Index of T-wave Variation as a predictor of Sudden Cardiac Death in Chronic Heart Failure Patients with Atrial Fibrillation

Alba Martín-Yebra[1,2], Iwona Cygankiewicz[3], Antoni Bayés-de-Luna[4], Pablo Laguna[2,5], Enrico G Caiani[1], Juan Pablo Martínez[2,5]

[1] Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy
[2] BSICoS Group, Aragón Institute of Engineering Research, IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain
[3] Department of Electrocardiology, Medical University of Lodz, Lodz, Poland
[4] Institut Català de Ciències Cardiovasculars, Santa Creu i Sant Pau Hospital, Barcelona, Spain
[5] CIBER en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Zaragoza, Spain

Abstract

Chronic heart failure (CHF) and atrial fibrillation (AF) are worldwide leading causes of morbidity and mortality in elders, a large part of them due to sudden cardiac deaths (SCD). The high irregularity of ventricular response in AF patients makes the use of standard SCD-risk markers inappropriate in this target population. The aim of this study was twofold: i) to propose a new index, suitable for AF patients, sensitive to ventricular repolarization changes; and ii) to evaluate its prognostic value in a CHF population with AF. Holter ECG recordings from 176 consecutive CHF patients with AF (22 SCD) were analyzed. The index of T-wave variation (I_{TV}), quantifying the average T-wave changes in pairs of consecutive beats under stable rhythm conditions, was computed using a fully-automatic method. Survival analysis was performed considering SCD as an independent endpoint. I_{TV} was higher for SCD than non-SCD victims (median (Q1;Q3): 12.44 (7.21;42.71) μV vs 8.57 (5.63;14.08) μV, p=0.06). In a survival analysis where a threshold on the third quartile of I_{TV} values was set, I_{TV}(+) outcome was successfully associated to SCD (Hazard Ratio (CI):3.217 (1.365,7.581) per μV, p=0.008). In conclusion, we show in this work that I_{TV} stratifies CHF patients with AF according to their risk of SCD, with larger I_{TV} associated to lower survival probability.

1. Introduction

Chronic heart failure (CHF) is the leading cause of morbidity and mortality worldwide, representing the major cause of hospitalizations together with atrial fibrillation (AF) in elderly ($\geq$65 years) patients. A number of mechanisms supporting both that CHF predispose to AF and that AF exacerbates CHF are reported [1]. Frequently both disorders coexist, exponentially increasing its incidence and prevalence with age and decreasing quality of life [2].

In particular, the prevalence of AF in patients with mild-to-moderate CHF (New York Heart Association, NYHA, classes II and III), ranges from 10% to 15% [1]. In this group of patients, a large portion of mortality is represented by sudden cardiac deaths (SCD), most of them being as a consequence of ventricular tachyarrhythmias.

Many questions arise regarding the underlying mechanisms that associate AF, CHF and SCD risk and a better understanding is still needed in order to adopt effective prediction and prevention strategies. Therapeutic options are mainly oriented to an adequate control of ventricular rate and to restore and maintain sinus rhythm. Implantable cardioverter-defibrillators (ICDs), by terminating ventricular tachyarrhythmias, protect from SCD, but identifying patients who benefit the most from this therapy is difficult, especially in the AF subgroup.

The spatio-temporal repolarization heterogeneity of ventricular activity, reflected on the T wave of the electrocardiogram (ECG), is commonly used to diagnose and assess SCD risk. Ventricular response during AF is highly irregular, mainly influenced by the properties of the atrioventricular (AV) node and atrial electrophysiology. Consequently, this makes not suitable the use of well established non-invasive indices for ventricular repolarization analysis, such as QT dispersion [3], the Tpeak-to-Tend interval [4] or T wave alternans (TWA) [5], as they require certain stability in rhythm to be properly assessed.

Our aim in this study was to propose a new index sensitive to ventricular repolarization changes based on a selective heart rate bin averaging technique as well as to evaluate whether it provides prognostic value in a CHF population with AF.

2. Study population

Consecutive patients with symptomatic CHF corresponding to NYHA classes II and III were enrolled in the multicenter MUSIC (MUerte Súbita en Insuficiencia Cardiaca) study, a prospective study designed to assess risk predictors for cardiovascular mortality in ambulatory CHF patients [6]. The 24-hour Holter ECG recordings of 176 patients (134 males) with AF aged 35-90 years (68.77±10.22 years) were available for the present study. ECG signals were acquired by using SpiderView records (ELA Medical, Sorin Group, Paris, France) and two or three orthogonal leads (X, Y, Z) sampled at 200 Hz were recorded for each subject. Collection of clinical data for this population was already reported elsewhere in [6, 7].

Patients were followed up every 6 months during 48 months. A total of 22 victims of SCD, 24 of other cardiac causes, 20 non-cardiac deaths and 110 survivors were included. SCD, 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, was considered as an independent endpoint in this study. Endpoints were reviewed an 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

We proposed the use of selective beat averaging technique that considers beats preceded by stable RR [8, 9] and compute the average T-wave variation waveform in pairs of consecutive beats defined by bins of stable RR.

3.1. Preprocessing

Preprocessing of ECG recordings included heart beat detection and labelling using the Aristotle ECG analysis software [10] and linear filtering of baseline wander. Finally, the ECG was low-pass filtered (with cut-off frequency of 15 Hz) to remove noise out of T-wave frequency range and down-sampled.

3.2. Selective beat averaging

Selective beat averaging was used to obtain averages of P-QRS-T complexes preceded by the same stable RR interval [8]. Based on this, we computed the RR interval series along the 24h Holter recording, being the RR interval associated to beat i, defined as the difference between the i and $(i-1)$ R-wave positions, as illustrated on Fig. 1. We then proceeded in this way:

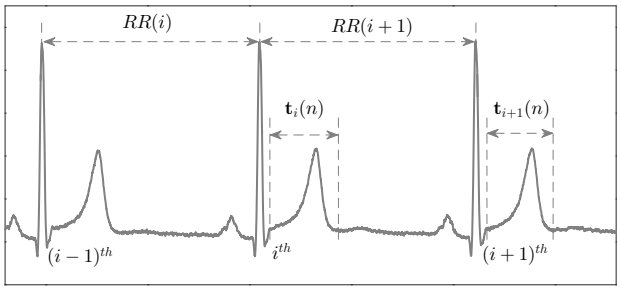

Figure 1. ECG signal with main explicative intervals.

1) Let us define S as the set of all consecutive beat pairs $(i, i+1)$, for any beat i in the Holter recording. S_{k}, $\mathrm{k} = 1, \ldots, \mathrm{K}$, are defined as the subsets of beat pairs in S such that $RR(i)$ is within the k^{th} defined RR interval bin, and the difference between $RR(i+1)$ is close enough to $RR(i)$. That is:

$$S_{\mathrm{k}} = \big\{ i : (i, i+1) \in S; RR(i) \in I_{\mathrm{k}}, \\ |RR(i+1) - RR(i)| \leq \Delta/2 \big\} \quad (1)$$

$$I_{\mathrm{k}} = \big\{ RR(i) : \mathrm{minRR} + (\mathrm{k}-1)\Delta \leq \\ \leq RR(i) \leq \mathrm{minRR} + \mathrm{k}\Delta - 1 \big\} \quad (2)$$

where K is the total number of bins within the considered RR range. We used Δ = 40 ms bins, initially between minRR = 300 ms and maxRR = 1600 ms.

2) At this point, once beats are grouped based on a heart-rate criteria and a certain stability can be assumed, for each pair of consecutive beats we computed the corresponding vectorcardiogram (VCG). Then, the variation waveform associated to the i^{th} pair of beats in S_{k} was defined as the difference of the two consecutive ST-T complexes. Using vector notation it is:

$$\mathbf{t}_{\Delta i}(n) = \mathbf{t}_{i+1}(n) - \mathbf{t}_i(n) \quad (3)$$

where vector $\mathbf{t}(n)$ denotes the ST-T complex (Fig. 1).

3) In order to make a robust estimation, as this variation of the ventricular activity could be within the range of non-visible microvolt sometimes comparable to the noise level, we replicate the analysis already presented in [11] in the context of TWA analysis, where all TWA waveforms were aligned in phase before the averaging. In this case, the phase-aligned waveform, $\mathbf{t}^{\mathbf{a}}_{\Delta i}$, was estimated as:

$$\mathbf{t}^{\mathbf{a}}_{\Delta i} = sign\left(\mathbf{t}^{\mathrm{T}}_{\Delta i}\mathbf{w}_1\right)\mathbf{t}_{\Delta i} \quad (4)$$

where $\mathbf{w}_1$ corresponds to the first eigenvector associated to the greatest eigenvalue λ_1 of the spatial correlation matrix $\mathbf{R}_{\mathbf{t}_\Delta}$ of all $\mathbf{t}_{\Delta i}$, (see [11] for more details).

4) Finally, the T-wave variation waveform associated to the k^{th} bin, i.e. associated the S_{k} subset, denoted as

$\bar{\mathbf{t}}^{\mathbf{a}}_{\Delta \mathrm{k}}$, is defined as the median waveform of all $\mathbf{t}^{\mathbf{a}}_{\Delta_i}$ computed for that bin.

3.3. Index of T-wave variation

The index of T-wave variation $\mathrm{I_{TV}}$ is then defined as the mean value of the final average waveform of all $\bar{\mathbf{t}}^{\mathbf{a}}_{\Delta \mathrm{k}}$:

$$\mathrm{I_{TV}} = \frac{1}{\mathrm{N}} \sum_{\mathrm{n}=1}^{\mathrm{N}} \left| \frac{1}{\mathrm{K}} \sum_{\mathrm{k}=1}^{\mathrm{K}} \bar{\mathbf{t}}^{\mathbf{a}}_{\Delta \mathrm{k}}(n) \right| \quad (5)$$

with N the total number of samples of the ST-T complex.

3.4. Statistical analysis

Data is presented as median (25^{th}; 75^{th} percentiles) for continuous variables, unless otherwise specified. Mann-Whitney test was applied to evaluate differences among groups. Survival analysis was performed by using Kaplan-Meier estimator and comparison of cumulative events by log-rank test. Prognostic value of $\mathrm{I_{TV}}$ in predicting SCD was determined with univariate and multivariates Cox proportional hazards analysis. For all tests, the null hypothesis was rejected for $\mathrm{p} \leq 0.05$.

4. Results

The average distribution of $\mathrm{I_{TV}}$ but computed for each single RR-bin S_{k}, for both the SCD and non-SCD groups is shown on Fig. 2. One can see that amplitudes differed from one group to the other, especially in the range from 300 to 600 ms, with higher values in the SCD group. From this observation and as a preliminary step, we decided to restrict the $\mathrm{I_{TV}}$ to this sub-range of RRs for the subsequent analysis. The $\mathrm{I_{TV}^{300\text{-}600}}$ was higher for the SCD in comparison to the non-SCD group (12.44 (7.21;42.71) μV vs 8.57 (5.63;14.08) μV, p=0.06). It should be noticed here that $\mathrm{I_{TV}^{300\text{-}600}}$ could not be computed in 12 subjects (1 from SCD and 11 from non-SCD group), either because only 2 leads were available (8 patients) or the methodology did not select any processable interval.

Patients were classified as $\mathrm{I_{TV}}$(+) and $\mathrm{I_{TV}}$(-), setting the cut point at the third quartile of $\mathrm{I_{TV}^{300\text{-}600}}$ (16.11 μV), what successfully predicted SCD (Table 1). In addition to the univariate Cox proportional model, two multivariate models were also constructed by adjusting for significant clinical covariates: (1) age, gender, NYHA class, left ventricular ejection fraction$\leq$35%, and diabetes and (2) use of antiarrhythmic drugs: beta-blockers (103 patients), digoxin (106) and amiodarone (27) plus covariables in 1. For all models, a $\mathrm{I_{TV}}$(+) outcome was the only variable associated with SCD risk, with an hazard ratio of 3.217, 3.050 and 3.508 for univariate, multivariate 1 and multivariate 2, respectively. Figure 3 shows the Kaplan-Meier survival curve for SCD.

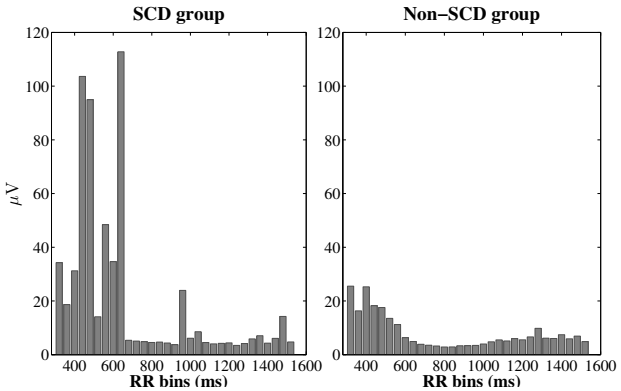

Figure 2. Average distributions of $\mathrm{I_{TV}}$ for each single RR-bin S_{k} in the SCD and non-SCD groups.

5. Discussion and conclusion

The underlying mechanisms between the association of AF with SCD are intriguing. Indeed, some studies suggested that AF is intrinsically proarrhythmic in the ventricle, increasing susceptibility to ventricular arrhythmias (and, consequently, SCD) whereas others support the hypothesis that AF is actually acting through other risk factors, like CHF, leading to the increase in SCD incidence [12]. A more comprehensive understanding of this phenomena is still needed to better adapt treatment strategies, and to find the answer to in what patients this proarrhythmic risk is higher using noninvasive methods will be of fundamental importance.

In this preliminary study based on observational results, we found that the index of T-wave variation $\mathrm{I_{TV}}$, quantifying the consecutive T-wave variation based on a selective beat averaging methodology, independently predicted SCD in CHF patients with AF.

In sinus rhythm, the predictive value of several ventricular-based indices, such as QT dispersion [3], the Tpeak-to-Tend interval [4] or TWA [5] among others has been widely demonstrated. However, the high irregularity of ventricular response in AF patients makes the use of those indices not extensive to this pathology. Data on SCD stratification in AF patients based on repolarization indices is still scarce. In a previous study based on HR information including a subset of 155 AF patients from our cohort, authors demonstrated that reduced irregularity of RR intervals in terms of approximate entropy (ApEn) during AF was also predictive of cardiac mortality as opposed to traditional indices [13]. These results encourage to continue research in this field. For example, the evaluation of combined both non-invasive indices of ventricular dispersion together with HR-derived indices, may improve this prediction. Also previous observations that short-long-short beat sequences may lead to VT/VF episodes [14] suggest the possibility of evaluating ventricular repolar-

Table 1. Association of $I_{TV}^{300\text{-}600}$ with SCD death in patients with heart failure and atrial fibrillation.

	Univariate		Multivariate 1*		Multivariate 2**	
	HaR (95% CI)	p-value	HaR(95% CI)	p-value	HaR(95% CI)	p-value
$I_{TV}^{300\text{-}600} \geq 16.11$	3.217 (1.365,7.581)	**0.008**	3.050 (1.282,7.256)	**0.012**	3.508 (1.410,8.724)	**0.007**

* Adjusted model includes age, gender, New York Heart Association class, left ventricular ejection fraction$\leq$35%, and diabetes.

** Adjusted model includes covariables in model 1 plus the use of antiarrhythmic drugs: beta-blockers (n=103), digoxin (106) and amiodarone (27)

ization activity by extending the methodology to new beat sequences. Improving the performance of SCD-risk stratification by using non-invasive methods is one of the main problems that public health systems are facing nowadays.

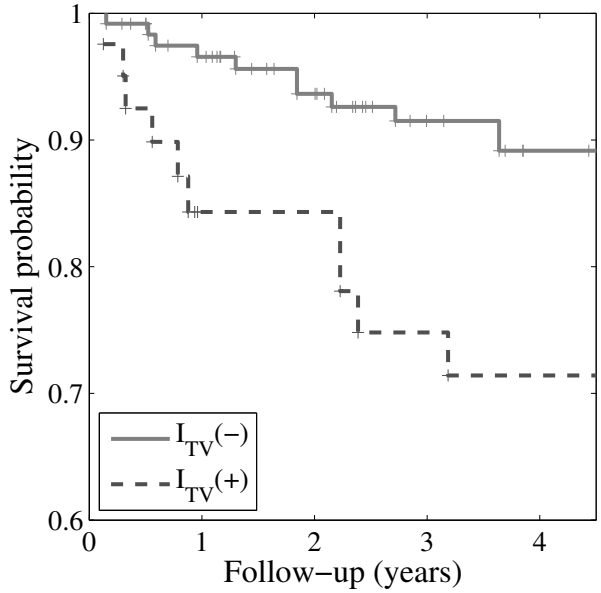

Figure 3. Long-term survival curves for sudden cardiac death according to $I_{TV}(+)$ and $I_{TV}(-)$ outcomes.

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Address for correspondence:

Alba Martín

DEIB, Politecnico di Milano Piazza Leonardo da Vinci, 32, 20.133, Milano, Italy

albapilar.martin@polimi.it