T-wave Morphology Restitution Dependency with Heart Rate Range and Its Association with Sudden Cardiac Death in Chronic Heart Failure

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Abstract

The index of T-wave morphology restitution (TMR) has recently been presented as a sudden cardiac death (SCD) predictor in a population of chronic heart failure (CHF) patients. This index quantifies the level of variation in the T-wave morphology per RR interval (RRI) increment. The impact of using different definitions of ranges of RRI (ΔRRI) and the study of the interaction between TMR and ΔRRI are relevant for both the optimization and the mechanistic interpretation of the index. This study aims to investigate the interaction between ΔRRI and TMR and to assess whether different definitions of ΔRRI (patients-independent or patient-specific) may affect the predictive value of TMR. Holter ECG recordings from 651 patients with CHF, including SCD, victims of other causes and survivors, were analyzed. Mann-Whitney test was used to evaluate significant differences between SCD victims and the rest of patients. In the patient-independent analysis, TMR values only showed significant differences when 0.25s$\leq$ ΔRR$\leq$0.3s, while in the patient-specific analysis TMR values were significantly different when ΔRR$\geq$0.6 of the maximum RR range, ΔRR_{max}. In conclusion, the index TMR is a predictor of SCD robust to variations in ΔRR values evaluated in segments comprising at least 0.6 of ΔRR_{max}.

1. Introduction

The action potential duration (APD) restitution (APDR) curve represents the interaction between local APD and local cycle length [1]. The morphology of the T-wave reflects the distribution of the repolarization sequence along the ventricle [2–4]. Therefore, the spatio-temporal inhomogeneity of the ventricular repolarization process as a response to changes in heart rate may be captured by an index measuring T-wave morphological changes.

In a recent study, the index of T-wave morphology restitution (TMR) was proposed and proved to predict sudden cardiac death (SCD) in a population of 651 chronic heart failure (CHF) patients [5]. The TMR is calculated as the difference in the morphology of two T-waves measured at two RR intervals (RRI) defining the maximum intra-subject RRI range, ΔRRI, and normalized by ΔRRI. The impact of using different definitions of ΔRRI and the study of the interaction between TMR and ΔRRI are relevant for both the optimization and the mechanistic interpretation of the index. This study aims to investigate the interaction between ΔRRI and TMR and to assess whether different definitions of ΔRRI may affect the predictive value of TMR.

In this study we calculated the evolution of the index TMR with an patient-independent and patient-specific change in ΔRR. Then, we calculated the SCD predictive value of TMR at each value of ΔRR and we compared the patient-independent and patient-specific results.

2. Materials and Methods

2.1. Materials

The study population included 651 consecutive patients with symptomatic CHF corresponding to NYHA classes II and III enrolled in the MUSIC study, a prospective, multicenter study designed to assess risk predictors for cardiovascular mortality in ambulatory patients with CHF [6]. A two- or three-lead 24-hour Holter ECG sampled at 200 Hz was recorded in each patient at enrolment using ELA Medical equipment (Sorin Group, Paris, France). Baseline demographic and clinical data in sinus rhythm were available for the analysis. The MUSIC study included patients with both reduced and preserved LVEF, ranging from 10% to 70%. The study protocol was approved by the institutional investigation committees and all patients signed informed consent. No medications were withdrawn during Holter

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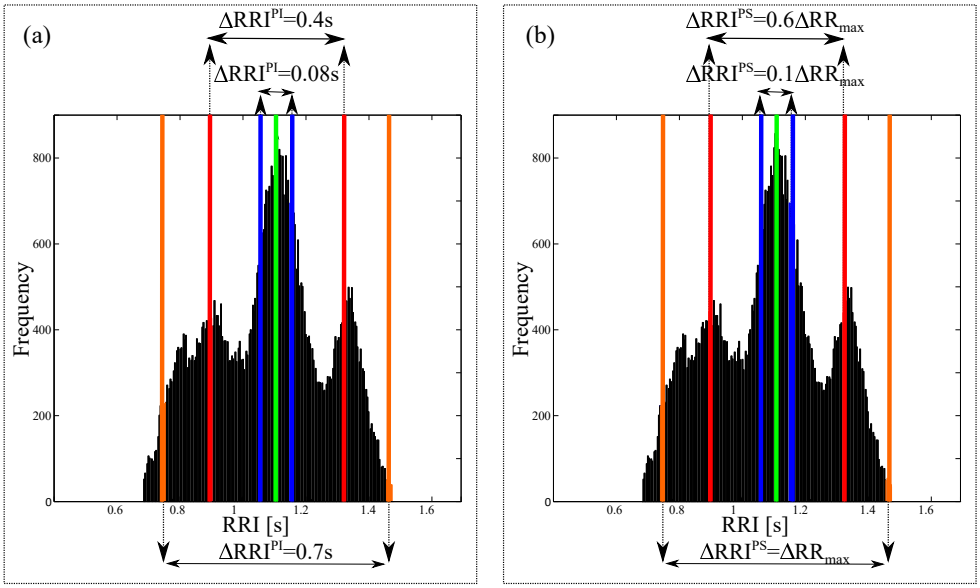

Figure 1. Selection of patient-independent (a) and patient-specific (b) ranges. Histogram of RR divided into 10-ms wide bins. Pairs of bins are selected by using fixed ΔRRI (a) or ΔRRI patient-specific to the maximum intra-subject ΔRR.

monitoring.

Patients were followed up every 6 months for a median of 48 months. SCD was defined as (1) a witnessed death occurring within 60 minutes from the onset of new symptoms unless a cause other than cardiac failure was obvious, (2) an unwitnessed death ($<$ 24 hours) in the absence of preexisting progressive circulatory failure or other causes of death, or (3) death during attempted resuscitation. End points were reviewed and classified by the MUSIC Study Endpoint Committee.

2.2. ECG Pre-processing

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 (PCA) was applied over the two-or-three available ECG leads to emphasize the energy of the T-wave and improve its delineation [7]. The PCA training matrix was built by only considering the samples from the T-waves on each lead. First, a single-lead-and-rules delineation technique was applied to select the samples from the T-wave and compute the PCA training matrix. Then, the first principal component was computed and delineated using a single-lead technique [8]. From the delineation marks, the RR interval series was obtained and the T-waves were selected using the known delimitation marks.

2.3. T-wave Morphology Restitution Using Patient-independent RR Ranges

Automatic quantification of the T-wave morphology restitution for patient-independent RR ranges was performed on every ECG recording in 4 steps:

1. **Selection of patient-independent ΔRRIs:** First, the histogram of the RR series was calculated during the entire 24-h recording, and it was divided into bins of 10 ms wide, showing a minimum frequency equal to 50. Next, a series of ΔRRI values, $\Delta RRI^{\text{PI}}(i)$, was defined as:

$$\begin{aligned} \Delta RRI^{\text{PI}}(i) &= RRI_2^{\text{PI}}(i) - RRI_1^{\text{PI}}(i), \quad i = 1, \cdots, N \\ RRI_1^{\text{PI}}(i) &= RRI_m - 10i, \\ RRI_2^{\text{PI}}(i) &= RRI_m + 10i, \end{aligned} \tag{1}$$

where RRI_m is the median RRI in the histogram and N is the maximum number of symmetric bins around RRI_m (Fig. 1 (a)). Then, the T-waves corresponding to the beats associated with $RRI_1^{\text{PI}}(i)$ and $RRI_2^{\text{PI}}(i)$ were considered for the analysis.

2. **Mean warped T-waves:** The mean warped T-waves of the T-waves within $RRI_1^{\text{PI}}(i)$ and $RRI_2^{\text{PI}}(i)$ were calculated by time-warping as in [9]. Each mean warped T-waves is a representative of the average T-wave morphology at $RRI_1^{\text{PI}}(i)$ and $RRI_2^{\text{PI}}(i)$, and compensate for the possible morphological differences introduced by eventual different histories of RRIs [5].

3. **Quantification of the T-wave morphological differences:** The morphological differences between the i-th

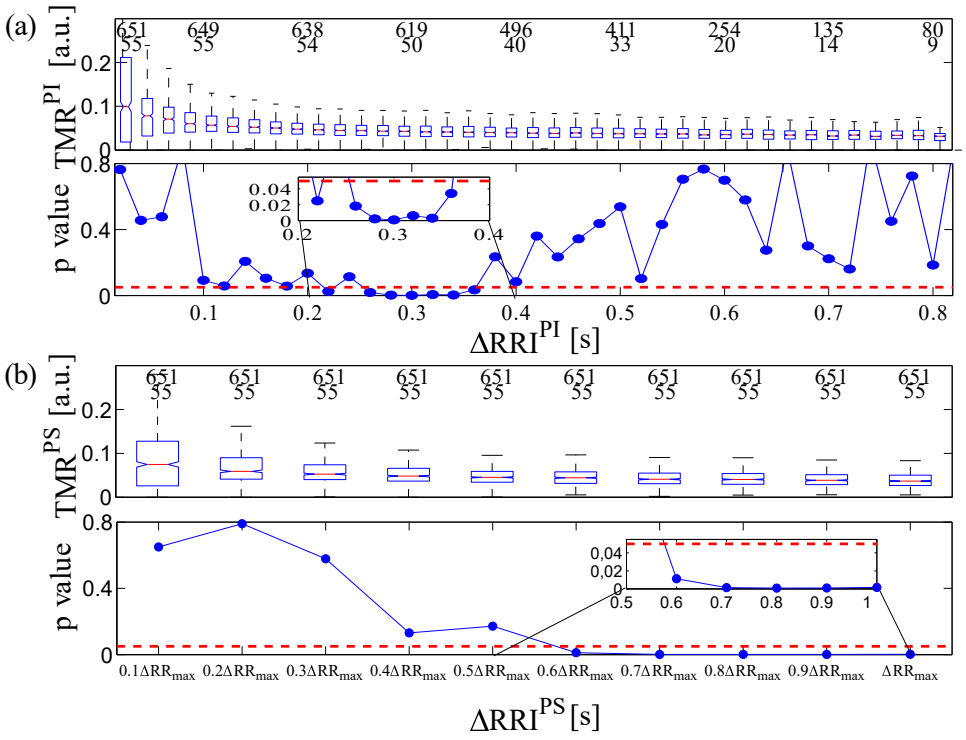

Figure 2. T-wave morphology restitution series using patient-independent (a) and patient-specific (b) RR ranges. Top panels show the boxplots of the TMR values, calculated across subjects, with respect to the patient-independent (a) and patient-specific (b) RR ranges. Bottom panels show the p-values of the Mann-Whitney test when comparing TMR values in SCD victims with respect to the rest of patients. The red dashed horizontal line marks the significance level, i.e. p=0.05. A zoom of the significant p-values is also provided. The first and second raw of numbers on top of each boxplot describes the total number of patients and the total number of SCD victims, respectively, in each boxplot.

pair of mean warped T-waves, corresponding to $RRI_1^{\text{PI}}(i)$ and $RRI_2^{\text{PI}}(i)$, were quantified by $d_w^{\text{PI}}(i)$, a time-warping-based index measuring the level of variation in the T-wave temporal domain [9]. Before applying the methodology, the gravity centres of both mean warped T-waves were aligned to only account on changes in the T-wave morphology, and not on global shifts (see [9] for details).

4. **T-wave morphology restitution series:** The series $TMR^{\text{PI}}(i)$ was, then, calculated by normalizing the variations in the temporal domain of each pair of mean warped T-waves by the corresponding RR range change:

$$TMR^{\text{PI}}(i) = \frac{d_w^{\text{PI}}(i)}{\Delta RRI^{\text{PI}}(i)}. \tag{2}$$

2.4. T-wave Morphology Restitution Using Patient-specific RR Ranges

The range of RR is highly subject-dependent and, thus, imposing a fixed increment in the range of RR for the TMR calculation might be a limitation. Then, for each subject, the maximum intra-subject RRI range, ΔRR_{max}, was divided into ten equally-spaced bins as follows (Fig. 1 (b)):

$$\begin{aligned} \Delta RRI^{\text{PS}}(j) &= 0.1j\Delta RR_{max}, \quad j = 1, \cdots, 10 \\ RRI_1^{\text{PS}}(j) &= RRI_m - \frac{0.1j\Delta RR_{max}}{2}, \\ RRI_2^{\text{PS}}(j) &= RRI_m + \frac{0.1j\Delta RR_{max}}{2}, \end{aligned} \tag{3}$$

and the T-waves corresponding to the RR intervals within $RRI_1^{\text{PS}}(j)$ and $RRI_2^{\text{PS}}(j)$ were considered for the subsequent analysis. The calculation of the mean warped T-waves and the computation of the series of temporal variations, $d_w^{\text{PS}}(i)$, was performed as described in the previous section. Finally, the series $TMR^{\text{PS}}(i)$ was obtained as:

$$TMR^{\text{PS}}(j) = \frac{d_w^{\text{PS}}(j)}{\Delta RRI^{\text{PS}}(j)}. \tag{4}$$

2.5. Statistical Analysis

Two-tailed Mann-Whitney test was used for univariate comparison of quantitative data.

3. Results and Discussion

Top panels in Fig. 2 show the boxplot of TMR, calculated across subjects, with respect to the patient-independent (a) and patient-specific (b) values of ΔRR. The first and second raw of numbers on top of each boxplot describes the total number of patients and the total number of SCD victims, respectively. In (a), this number is shown for each boxplot out of three due to the large number of boxplots. The p-value of Mann-Whitney's U test for comparison between SCD victims and the rest of patients is shown in the bottom panels, where each dot corresponds to a boxplot. The red dashed horizontal line marks the significance level, i.e. p=0.05.

TMR^{PI} was significantly different in SCD victims as compared to the rest of patients for ΔRRI values between 0.25 and 0.3 s (a). Moreover, only half the total number of patients had ΔRR values above 0.5s. This may be due to the fact that $\Delta RRI^{\text{PI}}(i)$ was set to be symmetrical around RRI_m and the histogram could be slightly skewed (Fig. 1 (a)). TMR^{PS} median values were consistently significantly different in SCD victims than in the rest of patients from $\Delta RRI^{\text{PS}}(j) \geq 0.6\Delta\text{RR}_{max}$. In addition, the number of patients in each boxplot was the same since the different values of $\Delta RRI^{\text{PS}}(j)$ are proportional to ΔRR_{max}.

Also, it can be appreciated that both the median value and variability of TMR^{PI} and TMR^{PS} are slightly larger for lower $\Delta RRI^{\text{PI}}(j)$ and $\Delta RRI^{\text{PS}}(j)$. This suggests that the morphological changes in the T-wave morphology as a response to small increments in $\Delta RRI^{\text{PI}}(j)$ and $\Delta RRI^{\text{PS}}(j)$ are comparable to those produced by noise.

TMR^{PI} and TMR^{PS} values showed the lowest p-value for SCD risk stratification when calculated at $\Delta RRI^{\text{PI}}(j)$=0.3 s (60000/(1000-150)-60000/(1000+150)=18 beats per minute) (p=0.0008) (Figure 2 (a)), and when calculated at $\Delta RRI^{\text{PS}}(j)$=0.8$\Delta\text{RR}_{max}$ (p=0.0008) (Figure 2 (b)), respectively.

4. Conclusions

The index of T-wave morphology restitution (TMR), hypothesized to be related to variations in dispersion of repolarization due to changes in heart rate, is a robust predictor of SCD when considering values of RR range as a fraction ($>$0.6) of the maximum intra-subject RR range or a fixed RR range between 0.25 and 0.35 s. Our results show that SCD victims manifest a significantly higher variation in the T-wave morphology per RR increment than the rest of patients when the RR range exceeds 0.6 of their maximum intra-subject RR range. When calculating TMR using patient-independent values of RR range, the predictive value of this index was not consistently significant as the RR range increases. Our results suggest that the variation in the T-wave morphology is patient-specific to the intra-subject range and, thus, patient-specific RR ranges should be considered in future studies using TMR for SCD risk prediction.

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