Repolarization variability in the risk stratification of MADIT II patients

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Received 26 February 2007; accepted after revision 12 June 2007; online publish-ahead-of-print 17 July 2007

Aims QT variability has been reported to be associated with ventricular arrhythmias and sudden cardiac death. There is limited data regarding variability in T-wave morphology and its prognostic value. In this study, we present a novel approach for the measurement of T-wave variability (TWV) reflecting changes in T-wave morphology, and we investigate the prognostic significance of Holter-derived TWV in patients with and without ventricular arrhythmias requiring appropriate implantable cardioverter defibrillator (ICD) therapy from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II).

Methods Study population consisted of 275 ICD patients from MADIT II after excluding patients with intraventricular conduction abnormalities or atrial fibrillation. TWV was measured based on amplitude variance of T-wave amplitude.

Results During 2-year follow-up, 58 (21%) patients had appropriate ICD therapy for ventricular tachycardia or fibrillation. Patients with appropriate ICD therapy had higher levels of TWV measures than those without arrhythmic events. After adjustment for heart rate, ejection fraction, and significant clinical predictors of arrhythmic events, a Cox proportional-hazards regression model revealed that dichotomized TWV values were predictive for ventricular tachyarrhythmias requiring appropriate ICD therapy (hazard ratio, 2.0; 95% CI; 1.2–3.5; \( P = 0.01 \)). On the basis of the comprehensive testing, TWV value above 59 \( \mu \text{V} \) was found predictive for arrhythmic events in MADIT II population.

Conclusion Our newly designed method for the assessment of repolarization variability in ambulatory Holter recordings detected transient variability of T-wave morphology, which was predictive for ventricular tachyarrhythmias in the MADIT II population.

Sudden cardiac death (SCD) from ventricular arrhythmias is a major public health issue with 300 000–400 000 deaths per year in the United States.1 Eighty per cent of patients who suffer from SCD are individuals with coronary heart disease. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) demonstrated that prophylactic therapy with implantable cardioverter defibrillator (ICD) significantly reduced mortality in post-infarction patients with severe left ventricular dysfunction. Ejection fraction was an effective risk stratifier in this study, although within MADIT II population there was a spectrum of patients with different degree of arrhythmia and SCD risk. The use of ICD in post-infarction patients with low ventricular ejection fraction represents a significant additional cost for the US health system. Estimated cost of ICD therapy is varying from $27 000 to $60 000 per life saved according to these studies.2,3 Following the current MADIT II criteria for ICD implantation, the number of implanted devices may reach 250 000 in year 2006.4 Thus, it would be helpful to develop non-invasive methods to identify post-infarction patients at increased or decreased risk for ventricular tachyarrhythmias (VT) and SCD in order to determine who will and will not benefit from ICD therapy.

Among the number of non-invasive risk stratifiers for the prediction of ventricular tachyarrhythmias and SCD, ECG measures of repolarization instability, namely T-wave alternans5–7 and QT variability,8 are of increasing interest. The spectral algorithm for the detection of T-wave alternans requires the patients to increase their heart rate to 100–110 beats per minutes through a controlled exercise. This requirement limits the diagnostic yield of the test since sick patients and those on proper dose of beta-blockers might not be able to sustain such level of heart rate for a prolonged time. T-wave alternans could also be
measured in regular Holter recordings signals. Since stable periods of sustained T-wave alternans might be difficult to identify in Holter recordings, one could consider variability of repolarization as another measure of electrical instability of myocardium, especially since increased repolarization variability has conceptually been considered as a prodrome to T-wave alternans. T-wave alternans might further, repolarization variability has conceptually been considered as a prodrome to T-wave alternans. T-wave alternans might be considered special case of T-wave variability (TWV) where 2:1 pattern is present. The analysis of QT variability using an algorithm developed by Berger and co-workers revealed that the QT variability is predictive for arrhythmic events in MADIT II patients. In the present study, we describe a novel algorithm for quantification of both TWV and T-wave alternans in Holter recordings and then evaluate this novel algorithm in the MADIT II population.

Methods

Study population

The study population for this project consisted of patients randomized to the ICD therapy in the MADIT II study. The patients were enrolled according to the MADIT II protocol described elsewhere. Each patient had a history of myocardial infarction (at least 1 month prior to enrollment) and an ejection fraction < 30%. No other risk stratifier was used for enrollment. For the purpose of this study, we excluded patients with intraventricular conduction disturbances [right or left bundle branch block (BBB)] since in MADIT II population patients with wide QRS complex had substantially higher mortality than patients with narrow QRS (unpublished data). We also excluded patients with atrial fibrillation (AF), a condition compromising T-wave alternans/variability analyses.

Endpoints

Appropriate ICD therapy for ventricular tachycardia and fibrillation was the primary endpoint for this analysis. Patients were followed up in each centre, and data concerning all ICD therapy were obtained at the time of device interrogation and retrieval of stored electrograms. Combination of ICD therapy or death, as well as death alone, were analysed as secondary endpoints.

Electrocardiogram recordings and processing

The Holter ECG signals were recorded using the Spacelab–Burdick digital Holter recorder (SpaceLab-Burdick, Inc., Deerfield, WI). This equipment provides 1000 Hz sampling frequency signals with 16-bit amplitude resolution. ECGs were acquired using pseudo-orthogonal X, Y, Z lead configuration for a period of 10 min. The standard silver-silver chloride electrodes were used (Blue Sensor, Linthicum, MD, USA). The ECG files were converted to the standard Holter format defined by the International Society for Holter and Non-Invasive Electrocardiology (ISHNE), the recordings were annotated and QRS detection was accomplished using the Holter scanning system, SyneScope 3.10 software (ELA Medical, Sorin Group, Paris, France). SyneTVar 3.10b was used for the analysis of TWV based on the vector magnitude VM = \sqrt{X^2 + Y^2 + Z^2}, VM was used as primary lead for the analysis. The SyneTVar includes a set of pre-processing steps involving a down-sampling to 200 Hz, an estimation of baseline and respiratory components, and the digital filtering of the signal for removing part of the noise components.

The methodology described below was used to quantify both T-wave alternans and TWV simultaneously from the same recording. The measurement of the variability of T-wave amplitude is based on the highest T-wave and expressed in per cent. The method selects the window (T) with the highest AW.

Measuring T-wave alternans

The technique quantifies the level of organization within the variation of the amplitude of the T-wave, namely, it identifies the occurrence of transient-alternans patterns within the selected periods. An alternans patterns is based on the alternans (Alt) definition, if Alt = 3, the alternans pattern includes four consecutive beats in which the T-wave amplitude alternates three times (+ + or − − −). The method counts the number of occurrence of this pattern and divides it by the number of total possible occurrences. We call this number the alternans weight (AW), and it is expressed in per cent. The method selects the window (T) with the highest AW.

Measuring T-wave variability

The distribution of each sample value for each window is normalized. Then, the level of variability is computed in each window based on the estimated variance of the average amplitude across beats in the selected window. The square root value is reported and expressed in microvolt. The window (T) revealing the highest level of TWV is selected.

Segment selection

The number of segments in which AW and TWV are computed may vary from one patient to another according to his/her number of beats available in the ECG recordings. We investigated both the median and maximum values of AW and TWV among all available segments.

Three factors might influence the results of this analysis: (1) the number of beats included in each segment (Nb = 60 beats in Figure 1), (2) the definition of a beat-to-beat alternation (Alt), and (3) the length of the non-overlapping window used to analyse the repolarization segment (WI, 100 ms in Figure 1). We designed a strategy based on the computation of various combinations of values for these three factors: factor Alt varying from 3 to 15 alternating beats, factor Nb varying from 5 to 60 consecutive beats, and factor WI equal to 20–100 ms by steps of 20 ms. We implemented several combinations of the Alt, Nb, and WI factors in order to estimate the role of these parameters in the predictive properties of T-wave alternans/variability.

Measurements of heart rate variability parameters

Time and frequency domain indexes of heart rate variability (HRV) were assessed including mean heart rate, standard deviation of normal to normal intervals (SDNN), root mean square of successive differences (RMSSD) in RR intervals, as well as low- and high-frequency components of the power spectrum. These measurements were obtained from the commercial Holter software (SpaceLab-Burdick, Milton, WI, USA) and they were computed on the overall 10 min recording. We evaluated HRV parameters since QT variability was previously reported to be related to HRV.
Statistical analysis

Cox regression models were used to assess the independent predictive values of the T-wave alternans/variability computed using various combinations of the factors Alt, Nb, and Wl. Hazard ratios were computed for TWV and considered dichotomized variables. When analysing the association between TWV and ICD therapy, primary endpoint for this analysis was time-dependent ICD therapy. For completeness, we also analysed combination of time-dependent ICD therapy and death, which ever comes first as a secondary endpoint. Kaplan-Meier curves were used to illustrate dichotomized parameters of interest. The highest quartile of the distribution of parameter values is used to define univariate threshold in the separation of our study groups. Non-parametric Wilcoxon test was used to compare median values between groups. A \( P \)-value of \(<0.05\) was considered significant.

Results

Population characteristics

Electrocardiogram Holter recordings were available in 632 MADIT II patients randomized to ICD therapy. Among this group, 22 patients did not have ICD and 1 patient did not have follow-up information. Thus, 609 patients were considered. Among them, 231 patients had BBB, 26 patients had AF, and an additional 18 patients had both AF and BBB. The risks of mortality in patients with BBB and/or AF was significantly higher than in patients without these conditions. Therefore, the BBB/AF subset of patients does not require further risk stratification being a high-risk group. Within the remaining group of 334 patients, 59 had too poor quality signals. Among the remaining 275 ICD patients, 58 patients developed ventricular tachycardia or fibrillation requiring ICD therapy, whereas 202 patients had no ICD therapy. There were 15 (5.4%) deaths among the 275 patients, and 73 (27.6%) patients experience either appropriate ICD therapy or died. There were no significant differences between 73 patients with and 202 patients without cardiac events in terms of age, gender distribution, body mass index (BMI), NYHA (dichotomized II to III vs. I), and the time between the myocardial infarction and the enrollment in the study. The blood urea nitrogen (BUN) was significantly increased in both groups of patients with ICD therapies only (22.2 ± 10.7 mg/100 mL, \( P = 0.05 \)) and the group of patients with ICD therapies and death (24.7 ± 13.1 mg/100 mL, \( P = 0.002 \)) in comparison with baseline.

T-wave alternans

The AW factor was not significantly associated with either appropriate ICD therapy, death, or their combination in the MADIT II population. Only sporadic transient episodes of TWA were identified in these resting Holter recordings, and this regardless of tested combination of investigated factors. For example for Alt = 12, mean AW was equal to 1.1 ± 4.1% in the group of patients with neither ICD therapy nor death, 0.7 ± 2.0% for the groups with ICD therapy or death, and 0.5 ± 1.6% for patients with ICD therapy only. The median values for the three groups were equal to 0. Therefore, we did not find significant alternans in the MADIT II population when using resting Holter recordings.

T-wave variability

We tested optimal combination of factors: Nb, the number of beats included in each segment, and Wl, the length of the window used to analyse the repolarization segment for defining TWV that might be predictive for arrhythmic events. On the basis of the median value of TWV from all available segments in each patient, TWV parameters based on \(<30\) beats (Nb = 30 beats) were predictive for arrhythmic event but especially those based on 60 beats (Nb = 60 beats). Cox analyses with the lowest deviance were utilized for optimally predicting arrhythmic events, we selected the following combination of factors for TWV measurement as optimally predicting arrhythmic events: number of beats (Nb = 60 beats) and window length (Wl = 40 ms). For
Nb = 60 beats, we obtained on average 11.0 ± 1.7 segments for each patient 10-min recording. We computed the median and the maximum value of TWV in all valid segments. We investigated the distribution of TWV across the repolarization intervals. Figure 2 provides a description of these results. The variability is unevenly distributed across the repolarization intervals. Variability is statistically higher in most windows when comparing patients with and without appropriate ICD therapy when these windows are in the interval between the J point and the J point +160 ms, and in the windows between 240 and 360 ms after the J point. When comparing the method based on the median or the maximum values from all windows, the median level of transient variability inside the T-wave was statistically significant, but not the maximum value. TWV was therefore defined as the median values among all available segments in the following analysis.

Electrocardiographic parameters

T-wave variability could not be computed in 59 subjects who did not meet technical requirements: 16 were removed because of frequent occurrence of non-sinus beats and 43 recordings because of both instable heart rate or/and non-sinus beats leading to a study population of 275 individuals including 58 patients with ICD therapy as their first event and 15 individuals who died prior to ICD therapy. Removing the 59 patients did not change the clinical characteristics of the study populations (Table 1).

Table 2 provides the values of the ECG parameters for the three groups of patients: no ICD therapy nor death (arrhythmia-free survivors), appropriate ICD therapy for ventricular tachycardia/fibrillation or death, and appropriate ICD therapy while censoring death. In comparison to arrhythmia-free survivors (without ICD therapy or death), heart rate was significantly increased in the group of individual with ICD therapy. SDNN, HF, and LF normalized values were somewhat, but not significantly lower in patients with cardiac events than those without cardiac events.

The amplitude variability was significantly higher in patients with ventricular tachycardia or ventricular fibrillation requiring ICD therapy than that in arrhythmia-free survivors (66 ± 68 vs. 58 ± 107 μV, respectively; P = 0.02). When ICD therapy was combined with death as the endpoint,

Table 1 Clinical characteristics of the study populations by: absence of ICD therapy or death, ICD therapy or death which ever comes first, and the presence of ICD therapy only

<table>
<thead>
<tr>
<th></th>
<th>No ICD therapy nor death (n = 202)</th>
<th>ICD therapy or death (n = 73)</th>
<th>ICD therapy only (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>16</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60 ± 11</td>
<td>62 ± 10</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>EF (%)</td>
<td>24 ± 5</td>
<td>23 ± 6</td>
<td>22 ± 6</td>
</tr>
<tr>
<td>BUN (mg/100 mL)</td>
<td>19.3 ± 8.3</td>
<td>24.7 ± 13.1** (*)</td>
<td>22.2 ± 10.7** (*)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.4 ± 5.2</td>
<td>29.0 ± 5.5</td>
<td>29.5 ± 5.6</td>
</tr>
<tr>
<td>NYHA class II–III (%)</td>
<td>58</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>MI before enrollment (months)</td>
<td>67 ± 68</td>
<td>74 ± 71</td>
<td>74 ± 69</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>73</td>
<td>63</td>
<td>64</td>
</tr>
</tbody>
</table>

None of the variables differed significantly between two groups.

*P = 0.06, **P = 0.002.
TWV was not significantly different in this group of patients in comparison with arrhythmia-free survivors. The value of TWV in nine patients who died was 48.1 ± 37.0 μV, it was not significantly different from the TWV level in arrhythmia-free survivors.

The threshold value for the TWV was pre-specified based on the study population’s highest quartile, which was 59 μV. Thirty-six per cent of the individuals with ICD therapy had only a TWV value above this threshold; it is significantly higher than in the group without ICD therapy and death (21%, P < 0.016). Similarly, 36% of patients in the group with ICD therapy or death had a TWV value superior to 59 μV, this was also statistically different in comparison with the group without ICD therapy and death (P = 0.017).

**Independent predictive value of T-wave variability**

We computed the Cox proportional hazard model including the parameters that were significantly different between the two groups (heart rate and EF) as well as the parameters that may have potential impact on the amplitude variance of the T-wave, namely NYHA class, BUN, gender, RMSSD, SDNN, HF, and LF. Among clinical parameters, only advanced NYHA class was predictive for arrhythmic events. We dichotomized the TWV parameters using upper quartile (TWV ≥ 59 vs. ≤ 59 μV). TWV ≥ 59 μV had hazard ratio equal to 2.01 (P = 0.011) for predicting arrhythmic events after adjustment for NYHA class (NYHA > II–III: ≤ I), the only other parameter that entered the model for predicting arrhythmia requiring ICD therapy (Table 3). This result shows a two-fold increased probability of having appropriate ICD shocks when TWV is > 59 μV. On the basis of this a priori chosen threshold (upper quartile), the Kaplan–Meier analysis (Figure 3) showed a significant separation in the risk of ventricular arrhythmia requiring ICD therapy in patients in the top quartile vs. three lower quartiles of TWV levels. It is important to emphasize that the above testing of the predictive value of T-wave variability was performed while excluding patients with wide QRS complex or AF.

**Effect of heart rate on T-wave variability**

The relationship between heart rate and repolarization variability of our study was investigated because TWV may lead to T-wave alternans when the heart rate is increased or the RR intervals are decreased. The averaged RR duration was computed from the sequence of beats used for the measurement of TWV. We investigated whether TWV was significantly associated with decreased RR intervals using the non-parametric Spearman rank correlation method. No significant relationship was found when considering the overall population (r² = 0.01, P = 0.17). We attributed this lack of relationship to a very limited range of heart rate recorded in these patients; they were recorded at rest in supine position.

**Discussion**

This study described a novel algorithm to quantify beat-to-beat changes in T-wave morphology that could be categorized as T-wave alternans or TWV and to determine whether this algorithm leads to development of parameters that could be used for predicting arrhythmic events. We demonstrated that TWV computed with our new algorithm based on Holter monitoring technology is predictive for arrhythmic events documented by ICD interrogation in MADIT II patients. It is worth emphasizing that increased levels of TWV were found predictive for arrhythmic events in MADIT II patients without AF and conduction disturbances.

The frequency-domain technique for the assessment of TWA is very rarely identified at resting heart rate, thus the need for a technique relying on resting ECG recordings would help risk stratifying all patients.
including the sickest individuals who may actually have high risk for SCD.

Our newly developed algorithm provides opportunity to quantify TWV and T-wave alternans, both phenomena reflecting electrical instability of myocardium. Previously, our group also attempted to quantify these electrical changes in repolarization using a correlation technique.\textsuperscript{24} We realize that T-wave alternans is relatively rare phenomenon, whereas repolarization variability is a more common finding, which could be observed in heart failure,\textsuperscript{25} coronary disease,\textsuperscript{24} or long QT syndrome patients.\textsuperscript{19,26} QT variability was recently found by our group\textsuperscript{27} as predictive for arrhythmic events in the same MADIT II population. This finding encouraged us to test our novel TWV algorithm using MADIT II population. Concordance of the findings by two different methods (Berger's and ours) indicates that phenomenon exists and might be considered as a risk stratifier.

The difference between Berger's and our method resides in the definition of the repolarization variability. Our method focuses on the variability of T-wave amplitude in the scalar ECGs, whereas Berger's method estimates the variability of the QT interval duration. In our previous investigation of beat-to-beat variability in patients with the LQT3 syndrome, we evidenced that both duration and amplitude of the T-wave were significantly increased in patients carrying the SCN5A mutation.\textsuperscript{28} In this study, we confirm that the presence of the variability in amplitude of the T wave is higher in patient with appropriate ICD therapy.

Predictive value of our TWV parameter was thoroughly tested in variety of signal-processing conditions that could potentially alter the results of testing. We changed number of beats continuously tested for TWV, we changed the minimum requirement for varying beats, we also changed the length of window during which amplitude of repolarization was continuously tracked for selected beats. Results of this comprehensive testing demonstrated that even 30-beat series could yield useful information about TWV, but 60-beat series provide more reliable and more significant predictive power.

Similar to the work of Haigney et al.,\textsuperscript{8} we did not observe significantly different values of TWV in 15 patients who died vs. arrhythmia-free survivors. Since the majority of death cases in ICD patients represents non-arrhythmic death (usually pump failure), it is plausible that TWV is not useful in predicting such mechanism of death. However, our sample size is too small to determine the association between TWV and non-arrhythmic fatal events. We looked at the level of QT variability within the population common to our study and Haigney's study, and we found a significant increased level of QT variability and TWV between patients with \((n = 51)\) and without \((n = 205)\) appropriate ICD therapy: \(0.23 \pm 0.20\) vs. \(0.22 \pm 0.50\), \(P = 0.02\) for QTVI and \(64 \pm 69\) vs. \(52 \pm 75\) \(\mu\)V, \(P = 0.05\) for TWV.

Limitations of this study include short-term, just 10-min, resting Holter recording, which precludes obtaining insight into dynamic behaviour of studied parameters quantifying the repolarization variability, eventually T-wave alternans. However, controlled recording conditions (supine resting) provide optimal opportunity to obtain reproducible data. Future studies with longer Holter recordings obtained in ambulatory setting with wider spectrum of heart rates are needed to evaluate further the predictive value of developed parameters and their reproducibility. Furthermore, almost 18\% of the ECG recordings did not meet the technical criteria for the method: 3 patients had frequent non-sinus beats, 21 patients had instable heart rate and 27 patients had both instable heart rate and occurrence of non-sinus beats. Several of these individuals had periods of important transient noise during which the analysis was not possible. One may hypothesize that in 24-hour ECG recordings, this percentage of the population to be excluded will be reduced.

Another limitation relates to the programming of the ICD devices, no mandated program was defined in MADIT II population thus we compared the survival curves for the ICD therapy for VT and ventricular fibrillation (VF) endpoints between patients with slow VT and patients with fast VT or VF. We did not find significant differences between these two groups reducing the probability for any selection bias in the study population.

This study should be considered as a pilot study, requiring further validation, apart from MADIT II subset of patients. Although this study population of 275 subjects is much larger than the study population of nested-case control cohort described by Verrier et al.\textsuperscript{29} for validating his T-wave alternans algorithm, we realize that our population served as development set and we need another independent validation set to prove further that T-wave variability...
measures using our algorithm is predictive both for arrhythmias as well as for mortality.

Acknowledgements

MADIT II trial was funded by unrestricted grant from Guidant Corporation to University of Rochester. The study was partially funded by unrestricted grant from ELA Medical to University of Rochester.

Conflict of interest: J.-P.C. and W.Z. are authors of the patent describing the method and they received consulting fees associated with this work.

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