T-Wave Morphology Restitution in Chronic Heart Failure Patient With Atrial Fibrillation

Flavio Palmieri[1,2], Laura Burattini[1], Juan Pablo Martínez[2,3], Julia Ramírez[4]

[1]Department of Information Engineering, Università Politecnica delle Marche, Ancona, Italy
[2]BSICoS Group, Aragón Institute of Engineering Research, IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain
[3]CIBER en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Spain
[4]William Harvey Research Institute, Queen Mary University of London, London, United Kingdom

Abstract

Chronic heart failure (CHF) represents one of the major public health problems that often end in sudden cardiac death (SCD). Atrial fibrillation (AF) is associated with an increased risk of SCD but nowadays there is no non-invasive method that accurately predicts that risk. The recently developed T-wave morphology restitution (TMR) index showed its specific association with SCD risk prediction in sinus rhythm subjects with CHF. The aim of this work was to investigate the SCD predictive value of this index in individuals with AF. TMR was computed from 171 24-hour ECG Holter recordings from CHF patients enrolled in the "MUerte Súbita en Insuficiencia Cardiaca" study with AF. There were 19 SCD victims after the 4 years' follow-up. The Mann–Whitney U test showed that TMR was not significantly different in SCD victims as compared to survivors (p=0.617). However, this might be due to the huge gap in sample size between both populations. Assuming a balanced case-control scenario, the TMR value distribution may approach to a normal distribution. Under this hypothesis, the t-test was performed under the condition of unequal variances between both populations, showing a significant difference in TMR between both groups (p=0.023). In conclusion, the predictive power of TMR index in AF rhythm should not be excluded, but it needs a more in-depth study.

1. Introduction

Chronic heart failure (CHF) is a progressive syndrome in which the heart is not able to pump enough blood to meet the body's needs [1]. One of the principal consequences of CHF is sudden cardiac death (SCD). Previous studies report that almost 85% SCDs result from arrhythmic causes [2], with atrial fibrillation (AF) being one of them. Patients with AF, which accounts for more than 20% of SCDs [3], have, on average, a 2.5-fold increased risk of SCD compared with patients without AF [3].

Many electrocardiogram (ECG) based indices have been proposed in the literature to quantify SCD risk in different populations (just to exemplify, see [4]). In particular, a novel ECG-based biomarker, the T-wave morphology restitution (TMR) index, demonstrated its SCD predictive value in CHF patients enrolled in the "MUerte Súbita en Insuficiencia Cardiaca" (MUSIC) dataset [5]. The TMR index was originally developed and tested in subjects with normal sinus rhythm.

In AF patients, the atria are activated in a non-organized way, and this electrical activity manifests on the ECG as a pattern of fibrillatory waves (f-waves) and the absence of P-waves. These f-waves often overlap with the T-waves, resulting in a large variability in T-waves morphology. In addition, ECG signals recorded from AF subjects show an extremely irregular QRS rate.

The aim of this work was to assess the predictive value of TMR in AF subjects selected from the MUSIC study. To overcome the special AF features present during AF rhythm, the original algorithm was purposely adapted.

2. Materials and Methods

2.1. Study population

The studied cohort consisted of patients with AF rhythm from the MUSIC study, a prospective and multicentre study designed to assess risk predictors of cardiac mortality and SCD in ambulatory patients with CHF [6]. A 2- (3%) or 3-lead (97%) 24-h ECG Holter recordings sampled at 200 Hz (using ELA Medical equipment - Sorin Group, Paris, France) were available for analysis in MUSIC study. The original cohort included 992 consecutive patients in AF, in sinus rhythm, in flutter and in pacemaker rhythm [6]. In this work, the study population included 171 subjects in AF rhythm, where 128

 ISSN: 2325-887X DOI: 10.22489/CinC.2018.177

patients (75%) were male. The age ranged between 35 years and 90 years. A total of 49 (29%) were classified as being in New York Heart Association (NYHA) class III, while the rest were in NYHA class II. The follow-up period was 4 years.

The primary endpoint of this study was SCD. The definition of SCD was considered as in [6]. All patients signed informed consent and the institutional investigation committees approved the study protocol.

2.2. Methods

2.2.1. ECG pre-processing

In this study, 171 ECG signals, sampled at 200 Hz were analysed. Pre-processing included low-pass filtering at 40 Hz to remove electric and muscle noise but allow QRS and T-wave analysis. Baseline wander was removed by high-pass filtering at 0.5 Hz. Single lead wavelet-based delineation was applied to each available lead to detect and delineate the QRS complexes [7]. Then, principal component (PC) analysis was applied over all the available ECG leads to emphasize the energy of the T-wave and improve its delineation [8]. The first PCs were finally delineated by using the same single-lead delineation technique [7] to derive the T-waves delineation marks (i.e. onset, peak and end position).

2.2.2. TMR index computation

The TMR index was calculated for each individual ECG recording. First, the T-waves delineated in the pre-processing stage were selected and grouped with respect to their RR interval. As a result, an RR histogram like that shown in Figure 1 was obtained for each ECG signal. This Figure illustrates the RR intervals from a particular ECG recording along the 24-h recording divided into bins of 10 milliseconds wide [5]. The number of RR values within each bin (i.e. the frequency) is depicted along the Y axis. The maximum intra-subject RR range, ΔRR, was defined as the maximum RR range symmetric with respect to the median RR interval (the green bin in Figure 1), by only using those bins with more than 50 RR interval values (the orange dotted line in Figure 1 shows this threshold) [5]. This limit was imposed to ensure a reliable estimation of the average T-wave morphology in each bin. In the case of the subject corresponding to Figure 1, the blue and the red bins define the lower and upper boundaries of ΔRR.

An RR-derived formula was implemented in this work to improve the delimitation of the T-wave end mark:

$$T_{Off_i} = T_{end_i} + 0.03 * RR_{i-1},$$

where T_{Off_i} is the new T-wave end for the i-th T-wave and T_{end_i} is the T-wave end resulting from the initial delineation. RR_{i-1} is the value of the previous R-to-R interval, and 0.03 is a correction factor that was tested directly on a reduced subset of ECG signals. This new implementation was a determinant task for AF ECG signal analysis. For instance, since the sampling period was 5 ms (i.e. 200 Hz), a T-wave delineation error of 5 samples (25 ms) due to f-wave noise could introduce a negative bias on the TMR computation. Obviously, that issue was not considered in the original algorithm, where only sinus rhythm ECG recordings were evaluated. In addition, a customized method was applied to avoid the presence of f-waves in the repolarization window after the accurate end of the T wave was located. This method was based a preliminary computation of the mean warped T-wave as proposed in [9]. This preliminary warped T-wave was only used to assess its length. Successively, all T-waves in the bin were truncated at that length to avoid the contribution from extra samples. These were adopted to evaluate the *warped-average* T-wave that was used to calculate the TMR index as in the original algorithm [9]. A second mean warped T-wave was computed in each red a blue bin by using the truncated T-waves. Then we calculated the Spearman's correlation coefficient between each individual T-wave in each bin and this second average T-wave. Thereafter, the mean warped T-wave was recalculated for the third time by only considering those with a Spearman's correlation coefficient greater than 0.98, obtaining the two T-waves representative of the average T-wave morphology corresponding to the blue and red RR intervals. The morphological differences between those last two *warped-average* T-waves along the temporal axis were quantified using the d_w index [9] that is an ECG-derived marker [9] that quantifies the amount of warping necessary to remove the temporal variation between two T-waves. Finally, the TMR index, quantifying the variation in the morphology of the T-wave per RR increment, was calculated as d_w normalized by ΔRR [9].

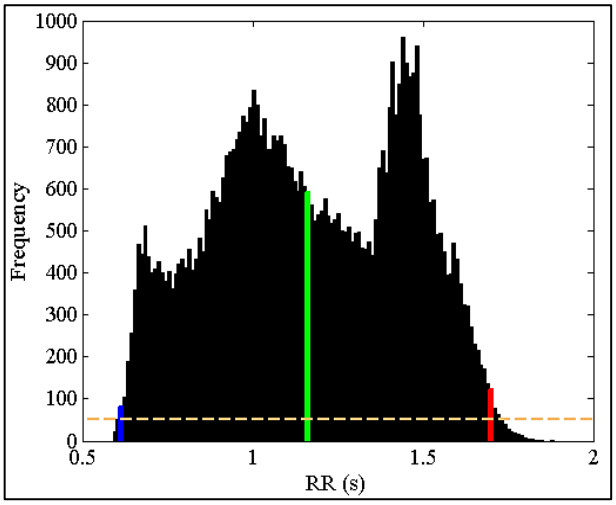

Figure 1: An example of RR histogram with 0.01 s wide bins from a particular subject. The blue and red bins are the boundary values of the maximum intra-subject RR range.

2.2.3. Statistical analysis

The Lilliefors normality test was performed to verify the normality of the distribution of TMR in the SCD, non-SCD, and whole population groups. Then, the Mann-Whitney U test was used to test for statistical differences in TMR between the SCD and non-SCD populations. Successively, under the hypothesis of unequal variances (that take into account the different number of patients in SCD and non-SCD groups) a two-sample T-test was performed to compare the means of TMR values in the SCD and non-SCD groups.

3. Results

Among the 171 subjects constituting the study population, 19 were categorised as SCD victims while 152 were categorised as survivors. For 8 patients from the non-SCD group, it was not possible to calculate the TMR index, as all the T waves in the selected RR bins had a Spearman's correlation coefficient lower than 0.98. Table 1 shows the descriptive statistics for continuous clinical variables, ΔRR, d_w and TMR in the SCD, non-SCD and whole population groups. Since age, ΔRR, d_w and TMR did not follow a normal distribution, the descriptives are shown as the median (interquartile range).

Boxplots in Figure 2 show the TMR values in the SCD and the non-SCD groups. Lilliefors normality test showed that the distribution of TMR was normal in the non-SCD group (p-value=0.001) but not in the SCD group (p-value = 0.199). Then, the Mann-Whitney U test indicated that TMR was not significantly different in the SCD group with respect to the non-SCD group (p-value= 0.617, Figure 2). On the other hand, the T-test showed that the mean of TMR was significant higher in the SCD group as compared to the non-SCD group (p-value=0.023).

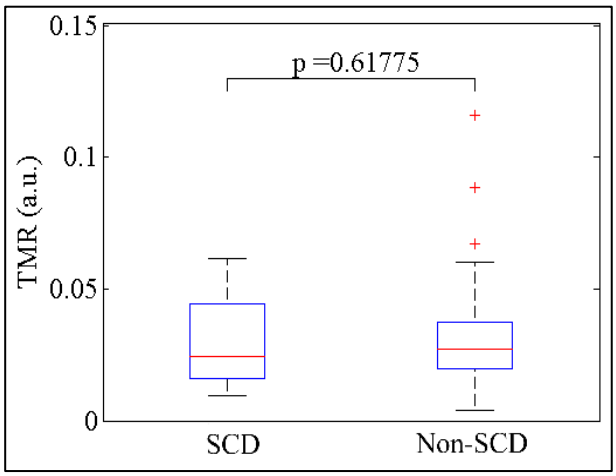

Figure 2: Boxplots of TMR in SCD and non-SCD victims. Red plus (+) signs indicated the outlier. The p-value from the Mann–Whitney U test is given.

Table 1: Descriptive statistics of clinical data, intra subject RR range ΔRR (ms), ECG marker d_w (ms) and T-wave morphology restitution TMR (a.u.). Age, follow-up, ΔRR, d_w and TMR were expressed as median (interquartile range). Binary data like gender, New York Heart Association (NYHA) class and missing variables are indicated as number (percentage) for sudden cardiac death (SCD) group, Non-SCD group and whole population

	SCD (N = 19)	Non-SCD (N = 152)	Overall (N = 171)
Gender [Male]	16 (84%)	112 (74%)	128 (75%)
Age [years]	71 (5.5)	71 (13.5)	71 (12.75)
NYHA class [III]	5 (26%)	44 (29%)	49 (29%)
Missing	0 (0%)	8 (5%)	8 (5%)
ΔRR (ms)	690 (303.12)	680 (140)	680 (155)
d_w (ms)	15.15 (18.13)	17.16 (10.46)	16.79 (10.81)
TMR (a.u.)	0.0242 (0.0282)	0.0272 (0.0176)	0.0271 (0.0182)

4. Discussion

The TMR index represents an innovative tool proposed to predict SCD risk in sinus rhythm subjects suffering from CHF. AF is associated with an increased risk of SCD and thus we tested this new biomarker in these patients, since it had never been investigated.

Due to the particular features of ECG signals recorded from AF subjects, several changes were performed to the original algorithm. First, the algorithm was customized to avoid the overlapping between the T-waves and the f-waves at the end of the analysis window. Second, a new T-wave end marker was computed to improve the definition of the repolarization window. The computation of this new end marker was crucial because the delineation performed in the original algorithm relied on the correct identification of the T-wave in all the leads. This was certainly safe in a non-pathological rhythm, but during AF, the f-waves overlap the T-waves and thus the T-wave end was not easily identifiable. Then, an incorrect T-wave end was often detected. On the other hand, the RR interval was always correctly assessed since R peaks were unequivocally identified and it was not affected by the noises or by errors in the delineator. Consequently, the T-wave duration was calculated based on the previous RR interval (as it strongly influences the actual heartbeat). Figure 3 depicts an example showing the overall effects of these improvements. These modifications allowed us to

apply the TMR index investigation in almost all the AF rhythm signals in this study. However, we were still unable to derive TMR from a 5% of subjects from the non-SCD group due to the presence of prominent f-waves, noise or other types of variability within the RR bins.

As the distribution of TMR in the SCD group did not pass the normality test, we applied the Mann–Whitney U test to assess differences in TMR between the SCD and non-SCD groups, but we did not find those differences to be statistically significant. However, this study with consecutive patients had a small number of patients in the SCD group. In this situation, it is known that the statistical power also declines [10], and the normality test could have failed even if the underlying distribution was normal [10]. Considering that, the t-test for groups of different variances was also tested showing significant differences between both groups (p=0.023). This finding suggests that the TMR prognostic value should not be excluded.

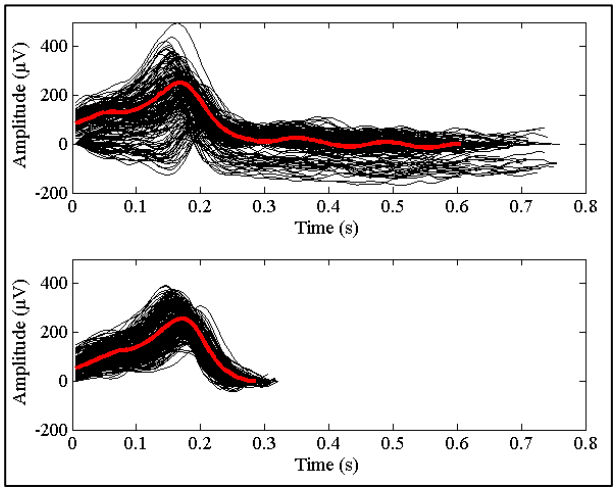

Figure 3: Combined effect of the overall improvements adopted in this work for the calculation of TMR from ECG recordings with AF rhythm. The average-warped T-waves are shown in red, on top of the individual, warped and aligned with respect to their onset T-waves from a particular RR bin, shown in black. Upper panel: Presence of f-waves within the analysis window. As a result, a long non-physiological "tail" is confused as part of the T-wave. Bottom panel: Correct delimitation of the T-wave thanks to the new modifications implemented in the original algorithm. Extra samples were discarded.

5. Conclusions

The T-test significant result in contrast with the one from Mann-Whitney U-test highlights that the SCD predictive power of TMR index in AF rhythm needs a more in-depth study. Future studies will include a wider pool of individuals in which there is a 1:1 case-control ratio to validate our hypothesis that TMR would predict SCD in CHF patients with AF if the SCD and Non-SCD group sample sizes were balanced.

Acknowledgements

This work was supported by CIBER in Bioengineering, Biomaterials & Nanomedicine (CIBER-BBN) through Instituto de Salud Carlos III and FEDER (Spain), project DPI2016-75458-R funded by MINECO and FEDER, and by Gobierno de Aragón and European Social Fund (EU) through BSICoS Group (T96). The computation was performed by the ICTS NANBIOSIS, specifically by the High Performance Computing Unit of the CIBER-BBN at the University of Zaragoza. JR acknowledges support from the Medical Research Council grant MR/N025083/1 and from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007/2013) under REA grant agreement 608765.

References

[1] P. A. McCullough et al., "Confirmation of a Heart Failure Epidemic: Findings From the Resource Utilization Among Congestive Heart Failure (REACH) Study," *J. Am. Coll. Cardiol.*, vol. 39, no. 1, pp. 60-69, Jan. 2002.

[2] M. W. Deyell et al., "Sudden Cardiac Risk Stratification," *Circ. Res.*, vol. 116, no. 12, pp. 1907-1918, Jun. 2015.

[3] A. Eisen et al., "Sudden Cardiac Death in Patients With Atrial Fibrillation: Insights From the ENGAGE AF-TIMI 48 Trial," *J. Am. Heart Assoc.*, vol. 5, no. 7, Jul 2016 Art. no. e003735.

[4] D. P. Morin et al., "Surface Electrocardiogram Predictors of Sudden Cardiac Arrest," *Ochsner J.*, vol. 16, no. 3, pp. 280-289, 2016.

[5] J. Ramírez et al., "T-Wave Morphology Restitution Predicts Sudden Cardiac Death in Patients With Chronic Heart Failure," *J. Am. Heart. Assoc.*, vol. 6, no. 5, May 2017, Art. no. e005310.

[6] R. Vazquez et al., "The MUSIC Risk Score: a Simple Method for Predicting Mortality in Ambulatory Patients With Chronic Heart Failure," *Europ. Heart J.*, vol. 30, no. 9, pp. 1088-1096, Feb. 2009.

[7] J. P. Martínez et al., "A Wavelet-Based ECG Delineator: Evaluation on Standard Databases," *IEEE Trans. on Biomed.*, vol. 51, no. 4, pp. 570-581, Mar. 2004.

[8] J. Ramírez et al., "Characterization of Cardiac Repolarization Response to Heart Rate Changes Provoked by a Tilt Test," *Computing in Cardiology*, vol. 39, pp.673-679, 2012.

[9] J. Ramírez et al., "Variability of Ventricular Repolarization Dispersion Quantified by Time-Warping the Morphology of the T-Wave," *IEEE Trans. on Biomed.*, vol. 64, no. 7, pp. 1619-1630, Jul. 2017.

[10] S. R. Jone et al., "An Introduction to Power and Sample Size Estimation," *Emerg. Med. J.*, vol. 20, pp. 453-458, Sep. 2003.

Address for correspondence
Julia Ramírez, Clinical Pharmacology, William Harvey Research Institute, John Vane Science Centre, Charterhouse Square, London EC1M 6BQ, United Kingdom. j.ramirez@qmul.ac.uk