < 0.05$). Consequently, Wilcoxon rank sum test has been used for group comparisons between healthy control subjects and MI patients. Table 1 shows the results of group discrimination for QT fluctuation parameters in time and amplitude in comparison to standard parameters. SDQT, $QTfluc_X$, $QTfluc_{X,norm}$, $QTfluc_Y$, $QTfluc_{Y,norm}$, and QTfluc show significant differences between healthy control subjects and MI patients ($P < 0.05$). QTV and QTfluc parameters are increased in Patients with MI compared to healthy subjects. Only TWA does not show this behavior ($P = 0.207$). By comparing SDQT with QTfluc in time, we found an in-
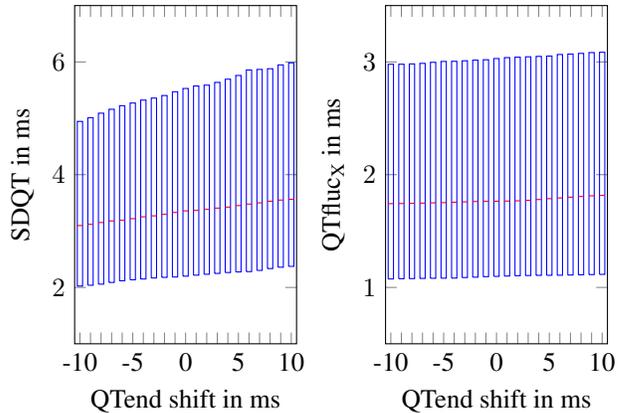

Figure 1. Standard deviation of QT intervals (SDQT) and QT fluctuation in time ($QTfluc_X$) for different delineations of the QT interval end (QTend) generated by shifting of the QTend boundary (QTend shift) in all datasets of the PTB diagnostic ECG database. Values are plotted as median and interquartile range.

creased effect size r from a small effect ($r_{SDQT} = 0.28$) to a medium effect ($r_{QTfluc_X} = 0.39$; $r_{QTfluc_{X,norm}} = 0.37$). In amplitude domain QTfluc showed higher effect sizes ($r_{QTfluc_Y} = 0.21$; $r_{QTfluc_{X,norm}} = 0.41$) compared to TWA ($r_{SDQT} = 0.11$). Calculating QTflux in time and amplitude domain showed the highest effect sizes for discriminating between both groups ($r_{QTfluc} = 0.45$). Compared to SDQT, the effect size of QTfluc showed a significant improvement group discrimination of up to 60 %.

Figure 1 shows the behavior of SDQT and $QTfluc_X$ to QTend shifts. SDQT increases the more QTend is shifted forward in time and decreases with negative QTend time shift. $QTfluc_X$ shows this behavior much less pronounced. Numerical results are shown in Table 2 by the median range and CV of the considered parameters. CV minimized from 0.039 (SDQT) to 0.004 ($QTfluc_X$) in healthy subjects and from 0.067 to 0.002 in MI patients. We found similar results for the $QTfluc_{X,norm}$ compared to SDQT. In both groups healthy subjects and MI QTfluc parameters show smaller CVs by factor 10 thus so more stable results regarding the delineation of the QTend.

Our results confirm previous findings that MI patients yield higher myocardial repolarization variability compared to healthy subjects. The introduced measure QTfluc to characterize such fluctuations in ECG shows better separation between groups. Especially in amplitude quantification, the normalization of QTfluc by T wave amplitude brings an increased group discrimination. This effect could be due to the relationship of QTV and T wave amplitude, which is an result of low signal-to-noise ratio by low T wave amplitudes [8]. Further investigations will analyze the interaction between QTfluc and the normalization in

Table 2. Effect of the QT interval end (QTend) boundary shifting on QT interval variability and QT fluctuation in healthy controls and patients with myocardial infarction (MI) of the PTB's diagnostic ECG database. QTend was shifted between -10 ms and 10 ms in 1 ms steps. Results are shown as median range and its coefficient of variation (CV).

	healthy		MI	
	median	CV	median	CV
SDQT, ms	2.61-2.95	0.0389	3.35-4.12	0.0667
$QTfluc_X$, ms	1.37-1.38	0.0038	2.45-2.47	0.0023
$QTfluc_{X,norm}$, 1	3.58-3.68	0.0093	6.14-6.29	0.0076

X, time domain; SDQT, standard deviation of QT intervals; $QTfluc_X$, QT fluctuation in time; $QTfluc_{X,norm}$, normalized QT fluctuation in time.

time and amplitude. By considering fluctuations of the entire waveform, more robust results could be obtained depending on the delineation of the QTend. This confirms the hypothesis that the ventricular repolarization process is highly complex and can be characterized much better by the analysis of the entire morphology of the QT interval than by its duration. In summary, the QTfluc parameter presented here provides a highly sensitive and at the same time more robust ECG-based measure for the characterization of ventricular repolarization. It enables the analysis of the fluctuation in time and amplitude.

4.   Conclusion

The proposed measure to quantify QT fluctuations shows significant improved characterization of ventricular repolarization lability in MI patients. Moreover, QTfluc shows more stable characteristics and is less dependent on QT interval end delineation. Further investigations will focus on the evaluation of additional datasets and the application to other quasiperiodic biosignals.

Acknowledgments

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Address for correspondence:

Martin Schmidt
Institute of Biomedical Engineering, TU Dresden
Fetscherstraße 29, 01307 Dresden, Germany
martin_schmidt@tu-dresden.de