Circadian Modulation on T-wave Alternans Activity in Chronic Heart Failure Patients

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Abstract

Average TWA activity has been shown to be an independent predictor of sudden cardiac death (SCD) in chronic heart failure (CHF) patients. However, the influence of circadian rhythms on TWA remains understudied. In this work, we aimed to assessed circadian TWA changes in a CHF population and to evaluate whether the prognostic value of TWA indices is sensitive to the circadian pattern. Holter ECG recordings from 626 consecutive CHF patients (52 SCD) were analyzed. Index of average alternans (IAA), quantifying the average TWA level, was measured in 4 consecutive 6-hour intervals using a multilead fully-automated method. Survival analysis was performed considering SCD as an independent endpoint. IAA changed along the day, with statistically significant lower values during the night than during daytime. This pattern is similar to the one observed in the mean HR. However, a low correlation (r=.18) was found between IAA and HR. After dichotomization of patients based on the third quartile of IAA indices, both $IAA_{06\text{-}12}$ and $IAA_{18\text{-}24}$ indices successfully predicted SCD (HR:2.34 per μV, IC: 1.33-4.13 and HR:1.87 per μV, IC: 1.04-3.36, respectively). In conclusion, time of the day should be considered for SCD risk prediction.

1. Introduction

A great part of deaths in patients with mild-to-moderate chronic heart failure (CHF) are represented by sudden cardiac deaths (SCD), being most of them as a consequence of ventricular tachyarrhythmias. In this context, implantable cardioverter-defibrillators (ICD) have been shown to be highly effective at terminating these life threatening arrhythmias. However, the cost-effectiveness of this therapy is still low and identifying patients at risk who would benefit the most from ICD therapy remains a clinical challenge.

T-wave alternans (TWA), a consistent beat-to-beat alternation in the amplitude or morphology of the ST segment and/or the T wave, reflects temporal and spatial heterogeneity of ventricular repolarization. It is presently regarded as a noninvasive risk marker for identifying patients at risk for SCD and ventricular vulnerability [1]. Although the long-term averaging of TWA activity in ambulatory recordings has been shown to be an independent predictor of SCD in CHF [2], the influence of circadian rhythms on TWA remains still understudied.

Our aim in this study was to assess circadian TWA changes in a CHF population as well as to evaluate whether the prognostic value of TWA is sensitive to this circadian pattern. To do that, a novel signal processing methodology, that improves TWA estimation under noisy conditions, has been proposed.

2. Study population

Consecutive patients with symptomatic CHF corresponding to New York Heart Association (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 [3]. The study protocol was approved by institutional investigator committees and all patients gave written informed consent. The 24-hour Holter ECG recordings of 626 patients (52 victims of SCD, 63 of other cardiac causes, 25 non-cardiac deaths and 486 survivors) with sinus rhythm and aged 18-89 years (62.7$\pm$11.9 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 available for each subject. Collection of clinical data

for this population was reported in previous studies [3, 4].

Patients were followed up every 6 months for a median of 48 months. 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.

3. Methods

3.1. Preprocessing

Preprocessing of ECG recordings included heart beat detection and labeled using the Aristotle ECG analysis software [5] and linear filtering of baseline wander. Finally, the ECG was low-pass filtered (with cut-off frequency of 15 Hz) and down-sampled to remove noise out of TWA frequency range.

3.2. TWA measurement

Index of average alternans (IAA), quantifying the average TWA level, was measured in consecutive 6-hour intervals (00.00-06.00 h; 06.00-12.00 h; 12.00-18.00 h; 18.00-24.00 h) using a multilead fully automated method based on periodic component analysis (πCA) combined with the Laplacian likelihood ratio method (LLRM) [2].

For each day interval, ECG signals were processed in segments of 128 consecutive beats (50% overlapped) with additional stability criterion imposed, as defined in [2], in order to consider only suitable segments for automatic analysis.

For estimating TWA amplitude of each segment ($\mathrm{V_k}$), we replicated the analysis performed in [2]: the three orthogonal leads were linearly combined in order to maximize the TWA content over noise by using πCA [6] and then, the LLRM [7] was applied in the new combined lead to estimate the TWA waveform of each segment, expressed as the median difference between ST-T complexes of even and odd beats.

The non-visible microvolt range of TWA, sometimes comparable to the noise level, makes the TWA detection a challenging task. At this point, a novel methodological step for the computation of the TWA amplitude was included in the analysis, consisting in the phase alignment of all TWA estimated waveforms before averaging.

In vector notation, the TWA estimated waveform of the $\mathrm{k^{th}}$ segment was defined as

$$\mathbf{y}_{\mathrm{k}}(n) = \left[y_{\mathrm{k}}(1) \ \ldots \ y_{\mathrm{k}}(N)\right]^T \tag{1}$$

First, a detrended version of each $\mathbf{y}_{\mathrm{k}}$, denoted as $\mathbf{y}_{\mathrm{k}}^{'}(n)$ was computed:

$$\mathbf{y}_{\mathrm{k}}^{'}(n) = \mathbf{y}_{\mathrm{k}}(n) - (a_{\mathrm{k}} + b_{\mathrm{k}} n) \tag{2}$$

The coefficients a_{k} and b_{k} were chosen as those that defined the linear interpolation between $y_{\mathrm{k}}(1)$ and $y_{\mathrm{k}}(N)$, whith the aim of eliminating any possible residual baseline component at the alternans frequency.

Then, the spatial correlation matrix of $\mathbf{y}_{\mathrm{k}}^{'}$, $\mathbf{R}_{\mathbf{y}'}$, was estimated as

$$\mathbf{R}_{\mathbf{y}'} = \frac{1}{\mathrm{N}} \sum_{\mathrm{k}=1}^{\mathrm{K}} \mathbf{y}_{\mathrm{k}}^{'} \mathbf{y}_{\mathrm{k}}^{'T} \tag{3}$$

being K the total number of suitable segments for the analysis.

To obtain the dominant waveform, that is, the first principal component, the following eigenvector equation for $\mathbf{R}_{\mathbf{y}'}$ was solved:

$$\mathbf{R}_{\mathbf{y}'} \mathbf{w}_1 = \mathbf{w}_1 \lambda_1 \tag{4}$$

where $\mathbf{w}_1$ corresponds to the first eigenvector and λ_1 the first eigenvalue of $\mathbf{R}_{\mathbf{y}'}$.

At this point, the phase-aligned waveform, $\mathbf{y}_{\mathrm{k}}^{a}$, was estimated as:

$$\mathbf{y}_{\mathrm{k}}^{a} = sign\left(\mathbf{y}_{\mathrm{k}}^{T} \mathbf{w}_1\right) \mathbf{y}_{\mathrm{k}} \tag{5}$$

Finally, the IAA was defined as the mean value of the average waveform of all $\mathbf{y}_{\mathrm{k}}^{a}$:

$$\mathrm{IAA} = \frac{1}{\mathrm{N}} \sum_{\mathrm{n}=1}^{\mathrm{N}} \left(\frac{1}{\mathrm{K}} \sum_{\mathrm{k}=1}^{\mathrm{K}} \mathbf{y}_{\mathrm{k}}^{a}(n) \right) \tag{6}$$

3.3. Statistical analysis

Data is presented as median (25^{th}; 75^{th} percentiles) for continuous variables, unless otherwise specified. Nonparametric Friedman test and Wilcoxon signed rank paired test with Bonferroni correction were applied to evaluate differences among time intervals. Survival analysis was performed by using Kaplan-Meier estimator and comparison of cumulative events by log-rank test. Prognostic value of TWA indices in predicting SCD was determined with univariate Cox proportional hazards analysis. For all tests, the null hypothesis was rejected for $\mathrm{p} \leq 0.05$.

4. Results

Distribution of HR and IAA for the four defined intervals are presented in Fig. 1. Significant differences were found between the night and all daytime periods. IAA was found minimal during the night period, reaching its maximum value for the interval defined from 12.00 to 18.00

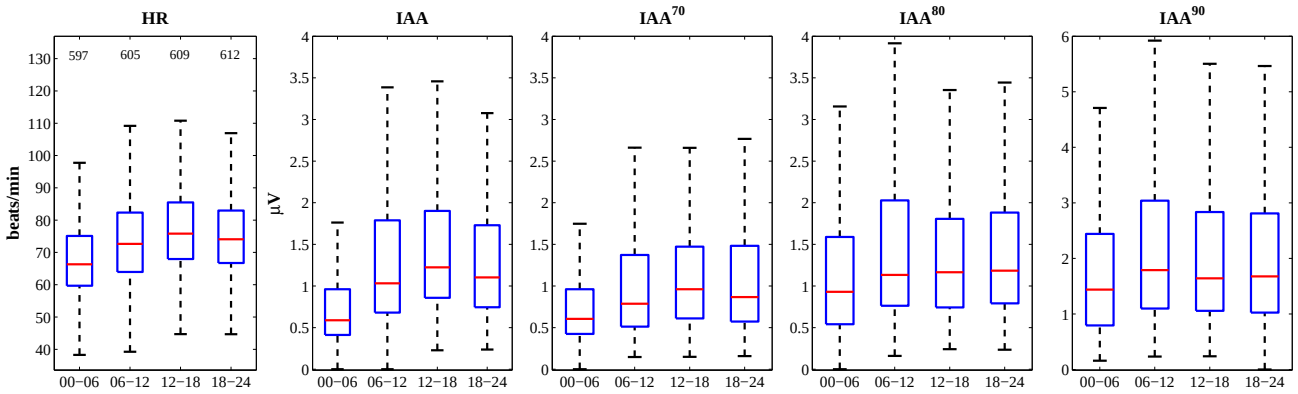

Figure 1. Distribution of HR and IAA indices for each day interval. Number of records in which IAA could be computed at each day period is indicated on left panel above the boxes.

h ($IAA_{00\text{-}06}$=0.58 (0.41;0.96) μV, $IAA_{12\text{-}18}$= 1.22 (0.86;1.90) μV, p<0.001). It should be noticed here that not all ECGs presented data for the total 24 hours, and consequently IAA could not be computed for each interval in all subjects (number of available recordings for each day period are indicated in Fig. 1, left panel).

The same trend was observed when considering average HR (Fig. 1, left panel). However, a weak correlation was found between IAA and average HR (r=0.18, p<0.001) and when considering IAA HR-restricted indices (IAA^{X}, $X = \{70, 80, 90\}$, HR ranging from X-10 to X beats/min) a similar oscillation pattern remains still visible. Additionally, an increasing tendency from IAA^{70} to IAA^{90} in all day periods, was evidenced.

Patients were classified as TWA(+) and TWA(-) based on the third quartile of IAA indices. By setting cut points $IAA_{06\text{-}12}$=1.789 μV and $IAA_{18\text{-}24}$=1.72 μV, both indices successfully predicted SCD (see Table 1). Survival probability curves for $IAA_{06\text{-}12}$ and $IAA_{18\text{-}24}$ are shown in Fig. 2.

Table 1. Assocaition of TWA indices with SCD death.

	Hazard ratio (95% CI)	**p-value**
$IAA_{00\text{-}06} \geq 0.961$	1.18 (0.60,2.30)	0.628
$IAA_{06\text{-}12} \geq 1.789$	**2.34 (1.33,4.13)**	**0.003**
$IAA_{12\text{-}18} \geq 1.900$	1.64 (0.91,2.9)	0.097
$IAA_{18\text{-}24} \geq 1.729$	**1.87 (1.04,3.36)**	**0.035**

5. Discussion and conclusion

Average TWA activity computed during both the morning (from 06.00 to 12.00 h) and the evening periods (18.00 to 24.00h) is associated with the risk of SCD in CHF patients. Interestingly, it coincides with the two circadian periods of elevated risk for SCD, whose distribution has been reported to present a primary peak of incidence from 7 to 11 a.m. and a secondary peak from 5 to 7 p.m. [8]. It should be remarked that the predictive value of both $IAA_{06\text{-}12}$ and $IAA_{18\text{-}24}$ indices, not only considerably reduces the required time for ECG monitoring from 24 to 6 hours, which implies some advantages in the clinical practice, especially for the patient, but also the computational cost of TWA analysis, also an important factor that should be considered.

The HR-restriction of IAA indices presented the same pattern for IAA^{70}, being similar when considering IAA^{80} and IAA^{90}. The increasing IAA indices from IAA^{70} to IAA^{90} are also consistent with the fact that TWA amplitudes for the same subject rises with instantaneous HR. However, only a weak correlation was found between average HR and IAA indices along the day, suggesting the influence of other HR-independent factors in IAA, which are known to be also determinant for TWA and related to higher cardiac electrical instability. Changes in autonomic neurotransmitters, with and increased activity of sympathetic nervous system during the day, especially more prominent at waking time, could be other determinant factors that significantly influence TWA [9]. Also, fluctuations in symptomatic and silent myocardial ischemia episodes, well-known to be linked to TWA phenomenon, have been reported to present this similar behavior [10]. All this supporting the hypothesis that IAA modulation along the day could be actually due to a circadian effect.

Automatic long-term averaging have been already shown to provide a reliable characterization of TWA in 24h-ECG recordings [2], avoiding the posterior visual verification usually needed when other methods, such as the modified moving average, are used [11]. The novel approach for computing IAA indices proposed in this work, including the phase alignment of TWA waveforms before

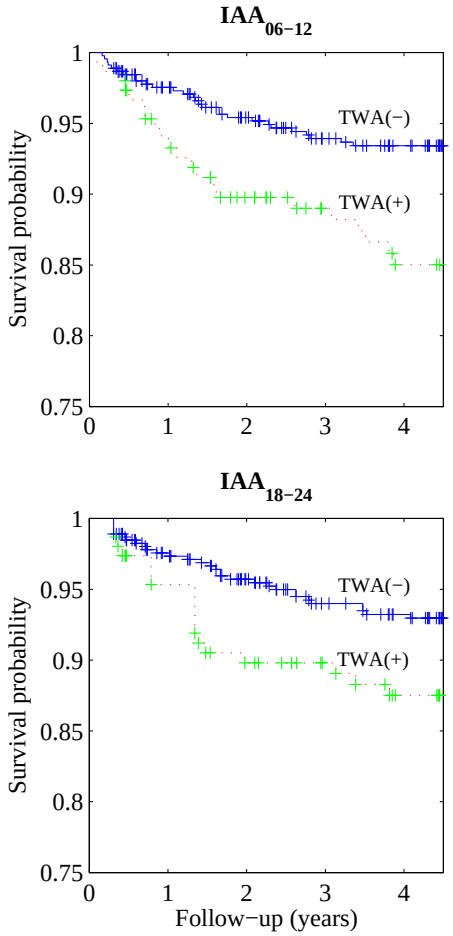

Figure 2. Survival curves for sudden cardiac death.

averaging, presents a more insensitive to noise solution, even in such an unfavorable condition when the TWA amplitude is at the noise level (i,e, a few microvolts).

In summary, results from a fully-automatic robuts methodology for TWA analysis suggest that circadian pattern modulates the IAA index, and time of the day should be considered for SCD risk prediction.

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References

[1] Verrier RL et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility – consensus guideline by International Society for Holter and Noninvasive Electrocardiology. J Am Coll Cardiol 2011;58(13):1309-24

[2] Monasterio V, Laguna P, Cygankiewicz I, et al. Average Twave alternans activity in ambulatory ECG records predicts sudden cardiac death in patients with chronic heart failure. Heart Rhythm 2012;9:383-389.

[3] Vázquez R, Bayés-Genís A, Cygankiewicz I, et al. The MUSIC risk score: a simple method for predictiong mortality in ambulatory patients with chronic heart failure. Eur Heart J 2009;30:1088 - 1096.

[4] Cygankiewicz I, Zareba W, Vázquez R, et al. Risk stratification of mortality in patients with heart failure and left ventricular ejection fraction $>$ 35 %. Am J Cardiol 2009;103:1003 - 1010.

[5] Moody GB, Mark RG. Development and evaluation of a 2-lead ECG analysis program. Computers in Cardiology 1982;9:39–44.

[6] Monasterio V, Clifford GD, Laguna P, Martínez JP. A multilead scheme based on periodic component analysis for T-wave alternans analysis in the ECG. Ann Biomed Eng 2010;38(8):2532-2541

[7] Martínez JP, Olmos S. Methodological principles of T wave alternans analysis: a unified framework. IEEE Trans Biomed Eng 2005;52(4):599-613

[8] Muller JE, Ludmer PL, Willich SN, et al. Circadian variation in the frequency of sudden cardiac death. Circulation 1987;75(1):131-138

[9] Verrier RL, Kumar K, Nearing BD. Basis for sudden cardiac death prediction by T-wave alternans from an integrative physiology perspective. Heart Rhythm 2009;6:416-422

[10] Nademanee K, Intarachot V, Josephson MA, et al. Circadian variation in occurrence of transient overt and silent myocardial ischemia in chronic stable angina and comparison with Prinzmental's angina in men. Am J Cardiol 1987;90:494-498

[11] Verrier RL, Nearing BD, Kwaku KF. Noninvasive sudden death risk stratification by ambulatory ECG-based T-wave alternans analysis: evidence and methodological guidelines. Ann Noninvasive Electrocardiol 2005;10:110-120

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