Circadian Pattern and Sex Differences of QT/RR and T-peak-to-end/RR Curvatures and Slopes in Chronic Heart Failure Patients

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Abstract

Increased QT/RR and T_{pe}/RR slopes have been shown to be independent predictors of sudden cardiac death (SCD) when analyzed over a 24-hour ECG recording. The circadian influence on the QT/RR slope is well-known but it has never been tested on the T_{pe}/RR slope. This work studied the inter-individual variability of the curvature and slope of QT/RR and T_{pe}/RR, as well as their circadian pattern in women and men. Holter ECG recordings of 385 patients with chronic heart failure (CHF) from the "MU-SIC" database were analyzed. ECGs were delineated using a single-lead procedure over the first principal component lead derived to emphasize the T-wave. RR, QT and T_{pe} series were obtained and for each patient, a regression equation was fitted, where γ is the QT/RR or T_{pe}/RR curvature, and Δ is the slope of the regression pattern evaluated at the medium RR value. The median (IQR) slope was Δ_{QT} = 0.194 (0.11), and $\Delta_{T_{pe}}$ = 0.018 (0.04). The median (IQR) curvature was γ_{QT} = 0.993 (0.17) and $\gamma_{T_{pe}}$ = 1.000 (0.04), respectively. The circadian pattern modulated the QT/RR and T_{pe}/RR curvature and slope, with statistically significant differences between day and night for QT/RR slope. No statistically significant differences in gender were found in this study. According to the results in this work, the time of the day should be considered when using QT/RR slope for SCD risk prediction, but the T_{pe}/RR slope is less sensitive to the circadian pattern.

1. Introduction

The QT interval and its correction for heart rate (HR), QTc, are the most extensively used indices of ventricular repolarization, but other T-wave-based electrocardiogram (ECG) indices have been investigated, including the interval between the T-wave peak and the T-wave end (T_{pe}) [1]. Increased QT/RR and T_{pe}/RR slopes have been shown to be independent predictors of sudden cardiac death (SCD) in patients with chronic heart failure (CHF) [2, 3]. The majority of previous studies investigated the QT/RR and T_{pe}/RR relationships by means of fixed regressions between simultaneously measured QT, T_{pe} and RR intervals. However, the QT/RR and T_{pe}/RR patterns do not necessarily follow the same regression relationship in different subjects. A recent study proposed numerical measurements of the curvatures of QT/RR and T_{pe}/RR patterns, after compensation for QT hysteresis effects [3, 4].

The circadian pattern has shown to be a strong modulator of ventricular repolarization, with previous studies demonstrating that the slope of the regression line between QT and RR intervals is steeper during the day than at night [5], and higher in women than in men [6, 7].

In this work, we study the inter-individual variability of the curvature and slope parameters of the QT/RR and T_{pe}/RR patterns, as well as their circadian pattern in women and men with CHF.

2. Materials and Methods

2.1. Materials

Consecutive patients with symptomatic CHF corresponding to New York Heart Association (NYHA) classes II and III were enrolled in the MUSIC (MUerte Súbita en Insuficiencia Cardiaca) study, a prospective, multicenter study designed to assess risk predictors for cardiovascular mortality in ambulatory CHF patients [8]. A two- or three-lead Holter ECG sampled at 200 Hz was recorded in each patient at enrolment. No medications were withdrawn during the Holter monitoring. The study protocol was approved by institutional investigation committees and all patients gave written informed consent.

The study population consisted of 625 patients but only 385 had ECG signal in every 6-hour segment considered for the circadian analysis. Therefore, the sample population consisted of 385 patients with sinus rhythm (243 men and 107 women) aged 18 to 89 years (mean 63 ± 12
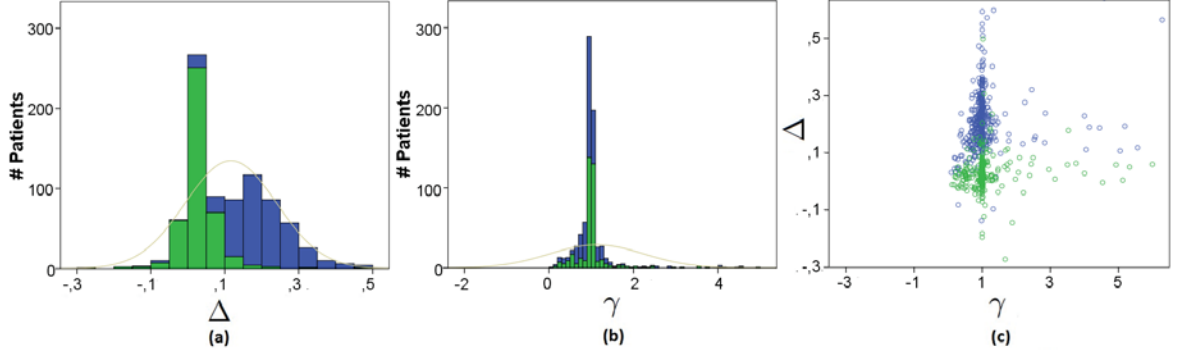
Figure 1. Histogram of slope (a) and curvature (b) values, and their scatter diagram (c) for QT/RR (blue) and T_{pe}/RR (green) regression patterns.

years).

2.2. Methods

2.2.1. ECG preprocessing and delineation

Preprocessing of the ECG signals included low pass filtering at 40 Hz to remove electric and muscle noise, cubic splines interpolation for baseline wander removal and ectopic beats detection.

Principal Component Analysis was applied over the three leads to emphasize the T-wave and improve delineation [3]. The first principal component was delineated using a single-lead technique [9] and, from the delineation marks, the RR, QT and T_{pe} interval series were obtained and subsequently interpolated at a sampling frequency f_s = 1 Hz.

2.2.2. Curvatures and slopes from ECG segments with unstable heart rate

To cope with measurements preceded by unstable HR, a previously proposed individual-specific model was used to quantify the hysteresis of QT and T_{pe} rate adaptation [10]. For this purpose, the 400-s history of RR intervals preceding each QT or T_{pe} interval measurement was obtained. Each time that the RR interval durations or HR are presented in the following text, the hysteresis compensated values are shown. Therefore, every QT or T_{pe} measurement is linked to its corresponding hysteresis-compensated RR value.

In order to quantify the curvature of the individual QT/RR and T_{pe}/RR patterns, the data of each subject were fitted with a non-linear regression function of the form [4]:

$$QT[i] = \chi + \phi(1 - RR[i]^{\gamma}), \qquad (1)$$

where $QT[i]$ and $RR[i]$ are individual QT and RR measurements, for each second "i", respectively, and γ is the numerical characteristic of the QT/RR curvature [4]. The
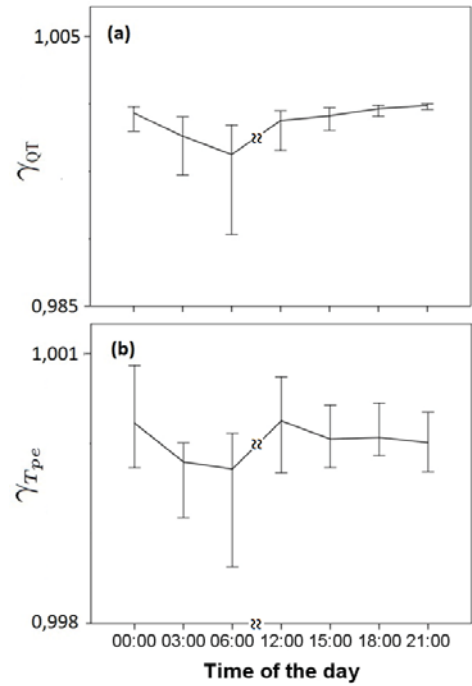

Figure 2. Circadian pattern of the curvature of QT/RR (a) and T_{pe}/RR (b).

same regression formula was applied to the T_{pe} interval series. χ and ϕ were derived from linear regression analysis and γ was optimized such that the regression leaded to the lowest residual error by using the so-called golden cut algorithm [4, 11], using the whole recording for each series of measurements in each subject independently, or, for the circadian pattern analysis, using 6-hour segments with a 3-hour overlapping.

The slope of the QT/RR and T_{pe}/RR pattern can be obtained via the derivative of equation (1) with respect to

$RR[i]$:

$$\Delta[i] = -\phi\gamma RR[i]^{(\gamma-1)} \quad (2)$$

Previously [3], Δ was shown to be predictor of SCD when evaluated at the averaged RR duration of the complete recording ($RR = \overline{RR}$). In this study, the slope was also evaluated at $RR = \overline{RR}$.

2.2.3. Statistical Analysis

Data are presented as median (IQR). In figures, data are presented as median (95% confidence interval). Day and night comparisons were performed by Mann-Whitney's U-test. Statistical significance was considered as p<0.05.

3. Results and Discussion

3.1. Inter-individual variability in 24 hours

The median (IQR) value of the curvature for QT/RR was $\gamma_{QT} = 0.993$ (0.17), and for T_{pe}/RR was $\gamma_{T_{pe}} = 1.000$ (0.04). These values were $\Delta_{QT} = 0.194$ (0.11) for QT/RR slope and $\Delta_{T_{pe}} = 0.025$ (0.004) for T_{pe}/RR slope.

The histograms of slope and curvature distributions showed non-normally distributed values (Figure 1). The curvature of QT/RR and T_{pe}/RR showed that the regression QT/RR and T_{pe}/RR patterns are not very different from a line in CHF patients, as opposed as in [4], where the curvature parameter spanned a wider range. The values of slopes showed higher inter-individual variability.

3.2. Analysis of circadian pattern

Figures 2 and 3 show the circadian modulation of the curvature and slope, respectively, for QT/RR and T_{pe}/RR, where the horizontal axis shows the central hour of the 6-hour analyzed segment. The "15:00" hour was chosen as the "day" segment and the "03:00" hour as the "night" segment, for statistical comparison.

The curvature of both QT/RR and T_{pe}/RR regression patterns changed along the time of the day, with lower values at night than during the day. However, no statistically significant values were found between day and night (Table 1).

In accordance with [6], the values of slope for QT/RR were higher during the day than at night, with these day-night differences for Δ_{QT} being statistically significant (Table 1). The slope of T_{pe}/RR did not follow a circadian pattern as clearly as the slope of QT/RR did, with flatter values at night and steeper values during the day, but not reaching the statistical significance.

Considering the value of QT/RR and T_{pe}/RR slope in predicting SCD [2,3], the peak observed at 06:00 h (Figure 3) would indicate a higher incidence of cardiac arrhythmias and SCD in the morning hours, as suggested by previous studies [12].
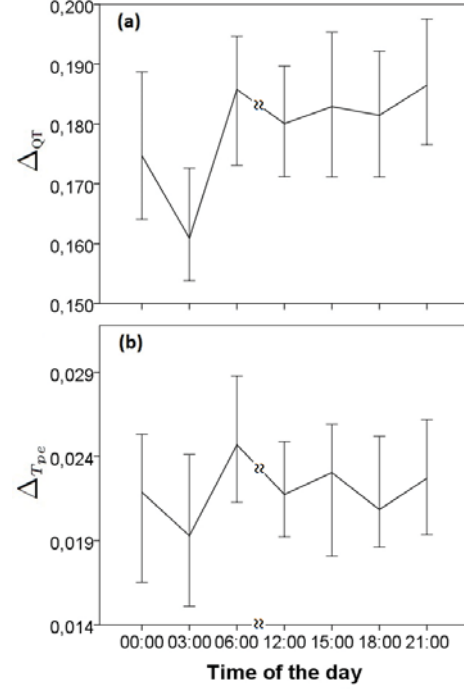

Figure 3. Circadian pattern of the slope of QT/RR (a) and T_{pe}/RR (b).

	day	night	p-value
γ_{QT}	0.999 (0.06)	0.998 (0.08)	0.130
Δ_{QT}	0.183 (0.13)	0.161 (0.11)	**0.003**
$\gamma_{T_{pe}}$	1.000 (0.02)	1.000 (0.02)	0.238
$\Delta_{T_{pe}}$	0.023 (0.04)	0.019 (0.04)	0.181

Significant differences between day and night are indicated in bold.

Data are represented as median (IQR).

Table 1. Circadian modulation of QT/RR and T_{pe}/RR curvature and slope.

3.3. Gender differences

Females had QT/RR and T_{pe}/RR regression patterns more curved than men both during the day and at night (Table 2), but this difference did not reach statistical difference (Figure 4). The slope for QT/RR regression pattern was higher in women, as suggested by [7], but without reaching significant levels. T_{pe}/RR slope was mildly steeper during the day and flatter at night in females than in males.

4. Conclusions

The curvature parameter, measured using 24-hour Holter ECG showed that CHF patients have almost linear QT/RR and T_{pe}/RR regression patterns. The circadian pattern modulated the QT/RR and T_{pe}/RR curvature and slope, with statistically significant differences between day
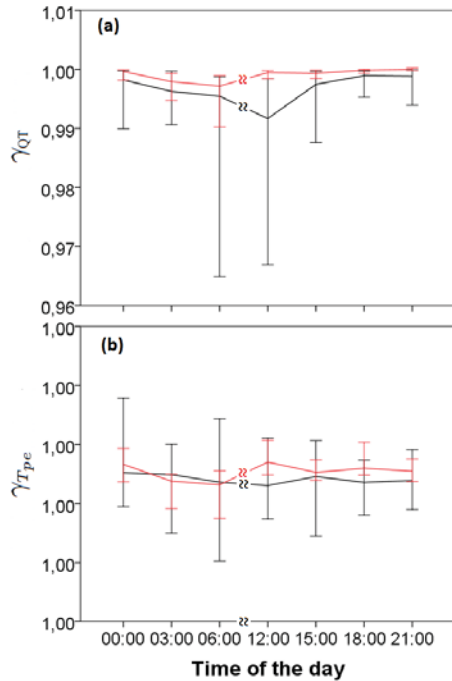
Figure 4. Circadian pattern of the curvature of QT/RR (a) and T_{pe}/RR (b) in women (black) and men (red).

	Women	Men	p-value
γ_{QT}			
Day	0.997 (0.08)	0.999 (0.05)	0.569
Night	0.996 (0.11)	0.998 (0.07)	0.959
Δ_{QT}			
Day	0.194 (0.11)	0.176 (0.13)	0.167
Night	0.167 (0.14)	0.159 (0.09)	0.331
$\gamma_{T_{pe}}$			
Day	1.000 (0.02)	1.000 (0.02)	0.330
Night	1.000 (0.02)	1.000 (0.01)	0.655
$\Delta_{T_{pe}}$			
Day	0.026 (0.06)	0.022 (0.04)	0.872
Night	0.017 (0.05)	0.020 (0.03)	0.448

Significant differences between day and night are indicated in bold.

Data are represented as median (IQR).

Table 2. Gender differences for day and night values of QT/RR and T_{pe}/RR curvature and slope.

and night for QT/RR slope. No statistically significant differences in gender were found in this study. According to the results in this work, the time of the day should be considered when using QT/RR slope for SCD risk prediction, but the T_{pe}/RR slope is less sensitive to the circadian pattern.

Acknowledgements

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