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QT/RR and T-peak-to-end/RR curvatures and slopes in chronic heart failure: Relation to sudden cardiac death☆

Julia Ramírez, MEng,[a,b,*] Pablo Laguna, PhD,[a,b] Antonio Bayés de Luna, MD, PhD,[c] Marek Malik, PhD, MD,[d] Esther Pueyo, PhD[a,b]

[a] Centro de Ingeniería Biomédica en Red (CIBER), Spain
[b] Aragón Institute of Engineering Research, IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain
[c] Institut Catalad'Ciencies Cardiovasculars, Hospital Santa Creu I Sant Pau, Barcelona, Spain
[d] St. Paul's Cardiac Electrophysiology, University of London, and Imperial College, London, UK

Abstract

Background: Previous studies investigated the QT/RR relationship by linear regressions of QT and RR intervals. However, the pattern of the QT/RR relationship is not necessarily linear. This study investigated the QT/RR and T-peak-to-end (Tpe)/RR curvatures and corresponding slopes in chronic heart failure (CHF) patients, and studied their differences between sudden cardiac death (SCD) victims and others.

Methods: Holter ECG recordings of 650 CHF patients were analyzed. RR, QT and Tpe series were obtained and for each patient, the data of each subject were fitted with a non-linear regression function of the form: $QT = \chi + \phi(1 - RR^{\gamma})$, where γ is the QT/RR curvature. The same regression formula was applied to the Tpe interval series. The slopes (dimensionless units) were calculated at the averaged RR intervals and at RR of 1 second.

Results: The median (difference between 75th and 25th percentile) of the curvature parameter was 0.226 (2.39) for QT/RR and −0.002 (3.64) for Tpe/RR in the overall sample. For the QT/RR slope, these values were 0.170 (0.12) and 0.190 (0.10) when evaluated at RR = 1 and at the averaged RR, respectively, while for the Tpe/RR slope the values were 0.016 (0.04) and 0.020 (0.04), respectively. The Tpe/RR slope showed high statistical significance for separation of SCD victims and others, particularly when evaluated at the averaged RR (median values of 0.040 vs 0.020, $p = 0.002$), but also when evaluated at RR = 1 second (0.026 vs 0.015, $p = 0.023$). Patients with values of Tpe/RR slope above 0.042 had double incidence of SCD, for the case of the slope being evaluated at RR = 1 second, and triple incidence for the case of the slope being evaluated at the averaged RR. The QT/RR slope and curvature, as well as the Tpe/RR curvature, were not different in SCD victims and in others.

Conclusions: Non-linear regression models based on curvature and slope characteristics, individually obtained for each patient, were used to characterize the QT/RR and Tpe/RR relationships. Steeper Tpe/RR slopes, obtained after adjusting for the curvature parameter, were associated with higher incidence of SCD. The curvature parameter itself did not show SCD predictive value.

Keywords: SCD; QT/RR; Tpe/RR; Regression curvature; ECG

Introduction

Sudden cardiac death (SCD) remains an important cause of mortality in patients with mild-to-moderate heart failure (HF). Although a number of SCD predictors have been proposed, such as the left ventricular ejection fraction (LVEF) [1] and T-wave alternans [2], their accuracy to identify patients at SCD risk is still weak, therefore further investigations are recommended.

The QT interval and its correction for heart rate (HR), QTc, are the most extensively used indices of ventricular

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* Corresponding author at: Aragón Institute of Engineering Research, IIS Aragón, Universidad de Zaragoza, Mariano Esquillor s/n, Lab. 4.0.04, 50018, Zaragoza, Spain.

E-mail address: Julia.Ramirez@unizar.es

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repolarization, but other T-wave-based electrocardiogram (ECG) indices have also been investigated, including the interval between the T-wave peak and the T-wave end (Tpe) [3]. The Tpe interval has been proposed by recent studies to reflect differences in the time for completion of repolarization of different ventricular regions [4,5]. Both QT and the Tpe intervals are HR dependent [6] and this dependence has also been related to arrhythmic risk [7]. Some studies concluded that increased daytime QT/RR slopes was an independent risk stratifier of all-cause mortality in patients with chronic heart failure [8], while others stated that the prognostic significance of the QT/RR slope needed prospective studies [9]. Watanabe et al. found that QT/RR slope was an independent predictor of SCD in CHF [10] and Iacoviello et al. showed how QT dynamicity improved arrhythmic risk stratification of dilated cardiomyopathy patients [11]. From a pathophysiological point of view, steeper QT/RR has been suggested to indicate decreased vagal tone and increased sympathetic activity reflecting the higher vulnerability of myocardium to arrhythmias [12]. Regarding the Tpe interval, in a recent large community-based study [13], the authors concluded that a prolonged Tpe interval was an independent risk marker of SCD, whereas in [14] the Tpe interval identified patients who died from any cause from survivors. For the best of our knowledge, there are no studies regarding Tpe/RR dynamicity in 24-hour Holter recordings as a SCD risk stratifier.

The majority of previous studies characterized the QT/RR relationship by linear regressions between simultaneously measured QT and RR intervals [15]. However, the pattern of the QT/RR relationship is not necessarily linear [16] and is known to be frequently steeper at fast HR. A recent study proposed numerical measurements of the curvatures of QT/RR patterns, after compensation for QT hysteresis effects, and evaluated such measurements in healthy subjects [17].

The present study characterized the QT/RR and T-peak-to-end (Tpe)/RR slopes and curvatures and investigated their association with SCD risk in patients with chronic heart failure (CHF).

Methods

Study population

Consecutive patients with symptomatic CHF of New York Heart Association (NYHA) classes II and III were enrolled in the MUSIC (MUerte Súbita en Insuficiencia Cardiaca) study, which was a prospective, multicenter study designed to investigate risk predictors of cardiovascular mortality in ambulatory CHF patients [18]. Patients were consecutively enrolled from the specialized HF clinics of eight university hospitals between April 2003 and December 2004. This study included patients with either depressed (<45%) or preserved (≥45%) LVEF. The latter were included if they had HF symptoms and a prior hospitalization for HF or some objective signs of HF confirmed by chest X-ray and/or echocardiography. Patients were excluded if they had recent acute coronary syndrome or severe valvular disease amenable for surgical repair. Patients with other concomitant diseases expected to reduce life-expectancy were also excluded. A two- or three-lead 24-hour Holter ECG (ELA Medical, Sorin Group, Paris, France) sampled at 200 Hz was recorded in each patient at enrollment. No medications were withdrawn during the Holter monitoring. The study protocol was approved by institutional investigation committees and all patients gave written informed consent.

Follow-up visits were conducted on an outpatient basis every 6 months, for a median of 44 months. SCD was defined as (a) a witnessed death occurring within 60 minutes from the onset of new symptoms unless a cause other than cardiac failure was obvious, (b) an unwitnessed death (<24 hours) in the absence of preexisting progressive circulatory failure or other causes of death, or (c) death during attempted resuscitation. SCD endpoint was reviewed and classified by the MUSIC Study Endpoint Committee [18].

ECG preprocessing and delineation

Preprocessing of the ECG signals was performed using custom-written software and 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 two-or-three ECG leads to emphasize the T-wave and improve delineation [19]. The first principal component was delineated using a single-lead technique [20] and, from the delineation marks, the RR, QT and Tpe interval series were obtained in a beat-to-beat basis and subsequently interpolated at a sampling frequency of 1 Hz using a fully automated method.

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 Tpe rate adaptation [21]. For this purpose, the 400-s history of RR intervals preceding each QT or Tpe 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 Tpe measurement represents the corresponding hysteresis-compensated value.

In order to quantify the curvature of the individual QT/RR and Tpe/RR patterns, the data of each subject were fitted with a non-linear regression function of the form [17]:

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

where QT[i] and RR[i] are individual QT and RR measurements (in seconds), respectively, and γ is the numerical characteristic of the QT/RR curvature [17]. The same regression formula was applied to the Tpe interval series. The optimum values of χ, ϕ and γ were obtained by minimizing the root mean square difference between the fitted and measured values of QT or Tpe, using the whole recording for each series of measurements in each subject independently.

The slope of the QT/RR and Tpe/RR pattern can be obtained via the derivative of Eq. (1) with respect to RR[i]:

$$\Delta[i] = -\phi.\gamma.RR[i]^{\gamma-1} \quad \text{(Dimensionless units)} \qquad (2)$$

Previously [17], Δ was shown to be substantially different between females and males when evaluated at RR of 1 second. In this study, the slope was evaluated at RR = 1 s and at the averaged RR duration of the complete recording $(RR = \overline{RR})$.

Statistical analysis

Two-tailed Mann–Whitney and Fisher exact tests were used for univariate comparison of quantitative and categorical data, respectively. Correlation was evaluated with Spearman's correlation coefficient since data distribution was not necessarily normal. ROC curves were used to identify the optimal cut-off point. Simultaneous maximization of sensitivity and specificity (minimum Euclidean distance from the ROC curve to the upper-left corner) was applied to select the threshold, with an area under the curve of >0.55 required for setting the classification cut-off point. Survival probability was estimated by using Kaplan–Meier methods with a comparison of cumulative events by using log-rank tests. Patients who died from non-SCD were censored at the time of death. The association of measurements with SCD endpoints was determined by univariate and multivariate Cox proportional hazard analyses. Five clinical covariates were chosen for the adjustment of multivariate Cox analysis (age, gender, LVEF, non-sustained ventricular tachycardia and NYHA class). A p-value of <0.05 was considered as statistically significant. Data were analyzed by using version 22.0 of SPSS software.

Results

The study population consisted of 650 patients with sinus rhythm (462 men and 188 women) aged 18–89 years (mean 63 ± 12 years). 82% of the patients were in heart failure NYHA class II and 55% of the patients had LVEF ≤35%.

During the 4-year follow up, 146 (22%) patients died. Of these, 119 (18%) were cardiac death (CD) victims and 27 (4%) non-CD victims. Among CD victims, 52 (8%) were categorized as SCD and 67 (10%) as deaths due to CHF progression.

Analysis of QT/RR dependence

The mean values of the curvature and slopes (evaluated at RR = 1 and at the averaged RR) for the QT interval (γ^{QT}, $\Delta^{QT}{}_{|RR=1}$ and $\Delta^{QT}{}_{|RR=\overline{RR}}$), established via Eqs. (1) and (2) for all patients were 0.364 ± 0.134, −0.027 ± 0.246 and 0.195 ± 0.005, respectively. The 25th, 50th and 75th percentiles were − 0.880, 0.226 and 1.507 for γ^{QT}, 0.112, 0.170 and 0.236 for $\Delta^{QT}{}_{|RR=1}$, and 0.146, 0.190 and 0.248 for $\Delta^{QT}{}_{|RR=\overline{RR}}$.

Table 1 shows the median (difference between 75th and 25th percentile) value of curvature and slopes in the overall sample as well as in the group of SCD victims and in the rest of patients. No statistical differences were found in median between SCD victims and in others for γ^{QT}, $\Delta^{QT}{}_{|RR=1}$ and $\Delta^{QT}{}_{|RR=\overline{RR}}$.

Table 1
Median (difference between 75th and 25th percentile) of γ^{QT}, $\Delta^{QT}{}_{|RR=1}$, $\Delta^{QT}{}_{|RR=\overline{RR}}$, γ^{Tpe}, $\Delta^{Tpe}{}_{|RR=1}$, and $\Delta^{Tpe}{}_{|RR=\overline{RR}}$ and association with SCD.

Variable	Overall sample (N = 650)	SCD victims (N = 52)	Non-SCD victims (N = 598)	p
γ^{QT}	0.226 (2.39)	−0.044 (4.30)	0.280 (2.29)	0.232
$\Delta^{QT}{}_{\|RR=1}$	0.170 (0.12)	0.151 (0.12)	0.171 (0.12)	0.170
$\Delta^{QT}{}_{\|RR=\overline{RR}}$	0.190 (0.10)	0.190 (0.10)	0.190 (0.10)	0.756
γ^{Tpe}	−0.002 (3.64)	−0.002 (4.32)	−0.002 (3.47)	0.671
$\Delta^{Tpe}{}_{\|RR=1}$	0.016 (0.04)	0.026 (0.05)	0.015 (0.04)	**0.023**
$\Delta^{Tpe}{}_{\|RR=\overline{RR}}$	0.020 (0.04)	0.040 (0.05)	0.019 (0.04)	**0.002**

Significant differences are indicated in bold.

Table 2 shows the correlation coefficients between the parameters under study and the HR-derived variables. No correlation was found between γ^{QT} and $\Delta^{QT}{}_{|RR=1}$ (added one at a time) and median HR or maximum HR. $\Delta^{QT}{}_{|RR=\overline{RR}}$, on the contrary, showed a statistical significant correlation with median HR and maximum HR. No correlation was found between γ^{QT}, $\Delta^{QT}{}_{|RR=1}$ or $\Delta^{QT}{}_{|RR=\overline{RR}}$ (added one at a time) and HR range.

Mann–Whitney U-test showed that increments in $\Delta^{QT}{}_{|RR=\overline{RR}}$ were not associated with increased female population (p = 0.058).

Analysis of T_{pe}/RR dependence

The same procedure was repeated for Tpe/RR curvature and slope parameters. The mean values of the curvature and slopes (evaluated at RR = 1 and at the averaged RR) for the Tpe interval (γ^{Tpe}, $\Delta^{Tpe}{}_{|RR=1}$ and $\Delta^{Tpe}{}_{|RR=\overline{RR}}$), established via Eqs. (1) and (2) for all patients were 0.797 ± 0.237, 0.906 ± 0.719 and 0.025 ± 0.002, respectively. The 25th, 50th and 75th percentiles were −1.363, −0.002 and 2.271 for γ^{Tpe}, 0.002, 0.016 and 0.040 for $\Delta^{Tpe}{}_{|RR=1}$, and 0.005, 0.020 and 0.042 for $\Delta^{Tpe}{}_{|RR=\overline{RR}}$.

No statistical differences were found between the median value of γ^{Tpe} in SCD victims and in others. Statistical differences were, however, found in median for $\Delta^{Tpe}{}_{|RR=1}$ and $\Delta^{Tpe}{}_{|RR=\overline{RR}}$ (Table 1).

No correlation was found between γ^{Tpe} and $\Delta^{Tpe}{}_{|RR=\overline{RR}}$ (added one at a time) and median HR. $\Delta^{Tpe}{}_{|RR=1}$, on the contrary, showed a statistical significant correlation with median HR. No correlation was found between γ^{Tpe}, $\Delta^{Tpe}{}_{|RR=1}$ or $\Delta^{Tpe}{}_{|RR=\overline{RR}}$ (added one at a time) with maximum HR or HR range (Table 2).

Fisher exact test showed that there were more women in the $\Delta^{Tpe}{}_{|RR=\overline{RR}} \geq 0.042$ group as compared to the $\Delta^{Tpe}{}_{|RR=\overline{RR}} < 0.042$ group (35% vs 27%, p = 0.048).

Fig. 1 shows the Tpe/RR regression pattern of an SCD victim (a) and of a survivor (b), whose slopes approximately coincide with the median values of each subgroup. A cut-off

Table 2
Correlation of γ^{QT}, $\Delta^{QT}_{|RR=1}$, $\Delta^{QT}_{|RR=\overline{RR}}$, γ^{Tpe}, $\Delta^{Tpe}_{|RR=1}$, and $\Delta^{Tpe}_{|RR=\overline{RR}}$ with median HR, maximum HR and HR range.

Variable	Median HR		Maximum HR		HR range	
	Spearman's correlation coefficient	p	Spearman's correlation coefficient	p	Spearman's correlation coefficient	p
γ^{QT}	−0.042	0.290	0.025	0.523	0.039	0.327
$\Delta^{QT}_{\|RR=1}$	0.016	0.683	0.016	0.679	−0.025	0.526
$\Delta^{QT}_{\|RR=\overline{RR}}$	0.325	$<\mathbf{10^{-17}}$	0.184	$<\mathbf{10^{-4}}$	0.026	0.518
γ^{Tpe}	−0.044	0.267	0.062	0.119	0.064	0.105
$\Delta^{Tpe}_{\|RR=1}$	−0.104	**0.008**	−0.020	0.606	−0.021	0.595
$\Delta^{Tpe}_{\|RR=\overline{RR}}$	0.015	0.713	0.032	0.414	−0.018	0.646

Significant differences are indicated in bold.

point of 0.042 showed to be optimal for both $\Delta^{Tpe}_{|RR=1}$ and $\Delta^{Tpe}_{|RR=\overline{RR}}$ (Fig. 2). Survival rate free of SCD was significantly higher in patients with $\Delta^{Tpe}_{|RR=1} < 0.042$ ($p = 0.024$) and in patients with $\Delta^{Tpe}_{|RR=\overline{RR}} < 0.042$ ($p = 0.002$). Univariate and Multivariate Cox analysis revealed that $\Delta^{Tpe}_{|RR=1} \geq 0.042$ and $\Delta^{Tpe}_{|RR=\overline{RR}} \geq 0.042$ outcomes were associated with SCD (Table 3). Multivariate Cox analysis was adjusted for gender, which was the only covariate statistically associated with SCD (hazard ratio of 2.32; 95% confidence interval (CI) 1.13–4.77, $p = 0.023$). Multivariate analysis showed that the time to SCD event was approximately doubled among patients with $\Delta^{Tpe}_{|RR=1} < 0.042$ in comparison to those with $\Delta^{Tpe}_{|RR=1} \geq 0.042$ and tripled among patients with $\Delta^{Tpe}_{|RR=\overline{RR}} < 0.042$ in comparison to those with $\Delta^{Tpe}_{|RR=\overline{RR}} \geq 0.042$ (Table 3). The Kaplan–Meier curves of SCD probability for $\Delta^{Tpe}_{|RR=1} < 0.042$ and $\Delta^{Tpe}_{|RR=1} \geq 0.042$ and for $\Delta^{Tpe}_{|RR=\overline{RR}} < 0.042$ and $\Delta^{Tpe}_{|RR=\overline{RR}} \geq 0.042$ patients were statistically different ($p = 0.012$, Fig. 3a and $p < 0.001$, Fig. 3b, respectively).

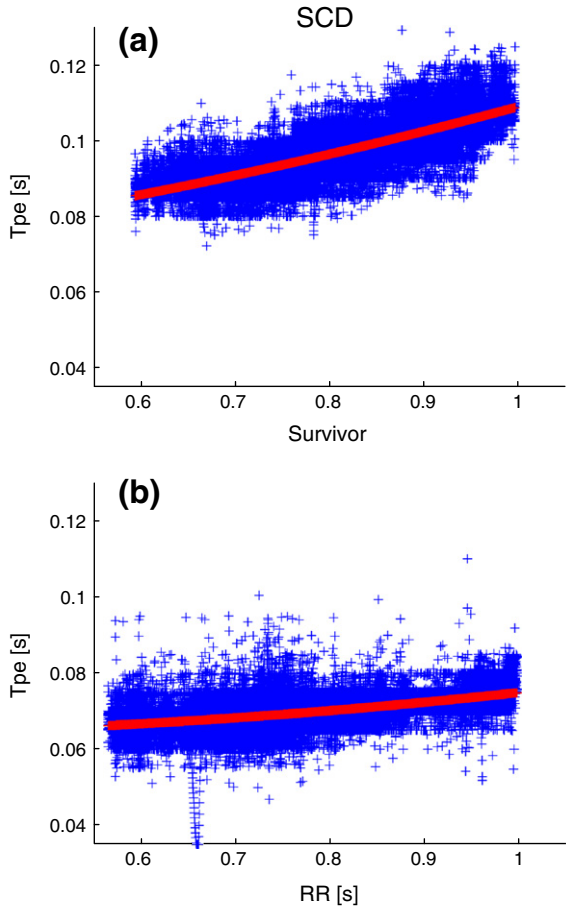

Fig. 1. Tpe/RR regression pattern (blue) and the fitted regression curvature (red) of an SCD victim (a) and of a survivor (b). (Color illustration online.)

Discussion

In this study, a fully automated method was presented to analyze the slopes and curvatures of QT/RR and Tpe/RR regression patterns from 24-hour ambulatory ECG recordings of CHF patients. QT/RR slope and curvature as well as Tpe/RR curvature were unrelated to SCD outcome. On the contrary, increased Tpe/RR slope appeared, in a univariate and multivariate analysis, to be statistically significantly associated with SCD in CHF patients. When evaluated at the averaged RR interval, the Tpe/RR slope appeared to be linked to SCD with higher statistical significance than when

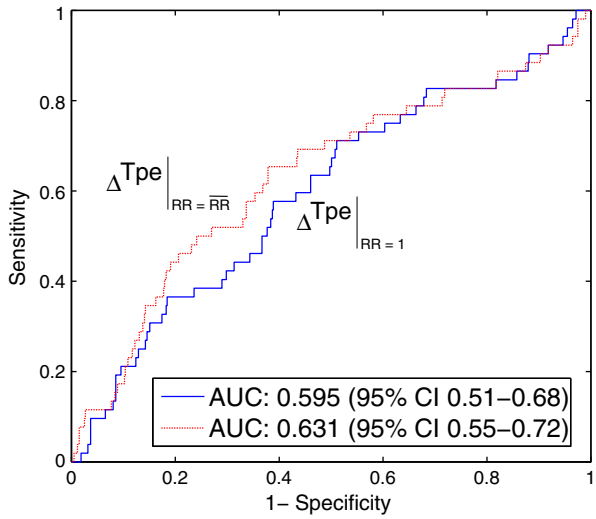

Fig. 2. ROC curve of $\Delta^{Tpe}_{|RR=\overline{RR}}$ (red) and $\Delta^{Tpe}_{|RR=1}$ (blue) association with SCD events during follow-up. The final chosen cut-off values were 0.042 for both $\Delta^{Tpe}_{|RR=\overline{RR}}$ and $\Delta^{Tpe}_{|RR=1}$ parameters. (Color illustration online.)

Table 3
Association of $\Delta^{Tpe}_{|RR=1}$ and $\Delta^{Tpe}_{|RR=\overline{RR}}$ with sudden cardiac death (SCD) in univariate and multivariate Cox analysis, after adjusting for significant clinical covariates.

Variable	Univariate Cox analysis	p	Multivariate Cox analysis	p
$\Delta^{Tpe}_{\|RR=1}$	2.03 (1.16–3.58)	**0.014**	2.15 (1.04–4.41)	**0.008**
$\Delta^{Tpe}_{\|RR=\overline{RR}}$	2.82 (1.64–4.86)	**$<10^{-3}$**	3.07 (1.77–5.30)	**$<10^{-4}$**

Significant differences are indicated in bold.

evaluated at RR = 1 s. Higher values of the Tpe/RR slope were associated with higher risk of suffering from SCD (double when evaluated at RR = 1 s and triple when evaluated at RR = $\overline{RR}$). To the best of our knowledge, a relationship between QT/RR and Tpe/RR curvatures and slopes and outcome in CHF patients has not been reported before.

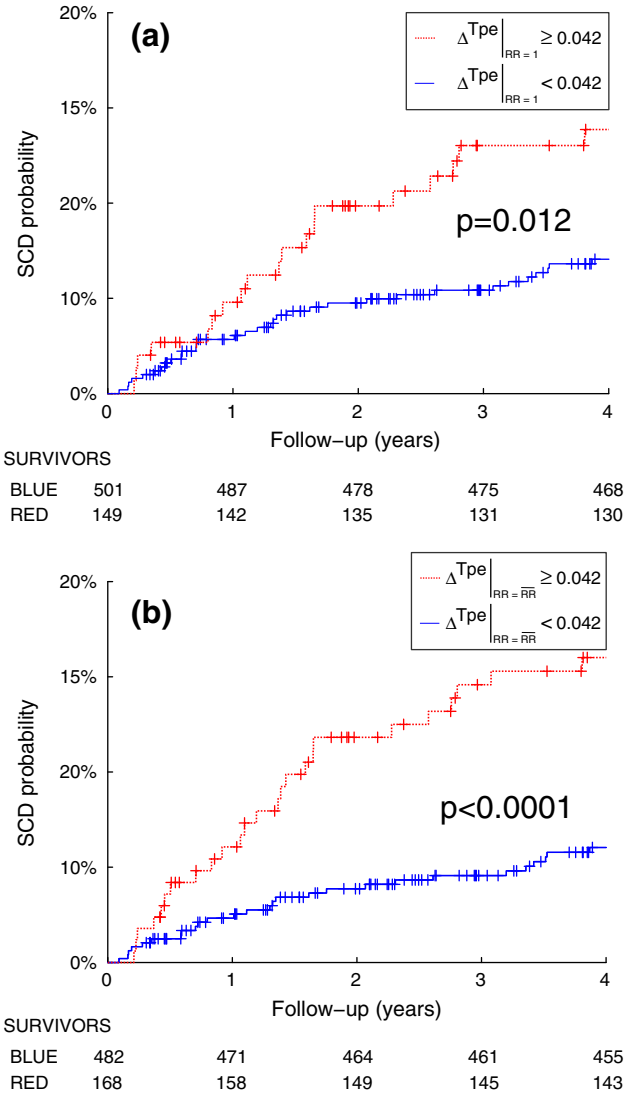

Fig. 3. Kaplan–Meier curves of SCD probability corresponding to $\Delta^{Tpe}_{|RR=1}$ in top panel (a) and to $\Delta^{Tpe}_{|RR=\overline{RR}}$ in bottom panel (b). Crosses show censored cases. Numbers of patients in each group at individual yearly interval are shown below the graphs. (Color illustration online.)

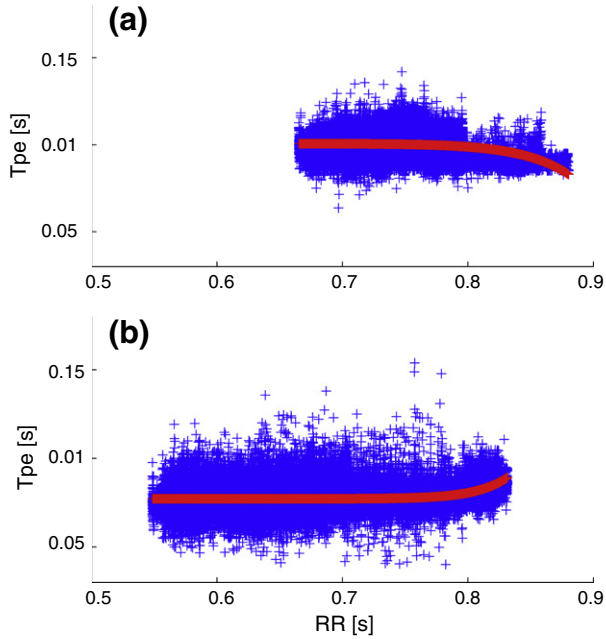

Fig. 4. Tpe/RR regression pattern (blue) and the fitted regression curvature (red) with negative (a) and positive (b) slope. (Color illustration online.)

Larger variability of Tpe/RR slopes was observed with values of $\Delta^{Tpe}_{|RR=1}$ as compared to values of $\Delta^{Tpe}_{|RR=\overline{RR}}$. A possible reason for this variability is presented in Fig. 4, which shows an example of a Tpe/RR regression pattern with a very negative slope (patient who died due to CHF progression) (when evaluated at RR = 1 s) (a) and with a very positive slope (survivor) (also when evaluated at RR =1) (b). Parameters from Eq. (1) have been optimized in order to minimize the residual error by fitting the Tpe and RR data. If there are no Tpe data in RR = 1, Tpe values must be extrapolated for the analysis, thus, due to the curvature, producing higher absolute values of the slope when evaluated at RR = 1 s than when evaluated at the averaged RR interval. Although evaluation of the slope at RR = 1 s allows assessing this characteristic of the Tpe/RR patterns at the same heart rate for all patients, the recordings of many patients of this study did not contain RR values around 1 s, which led to substantial extrapolation of the $\Delta^{Tpe}_{|RR=1}$ measurements.

The SCD predictive capacity of $\Delta^{Tpe}_{|RR=\overline{RR}}$ cannot be attributed to HR-related differences, since correlation analysis between $\Delta^{Tpe}_{|RR=\overline{RR}}$ and median HR, maximum HR and HR range confirmed that only very weak relations exist. $\Delta^{Tpe}_{|RR=1}$ was correlated to the median HR. As explained above, RR values around 1 s were needed to obtain reliable measurements of $\Delta^{Tpe}_{|RR=1}$, thus adding a dependency on heart rate.

The results obtained in this study show that the mean value of the QT/RR curvature parameter (0.364 ± 0.134) is smaller than the mean value of QT/RR curvature parameter obtained in [17] for both women (0.544 ± 0.661) and men (0.797 ± 0.706), suggesting that QT/RR regression patterns in CHF patients are more curved than in healthy subjects.

Regarding the QT/RR slope, the results obtained in this study show that CHF patients have steeper QT/RR regression patterns than healthy subjects, indicating faster QT adaptation to changes in RR. Malik et al concluded in [17] that QT/RR patterns in women were not only steeper than those in men but also more curved. We found borderline association ($p = 0.058$) between the continuous variable of QT/RR pattern slope (when evaluated at $RR = \overline{RR}$) and gender, with higher values of $\Delta^{QT}{}_{|RR=\overline{RR}}$ being associated with female gender, as shown in [17]. Regarding Tpe/RR regression pattern, we found a sex-dependent relationship in the dichotomized Tpe/RR slopes, with $\Delta^{Tpe}{}_{|RR=\overline{RR}} \geq 0.042$ and $\Delta^{Tpe}{}_{|RR=1} \geq 0.042$ both being associated with female gender, in concordance with the results published in [22], where linear Tpe/RR slopes were significantly steeper in women than in men. However, before dichotomization, the continuous Tpe/RR slope variable was not statistically separable by gender.

Regarding SCD prediction, we did not find any significant association between QT/RR slopes and SCD, as opposed to the results reported in [11] and [12]. Steeper Tpe/RR slopes showed a strong association with SCD. We are not able to compare our Tpe/RR slope results with any other work because, as far as we are aware, the association of Tpe dynamicity with SCD has not been reported before.

Our results are consistent with a previous investigation [23], which evaluated the index $\Delta\alpha$ [24] in the same population. The Tpe/RR slope computed at the averaged RR interval may estimate $\Delta\alpha$ differently to the original definition [24]. Larger heterogeneities in repolarization restitution within the ventricles could lead to increased Tpe/RR slopes and could possibly contribute to increased arrhythmic risk. However, further studies are needed to confirm the value of the Tpe/RR slope variable as SCD risk stratifier and to elucidate its underlying mechanisms.

Limitations

This study used fully automated ECG measurements that are likely to suffer imprecision especially when applied to abnormal ECGs in CHF patients (see the outliers in Figs. 1 and 4). Until detailed visual inspection is used to verify the measurements, the results can only be considered preliminary. A retrospective study of this kind may only be hypothesis generating. Prospective studies are needed to verify that the observations presented here have a role in SCD prediction in CHF patients. The definition of SCD used in this study was the same as in other similar studies but might not be uniform in respect of the underlying pathophysiology. Both tachycardia and bradycardia cases were likely included. The number of SCD victims was relatively low not only in comparison with survivors but also with victims of other modes of death. This might have imposed some limitations on the statistical comparisons. Future studies may include the splitting of the data into training and test sets so that the thresholds developed in the training set could be evaluated in the test set. Also, further studies may aim at separately analyzing patients with and without ventricular conduction defects to assess potential differences in their QT/RR and Tpe/RR regression patterns.

Conclusions

A non-linear regression model based on curvature and slope characteristics, individually obtained for each patient, was used to characterize the QT/RR and Tpe/RR relationships. Steeper Tpe/RR slopes, obtained after adjusting for the curvature parameter, were associated with higher incidence of SCD. The curvature parameter itself did not show SCD predictive value.

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[10] Watanabe E, Arakawa T, Uchiyama T, Tong M, Yasui K, Takeuchi H, et al. Prognostic significance of circadian variability of RR and QT intervals and QT dynamicity in patients with chronic heart failure. Heart Rhythm 2007;4(8):999–1005.
[11] Iacoviello M, Forleo C, Guida P, Romito R, Sorgente A, Sorrentino S, et al. Ventricular repolarization dynamicity provides independent prognostic information toward major arrhythmic events in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2007;50(3):225–31.
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[23] Ramírez J, Mincholé A, Bolea J, Laguna P, Pueyo E. Prediction of sudden cardiac death in chronic heart failure patients by analysis of restitution dispersion. Comput Cardiol 2013;40:1–4.
[24] Mincholé A, Pueyo E, Rodríguez JF, Zacur E, Doblaré M, Laguna P. Quantification of restitution dispersion from the dynamic changes of the T wave peak-to-end, measured at the Surface ECG. IEEE Trans Biomed Eng 2011;58:1172–82.

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Erratum

Erratum: QT/RR and T-peak-to-end/RR curvatures and slopes in chronic heart failure: Relation to sudden cardiac death

Julia Ramírez, MEng,[a,b] Pablo Laguna, PhD,[a,b] Antonio Bayés de Luna, MD, PhD,[c] Marek Malik, PhD, MD,[d] Esther Pueyo, PhD[a,b]

[a] Centro de Investigación Biomédica en Red (CIBER), Spain
[b] Aragón Institute of Engineering Research, IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain
[c] Institut Català de Ciències Cardiovasculars, Hospital Santa Creu i Sant Pau, Barcelona, Spain
[d] St. Paul's Cardiac Electrophysiology, University of London, and Imperial College, London, UK

This erratum is published due to an editing misunderstanding in the final submission of the manuscript by Ramirez et al (J Electrocardiol. 2014 Nov-Dec;47(6):842-8), the printed version included a number of errors and inconsistencies that are reported in this erratum, corresponding to one Affiliation, one paragraph in the Introduction section, two paragraphs in the Discussion section and fifteen references in the Bibliography list. Below we provide the location of each of them within the original article and the corrected final edition:

- Affiliation [a] should read:

[a] Centro de Investigación Biomédica en Red (CIBER), Spain

- Introduction

- The lines from the eighth sentence of the second paragraph in the Introduction starting as "Both QT and the Tpe intervals are HR dependent [6] and this dependence has..." (p-2, line 6) until the third sentence of the third paragraph ending as "...relationship by linear regressions between simultaneously measured QT and RR intervals [15]." (p-2, line 30) should be replaced with the following text:

"Both QT and Tpe intervals are HR dependent [6, 7]. Regarding QT dynamics, increased QT/RR slopes have been related to arrhythmic risk in post-myocardial infarction patients [8] and dilated cardiomyopathy patients [9]. In patients with chronic HF (CHF), increased QT/RR slope has been shown to be an independent predictor of SCD [10] and also QT/RR slopes evaluated during the day have been shown to be associated with higher risk of cardiac death [11] and total mortality [12]. From a pathophysiological point of view, steeper QT/RR has been suggested to indicate decreased vagal tone and increased sympathetic activity, reflecting the higher vulnerability of the ventricular myocardium to arrhythmias [13]. As for the Tpe interval, controversy exists regarding its value as a risk marker. In a large community-based study, prolongation of Tpe has been shown to be an independent risk marker of SCD [14], whereas this concept has been challenged in other studies [15]. To the best of our knowledge, there are no investigations evaluating Tpe/RR dynamicity in 24-h Holter recordings as a SCD risk stratifier.

The majority of previous studies have characterized the QT/RR relationship by linear regressions between simultaneously measured QT and RR intervals."

- Discussion

- The lines from the first sentence of the fifth paragraph in the Discussion, starting as "Regarding SCD prediction, we did not find any significant association between QT/RR slopes and SCD, as..." (p-6, line 19) to the third sentence of the fifth paragraph, ending as "...opposed to the results reported in [11] and [12]." (p-6, line 21) should be replaced with the following text:

"Regarding SCD prediction, we did not find any significant association between QT/RR slopes and SCD, as opposed to previous results in other patient populations reporting association between QT/RR slopes and arrhythmic risk [8, 9, 10, 23]."

- The lines from the first sentence of the sixth paragraph in the Discussion, starting as "Our results are consistent with a previous investigation [23], which evaluated the index $\Delta\alpha$ [24] in the same..." (p-6, line 26) to the fifth sentence of the sixth paragraph, ending

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as "…interval may estimate Δα differently to the original definition [24]." (p-6, line 30) should be replaced with the following text:

"Our results are consistent with a previous investigation [24], which evaluated the index Δα [25] in the same population. The Tpe/RR slope computed at the averaged RR interval may estimate Δα differently to the original definition [25]."

- References

The reference list from [4] to [5] should be replaced with the following:

[4] Antzelevitch C, Sicouri S, Di Diego JM, et al. Does Tpeak-Tend provide an index of transmural dispersion of repolarization? Heart Rhythm 2007; 4(8): 114–6.
[5] Izumi D, Chinuski M, Lijima K, Furushima H, Hosaka Y, Hasegawa K, et al. The peak-to-end of the T wave in the limb ECG leads reflects total spatial rather than transmural dispersion of ventricular repolarization in an anthopleurin-A model of prolonged QT interval. Heart Rhythm 2012; 9:796–803.

The reference list from [7] to [16] should be replaced with the following:

[7] Smetana P, Batchvarov V, Hnatkova K, John Camm A, Malik M. Sex differences in the rate dependence of the T wave descending limb. Cardiovasc Res 2003; 58(3): 549–54.
[8] Szydlo K, Trusz-Gluza M, Wita K, Filipecki A, Orszulak W, Urbanczyk D, et al. QT/RR relationship in patients after remote anterior myocardial infarction with left ventricular dysfunction and different types of ventricular arrhythmias. Ann Noninvasive Electrocardiol 2008 Jan; 13: 61–6.
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[11] Watanabe E, Arakawa T, Uchiyama T, Tong M, Yasui K, Takeuchi H, et al. Prognostic significance of circadian variability of RR and QT intervals and QT dynamicity in patients with chronic heart failure. Heart Rhythm 2007; 4(8): 999–1005.
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[16] Garnett CE, Zhu H, Malik M, Fossa AA, Zhang J, Badilini F, et al. Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects. Am Heart J 163: 912–930, 2012.

The reference list from [23] to [24] should be replaced with the following:

[23] Pueyo E, Smetana P, Caminal P, de Luna AB, Malik M, Laguna P, et al. Characterization of QT interval adaptation to RR interval changes and its use as a risk-stratifier of arrhythmic mortality in amiodarone-treated survivors of acute myocardial infarction. IEEE Trans Biomed Eng 2004; 51(9): 1511–20.
[24] Ramírez J, Mincholé A, Bolea J, Laguna P, Pueyo E. Prediction of sudden cardiac death in chronic heart failure patients by analysis of restitution dispersion. Computing in Cardiology 2013; 40: 1–4.

Finally, an extra reference ([25]) should be added:

[25] Mincholé A, Pueyo E, Rodríguez JF, Zacur E, Doblaré M, Laguna P. Quantification of restitution dispersión from the dynamic changes of the T-wave peak-to-end, measured at the Surface ECG. IEEE Trans Biomed Eng 2011; 58: 1172–82.