Analysis of T-Wave Morphology From the 12-Lead Electrocardiogram for Prediction of Long-Term Prognosis in Male US Veterans

Markus Zabel, MD; Marek Malik, PhD, MD; Katerina Hnatkova, PhD; Vasilios Papademetriou, MD; Andreas Pittaras, MD; Ross D. Fletcher, MD; Michael R. Franz, MD, PhD

Background—The aim of the present study was to assess the prognostic value of novel repolarization descriptors from the 12-lead ECG in a large cohort of US veterans.

Methods and Results—Male US veterans (n = 813) with cardiovascular disease had digital 12-lead ECGs recorded at the VA Medical Center, Washington, DC, between 1984 and 1991. The patient series was retrospectively compiled in 1991; follow-up was prospectively assessed until 2000. Novel ECG variables characterizing repolarization and the T-wave loop were automatically analyzed. Of 772 patients with technically analyzable data, 252 patients (32.6%) died after a mean follow-up of 10.4 ± 3.8 years. Direct comparison between dead and alive patients showed that the so-called T-wave residua (the absolute and relative amount of nondipolar contents within the T wave) predicted mortality (111 900 ± 164 700 versus 85 600 ± 144 800 between dead and alive patients, P < 0.0002; and 0.43 ± 0.62% versus 0.33 ± 0.56%, P < 0.0005 for the absolute and relative T-wave residuum, respectively). On Cox regression analysis entering age, left ventricular ejection fraction, echocardiographic left ventricular hypertrophy, and either of the T-wave residua, risk prediction was independent for the absolute (P = 0.022) and for the relative (P = 0.006) T-wave residuum, respectively, with age (P < 0.0001), presence of left ventricular hypertrophy (P = 0.002), and left ventricular ejection fraction (P = 0.004) also being predictors of survival.

Conclusions—The heterogeneity of myocardial repolarization, measured by the so-called T-wave residuum in the ECG, confers long-term independent prognostic information in US veterans with cardiovascular disease. (Circulation. 2002; 105:1066-1070.)

Key Words: death, sudden ■ risk factors ■ waves ■ electrocardiography

Noninvasive identification of patients at increased risk for sudden cardiac death remains an important goal. In assessing the pathophysiology of ventricular repolarization, T-wave alternans has been demonstrated to be a useful noninvasive risk predictor, which requires an exercise test. From the resting 12-lead surface ECG, QT interval dispersion (QTd) had shown initial promise as a simple marker of spatial dispersion of ventricular repolarization, but its clinical use was limited by measurement inaccuracies, and prognostic utility was not confirmed in prospective studies. Moreover, it was recently shown that QTd was caused by different projections of a common T-wave vector onto the leads of the surface ECG rather than to reflect regional heterogeneity of myocardial repolarization. The failure of the assumed pathophysiologic basis of QTd was subsequently proven by Malik et al. Instead, the authors hypothesized that the nondipolar contents of the 12-lead ECG T wave, that is, the signal beyond the 3-dimensional T-wave vector, reflects the true heterogeneity of ventricular repolarization. This variable was termed the T-wave residuum (TWR). This study tested the hypothesis that TWR and/or other ECG variables of T-wave morphology predict long-term survival in US veterans with cardiovascular disease.

Methods

Patients
A cohort of 813 US male veterans with cardiovascular disease had a digital 12-lead surface ECG recorded during their initial diagnostic workup at the Veterans Affairs Medical Center Washington, DC between 1984 and 1991. The patient series was retrospectively compiled in 1991 with the use of the VA Medical Center Washington, DC digital patient file system (DHCP) and followed up prospectively until 2000. Coronary angiography was performed to assess the presence of coronary artery disease (CAD) and its severity. Left ventricular ejection fraction (LVEF) was evaluated by means of left ventricular angiography. Echocardiography was performed...
TABLE 1. Clinical and Echocardiographic Variables in Patients With and Without Events (Deaths) During Follow-Up

<table>
<thead>
<tr>
<th>Events (Deaths) During Follow-Up</th>
<th>Alive (n=520)</th>
<th>Dead (n=252)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60±11</td>
<td>64±18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>56±16</td>
<td>53±18</td>
<td>0.03</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>2.10±0.20</td>
<td>2.05±0.21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.3±3.9</td>
<td>22.4±4.0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>LVH, positive</td>
<td>329/520 (63%)</td>
<td>201/252 (80%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

formed for detection and quantification of left ventricular hypertrophy (LVH). Hypertension and hypertensive heart disease were clinically diagnosed as previously described. Cardiac medications were assessed at the time of the study entry. Body surface area (BSA) and body mass index were calculated from the patient’s weight and height.

ECCG Recordings and Analysis

In all patients, a digital 12-lead surface ECG sampled at 250 Hz was recorded on Marquette standard equipment and was stored on a MUSE network (GE Marquette). Utilizing recently validated algorithms, ECG variables characterizing the T-wave loop and other repolarization features were calculated automatically and blindly (ie, by coworkers who did not have access to the clinical and follow-up data). T-wave loop dispersion, the normalized T-wave loop area, the total cosine R-to-T (TCRT), and T-wave morphology dispersion (TMD) were calculated as recently described. In addition, the relative and absolute TWR was determined. Briefly, after singular value decomposition, the ECG was reconstructed in an orthogonal 8-lead system. In this lead system, the first 3 orthogonal components represent the signal of the traditional 3-dimensional T-wave vector or dipolar signal contents, whereas the remaining 4th to 8th orthogonal lead components relate signal components beyond the single dipole movement. These so-called nondipolar components reflect repolarization signals that are contained within the ECG but are not reflected in the global reconstructed T-wave vector. Thus, they are expected to represent true heterogeneity of ventricular repolarization within the ECG. In this study, the absolute and relative TWR were calculated as the sum of squares of the 4th to 8th eigenvalues of the T-wave signal and as the proportion of this sum to the sum of squares of all 1st to 8th eigenvalues. The absolute TWR is given in clinical units, dependent on the numerical representation of the native ECG signal (which was the same for all ECGs in the study); the relative TWR is unitless and is given in percent. Although repeatability of the TWR from a single recording is 100%, reproducibility from repeated recordings in several patient populations is fully acceptable, with coefficients of variance between 0.24 and 0.34 among 10 repeated ECGs. For comparison, the average QT interval and the complexity ratio (CR) from principal component analysis were also computed from the ECG.

Clinical Follow-Up

Prospective collection of follow-up information was ensured through the VA health care system until June 2000. To avoid misclassification among cardiac, arrhythmic, and noncardiac mortality, total mortality was defined as the end point of the study. The exact date of death was retrieved from the VA records.

Statistics

Continuous values are reported as mean±SD. Comparisons between patients with and without events, and the relation of ECG variables to categorical clinical variables were tested by means of a nonparametric U test. Distributions of categorical variables were tested by χ² test. Kaplan-Meier event-probability curves were computed, dichotomizing patient groups by the median value of the given variable, and compared by the log-rank test. Cox regression analysis for determination of the independent correlation of multiple variables with the timing of events during follow-up was performed with a stepwise backward removal of the respective least significant variable. Continuous variables were categorized by median value. A value of P<0.05 was considered statistically significant.

Results

Clinical and Follow-Up Data

The mean age at study entry was 61±10 years. The ECG recordings of 41 of 813 patients were technically not analyzable (eg, because of excessive noise) and were excluded from the final data analysis. CAD was diagnosed in 563 of 772 (73%) of the patients included; 6% (46 of 772) had dilative cardiomyopathy. LVEF averaged 55±17%. Five hundred seventeen of 772 (67%) patients had hypertension, with 185 of 772 patients (24%) classified as having hypertensive heart disease. LVH (LV mass index ≥131 g/m²) was found in 522 of 772 (67.6%) patients. ACE inhibitors were taken by 226 of 772 (29.3%) patients, diuretics by 259 of 772 (33.5%) patients, and digoxin by 102 of 772 (13.2%) patients, respectively. A total of 53 of 772 (6.9%) patients were treated with class I or III antiarrhythmic drugs. During a mean follow-up of 10.4±3.8 years, 252 patients (32.6%) died. On univariate analysis (Table 1), age, LVEF, BSA, and body mass index were predictive of events. The presence of CAD as well as the

TABLE 2. T-Wave Morphology Variables in Patients With and Without Events (Deaths) During Follow-Up

<table>
<thead>
<tr>
<th>Events (Deaths) During Follow-Up</th>
<th>Alive (n=520)</th>
<th>Dead (n=252)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT interval, ms</td>
<td>478±48</td>
<td>482±50</td>
<td>ns</td>
</tr>
<tr>
<td>Complexity ratio</td>
<td>0.23±0.14</td>
<td>0.25±0.13</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>T-wave morphology dispersion, degrees</td>
<td>42±27</td>
<td>47±26</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Total cosine R-to-T</td>
<td>−0.11±0.65</td>
<td>−0.23±0.60</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Normalized T-wave loop area</td>
<td>0.51±0.17</td>
<td>0.49±0.17</td>
<td>ns</td>
</tr>
<tr>
<td>T-wave loop dispersion</td>
<td>37±6</td>
<td>37±5</td>
<td>ns</td>
</tr>
<tr>
<td>Absolute T-wave residuum, t.u.</td>
<td>85 601±144 844</td>
<td>111 913±164 711</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Relative T-wave residuum, %</td>
<td>0.33±0.57</td>
<td>0.43±0.62</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

t.u. indicates technical units; ns, not significant.
number of vessels involved was not related to the risk of death.

T-Wave Morphology Analysis: Univariate Prognostic Value
Table 2 shows mean values for the studied ECG variables for patients who died during follow-up as compared with the 520 survivors. The most striking difference was found for variables of nondipolarity (P < 0.0002 and P < 0.0005 for absolute and relative TWR, respectively), indicating a higher degree of repolarization heterogeneity in patients who had events during long-term follow-up. Among the other variables studied, CR (P < 0.03), TMD (P < 0.02), and TCRT (P < 0.02) had significant differences.

T-Wave Morphology Analysis: Kaplan-Meier Curves
Patients with a relative TWR above the median (ie, > 0.15%) showed a significantly worse survival rates as compared with patients with values below (P < 0.0002, Figure, A). Similarly, patients with an absolute TWR above the median (ie, > 51042) had worse survival rates than did patients with values below (P < 0.0004, Figure, B). The median value of CR also allowed stratification of patient risk, with values above the median (ie, > 0.208) indicating a higher probability for end points (P < 0.004). Stratification of patient subsets by the median of TCRT, TMD, and normalized T-wave loop area did not result in different event probabilities.

Multivariate Risk Assessment
For Cox regression analysis, clinical variables (age, LVEF, BSA), presence of LVH, and T-wave morphology descriptors (relative TWR, absolute TWR, CR, TCRT and TMD), which were univariately predictive of events, were entered as independent categoric variables dichotomized by their median. Because of similarity, relative and absolute TWR, as well as CR, TCRT and TMD were not entered together. Age (P < 0.0001) and presence of LVH (P = 0.002) as well as LVEF (P = 0.004) were predictors of prognosis, whereas either relative TWR (P = 0.006) or absolute TWR (P = 0.022) were the only independent T-wave morphology variables remaining in the final regression equation (Table 3).

Discussion
This study in a large number of male US veterans is the first to demonstrate that a new parameter—the so-called TWR, which characterizes heterogeneity of ventricular repolarization by calculating the absolute and relative nondipolar signal contents within the 12-lead surface ECG—permits risk stratification in patients with cardiovascular disease over a long-term follow-up of > 10 years. This new parameter, TWR, is available within a single beat of the ECG and can be measured automatically, instantaneously, and with a practically acceptable reproducibility.14

Repolarization Heterogeneity: Noninvasive Assessment and Relevance for Prognosis
A close link between an increased heterogeneity of ventricular repolarization and arrhythmogenicity has been demonstrated in many previous as well as very recent experimental studies.22–25 Searching for a noninvasive measurement of this substrate, body surface potential mapping proved successful26–29 but is impractical for wide clinical use. Measurement of QTd from the 12-lead surface ECG was proposed a decade ago3 and was believed to provide a reasonably good reflection of the true myocardial heterogeneity of repolarization.30,31 Because of its simplicity and wide availability, QTd has been evaluated in a large number of clinical studies.6 Whereas initial retrospective studies3–5 seemed to support the use of QTd as a risk stratifier, more recent prospective trials11,12 did not confirm its clinical usefulness. Among other methodological limitations6,31 an important concern stemmed from ECG lead theory. A study by Kors et al13 convincingly showed that QTd relates to different projections of the T-wave loop onto the surface ECG leads and therefore cannot provide regional repolarization information. Their study assumed an entirely
dipolar nature of the T wave, which is true for a substantial portion but not the entire extent of the ECG signal.\textsuperscript{32,33} To further clarify the genesis of QTd in the ECG, Malik et al\textsuperscript{14} designed a methodological study in clinically well-defined populations. For comparison with traditional QTd, they reconstructed the 3D T-wave vector from the 12-lead ECG and quantified the nondipolar signal contents, that is, the extent to which an individual ECG lead differs from the projection of the T-wave vector into the same lead. The rationale of this approach is that those repolarization signals not reflected by a common 3D T-wave vector do represent true heterogeneity of ventricular repolarization. These nondipolar signal contents can be expressed in absolute terms or relative to the overall signal power involving dipolar and nondipolar contents and were termed absolute and relative TWR. Importantly, there was no significant correlation between the T-wave residua and QTd, neither in the overall population nor in subgroups, proving that an entirely new concept is used. Consistent with the concept that heterogeneity of ventricular repolarization increases with myocardial disease states, significantly higher values were found for the T-wave residua in patients after myocardial infarction as compared with normal subjects. Nonetheless, the absolute values of the relative TWR appear very small; the differences between patients after myocardial infarction and normal subjects were reported in normal subjects\textsuperscript{14} than in patients with CAD after myocardial infarction.\textsuperscript{18} However, it was only univariately associated with events in the current study. Similarly, CR from principal component analysis\textsuperscript{20} and TMD\textsuperscript{17,18} exhibited univariate but not independent predictive value in this study. The fact that a more general population with cardiovascular disease and with preserved LV function at study entry was investigated may explain the differences between this and the previous study in patients after infarction.

**Limitations**

The study was retrospective because the digital ECG analysis techniques used have only recently become available. On the other hand, the VA Medical Center in Washington, DC, is unique in enabling a long-term follow-up of patients with standard ECGs recorded and stored digitally since over 15 years. Therefore, the design used was the only possible to evaluate the long-term prognostic implications of digitally analyzable ECG variables.

Technically, the noise level of an ECG recording influences the T-wave residua. A major influence on the prognostic utility of this variable was ruled out, however, by calculation of the respective residua of QRS, which were evenly distributed among patients with and without events.

Finally, the pathophysiology of the T-wave residua and other new T-wave morphology variables has not been studied in experimental models, so potential mechanisms as to why these markers can predict arrhythmias can only be theoretically discussed. Experimental protocols to answer these pertinent questions are underway and will become available soon.

**References**


**TABLE 3. Independent Prognostic Value of Risk Stratifiers for Prediction of Mortality After Entering All Univariately Predictive Clinical and T-Wave Loop Morphology Variables Into a Stepwise Backward Cox Regression Analysis**

<table>
<thead>
<tr>
<th>Risk Stratifier</th>
<th>Adjusted Risk Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.69 (1.31–2.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVH</td>
<td>1.59 (1.19–2.08)</td>
<td>0.002</td>
</tr>
<tr>
<td>LVEF</td>
<td>1.54 (1.18–1.99)</td>
<td>0.004</td>
</tr>
<tr>
<td>Relative T-wave residuum</td>
<td>1.47 (1.14–1.92)</td>
<td>0.006</td>
</tr>
<tr>
<td>Absolute T-wave residuum</td>
<td>1.37 (1.06–1.79)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

P values and absolute risk ratios are at last regression step. Variables were categorized by their median to correct for the skewed absolute values of TWR and other T-wave loop morphology variables. Absolute and relative TWR were not entered into the model at the same time because of their similarity.


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