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Prognostic value of average T-wave alternans and QT variability for cardiac events in MADIT-II patients

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Abstract

Background: Identifying which patients might benefit the most from ICD therapy remains challenging. We hypothesize that increased T-wave alternans (TWA) and QT variability (QTV) provide complementary information for predicting appropriate ICD therapy in patients with previous myocardial infarction and reduced ejection fraction.

Methods: We analyzed 10-min resting ECGs from MADIT-II patients with baseline heart rate >80 beats/min. TWA indices IAA and IAA_{90} were computed with the multilead Laplacian Likelihood ratio method. QTV indices QTVN and QTVI were measured using a standard approach. Cox proportional hazard models were adjusted considering appropriate ICD therapy and sudden cardiac death (SCD) as endpoints.

Results: TWA and QTV were measured in 175 patients. Neither QTV nor TWA predicted SCD. Appropriate ICD therapy was predicted by combining IAA_{90} and QTVN after adjusting for relevant correlates.

Conclusion: Increased TWA and QTV are independent predictors of appropriate ICD therapy in MADIT-II patients with elevated heart rate at baseline.

Keywords: T-wave alternans; Holter ECG; Sudden cardiac death; ICD therapy; MADIT-II

Introduction

Cardiovascular diseases are the major cause of death in adults worldwide. The presence of electrical instability and the presence of severely depressed left ventricular function have been studied as markers for an arrhythmic death in many clinical trials for primary prevention of sudden cardiac death (SCD): MADIT I[1] and II,[2] MUSTT,[3] SCD-HeFT,[4] DINAMIT,[5] and more recently in MADIT-CRT.[6] Most of these trials have shown that prophylactic therapy with an implantable cardioverter defibrillator (ICD) significantly reduces overall mortality in post-infarction patients with severe left ventricular dysfunction (LVEF ≤30%). In MADIT-II,[2] defibrillator implantation was associated with a significant improvement in survival compared to medication therapy. 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, clinicians lack 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.

Electrocardiographic markers of the presence of myocardial vulnerability, such as the frequency of ventricular ectopic beats and the presence of sustained/non-sustained ventricular arrhythmias, help the clinicians to assess the presence of electrical susceptibility to life-threatening arrhythmias. Generally, they are considered in combination with New York Heart Association (NYHA) class and left ventricular ejection fraction (LVEF), which reflect the loss of cardiac reserve and adversely affect the prognosis of patients with structural heart disease.[7]

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In this work, we propose to investigate electrocardiographic markers of repolarization instability in combination with relevant clinical markers in order to predict ICD therapies and SCD in MADIT-II patients. We hypothesize that our new method to measure T-wave alternans (TWA), which successfully predicts SCD in patient with chronic heart failure,[8] could help identifying the patients who would benefit the most from ICD implantation. In the previous work[8] 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: the index of average alternans (IAA) and the average alternans activity in the heart rate (HR) range of 80–90 beats/min (IAA_{90}). The aim of the present study is to validate those findings and to combine the measurements of TWA with measures of QT variability (QTV) in order to evaluate their complementarity in MADIT-II patients.

Methods

Study population

The study population consisted of patients enrolled in the MADIT-II trial.[2] Each patient had a history of myocardial infarction at least 30 days prior to enrollment, and LVEF≤30%. No other risk stratifier was used at enrollment. 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 enrollment in the study for 902 of the 1232 enrolled patients. For this study, we excluded patients with atrial fibrillation (AF) because AF is a condition compromising the measurement of TWA. Furthermore, the patients who presented a HR < 80 beats/min during the whole ECG were also excluded because TWA requires elevated HR.[9] Therefore, our study population consisted of those MADIT-II patients with sinus rhythm who presented a HR≥80 beats/min during 10-min rest ECG.

Definition of endpoints

The occurrence of VT or VF requiring ICD therapy (either antitachycardia pacing or defibrillator shock) was determined by periodic interrogation of the implanted device. The results of these interrogations were reviewed by the MADIT-II Data Coordinating Center, which determined the appropriateness of therapy.[2] 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.

Measurement of TWA

Holter ECGs 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.

Automatic TWA analysis was performed using a multilead version of the Laplacian Likelihood Ratio (LLR) method.[10] 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[11]) uses periodic component analysis (πCA) 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) and then 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 patients.[8]

In this study, we replicated the procedure presented in[8] to automatically analyze TWA. ECGs were analyzed beat-to-beat in segments of 16 beats. The procedure 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 segment 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 ≤300 μV.
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:

   $$combined\ lead = a\ lead\ X + b\ lead\ Y + c\ lead\ Z,$$

   where the coefficients a, b, and c were specifically computed for each 16-beat segment using πCA. This automated combination made it unnecessary to manually select the best ECG channel in each segment. In the combined lead the median difference between ST-T complexes of even and odd beats was computed with the LLR method,[10] obtaining an estimation of the median TWA waveform in the segment. The amplitude of TWA in each segment was measured as the absolute value of the mean of the estimated TWA waveform (Fig. 1).
3. Two TWA indices were computed. First, the Index of Average Alternans (IAA), which reflects the average TWA activity during the whole ECG recording, was computed as the average TWA amplitude of all analyzed segments in the ECG. Second, the HR-restricted Index of Average Alternans (IAA_{90}), which

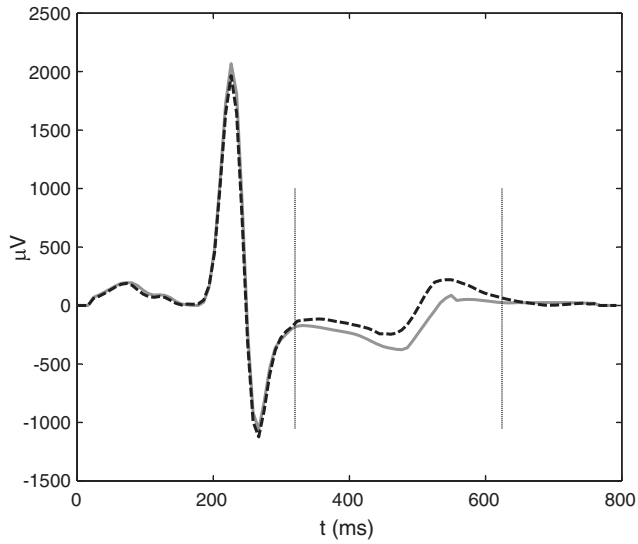

Fig. 1. Example of application of the multi-LLR method for TWA quantification. The plot shows the median of even beats (black dotted line) and the median of odd beats (grey line) in a new combined lead, which is recomputed for each 16-beat ECG segment to specifically reveal TWA. Vertical lines delimit the ST-T segment. In the example, TWA amplitude was 35 μV at the time shown and TWA indices for the whole record were IAA = 8.8 μV and IAA_{90} = 10.2 μV.

reflects the average TWA activity in ECG periods with heart rate ranging between 80 and 90 beats/min, was computed as the average of the TWA amplitudes measured in segments with an average HR between 80 and 90 beats/min.

Measurement of QTV

Normalized QTV (QTVN) and QTVI (QTVN adjusted for HR variance) data were extracted from a previous work by Haigney et al. on the MADIT-II trial.[12] In,[12] QTV was assessed using the algorithm described by Berger et al.[13] For each 10-min ECG, they computed the HR mean (HRm), HR variance (HRv), QT interval mean (QTm) and QT interval variance (QTv). Then, QTV indices were derived as $QTVN = QTv/QTm^2$ and $QTVI = \log_{10}[(QTv/QTm^2)/(HRv/HRm^2)]$. We extracted QTV values only from subjects in whom the TWA parameters could be computed, so the list of patients reported in this study is different from the one in.[12]

Statistical analysis

Data are presented as mean value and standard deviation for continuous variables and as number and percentage for categorical variables. Correlation between repolarization measures 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 prognostic value of TWA and QTV indices in predicting appropriate ICD therapy and SCD as single and combined endpoints was determined with multivariable Cox proportional hazards models. TWA and QTV indices were entered into the models as continuous variables. Multivariable analyses included the following confounding variables: ICD treatment (only for association with SCD/ICD therapy), QRS duration, NYHA class II or III, blood urea nitrogen (BUN) >25mg/dL, diabetes, and creatinine (mg/dL). No association was found between LVEF and any single or combined endpoints in our study, so it was not included as a correlate in the multivariable model. 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.

Results

Study population

Among the 902 patients with at least one Holter recording in the overall MADIT-II population, 46 patients experienced AF. After excluding these patients, and the patients with HR <80 beats/min during the whole ECG (n=518), the final study population consisted of 338 subjects (Fig. 2). The average follow-up of patients was 1.8 ± 1.03 years. IAA could not be computed in 16 patients because all segments of their ECGs were rejected for automatic analysis by the TWA algorithm, due to unstable HR, high baseline changes and/or frequent abnormal beats. Therefore, 322 patients had IAA values available (Group 1). In Group 1, 115 individuals had ECGs in which all segments between 80–90 beats/min were rejected for automatic analysis, so IAA_{90} could be computed for a subset of 207 patients (Group 2, n=207). We assessed if clinical characteristics of patients with and without IAA_{90} values differed (Group 1 vs. Group 2), and we did not find any significant differences (Table 1).

QTV measurements were available in 84% (n=761) of the initial population. In Group 1, 54 subjects had ECGs in which QTV could not be measured, thus we had n=269 subjects with both QTV and IAA values (Group 1a). In Group 2, 32 patients had ECGs in which QTV could not be measured (Group 2a, n=175). We assessed if clinical characteristics of patients with and without QTV values differed (Group 1 vs. 1a and Group 2 vs. 2a), and we did not find any significant differences (Table 1). We investigated the association between repolarization measurements and the baseline HR (QTVI, QTVN, IAA, IAA_{90} vs. HR) and did not find any significant correlation.

Tables 2 and 3 report the clinical and electrocardiographic characteristics of the subset of the patients from the ICD arm, i.e. patients in whom information about the presence or absence appropriate ICD therapy for VT/VF was available. In Group 1, 198 patients were identified (ICD group 1), and 131 in Group 2 (ICD group 2) (see Fig. 2). The percentage of patients who received appropriate ICD therapy was comparable in ICD group 1 and ICD group 2 (28.8% vs. 30.5%, $P = .814$).

TWA indices in patients with and without appropriate ICD therapy

In Group ICD 1, QRS duration and IAA measurements were the only factors showing significant differences between subjects with and without ICD therapy (Table 2). A larger QRS duration was present in patients with

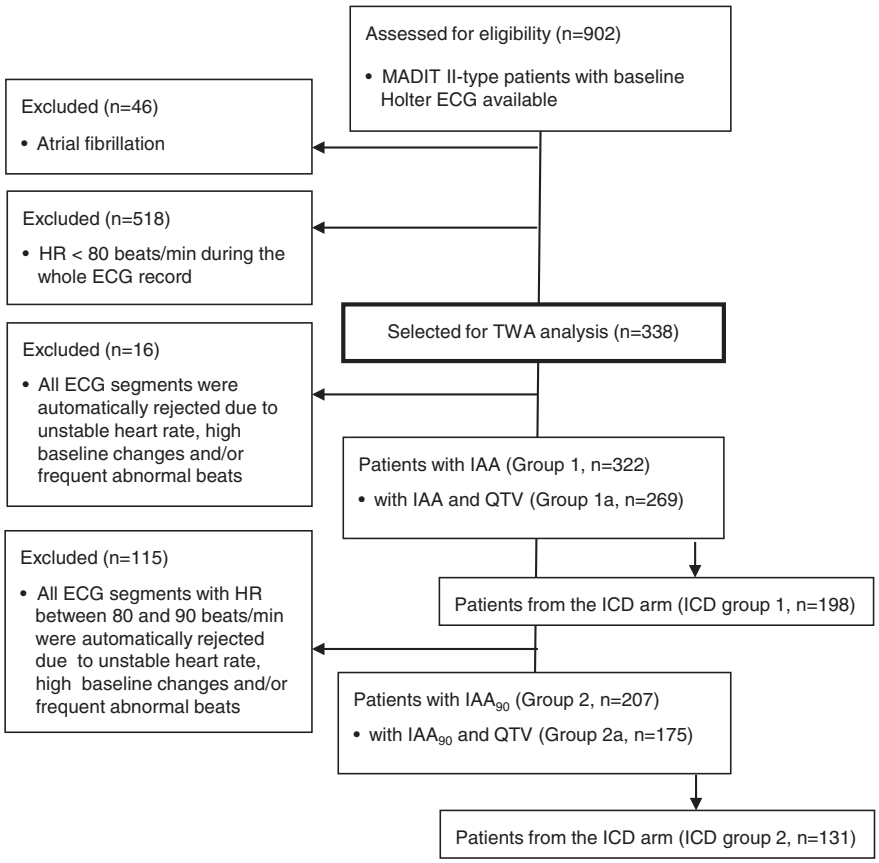

Fig. 2. Flow chart of the study population. The box in bold line indicates the initial population of patients pre-selected for TWA analysis.

appropriate therapy (125.4±33.7 vs. 111.5±25.2 ms, $P = .01$) while their IAA_{90} values were also statistically higher (13.7±10.1 vs. 9.7±5.6 μV, $P = .01$). These trends were confirmed in ICD group 2, where QRS differences were even stronger (129.3±34.1 vs. 109.7±24.3 ms, $P = .002$) and both IAA and IAA_{90} were statistically higher in patients with appropriate therapy (Table 3). The Kaplan-Meier plot for ICD group 2 revealed that patients with IAA_{90} above the first quartile (IAA_{90} >6.0 μV) were at increased risk of experiencing appropriate ICD therapy, 2 years after implantation (Fig. 3). No other clinical factor revealed differences between patients with and without VT/VF events.

TWA indices as predictors of appropriate ICD therapy and SCD

There were 25 SCD events in Group 1, 20 in Group 1a, 18 in Group 2, and 15 in Group 2a. We evaluated the predictive value of IAA indices for SCD and appropriate ICD therapy 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 in groups 1 and 2. However, when considering appropriate ICD therapy as a single endpoint, IAA_{90} was found to be an independent predictor in ICD group 2. Precisely, there was a 5% increase chance for a patient to have an ICD shock with each 1 μV increase in IAA_{90} (hazard ratio: 1.05, 95%CI: 1.01–1.09, $P = .008$).

Table 1
Clinical characteristics of the study population.

	Group 1	Group 1a	Group 2	Group 2a
N	322	269	207	175
Age (yrs)	62±11	62±11	61±11	61±11
Gender (%f)	17.4	18.4	20.3	20.5
QRS (ms)	116±28	117±28	116±28	117±28
NYHA class II or III (%)	69.4	67.3	66.8	64.7
BUN (mg/dL)	23±13	29±13	23±14	23±14
Diabetes (%)	43.1	42.1	43.7	43.7
Creatinine (mg/dL)	1.2±0.5	1.2±0.5	1.2±0.6	1.2±0.6

Table 2
Descriptive statistics for patients from the ICD arm in whom IAA values could be computed (ICD group 1).

	All	Shock	No-shock	*P*-value
N	198	57	141	
Age (yrs)	61.4±10.6	62.8±9.8	60.8±10.9	.25
Gender (%f)	18.2	17.5	18.4	.88
QRS (ms)	**115.6±28.6**	**125.4±33.7**	**111.5±25.2**	**.01**
NYHA class II or III (%)	69.8	78.9	65.9	.07
BUN (mg/dL)	22.9±13.5	24.1±12.1	22.5±14.0	.12
Diabetes (%)	42.9	36.8	45.3	.27
Creatinine (mg/dL)	1.2±0.5	1.2±0.4	1.2±0.6	.76
QTVI	−0.74±0.59	−0.64±0.55	−0.78±0.60	.28
QTVN	0.52±1.47	0.98±2.6	0.35±0.54	.18
IAA	11.1±6.9	11.5±5.8	12.0±7.2	.19
IAA90	**10.9±7.5**	**13.7±10.1**	**9.7±5.6**	**.01**

Bold values signify $p < 0.05$.

Table 3
Descriptive statistics for patients from the ICD arm in whom IAA_{90} values could be computed (ICD group 2).

	All	Shock	No-shock	*P*-value
N	131	40	91	
Age (yrs)	60.5±11.4	62.3±10.4	59.8±11.8	.20
Gender (%f)	20.6	22.5	19.8	.72
QRS (ms)	**115.7±29.0**	**129.3±34.1**	**109.7±24.3**	**.002**
NYHA class II or III (%)	68.7	75.0	65.9	.30
BUN (mg/dL)	22.9±13.9	22.4±10.4	23.2±15.3	.59
Diabetes (%)	44.2	37.5	47.2	.30
Creatinine (mg/dL)	1.2±0.6	1.2±0.4	1.3±0.7	.66
QTVI	−0.71±0.55	−0.66±0.50	−0.73±0.57	.72
QTVN	0.53±1.47	0.98±2.58	0.35±0.54	.18
IAA	**10.9±5.6**	**12.6±6.3**	**10.2±5.1**	**.02**
IAA90	**10.9±7.5**	**13.7±10.2**	**9.7±5.6**	**.01**

Bold values signify $p < 0.05$.

Combination of TWA and QTV

In MADIT-II patients, QTVI and QTVN were reported to be associated with ICD therapy, but not with mortality.[12] In the present study we found a similar association between QTVN and arrhythmias in ICD group 1 (hazard ratio: 1.20, 95%CI: 1.06–1.36, $P = .004$). When combining IAA parameters with QTVN, we found that IAA_{90} and QTVN were complementary and both associated with an increased probability of appropriate ICD therapy (ICD group 2). The hazard ratios were 1.19 (95% CI: 1.03–1.37, $P = .02$) and 1.05 (95%CI: 1.01–1.09, $P = .02$) for QTVN and IAA_{90}, respectively (Table 4).

Discussion

The prognostic value of TWA has been subject to extensive research.[14,15] In MADIT-II-like patients, TWA identified a low-risk group unlikely to benefit from ICD therapy,[16] although there is conflicting evidence suggesting that in ICD-treated patients the risk of VT/VF events does not differ according to TWA classification.[17] Such discrepancy has been addressed by recent meta-analyses,[14,15] which questioned the suitability of appropriate ICD therapy as a surrogate for SCD in clinical trials. The commonly proposed mechanism of SCD involves the development of VT, which degenerates into VF, and which ultimately leads to asystole and death. Therefore, ICD shocks triggered by VT/VF episodes ("appropriate" shocks) have been considered as a surrogate for SCD. However, even when ICD shocks are deemed "appropriate", they are not necessarily equivalent to a life saved, as some episodes may have been nonfatal events which would have terminated spontaneously. In this study, we found that the TWA index IAA_{90} predicted appropriate ICD therapy in ICD-recipients, but did not predict SCD in non-ICD patients, which supports the hypothesis that appropriate ICD therapies may not be an adequate surrogate for SCD.

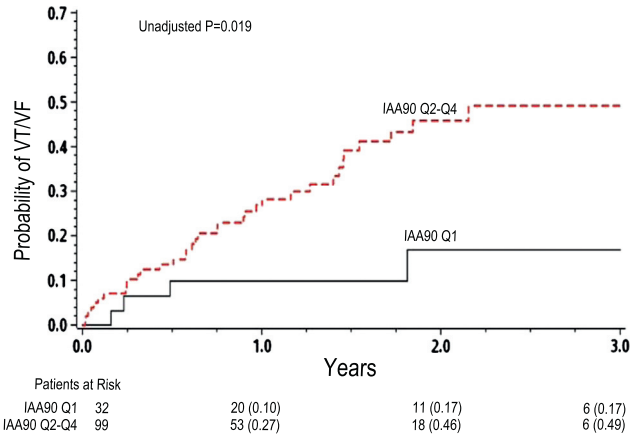

Fig. 3. Kaplan–Meier estimates of the probability of appropriate ICD therapy in MADIT-II patients from the ICD arm with elevated resting HR (ICD group 2). Color illustration online.

In studies conducted to evaluate TWA as a risk stratifier, TWA is usually measured either in exercise stress test ECGs or in ambulatory ECGs.[15] The clinical gain of stress test TWA remains inconclusive because of contradictory reports in large prospective and retrospective studies such as the MASTER[17] trial, the ABCD[18] trial, and the SCD-HeFT[19] substudy. TWA did not predict SCD or ICD discharge in both the MASTER and the SCD-HeFT substudy, and therefore the use of spectral TWA method to support the decision of ICD implantation has not been accepted. Stress test TWA failed to predict events in the ABCD trial but the complementarity of TWA and electrophysiology tests emerged. Unfortunately the clinical gain of implementing TWA did not balance with the clinical burden associated with the implementation of an additional test in these patients.

Analysis of ambulatory ECGs was proposed as an alternative[20] to stress test TWA. Long-term ECG recordings, such as 24-h Holters, allow measuring TWA at specific periods of increased vulnerability to SCD, which may improve the prognostic value of the test. Studies such as [21] and [22] have reported promising risk stratification results for TWA analysis on ambulatory ECG. Ambulatory records, however, contain high amounts of noise that make it necessary to visually discard false TWA measurements, which may compromise the accuracy and repeatability of the TWA test.

In our study, we applied a fully automated TWA method which eliminates the need of subjective assessment of the quality of TWA measures, and which might therefore improve the repeatability of the test, and also its accuracy when applied by non-experts. Besides, we were able to

Table 4
Multivariable risk predictors of appropriate ICD therapy in MADIT-II patients from the ICD arm with elevated resting HR (ICD group 2).

	Hazard ratio	95% CI	*P*-value
IAA_{90} per μV	1.05	1.01–1.09	**.02**
QTVN	1.18	1.02–1.37	**.02**
QRS (>120 ms)	2.90	2.20–15.4	**.0004**
NYHA class II or III	1.90	0.86–4.21	.11
BUN >25 mg/dL	2.04	0.82–5.11	.13
Diabetes	0.37	0.18–0.76	**.007**
Creatinine	0.56	0.26–1.22	.15

Bold values signify $p < 0.05$.

extract useful TWA information from 10-min rest ECGs, as opposed to stress test or 24-h ECG recordings. To our best knowledge, this is the first study to report a significant association between TWA measured in rest ECGs and arrhythmic events in MADIT-II patients. We 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, thus overcoming some limitations of exercise or ambulatory TWA tests.

The mechanisms involved in the genesis of alternans and variability of the T-wave on the surface ECG remain to be fully elucidated. Yet, TWA has been described as a result of both temporal and spatial dispersion of repolarization. The spatial component is primarily driven by the regional differences in action potential duration (APD) and conduction velocity while the temporal dispersion is linked to mechanism of steep restitution of the APD. It is believed that TWA is primarily driven by calcium loading. QTV, on the other hand, is primarily driven by temporal instability of repolarization and heart rate variability (for QTVN). The link between an increased variability (QTVN) and a propensity for arrhythmic events resides in the required presence of heterogeneity of excitability. We believe the two mechanisms of TWA and QTV could play an independent arrhythmogenic role and our results are consistent with such hypothesis.

TWA indices did not predict SCD in our group, while IAA was found to be an independent predictor of SCD in the MUSIC trial.[8] It is noteworthy that in MADIT-II the ECG recordings were not ambulatory and short in duration (10 minutes), so the global index IAA in our study reflects TWA activity over a much shorter period, with a narrower HR range than in ambulatory 24-h Holter ECGs. Furthermore, the number of events in the subgroup of patients with reported SCD was rather low. Therefore, our study is not conclusive about the clinical value of TWA for prediction of SCD in MADIT-II patients.

As expected in MADIT-II population, QRS duration was a strong confounding factor in the predictive model for VT/VF. QRS duration is expected to be longer in patients with very high risk, that is, patients with comorbidities and advanced cardiac disease.[23] Our patients were pre-selected based on HR (>80 beats/min) and thus are likely to include the sicker patients. Therefore, it is not surprising to find QRS duration as strong predictor of events in this population. The multivariable model was adjusted for QRS duration, and despite this adjustment both QTV and TWA remained predictive.

Our investigation has evaluated the prognostic value of TWA measured in short-term ECGs recorded in MADIT-II patients at the time of their enrollment in the study. There is a lack on consistencies between studies which have investigated the role of TWA in stratifying patients who would benefit from ICD implantation. Our results suggest that TWA measured at rest in MADIT-II patients are stronger in patients who will experience ICD therapy.

Unfortunately, the major limitation of our results is the small size of the final study population, resulting from the HR-based pre-selection for TWA analysis and from the further exclusion of patients for technical reasons. Additional validation in a larger independent cohort would be required for assessing the applicability of the IAA_{90} cut point in terms of specificity, sensitivity and predictive value at the end of the follow-up period, since the final population in our study is too small to be sufficiently representative of the potential target population (ICD recipients with elevated resting heart rate). 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.

Conclusion

Increased TWA measured in rest ECGs was found to predict appropriate ICD therapy in patients with elevated resting HR from the ICD arm of the MADIT-II trial. IAA_{90} and QTVN were found to be complementary and both associated with an increased probability of arrhythmic events. Our results suggest that MADIT-II –type patients with elevated resting HR could be pre-selected for ICD implantation based on a 10-minute ECG test.

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