

T-wave Alternans Predicts ICD Discharge in MADIT II Patients with Elevated Resting Heart Rate

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Abstract

The identification of MADIT II patients who might benefit the most from implantable cardioverter defibrillator (ICD) therapy remains a clinical challenge. In this work we measure T-wave alternans (TWA) using the multilead Laplacian likelihood ratio method (mLLR) in MADIT II patients, and we evaluate its ability to predict ventricular tachycardia or ventricular fibrillation events requiring an ICD shock and to predict sudden cardiac death (SCD). Our results indicate that the average TWA measured between 80 and 90 beats/min in resting ECGs is associated with future ICD therapy in MADIT II patients with elevated resting heart rate.

1. Introduction

Prophylactic therapy with an implantable cardioverter defibrillator (ICD) has been shown to significantly reduce overall mortality in post-infarction patients with severe left ventricular dysfunction. In the clinical trial MADIT II [1], defibrillator implantation was associated with a significant improvement in survival compared to medication therapy alone. Patients treated only with medication presented a 78% survival rate after two years whereas patients treated with an ICD and medication had an 84% survival. Yet, only a small fraction of patients with ICDs actually receive life saving therapy from the devices.

Therefore, there is a need for risk markers which identify patients at a higher risk of experiencing ventricular tachycardia (VT) or ventricular fibrillation (VF) requiring an ICD shock, so that prophylactic ICD therapy can be selectively applied only to those patients who will benefit the most from it.

In this work, we propose to investigate the utility of T-wave alternans (TWA), an electrocardiographic marker of repolarization instability, to predict ICD therapies and SCD in MADIT-II patients. In our previous works [2-3]

we studied the prognostic value of different measures of average and maximum TWA activity over heart rates ranging from 60 to 110 beats/min, and found two indices which predicted SCD in a population of chronic heart failure (CHF) patients: the index of average alternans (IAA) and the average alternans activity in the heart rate (HR) range of 80-90 beats/min (IAA₉₀). The aim of the present study is to validate those findings in the MADIT-II population.

2. Dataset

A subset of 269 patients enrolled in the MADIT-II trial [1] was analyzed in the present study. Each patient had a history of myocardial infarction at least 30 days prior to enrolment, and left ventricular ejection fraction (LVEF) \leq 30%. Patients were randomized to either ICD therapy or conventional medication therapy. Holter ECGs were recorded for 10 minutes at rest in supine position at the time of enrolment. Only patients with sinus rhythm who presented a HR \geq 80 beats/min at any point during the 10-min baseline ECG were included in the study population. The average follow-up of patients was 1.8 \pm 1.0 years.

3. Methods

Holter ECG signals were recorded using Spacelab-Burdick digital recorders (SpaceLab-Burdick, Inc., Deerfield, WI). Data from XYZ orthogonal leads were sampled at 1000 Hz with an amplitude resolution of 16-bit for an average of 10 minutes. Heart beats were automatically detected and then manually annotated by ECG expert technicians from the Heart Research Follow-up Program in Rochester, NY.

3.1. Measurement of TWA

Automatic TWA analysis was performed using a multilead version of the Laplacian Likelihood Ratio

(LLR) method [4]. The LLR method assumes that ECG noise follows a Laplacian distribution (which accounts for outliers and extreme values, as opposed to a Gaussian distribution), and quantifies TWA using the median operator instead of the mean in order to make results less sensitive to noise bursts, sudden artifacts or ectopic beats. The multilead version of the LLR method (multi-LLR method [5]) uses periodic component analysis (π CA) to find the combination of ECG leads that maximizes the visibility of TWA (thus revealing TWA episodes embedded in noise that could be undetectable if leads were analyzed separately). Then, it applies the LLR method to the combined lead. The multi-LLR method has been successfully applied to the analysis of Holter ECGs, producing TWA measures which predict SCD in a population of chronic heart failure (CHF) patients [2-3].

In this study, we replicated the procedure presented in [2-3] to automatically analyze TWA (Figure 1). ECGs were analyzed beat-to-beat in segments of 16 beats. The procedure for each 10-min ECG consisted of 3 steps: 1) selection of ECG segments that were suitable for automatic analysis, 2) quantification of the TWA amplitude in those segments, and 3) computation of TWA indices characterizing the whole ECG recording:

1. Each 16-beat segment k was included in automatic TWA analysis if (a) the difference between the maximum and the minimum instantaneous HR was < 20 beats/min and (b) at least 75% of the beats fulfilled three conditions: the beat was labeled as a normal sinus beat, the difference between the RR interval of that beat and the previous RR interval was ≤ 150 ms, and the difference between the baseline voltage measured at the PQ segment in that beat and the one measured in the preceding beat was $\leq 300 \mu\text{V}$.

2. The three leads of each ECG segment were linearly combined to obtain a new lead in which the visibility of TWA over noise was maximized. This combination can be expressed as:

$$\text{combined lead} = a \cdot \text{lead X} + b \cdot \text{lead Y} + c \cdot \text{lead Z},$$

where the coefficients a , b , and c were specifically computed for each 16-beat segment using π CA (Figure 1(B)). In the combined lead the median difference between ST-T complexes of even and odd beats was computed with the LLR method [4], obtaining an estimation of the median TWA waveform in the segment. The amplitude of TWA in each segment (V_k) was measured as the absolute value of the mean of the estimated TWA waveform (Figure 1(C)).

3. Several TWA indices were evaluated in previous works [2-3] and two of them were found to predict cardiac risk: the Index of Average Alternans (IAA), which reflects the average TWA activity during the whole ECG recording, and the HR-restricted Index of Average Alternans (IAA₉₀), which reflects the average TWA activity in ECG periods with heart rate ranging between 80 and 90 beats/min. In the present study, we computed the IAA as the average TWA amplitude of all analyzed segments in the ECG, and the IAA₉₀ as the average of the TWA amplitudes measured in segments with an average HR between 80 and 90 beats/min.

3.2. Statistical analysis

Correlation between TWA indices and HR was evaluated with Spearman's correlation coefficient. Two-tailed Mann-Whitney and Fisher exact tests were used for univariate comparison of quantitative and categorical data, respectively. The primary endpoints for the present study were appropriate ICD therapy for VT/VF in patients randomized to ICD therapy, and SCD in patients randomized to conventional therapy. The prognostic value of TWA indices in predicting the endpoints was determined with a multivariable Cox proportional hazards model. TWA indices were entered into the model as continuous variables, and the following confounding

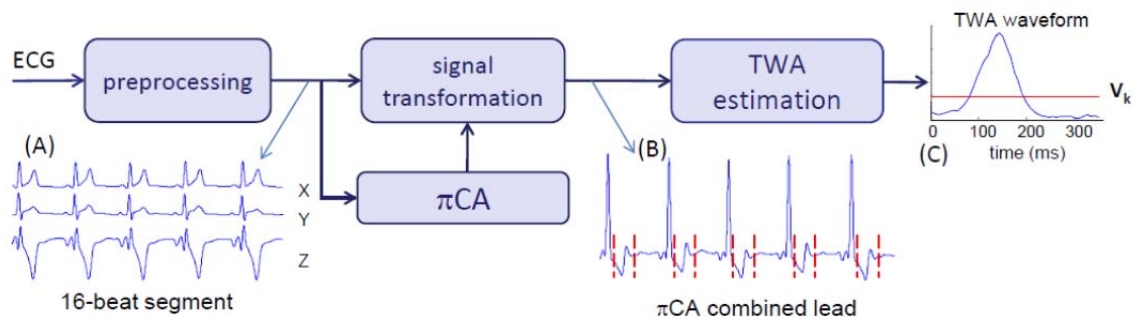


Figure 1. Block diagram of the TWA amplitude estimation method. An ECG segment selected for automatic analysis after low-pass filtering and baseline cancellation is labelled as (A). The new combined lead, computed with π CA is labelled as (B). The TWA waveform estimated with the Laplacian likelihood ratio method is shown with the label (C). V_k is then computed as the mean of the estimated waveform. (Adapted from [2]).

variables were considered: ICD treatment (only for the association with the combined endpoint SCD/ICD therapy), QRS duration, New York Heart Association (NYHA) class II or III, blood urea nitrogen (BUN) > 25mg/dL, diabetes, and creatinine (mg/dL). Statistical analysis was conducted at University of Rochester Medical Center using SAS software (SAS Institute Inc., Cary, NC). The computation of TWA indices was done in University of Zaragoza. The group from Zaragoza was blinded to the study endpoints during their analysis.

4. Results

The general index IAA was computed for all the patients of the study population. Within the initial population, 94 individuals had ECGs in which all segments between 80-90 beats/min were rejected for automatic analysis, so IAA₉₀ could be computed for a subset of 175 patients (Figure 2). We assessed if the clinical characteristics of patients with and without IAA₉₀ values differed (initial population vs. group of 175 patients), and we did not find any significant difference. The clinical characteristics of the subset of patients with valid IAA₉₀ values are presented in Table 1. No significant correlation was found between TWA indices and the baseline HR.

In patients from the ICD arm, both IAA and IAA₉₀ were statistically higher in patients who experienced appropriate ICD shocks (Table 2). The Kaplan-Meier plot revealed that patients with IAA₉₀ above the first quartile (IAA₉₀ > 6.0 μ V) were at increased risk of experiencing appropriate ICD shocks, 2 years after implantation (Figure 3). No other clinical factor revealed differences between patients with and without appropriate ICD shocks.

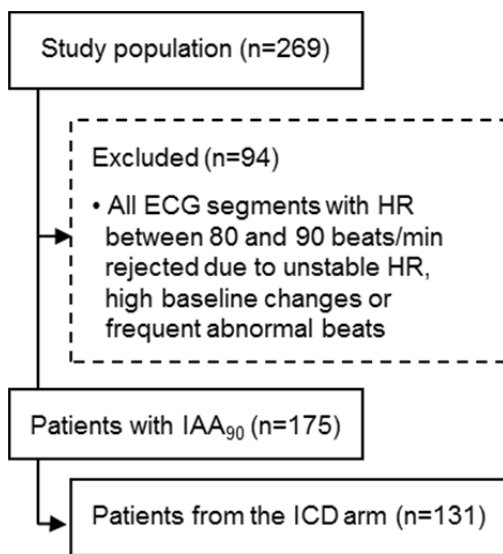


Figure 2. Flow chart of the study population

Table 1. Clinical characteristics of the patients with valid IAA₉₀ values.

N	175
Age (yrs)	61±11
Gender (%f)	20.5
QRS (ms)	117±28
NYHA class II or III (%)	64.7
BUN (mg/dL)	23±14
Diabetes (%)	43.7
Creatinine (mg/dL)	1.2±0.6

Table 2. TWA indices in patients from the ICD arm.

	All	Shock	No-shock	p-value
N	131	40	91	
IAA	10.9±5.6	12.6±6.3	10.2±5.1	0.02
IAA ₉₀	10.9±7.5	13.7±10.2	9.7±5.6	0.01

Table 3. Multivariable risk predictors of appropriate ICD shocks in patients from the ICD arm.

	Hazard ratio	95% CI	p-value
IAA ₉₀ per μ V	1.05	1.01-1.09	0.008
QRS (>120ms)	4.34	1.68-11.26	0.002
NYHA class II or III	1.63	0.77-3.46	0.20
BUN >25 mg/dL	2.37	0.98-5.71	0.05
Diabetes	0.57	0.29-1.10	0.09
Creatinine per mg/dL	0.54	0.26-1.16	0.12

There were 20 SCD events in the initial population and 15 in the group of patients with valid IAA₉₀ values. We evaluated the predictive value of TWA indices for SCD and appropriate ICD shocks as single and combined endpoints. After adjustment for relevant clinical factors, we did not find any association between TWA indices and SCD either as a single endpoint or when combined with appropriate ICD therapy. However, when considering appropriate ICD therapy as a single endpoint, AAI₉₀ was found to be an independent predictor in patients from the ICD arm. Precisely, there was a 5% increase chance for a patient to have an ICD shock with each 1 μ V increase in IAA₉₀ (Table 3).

5. Discussion and conclusions

In this work we evaluated the prognostic value of TWA in MADIT-II patients. There is a lack of consistency between studies investigating the role of TWA in stratifying patients who would benefit from ICD implantation [6-8]. Our results suggest that TWA measured at rest in MADIT-II patients is higher in

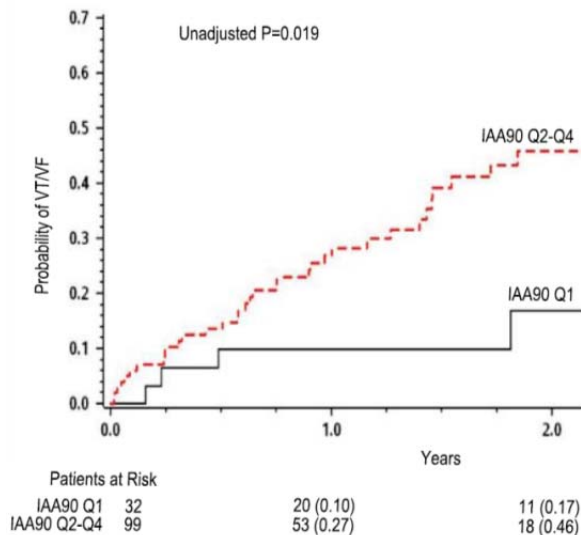


Figure 3: Kaplan-Meier plot for IAA₉₀ index considering appropriate ICD shocks in patients from the ICD arm.

patients who will experience ICD therapy. We found a significant association between TWA measured in rest ECGs and arrhythmic events, and also found that these patients may not need to have very high HR (>100 beats/min) but rather develop detectable TWA at HR in the 80-90 beats/min range. Such observations may support the development of a simple protocol to perform TWA testing in rest ECGs, perhaps by slightly increasing the resting HR of patients using appropriate drugs.

The general index IAA did not predict cardiac events in our study, while it was found to be an independent predictor of SCD in the MUSIC trial [3]. This discrepancy may not only be caused by the change of clinical population (MADIT-like vs. CHF patients), but might also be due to the differences in ECG acquisition. In the MUSIC trial, ECGs were ambulatory and 24 hours long, whereas in the present work they were recorded at rest and during a much shorter period (10 minutes), so the global index IAA in our study reflects TWA activity over a much shorter period and with a narrower HR range. Since IAA is computed as an average over the whole ECG duration, the same TWA episode would produce higher IAA values in shorter records. Moreover, TWA episodes are thought to be less frequent at lower heart rates. The differences in the mean IAA values ($3.3 \pm 2.1 \mu\text{V}$ in MUSIC [3], vs. $10.9 \pm 5.6 \mu\text{V}$ in this study) would corroborate the idea that IAAs obtained from ECGs recorded in such different conditions are not directly comparable. Therefore, a study on 24-h ambulatory ECGs might be worthwhile before ruling out IAA as a useful index for MADIT-II patients.

Unfortunately, the major limitation of our results is the small size of the study population, resulting mainly from the HR-based pre-selection for TWA analysis (as only patients with elevated resting HR can be tested).

Additional validation in a larger independent cohort would be required for confirming the applicability of the IAA₉₀ cut point, since the final population in our study is too small to be sufficiently representative of the potential target population (ICD recipients with elevated resting HR). Finally, as we did not evaluate any risk factors in non-preselected patients, our findings should not be extrapolated to the general MADIT-II population.

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