Sudden Cardiac Death Prediction in Chronic Heart Failure Patients by Periodic Repolarization Dynamics

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Abstract

Chronic heart failure (CHF) is a clinical syndrome associated with high mortality due to pump failure death (PFD) resulting from heart failure progression as well as to ventricular arrhythmias leading to sudden cardiac death (SCD). CHF patients are known to experience autonomic nervous system imbalance, which is expected to be reflected in the electrocardiogram (ECG). Periodic Repolarization Dynamics (PRD) quantifies low-frequency oscillations in the T wave of the ECG and has been related to sympathetic modulation of ventricular repolarization. In this study, we assessed the capacity of PRD to predict PFD and SCD in a CHF population. 20-minute 3-lead ECG recordings of 569 patients with symptomatic CHF and normal sinus rhythm were analyzed. PRD values were measured by analyzing 5-minute segments with 4-minute overlap. Each patient was assigned with the minimum PRD value over segments. PRD was higher in SCD victims than PFD victims and even more so than survivors and non-cardiac death victims, although differences were not statistically significant. Low- and high-risk groups were defined by dichotomization according to median PRD in the population. Hazard ratio [95% Confidence Interval] for SCD from univariate Cox regression was 1.808 [1.031-3.169] deg (p=0.039). In conclusion, PRD predicts SCD in a CHF population, with SCD victims presenting enhanced sympathetic-induced oscillations of ventricular repolarization.

1. Introduction

Chronic heart failure (CHF) is a cardiac syndrome with high morbidity and mortality rates worldwide. Only in the United States, there are currently around 6 million people suffering from CHF and projections indicate that more than 8 million people will suffer from this condition by 2030 [1]. CHF is characterized by functional and structural abnormalities in the heart that hamper its ability to pump blood sufficiently to maintain the body's needs. Importantly, autonomic imbalance has been shown to occur in CHF, with increased sympathetic activity and withdrawal of parasympathetic activity, altogether leading to further worsening of CHF prognosis [2].

Sudden cardiac death (SCD), defined as unexpected death caused by loss of heart function, represents the main underlying cause of mortality in CHF patients. Another common cause of death in CHF is pump failure death (PFD), resulting from a deterioration of heart failure. Prediction of these two modes of death is of major importance, as it can help in the application of more tailored therapies, which can lead to an improvement in the quality of life of affected patients.

A number of non-invasive markers measured from the electrocardiogram (ECG) have been proposed for PFD and SCD risk stratification in CHF. Among others, QT dispersion [3], Tpeak-to-Tend interval [4] and T wave alternans [5] have been evaluated. Periodic Repolarization Dynamics (PRD) has been recently proposed to assess sympathetic modulation of ventricular repolarization by measuring low-frequency (below 0.1 Hz) oscillations in the T wave vector [6]. The capacity of PRD to predict total and arrhythmic mortality and to identify benefit from ICD implantation in post-myocardial infarction populations has been demonstrated [6, 7]. The aim of this work is to assess the capacity of PRD to risk stratify for PFD and SCD in a cohort of CHF patients.

2. Study Population

The study population consisted of 569 patients with symptomatic CHF, New York Heart Association (NYHA)

classes II and III, enrolled in the MUSIC (MUerte Subita en Insuficiencia Cardiaca) study, a prospective, multicenter, longitudinal study designed to assess risk predictors of cardiac mortality and SCD in CHF ambulatory patients [8].

20-minute high-resolution (1000 Hz) ECG recordings were acquired at rest by using SpiderView recorders (ELA Medical, SorinGroup, Paris, France). Three orthogonal leads were analyzed for each patient.

Patients were followed up every 6 months on an outpatient basis for an average of 48 months. The study group included 53 victims of SCD, 53 victims of PFD, 37 non-cardiac death victims and 426 survivors. Death was defined as SCD if it was: (i) a witnessed death occurring within 60 minutes from the onset of new symptoms, unless a cause other than cardiac was obvious; (ii) an unwitnessed death ($<$ 24 hours) in the absence of preexisting progressive circulatory failure or other causes of death; or (iii) a death during attempted resuscitation. Endpoints were reviewed and classified by the MUSIC Study Endpoint Committee. The study protocol was approved by institutional investigator committees and all patients gave written informed consent.

3. Methods

3.1. Preprocessing

Preprocessing of ECG signals included noise removal using a 50 Hz notch filter, heart beat detection and labelling using Aristotle ECG analysis software [9]. Since subsequent analysis focused on the T wave, a 40 Hz low-pass filter was applied to remove noise without altering the T wave shape. Finally, cubic splines interpolation was applied to estimate and remove baseline wander.

A window including the T wave was defined from T wave onset, T_{on_i}, to T wave end, T_{off_i}, defined according to the following rules, expressed as a function of the corresponding QRS mark (QRS_i) and RR interval (RR_i), with i denoting beat index:

- If $RR_i < 720$ ms,

$$T_{on_i} = QRS_i + 90 \text{ ms}$$
$$T_{off_i} = QRS_i + \min(360, \tfrac{2}{3} RR_i) \text{ ms}.$$

- If $RR_i \geq 720$ ms,

$$T_{on_i} = QRS_i + 90 \text{ ms}$$
$$T_{off_i} = QRS_i + 360 \text{ ms}.$$

A noise level was defined for each T wave by measuring the high-frequency components (above 15 Hz) [10]. The defined T wave window boundaries were discarded for low-quality beats (noise level $>$140 μ V) but the associated QRS marks were retained.

Two types of incidences were found in the identification of QRS marks: QRS marks defined in the absence of a beat and QRS marks not defined for existing beats. An automatic algorithm was used to replace ectopic and erroneously detected beats by normal beats [11]. If two consecutive QRS marks still remained within 50 ms, the second one was disregarded.

3.2. Periodic Repolarization Dynamics

The angles between consecutive T waves were calculated from the preprocessed ECG signals by an updated method, defined in [12], based on the original method proposed in [6]. The method included the following steps:
1. The boundaries of each T wave window were identified according to the method described in section 3.1.
2. A constant value was subtracted from each T wave in each of the analyzed leads so that the amplitude at the T wave end boundary was set to 0 mV.
3. An average T wave vector was calculated for each T wave window. The angle dT° between two consecutive T waves, which is associated with the instantaneous degree of repolarization instability, was calculated by using the dot product of the two average T wave vectors.
4. A 10th-order median filter was applied to the dT° time series to attenuate outliers and avoid very abrupt changes.

To compute PRD from the dT° series, a phase-rectified signal averaging (PRSA)-based method was used [13], which included:
5. Anchor points were defined by comparing averages of M=9 values of the dT° series prior and posterior to each anchor point candidate x_i. A beat i was considered an anchor point if:

$$\frac{1}{M} \sum_{j=0}^{M-1} x_{i+j} > \frac{1}{M} \sum_{j=1}^{M} x_{i-j}. \tag{1}$$

The use of M=9 allows detecting frequencies in the range of interest (from 0.025 to 0.1 Hz).
6. Windows of W=40 values were defined around each anchor point. If an anchor point was so close to the beginning or to the end of the dT° series that there were not enough samples before or after it, it was disregarded.
7. PRSA series was obtained by averaging the dT° series over all defined windows of length W described in the previous step.

PRD was defined as the difference between the maximum and minimum values of the PRSA series. Each 20-minute ECG recording was divided into 5-minute segments with 4-minute overlap and PRD was measured in each of those segments. Finally, each patient was assigned with the minimum PRD value over segments.

3.3. Statistical analysis

PRD values in patient subgroups are presented as median [interquartile range (IQR)]. The Mann-Whitney U test

(or Wilcoxon rank-sum test) was used for univariate comparisons of PRD values between patient groups. Survival probability was estimated and graphically shown according to the Kaplan-Meier method, with comparisons between survival times performed by the log-rank test. The Cox proportional hazards regression model was used in the prediction of SCD, with hazard ratios (HAR) and 95% confidence intervals used for characterization. P values <0.05 were considered as statistically significant. Variables providing significantly different survival times between groups were entered into the Cox regression model. MATLAB R2017a (9.2) and SPSS (version 24.0) were used for the analysis.

4. Results

4.1. Association with cardiac mortality

Figure 1 presents boxplots showing statistical distributions of PRD in three analyzed patient subgroups, namely SCD victims, PFD victims and the rest of patients (survivors plus non-cardiac death victims). Although no significant differences were found between these groups, PRD showed a trend towards higher values in SCD victims (with median [IQR] being 1.57 [1.21] deg) than in PFD victims (1.41 [0.91]) and even more than in survivors and non-cardiac death victims (1.24 [1.28] deg).
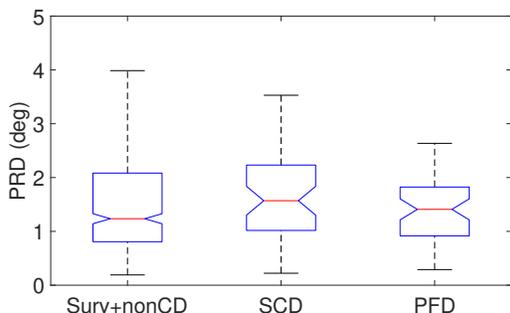

Figure 1. Boxplots of PRD for three patient subgroups: SCD, PFD and the rest of patients (survivors plus non-cardiac death victims).

4.2. Survival analysis

The median PRD value in the study population was used to define low-risk (PRD < 1.31 deg) and high-risk (PRD $\geq$ 1.31 deg) groups. When PFD was considered as endpoint, no significant differences in the survival times were found between those two groups. For SCD as endpoint, differences between survival times in the low-risk and high-risk groups were statistically significant ($p = 0.036$). The

probability curves for survival to SCD along follow-up are presented in Figure 2.
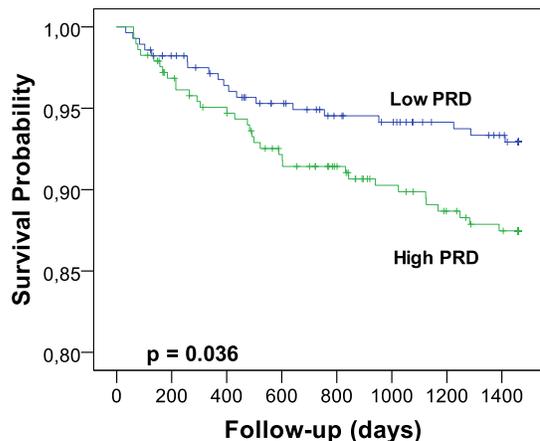

Figure 2. Estimated probability of survival to SCD for two patient subgroups dichotomized according to PRD.

In univariate Cox proportional model using PRD as the predictor variable, the hazard ratio [95% confidence interval] for SCD was 1.808 (1.031-3.169), $p = 0.039$.

5. Discussion and conclusions

Low-frequency oscillations in the T wave of the ECG were non-invasively measured by quantifying the PRD marker in 20-minute ECG recordings of CHF patients. PRD has been associated with sympathetic modulation of ventricular electrical activity [6]. Clinical, experimental and theoretical studies have shown that sympathetic provocation leads to increased magnitude of low-frequency oscillations of ventricular repolarization as measured from the T wave of the ECG, from activation recovery intervals of electrograms and from cellular action potentials [7, 14–16]. Potential mechanisms underlying those sympathetic-induced increases have been postulated, involving synergistic β-adrenergic and mechanical effects [14, 17].

When investigating PRD values separately in PFD victims, SCD victims and the rest of patients, differences were found, even if not reaching statistical significance. The highest PRD values were measured in SCD victims, which could possibly be indicative of higher sympathetic modulation of repolarization in those patients. After dichotomizing the study population into low- and high-risk groups based on median PRD, we found that SCD probability during follow-up was almost double in the high-risk than in the low-risk group ($p = 0.036$). This is in agreement with clinical and theoretical studies showing a relationship between increased PRD and enhanced arrhythmic risk [6, 7, 14, 17].

An interesting feature of this research is that PRD was calculated in 20-minute resting ECG recordings, thus facilitating generalization of PRD evaluation for risk stratification purposes. Other ECG indices, such as heart rate turbulence, deceleration capacity [18] or microvolt T wave alternans [5] are commonly measured from ambulatory ECG recordings or using specific protocols like stress tests.

In conclusion, this study indicates that PRD, a non-invasive marker of repolarization instability measuring low-frequency T wave oscillations, has the potential to predict SCD in CHF from short resting ECG recordings, with higher PRD values indicative of higher SCD risk.

Acknowledgements

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