Sudden Cardiac Death Prediction in Chagas Heart Disease Patients from ECG-derived Biomarkers of Ventricular Restitution

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Abstract

Sudden cardiac death (SCD) remains an important cause of mortality in patients with Chagas heart disease (ChHD). The aim of this study is to compare the SCD predictive value of ECG-derived indices of ventricular restitution, the response to heart rate changes of the QT ($\Delta\alpha^{QT}$) and T-peak-to-T-end (Tpe, $\Delta\alpha^{Tpe}$) intervals, the T-wave morphology restitution index (TMR) and Tpe morphology restitution index ($TpeMR$) in a population with ChHD. We derived these indices from Holter ECG recordings from 140 patients with ChHD and evaluated their association with SCD. SCD victims showed significantly higher values of $\Delta\alpha^{Tpe}$ and $TpeMR$ compared to the rest of patients (p <.001). Multivariate Cox analyses after adjusting for the Rassi score showed that individuals with $\Delta\alpha^{Tpe}$ and $TpeMR$ values greater than 0.036 and 0.021 had a hazard ratio (HR) of 2.93 (p <.001) and 2.02 (p=0.023), respectively. In conclusion, $\Delta\alpha^{Tpe}$ and $TpeMR$, both quantifying end-stage ventricular restitution, are strongly and independently associated with SCD. The lack of predictive value of $\Delta\alpha^{QT}$ and TMR might be associated to other effect of ChHD on the early stages of ventricular repolarization unrelated to SCD.

1. Introduction

Chagas heart disease (ChHD) is a parasitic condition caused by the protozoan *Trypanosoma cruzi* with a strong link to sudden cardiac death (SCD). Specifically, 65% of ChHD patients suffer a SCD event at a rate of 24 per 1000 patients per year, while the remainder may be at risk of dying from chronic heart failure [1]. The Rassi score is currently the only clinical score with a strong association with mortality, but it lacks specificity when identifying individuals at risk of SCD [2].

ChHD particularly affects the left ventricle, causing an abnormal ventricular repolarization [3]. It has been shown that one of the electrophysiological substrates that can lead to SCD is an abnormal action potential duration restitution dynamics (APDR) in the ventricles [4]. However, large-scale assessment of APDR is unfeasible due to its invasive nature, as well as being costly, motivating the search and use of non-invasive techniques.

Previous studies have reported several methods to indirectly estimate APDR by only making use of the T-wave morphology on the surface electrocardiogram (ECG). Multiple biomarkers have been proposed, such as the response to heart rate changes of the QT ($\Delta\alpha^{QT}$) [5] and T-peak-to-T-end (Tpe) intervals ($\Delta\alpha^{Tpe}$) [6]. More recently, the T-wave morphology restitution index (TMR), quantifying the variations in the overall morphology of the T-wave with heart rate, showed a strong association with SCD in chronic heart failure and general population [7, 8]. TMR was later adapted to specifically quantify variations in the Tpe morphology with heart rate, $TpeMR$, also showing a strong association with SCD [9] and arrhtymia risk [10].

In this work, we hypothesised that the above ECG-derived indices could also be useful for predicting the risk of SCD in subjects with ChHD. To this end, this project will analyse a database of patients with ChHD, derive $\Delta\alpha^{QT}$, $\Delta\alpha^{Tpe}$, TMR and $TpeMR$ and assess their association with SCD risk. The aim is to establish whether indexes over certain values are associated with SCD.

2. Materials and Methods

2.1. ChHD database

A total of 220 patients with ChHD were enrolled in the protocolized clinical follow-up program of patients of the ChHD outpatient clinic from University Hospital Clementino Fraga Filho of Federal University of Rio de

Janeiro (HUCFF-UFRJ) between 1992 and 2017 [1]. Figure 1 shows the flowchart of the study population and Table 1 describes the characteristics of the population. The exclusion criteria were: (i) High-risk Rassi score (12-20 points), (ii) pacemaker or defibrillator implantation or ablation surgery before the ECG-Holter, (iii) death from other causes within the follow-up period, (iv) anomalies in analog-to-digital conversion and (v) short duration recordings without enough heartbeats. The main endpoint of the study was defined as SCD, pacemaker or defibrillator implantation, or ablation surgery occurring within the follow-up period. The median follow-up was 5 years.

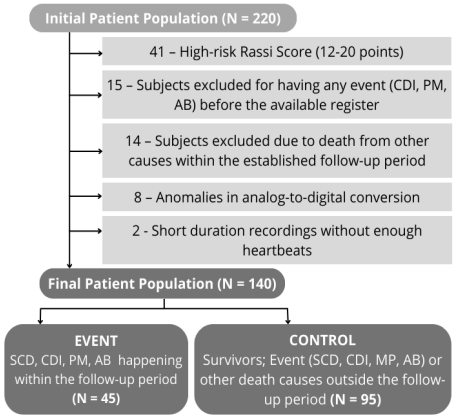

Figure 1: Inclusion and exclusion criteria.

2.2. ECG Pre-processing

Preprocessing of the ECG signals included interpolation at a sampling frequency fs = 1000 Hz, high pass filtering at 0.5 Hz to remove baseline wander, low pass filtering at 40 Hz to remove electric and muscle noise and ectopic beats detection. A fully automated delineation system with a posterior visual inspection to remove any possible error was used to annotate QRS and T-wave onset and offset timings. Each T-wave was further low-pass filtered with a sixth order Butterworth filter at 20 Hz cut-off frequency for subsequent use for ECG analysis [8].

2.3. ECG indices of ventricular restitution

First, the RR interval (RRI) histogram was calculated during the entire 24-hour recording, and it was divided into 10 milliseconds wide bins. Only those RRI bins with fewer than 75 occurrences were discarded. Next, the 2 most distant RRI bins from the median, RRI_2, and RRI_1, distributed symmetrically around this median, were chosen as those defining the maximum intrasubject RRI range, ΔRRI, ie, $\Delta RRI = RRI_2 - RRI_1$. Then, the beats associated with the RR interval within these two bins were considered for the computation of $\Delta\alpha^{QT}$ and $\Delta\alpha^{Tpe}$:

$$\Delta\alpha^{QT} = \frac{|QT^m_{RR1} - QT^m_{RR2}|}{\Delta RRI} \tag{1}$$

$$\Delta\alpha^{Tpe} = \frac{|Tpe^m_{RR1} - Tpe^m_{RR2}|}{\Delta RRI}, \tag{2}$$

where QT^m_{RR1} and QT^m_{RR2}, Tpe^m_{RR1} and Tpe^m_{RR2} measure the median duration of the QT and Tpe intervals, respectively, of the beats contained in each RRI_2, and RRI_1 bins.

To calculate the two remaining ECG-derived indices, two mean warped T-waves (TW) representing the average T-wave morphology for RRI_1 and RRI_2, respectively, were computed using a warping method (Figure 2) [7]. These mean warped T-waves capture information about repolarization dispersion variations between RRI_1 and RRI_2 bins, and the level of warping needed to optimally align any two mean T-waves is quantified, in ms, by the warping parameter d_w (Figure 2):

$$d_w = \frac{1}{N_r}\sum_{n=1}^{N_r} |\gamma^*(\boldsymbol{t}^r(n)) - \boldsymbol{t}^r(n)| \tag{3}$$

The optimal warping function $\gamma^*(t^r)$ optimally relates the temporal vectors of each mean warped T-wave.

The index TMR was calculated by dividing d_w by ΔRRI:

$$TMR = \frac{|d_w^{TW}|}{\Delta RRI} \tag{4}$$

Regarding $TpeMR$, only the morphology of the mean warped T-waves corresponding to the Tpe interval was considered:

$$TpeMR = \frac{|d_w^{Tpe}|}{\Delta RRI} \tag{5}$$

2.4. Statistical Analyses

The two-tailed Mann-Whitney test was used to evaluate the association of $\Delta\alpha^{QT}$, $\Delta\alpha^{Tpe}$, TMR and $TpeMR$ with SCD. First, receiver operating curves (ROC) were derived using the pROC package from R. We estimated the optimal cutoff as the value that jointly maximised sensitivity and specificity. Kaplan-Meier curves were derived using the optimal cutoff values, with a comparison of cumulative events performed by using log-rank tests.

Univariate and multivariate Cox regression analyses were performed one at a time, adjusting for Rassi score for the latter. The Rassi score was developed as described in the original publication [2]. Statistical analyses were performed using RStudio version 2023.12.1.

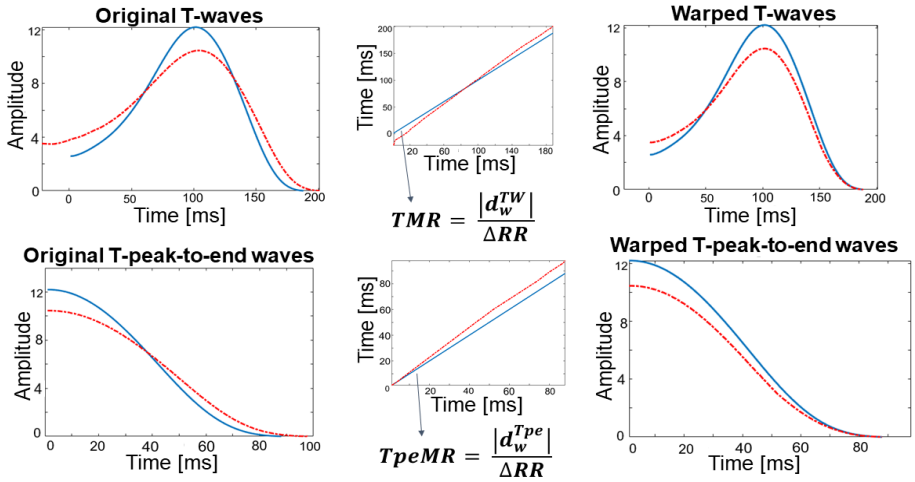

Figure 2: Calculation of the T-wave and T-peak-to-end morphology restitution indices, TMR and $TpeMR$

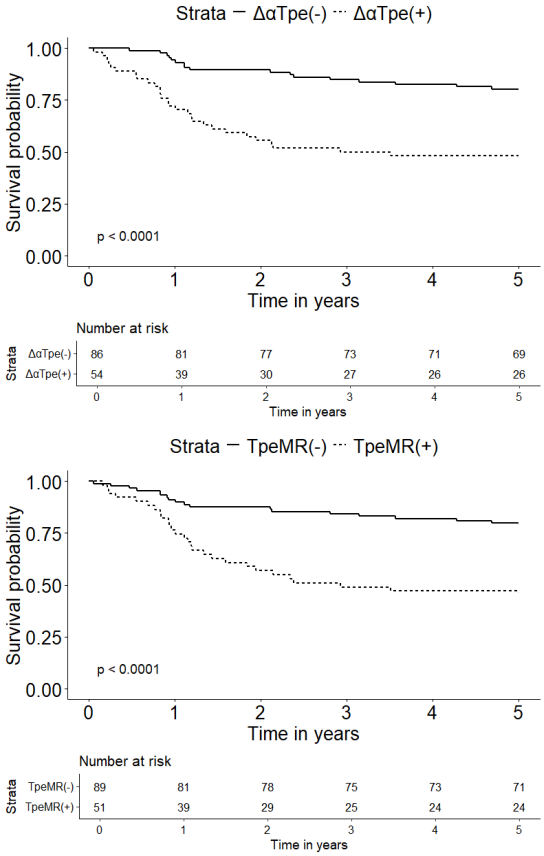

Figure 3: Kaplan-Meier survival curves

3. Results

Overall, 140 subjects were included in the final population, and 45 (32.14%) had the primary endpoint within the follow-up period (Table 1). Upon comparison of variables between SCD and non-SCD groups, significant differences were found for Rassi score, $\Delta\alpha^{Tpe}$ and $TpeMR$. The area under the ROC curve for $\Delta\alpha^{Tpe}$ and $TpeMR$ was 0.683 (95% CI: 0.586-0.779) and 0.673 (95% CI: 0.571-0.775), respectively.

Patients were dichotomized into $\Delta\alpha^{Tpe}$ positive ($\Delta\alpha^{Tpe}+$) and negative ($\Delta\alpha^{Tpe}-$) groups according to their optimal cut-off point of 0.036. Similarly, patients were dichotomized into $TpeMR+$ and $TpeMR-$ groups according to the optimal cut-off point of 0.021. Figure 3 shows Kaplan-Meier survival probabilities for the 2 groups defined by $\Delta\alpha^{Tpe}-$ and $\Delta\alpha^{Tpe}+$ (top panel) and $TpeMR-$ and $TpeMR+$ (bottom panel).

Univariate Cox analysis revealed that $\Delta\alpha^{Tpe} > 0.036$ ($\Delta\alpha^{Tpe}+$) and $TpeMR > 0.021$ ($TpeMR+$) were significantly associated with SCD risk (Table 2), with a hazard ratio (HR) of 3.54 (95% confidence interval [CI]: 1.93-6.48; $p < .0001$) and 3.33 (95% CI: 1.82-6.06; $p < .0001$), respectively. Multivariate Cox analysis, adjusting for the Rassi score, showed that $\Delta\alpha^{Tpe}+$ and $TpeMR+$ remained significantly associated with SCD with a HR of 2.93 ($p < .001$) and 2.02 ($p = 0.0238$), respectively.

4. Discussion and conclusions

In this work, we demonstrate that $\Delta\alpha^{Tpe}$ and $TpeMR$, both ECG indices quantifying restitution properties of the late phase of ventricular repolarization, are strongly associated with an increased risk of SCD in ChHD, independently from the Rassi score. From a physiological perspective, studies show that ChHD often causes injuries concentrated in the endocardium [11]. This damage can potentially increase transmural dispersion of repolarization, associated with reentrant arrhythmias.

Consequently, these two indices could be used to non-invasively identify ChHD patients at risk of SCD who

Table 1: Characteristics of patients.

	Overall population (N = 140)	SCD (N = 45)	Non-SCD (N = 95)	p-value
Age (y)	43.7 (13.4)	43.5 (11.9)	43.8 (14.1)	0.603
BMI (kg/m^2)	28 (2.25)	28 (3)	28 (3)	0.126
Rassi score	5 (9)	11 (3)	3 (3)	**<.0001**
DM2	19 (13.5%)	9 (20%)	10 (10.5%)	0.128
$\Delta\alpha^{QT}$	0.148 (0.101)	0.161 (0.110)	0.147 (0.103)	0.890
$\Delta\alpha^{Tpe}$	0.024 (0.049)	0.043 (0.076)	0.019 (0.033)	**<.001**
TMR	0.034 (0.025)	0.035 (0.031)	0.034 (0.024)	0.334
$TpeMR$	0.014 (0.024)	0.027 (0.045)	0.012 (0.015)	**<.001**

[1]Data presented as absolute frequencies and percentages and median with IQ range. Significant differences between SCD and non-SCD groups are indicated in bold. BMI: Body Mass Index; DM2: Diabetes Mellitus type 2.

Table 2: Univariate and Multivariate Cox analyses

	Univariate		Multivariate[2]	
ECG variables	HR (95% CI)	p-value	HR (95% CI)	p-value
$\Delta\alpha^{Tpe} > 0.036$	3.54 (1.93-6.48)	**<.0001**	2.93 (1.58-5.41)	**<.001**
$TpeMR > 0.021$	3.33 (1.82-6.06)	**<.0001**	2.02 (1.09-3.73)	**0.023**

[2]Adjusted model includes Rassi score. Statistically significant values are marked in bold. HR: Hazard Ratio; CI: Confidence Interval.

might benefit from more effective preventive strategies, such as implantation of cardiac defibrillators.

In contrast, the TMR index, which quantifies the change in the overall morphology of the T-wave, and $\Delta\alpha^{QT}$ were not associated with SCD. This result points to some possible mechanism in which ChHD may have an SCD unrelated effect on early phase of ventricular repolarization, masking the arrhythmogenic substrate specifically linked to SCD.

Acknowledgments

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References

[1] Cavalcante CHL, et al. Sudden cardiac death multiparametric classification system for Chagas heart disease's patients based on clinical data and 24-hours ECG monitoring. Math Biosci Eng Mar. 2023;20(5):9159–9178.

[2] Anis Rassi J, et al. Development and validation of a risk score for predicting death in chagas' heart disease. New England Journal of Medicine 2006;355(8).

[3] Pinto Dias JC, et al. II Consenso Brasileiro em Doença de Chagas. Epidemiol Serv Saúde Brasília 2016;25(esp):7–86.

[4] Laurita KR, et al. Modulation of ventricular repolarization by a premature stimulus: role of epicardial dispersion of repolarization kinetics demonstrated by optical mapping of the intact guinea pig heart. Circulation Research Sept. 1996;79(3).

[5] Zareba W, et al. QT dynamics and variability. Annals of Noninvasive Electrocardiology Apr. 2005;10(2):256–262.

[6] Mincholé A, et al. Quantification of restitution dispersion from the dynamic changes of the T-wave peak to end, measured at the surface ECG. IEEE Transactions on Biomedical Engineering May 2011;58(5):1172–1182.

[7] Ramírez J, et al. Variability of Ventricular Repolarization Dispersion Quantified by Time-Warping the Morphology of the T-Waves. IEEE Trans Biomed Eng 2017;64(7):1619–1630.

[8] Ramírez J, et al. T-Wave Morphology Restitution predicts Sudden Cardiac Death in patients with Chronic Heart Failure. Journal of the American Heart Association Apr. 2018; 6(5).

[9] Ramírez J, et al. Comparison of ECG T-wave duration and morphology restitution markers for sudden cardiac death prediction in chronic heart failure. In 2017 Computing in Cardiology (CinC). IEEE ;1–4.

[10] Gómez N, et al. Changes in T-peak-to-T-end Morphology Measured by Time-Warping are associated with ischemia-induced Ventricular Fibrillation in a porcine model. In 2022 Computing in Cardiology (CinC). IEEE ;1–4.

[11] Santos JBF, et al. Analysis of three-dimensional scar architecture and conducting channels by high-resolution contrast-enhanced cardiac magnetic resonance imaging in chagas heart disease. Revista da Sociedade Brasileira de Medicina Tropical Oct. 2022;55(e06882021).

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