Analysis of T-Wave Alternans in ambulatory recordings using the ADTWA index

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***Abstract*— Implantable cardioverter defibrillators (ICD) are the most effective way of preventing sudden cardiac death (SCD). However, the implantation of an ICD is an invasive procedure with associated risks and a high cost. Therefore, it is necessary to determine non-invasive risk markers that identify patients at a higher risk of suffering malignant arrhytmias.One of the most promising non-invasive indices is T-wave alternans (TWA). This work assesses T-wave alternans using the Amplitude of Dominant T-Wave Alternans (ADTWA), that is derived from the dominant T wave associated to a number of consecutive beats. Data from 650 patients with heart failure enrolled in the MUSIC study were analyzed. ADTWA have higher values increasing heart rate. ADTWA was also significantly higher in SCD patients than in survivors (survivors vs. SCD: 6.60 ± 1.98 vs. 7.55 ± 2.53, p=0.01). ADTWA seems a promising index to identify patients with heart failure at higher risk of SCD.**

I. INTRODUCTION

Cardiovascular diseases are the major cause of death in adults and the elderly in the majority of the developed countries and in many developing countries. Many of these deaths occur suddenly, shortly after the onset of the first symptoms, and are related to malignant ventricular arrhytmias that lead to a heart attack. This kind of outcome is known as *sudden cardiac death* (SCD).

Implantable cardioverter defibrillators (ICD) are the most effective way of preventing SCD [2]. However, the implantation of an ICD is an invasive procedure with associated risks and a high cost. Therefore, it is necessary to determine *non-invasive risk markers* that identify patients at a higher risk of suffering malignant arrhytmias, so that invasive diagnostic test and treatments can be selectively applied only to those patients who will benefit the most, saving risk for the patients and also health-care costs.

Various non-invasive indices have been proposed to predict the risk of arrhytmias. Most of them are based either on the analysis of echocardiographic images [3] or on the analysis of electrocardiographic signals (QRS duration, QT dispersion, heart rate variability, etc.) [4]. The main limitation of existing indices is their low specificity and predictive value. One of the most promising non-invasive indices is T-wave alternans (TWA) [5]. Its prognostic value has been intensively studied and significant evidence of the relation between TWA and the susceptibility to ventricular fibrillation has been found in recent years [5]. TWA is a beat-to-beat alteration in morphology and amplitude of T-wave of the order of magnitude of a few microvolts. It is usually invisible at a naked eye and may be difficult to discern by a computerized method due to intrinsic noise of electrocardiograms.

Different methods have been proposed to measure TWA. The most used ones in clinical practice are Spectral Method (SM) [7] and Modified Moving Average Method (MMAM) [8]. They are single - lead methods, with proven clinical efficacy [5] and commercial systems.

The SM has been used to measure TWA in some specific clinical procedures such as stress tests and, in any case, analysis is restricted on heart rates comprised between 100 and 125 bpm [9] while the MMAM has been applied to Holter recordings, requiring visual inspection of the segments with TWA.

In 2010 a new multilead index based on the Laplacian Likelihood Ratio method combined with Periodic Component Analysis, was developed [10] which detected TWA by maximizing the ECG components at the TWA frequency, *i.e.*, 0.5 cycles per beat (cpb). In a second study [11] the method was used to measure TWA on a database of 650 Holter ECG recordings (MUSIC [12]). This work tests a method meant to evaluate presence of TWA in ambulatory recordings (ADTWA, *Amplitude of Dominant T-Wave Alternans*), recently introduced [13]. This method is multilead and based on the paradigm of the Dominant T-Wave (DTW), which in turn was derived by a physiological model of T-wave genesis. The methodological efficacy of the index had already been proved [15].

The purpose of this study is to assess the feasibility of quantifying this index in ambulatory recordings and the clinical relevance of this method, *i.e.*, its prognostic value in predicting cardiovascular diseases in a large population of subjects. This is the first time that such method is tested in the clinical practice and not on simulated signals.

II. STUDY POPULATION

Data from the MUSIC study [12] have been used in this work. MUSIC is a prospective study which enrolled patients in 9 centers in Spain between April 2003 and December 2004 who suffered from symptomatic heart failure (CHF, II-III NYHA functional classes). The study was designed to assess risk predictors for cardiovascular mortality in ambulatory patients with CHF. 992 ambulatory patients with CHF were

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included in the MUSIC study (718 men and 274 women), aged 18-89 years (mean 65 $\pm$ 12). Most patients (78.4%) were in NYHA class II. For our analysis we considered a subset of 650 patients which presented sinus rhythm.
As far as the follow-up phase is concerned, visits were conducted on an outpatient basis every 6 months, for a median of 44 months.
The total number of recorded deaths was 146 (22.5%), the most part of which had a cardiovascular origin. Among these, 66 (10.1%) were due to pump failure (PF) and 52 (8%) due to sudden cardiac death (SCD).
Twenty-four-hour ambulatory Holter recordings (XYZ orthogonal leads, 200-Hz sampling rate) were performed by using SpiderView recorders (ELA Medical, Sorin Group, Paris, France).

III. METHODS

A. Amplitude of Dominant T-Wave Alternans (ADTWA)

Amplitude of Dominant T-Wave Alternans (ADTWA) [13] offers a new perspective in the detection of T-wave alternans, that is defined as a beat–to–beat alteration in the repolarization morphology repeating every other heart beat. T-wave alternans is the manifestation of the spatial dispersion of the ventricular repolarization, which is a natural property of the human heart. Thus an increased T-wave alternans mirrors an increased dispersion in ventricular repolarization. A metric of ECG repolarization heterogeneity has been presented by Sassi and Mainardi in 2011 (*V-index*) [16]. This metric was derived from the analysis of a biophysical model of the ECG, where repolarization is described by the Dominant T-Wave (DTW) paradigm. The model explains the shape of T-waves in each lead as a projection of a main waveform (the DTW) and its derivatives weighted by scalars, the lead factors. In the ADTWA derivation, using the definition of alternans, a mathematical relation is then derived, in which each term has a clear physiological meaning.
TWA can be quantified, in each lead l, by considering the maximum absolute differences in the T waves of even and odd beats:

$$TWA = \max_t |\Psi_e - \Psi_o| \approx |A(\Delta\rho_e - \Delta\rho_o)| \max_t |T_D| \quad (1)$$

Where :

- Ψ_e is a matrix containing the average of the surface T-waves for even beats;
- Ψ_o is a matrix containing the average of the surface T-waves for odd beats;
- A is an transfer matrix, that accounts for both the volume conductor properties (geometry and conductivity) and the solid angle under which the single source, *i.e.* myocytes or group of contributes to the potential in each lead;
- $\Delta\rho_e$ is a vector containing the distance from the mean repolarization time of each node in even beats;
- $\Delta\rho_o$ is a vector containing the distance from the mean repolarization time of each node in odd beats;
- T_D is the dominant T-wave, which is the first derivative of the repolarization curve of the myocites' transmembrane action potential (TMP).

The remarkable aspect of Eq. 1 is that information on TWA is summarized into 2 factors:

- The $\max_t |T_D|$ term, which is related to the repolarization phase of the myocites transmembrane action potentials (TMPs).
- The difference $|A(\Delta\rho_e - \Delta\rho_o)|$, which accounts for differences in the repolarization times among *even and odd beats*

A single index of alternans can the be obtained across leads, l, as

$$I = \max_l |A(\Delta\rho_e - \Delta\rho_o)| \max_t |T_D| \quad (2)$$

where the first maximum is taken across the rows of the vector $|A(\Delta\rho_e - \Delta\rho_o)|$. The index can be rewritten as:

$$I = ADTWA = \max_l |\lambda_e u_e - \lambda_o u_o| \max_t |T_D| \quad (3)$$

Where:

- u_e and u_o are the first column of the matrix **U** obtained by singular value decomposition (SVD) of Ψ_e and Ψ_o which are the median templates for T-waves in even and odd beats respectively;
- λ_e and λ_o are the corresponding eigenvalues;
- t_D is the Dominant T-Wave, which is estimated as the first column of the matrix **V** obtained by SVD of the matrix $\Psi = (\Psi_e + \Psi_o)/2$.

B. Beat selection

Ectopic beats were excluded from the analysis, as they mirror non-physiological dynamics. ECGs were analyzed in segments of 128 beats with a 50% overlap between adjacent segments. A segment was included in automatic TWA analysis, following the same criteria as in [11], if:

1) the difference between the maximum and the minimum instantaneous heart rate (HR) during the segment was lower than 20 beats/min.
2) at least 80% of the beats fulfilled the following conditions:
    - it was labeled as normal sinus beat
    - the difference between each RR interval and the previous one was lower than 150 ms,
    - the difference between the baseline voltage measured at the PQ segment in that beat and the one measured in the preceding beat was inferior to 300 microvolts.

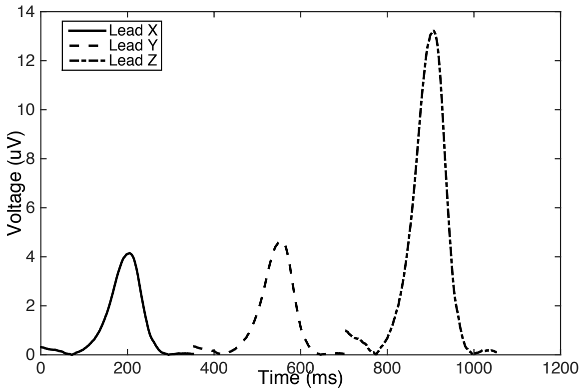

Fig. 1. T - wave alternans waveform on a single segment. Its maximum is taken as an index of alternans.

C. Practical ADTWA estimation: the AM method

The method used to calculate ADTWA on ECG recordings was named AM method (*Average of Maximum*). The following steps are followed:

- In each segment, beats are aligned and the median templates for even beats (Ψ_e), for odd beats (Ψ_o) and for all the beats (Ψ) are calculated.
- SVD of the matrices Ψ_e, Ψ_o and Ψ is performed and the index I of ADTWA is calculated as $\max_l |\lambda_e u_e - \lambda_o u_o| \max_t |t_D|$. This is the maximum of the waveform of alternans on a single segment (see fig. 1);
- This procedure is repeated for every segment valid for analysis.
- A global average of the calculated indexes is obtained.

Indexes of alternans have been evaluated by averaging all the segments composing the recording and separating them into heart rate bins as in [11] (60-70 bpm, 70-80 bpm, 80-90 bpm, 90-100 bpm, 100-110 bpm).

D. Statistical analysis

ROC curves have been calculated in order to get the best value which could discriminate subjects positive to our TWA test. Student's t-test has been used in order to compare the distribution of ADTWA in the group of patients who survived during the follow-up with the group of patients who died from SCD. A two-tailed value of $p < 0.05$ was considered significant.

IV. Results

The mean value of ADTWA in the study population was 6.74 $\pm$ 2.11 μV, and the 25th, 50th, and 75th percentiles were 5.34, 6.47 and 7.80 μV, respectively.

Boxplots for the different measured alternans indices, divided by heart rate bins, are shown in Fig 2. The mean values of ADTWA increased with local HR, and there were significant differences between indices from all adjacent HR intervals. TWA depends on heart rate and, as expected, it is higher for higher values of heart rate.

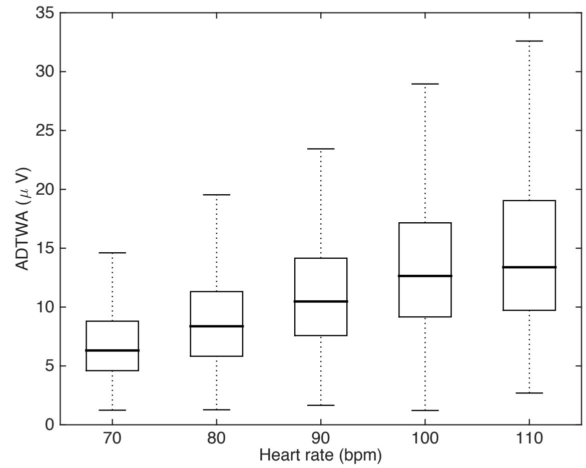

Fig. 2. Boxplot of alternans indexes calculated with AM Method.

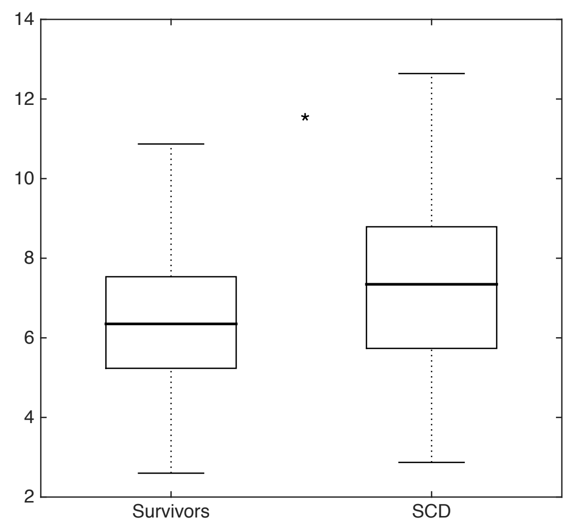

Fig. 3. Boxplots comparing distribution of TWA in patients who survived during the follow-up phase (Survivors) and patients who died from SCD (*p $<$ 0.05).

Figure 3 shows the boxplot comparing the distribution of ADTWA in the two populations:

- People who survived (Survivors);
- People who died from Sudden Cardiac Death (SCD).

ADTWA was significantly higher among the SCD group than among survivors (p=0.01). In particular for survivors ADTWA was 6.60 $\pm$ 1.98, whereas for patients dying from SCD ADTWA was 7.55 $\pm$ 2.53, p=0.01.

The ROC curve is shown in fig. 4. The area under the curve is 0.61. The optimal value of ADTWA, *i.e.*, the value maximizing the accuracy, to discriminate survivors from patients who died from SCD is $6.774\mu V$.

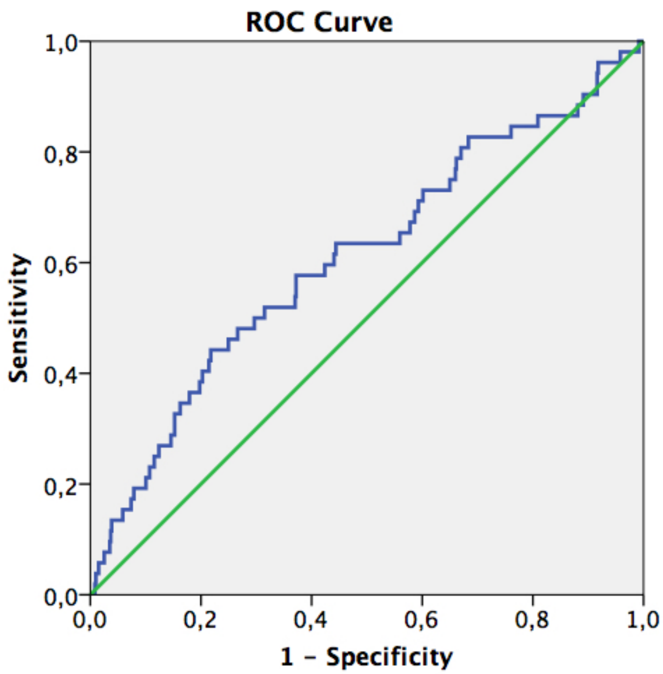

Fig. 4. Roc Curve for AM Method (ADTWA threshold = $6.774\mu V$)

V. Discussion and Conclusion

The aim of the present work was to assess whether the ADTWA index, a simple, multi-lead and based on a physiological model index, could be associated to the risk of SCD in patients with symptomatic heart failure. The TWA waverform was obtained on a 128-beat segment and the maximum of the mean waveform - on the 24 hours - was taken as an index of TWA. To obtain a single reliable measurement from each recording, we used a method similar to that used in [11], consisting in averaging the ADTWA value obtained in processable 128-beat segments during all the recording. This was also done by averaging ADTWA values from segments in different ranges of heart rate. The results show that ADTWA values had an increasing trend, and also were more spread out when computed in segments with higher heart rate. A similar behaviour has been shown in previous works [11]. ADTWA was also significantly higher in SCD patients than in survivors. These results suggest that a TWA index based on the paradigm of the dominant T wave and computed in standard Holter recordings may discriminate patients with increased risk of SCD. Finally, results from the ROC curve can be used in future studies to assess ADTWA as predictor of SCD in patients with heart failure. It is worth highlighting that ADTWA involves easy computations and is derived from a physiological model of alternans.

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