Analysis of 12-Lead T-Wave Morphology for Risk Stratification After Myocardial Infarction

Markus Zabel, MD; Burak Acar, PhD; Thomas Klingenstein, MD; Michael R. Franz, MD, PhD; Stefan H. Hohnloser, MD; Marek Malik, PhD, MD

**Background**—The stratification of post–myocardial infarction (MI) patients at risk of sudden cardiac death remains important. The aim of the present study was to assess the prognostic value of novel T-wave morphology descriptors derived from resting 12-lead ECGs.

**Methods and Results**—In 280 consecutive post-MI patients, a 12-lead ECG was recorded before discharge, optically scanned, and digitized. For the present study, 5 T-wave morphology descriptors were automatically calculated after singular value decomposition of the ECG signal. The total cosine R-to-T (TCRT [describes the global angle between repolarization and depolarization wavefront]) and the T-wave loop dispersion were univariately associated ($P=0.0002$ and $P<0.002$, respectively, $U$ test) with 27 prospectively defined clinical events in 261 patients (mean follow-up 32±10 months). Kaplan-Meier event probability curves for strata above and below the median confirmed the strong risk discrimination by TCRT and T-wave loop dispersion ($P<0.003$ and $P<0.001$, respectively, log-rank test). On Cox regression analysis, with the entering of age, left ventricular ejection fraction, heart rate, QRS width, reperfusion therapy, β-adrenergic–blocker treatment, and standard deviation of R-R intervals on 24-hour Holter monitoring, TCRT ($P<0.03$) yielded independent predictive value, whereas T-wave loop dispersion was of borderline independence ($P=0.064$). Heart rate ($P<0.02$), left ventricular ejection fraction ($P<0.02$), and reperfusion therapy ($P<0.02$) also remained in the final model.

**Conclusions**—Computerized T-wave morphology analysis of the 12-lead resting ECG permits independent assessment of post-MI risk and an improved risk stratification when combined with other risk markers. (Circulation. 2000;102:1252-1257.)

**Key Words:** myocardial infarction ■ death, sudden ■ risk factors ■ waves ■ electrocardiography

The noninvasive identification of individuals at risk for sudden cardiac death still presents a significant clinical dilemma. Lately, interest has focused on ECG T-wave heterogeneity, reflecting a dispersion of myocardial repolarization, which may facilitate ventricular tachycardia (VT) or fibrillation (VF). Although a variety of studies have assessed QT variability, QT dispersion (QTD), QT interval alternans, ventricular repolarization alternans, and T-wave loop dispersion have shown promise for VT risk stratification and are being evaluated in large controlled trials. However, none of these approaches embodies combined the temporospatial features of repolarization dispersion.

We hypothesized that composite temporospatial measures of ECG repolarization dispersion would improve risk stratification for post–myocardial infarction (MI) ventricular arrhythmias and sudden cardiac death in comparison with stratifiers such as QTD, left ventricular ejection fraction (LVEF), or thrombolytic therapy. In particular, we applied recently developed novel quantitative repolarization analyses that are accessible from a single ECG beat. The total cosine R-to-T (TCRT) reflects the spatial angle between depolarization and repolarization, akin to the venerable concept of the ventricular gradient. T-wave loop dispersion extends this concept, reflecting variability of the T-wave vector loop. The normalized T-wave loop area measures heterogeneity of principal components of the T wave within its loop, whereas T-wave morphology dispersion expresses morphological heterogeneity within the 12-lead ECG. Conceptually similar but distinct examinations of repolarization complexity were recently successful in stratifying arrhythmic risk in the long QT syndrome and arrhythmogenic right ventricular dysplasia.

We therefore set out to determine the usefulness of our analyses in temporospatial dispersion for the stratification of arrhythmic risk and death in a series of prospectively studied post-MI patients. This analysis resulted in a surprisingly...
powerful accuracy of the prediction of cardiac mortality from the 12-lead resting ECG.

Methods

Patient Population and ECG Recordings

For the present study, the digital ECG recordings of a recently published prospective study on the prognostic value of QTD were reevaluated with the new T-wave morphology analysis. Characteristics of the patient group have been described elsewhere. In brief, 280 consecutive patients (229 men and 51 women, mean age 58±11 years) were enrolled into the study 9±3 days after their index MI. Twelve-lead resting surface ECGs were recorded with a paper speed of 50 mm/s and converted into digital ECGs with a customized method that involved scanning, editing of the resulting image file, and digitization at 1 kHz by means of a custom-written Labview program. For each ECG, the digital signal of 1 beat of each lead was used in this study.

T-Wave Morphology Descriptors

Analysis of the digital ECG recordings was performed in a fully automatic manner with a custom-developed software implemented on a personal computer. The study was conducted in a strictly blinded manner: digital ECGs were sent from Germany to London for processing without any clinical data. The analytical results were returned to the German center as an unlabeled numerical spreadsheet. Only after completion of the statistical analyses were the German center workers given the description of the analytical procedures.

The analysis program performs a singular value decomposition of the ECG signal into a minimum dimensional space. From singular value components, principal component analysis (PCA) was performed as recently described. Complex ratio (CR) was the ratio of the singular value of the second most significant component to the square root of the sum of the squares of all 8 singular values.

Based on the decomposition, several descriptors were calculated that involved spatial and temporal variations of T-wave morphology and repolarization wavefront direction (Figure 1). (1) The so-called T-wave morphology dispersion measures the variation of the ECG vector (ie, the variation of the interlead relations among domain of interlead relations spanned by the ECG vector). This variable is unitless; its maximum value is 100. (2) The so-called normalized T-wave loop area describes the shape and irregularity of the T-wave loop by expressing its area as a fraction of the rectangle that encompasses the loop. The variable is unitless. (3) The so-called T-wave loop area is calculated as fraction of loop area (marked by stripes) of encompassing rectangle. Bottom right, reconstruction vectors of different ECG leads onto T-wave loop. T-wave morphology dispersion is calculated by averaging angle between all possible reconstruction vector pairs. Angle between reconstruction vectors is shown in figure. See Methods for more detailed explanation.

Statistical Analysis

Statistical evaluation was processed independent of the T-wave analyses. For comparison, the results for conventional QTD variables (QRS width, QTD, JT dispersion, T peak-to-end interval, area under the T wave), for other risk stratifiers (SDNN from Holter recordings, QRS width, QTD, JT dispersion, T peak-to-end interval, area under the T wave), other statistics. Continuous values are reported as mean ±SD. Comparisons between patients with and without events during follow-up were performed by the nonparametric U test. Pearson’s correlations between ECG and clinical variables was tested by a U test. For comparison, the results for conventional QTD variables (QRS width, QTD, JT dispersion, T peak-to-end interval, area under the T wave), for other risk stratifiers (SDNN from Holter recordings, LVEF), and for clinical variables (age, reperfusion therapy, beta-blocker treatment, heart rate from the study ECG) were taken from the previous study of this cohort. Data were analyzed with SPSS Version 7.0 for Windows for Cox regression analysis and JMP-3.1 software (SAS Institute) for all other statistics. Continuous values are reported as mean ±SD. Comparisons between patients with and without events during follow-up were performed by the nonparametric U test. Pearson’s correlations between ECG and clinical variables were used. The relation of ECG variables to categorical clinical variables was tested by a χ² test.

Follow-Up

Follow-up data and information on clinical end points were unchanged from the initial publication of the same post-MI patient group. The prospectively defined primary end point combined all-cause mortality, sustained VT, and resuscitated VF. The secondary end points consisted of arrhythmic events: sudden cardiac death, documented sustained VT, and resuscitated VF.
TABLE 1. Overview of Clinical Variables in Patients With and Without Primary Events During Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=261)</th>
<th>Patients Without LBBB (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±11</td>
<td>65±8</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68±11</td>
<td>75±15</td>
</tr>
<tr>
<td>LVEF</td>
<td>48±11</td>
<td>39±13</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>98±42</td>
<td>72±25</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>196 (84)</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Reperfusion therapy, n (%)</td>
<td>129 (55)</td>
<td>6 (22)</td>
</tr>
</tbody>
</table>

Patient groups: Negative (n=234) and Positive (n=27). Statistical significance was considered for P<0.05.

Clinical Events
During a 32±10-month follow-up, 20 patients died (10 of sudden cardiac death, 5 of pump failure, 5 of noncardiac causes). Sustained VT was noticed in 5 patients, and 2 patients were resuscitated from VF. According to the prospective criteria, a total of 27 of 261 patients reached the primary end point. The secondary end point (arrhythmic events) was met in 17 patients. Of 9 patients with LBBB, 4 reached a primary end point, including 3 arrhythmic events. Table 1 shows the relationships of clinical variables included in the multivariate analysis to the occurrence of primary end points.

T-Wave Morphology Analysis: Correlations With Conventional QTD Variables and Clinical Data
Pearson’s correlation coefficients were determined for pairs of T-wave morphology variables. All r values were <0.25 and thus of no clinical relevance. Specifically, TCRT and T-wave loop dispersion were unrelated (r=0.11, P=NS). For pairs with conventional QTD variables and QRS width, an intermediate inverse relationship with the average area under the T wave was found for CR (r=-0.40, P<0.001). Patients with LBBB (n=9) had TCRT of -0.77±0.25, whereas patients without LBBB (n=252) had an average TCRT of 0.11±0.12 (P=0.005). T-wave loop dispersion exhibited a borderline difference related to LBBB (33±4 with LBBB versus 35±5 without LBBB, P=0.044), whereas all other T-wave variables were not influenced by LBBB. All other correlations were not practically relevant, including several significant r values between 0.17 and 0.25. Right bundle-branch block was not associated with the T-wave morphology variables. Moreover, none of the continuous clinical variables, including heart rate, age, SDNN from Holter, and LVEF, were related to the T-wave morphology variables. This was also true for other clinical variables, such as sex, use of reperfusion therapy, β-blocker treatment, or infarct location.

T-Wave Morphology Analysis: Univariate Prognostic Information
Of 280 ECGs, 19 were excluded due to insufficient data quality or missing leads. Tables 2 and 3 summarize the values for T-wave morphology variables for 27 patients with events compared with 234 event-free patients. Tables 2 and 3 also show the same comparison between 17 patients with and 244 patients without arrhythmic events. CR exhibited paradoxically lower rather than theoretically expected higher values in the event group, with a borderline significance (P<0.07). The comparison for patients with and without arrhythmic events was not significant. TCRT was lower in the patient group with events (P<0.0002) and in patients with arrhythmic events (P<0.004). Similarly, T-wave loop dispersion was lower in patients with primary end points (P<0.002) and arrhythmic events (P<0.003). No difference was found for T-wave morphology dispersion and normalized T-wave loop area.

T-Wave Morphology Analysis: Kaplan-Meier Event Probabilities
Patients with a TCRT below the median had decreased survival (P<0.003, Figure 2A) and a higher incidence of arrhythmic events (P<0.007). The median value of T-wave loop dispersion also discriminated patients at risk of overall end points (P<0.001, Figure 2B) and arrhythmic events (P<0.004). CR, T-wave morphology dispersion, and normalized T-wave loop area did not result in different Kaplan-Meier event probabilities. In an analysis of the patients without LBBB (n=252), the results were similar with TCRT (P=0.022 and P<0.04, respectively, for primary and arrhythmic end points) and T-wave loop dispersion (P=0.003 and P=0.014, respectively).

TABLE 2. T-Wave Morphology Variables for Patients With and Without Primary Events During Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=261)</th>
<th>Patients Without LBBB (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (n=234)</td>
<td>Positive (n=27)</td>
</tr>
<tr>
<td>Complexity ratio</td>
<td>0.26±0.15</td>
<td>0.21±0.13</td>
</tr>
<tr>
<td>T-wave morphology dispersion, °</td>
<td>57.0±27.5</td>
<td>63.7±23.8</td>
</tr>
<tr>
<td>TCRT</td>
<td>0.16±0.57</td>
<td>-0.31±0.57</td>
</tr>
<tr>
<td>Normalized T-wave loop area</td>
<td>0.56±0.16</td>
<td>0.48±0.20</td>
</tr>
<tr>
<td>T-wave loop dispersion</td>
<td>35.6±4.7</td>
<td>32.9±6.2</td>
</tr>
</tbody>
</table>

Despite the strong relationship of total cosine R-to-T to LBBB, the univariate relationship with primary end points remains significant for patients without LBBB.
Multivariate Analysis of Risk Factors

Clinical variables (age, reperfusion therapy, LVEF, \(\beta\)-blocker treatment, QRS width, heart rate), Holter parameters (SDNN), and T-wave morphology descriptors (TCRT, T-wave loop dispersion) that were univariately predictive of follow-up endpoints were entered as independent variables into a Cox regression model with stepwise backward removal (Tables 4 and 5). At least 1 T-wave morphology variable remained in the equation at the last regression step, namely, TCRT for the prediction of primary end points and T-wave loop dispersion for the prediction of arrhythmic events. By entering only univariately predictive T-wave morphology variables into the Cox regression model (TCRT, T-wave loop dispersion, normalized T-wave loop area) and by considering only patients without LBBB (n=252), we showed that T-wave loop dispersion (\(P=0.009\) and \(P=0.003\), respectively) and TCRT (\(P=0.006\) and \(P=0.07\), respectively) were independently predictive of primary end points and arrhythmic events.

Discussion

This post hoc analysis of a prospective study in 280 consecutive post-MI patients demonstrates that novel T-wave morphology descriptors from the 12-lead surface ECG\(^{11}\) permit the accurate risk stratification of post-MI patients. This was found in a patient population where conventional variables of ventricular repolarization dispersion had failed to discriminate risk.\(^{15}\) The new variables require digital recording of the ECG but otherwise are readily accessible at the patient’s bedside. On multivariate analysis, \(\geq 1\) T-wave morphology descriptor remained in the model, adding independent information to other risk stratifiers such as heart rate, LVEF, and the administration of reperfusion therapy.

Comparison With PCA and Conventional QTD

In a comparison with PCA of the T wave,\(^{13,14}\) 2 of the proposed T-wave morphology descriptors were superior. At best, PCA yielded borderline significance in the univariate model with stepwise backward removal (Tables 4 and 5). At least 1 T-wave morphology variable remained in the equation at the last regression step, namely, TCRT for the prediction of primary end points and T-wave loop dispersion for the prediction of arrhythmic events. By entering only univariately predictive T-wave morphology variables into the Cox regression model (TCRT, T-wave loop dispersion, normalized T-wave loop area) and by considering only patients without LBBB (n=252), we showed that T-wave loop dispersion (\(P=0.009\) and \(P=0.003\), respectively) and TCRT (\(P=0.006\) and \(P=0.07\), respectively) were independently predictive of primary end points and arrhythmic events.

### Table 3. T-Wave Morphology Variables in Patients With and Without Arrhythmic Events During Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=261)</th>
<th>Patients Without LBBB (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (n=244)</td>
<td>Positive (n=17)</td>
</tr>
<tr>
<td>Complexity ratio</td>
<td>0.26±0.15</td>
<td>0.20±0.13</td>
</tr>
<tr>
<td>T-wave morphology dispersion, °</td>
<td>57.3±27.3</td>
<td>63.4±25.6</td>
</tr>
<tr>
<td>TCRT</td>
<td>0.14±0.58</td>
<td>−0.31±0.60</td>
</tr>
<tr>
<td>Normalized T-wave loop area</td>
<td>0.56±0.16</td>
<td>0.50±0.20</td>
</tr>
<tr>
<td>T-wave loop dispersion</td>
<td>35.5±4.9</td>
<td>31.8±4.4</td>
</tr>
</tbody>
</table>

Values are given for patient groups including (n=261) and excluding (n=252) LBBB.
TABLE 5. Independent Prognostic Value of Risk Stratifiers After Entering All Univariately Predictive Clinical, Holter, and T-Wave Morphology Variables Into a Stepwise Backward Cox Regression Analysis (P Values at Last Regression Step) and With Arrhythmic Events as the Dependent Variable

<table>
<thead>
<tr>
<th>Risk Stratifier</th>
<th>P (all patients, n=261)</th>
<th>P (patients without LBBB, n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperfusion therapy</td>
<td>0.012</td>
<td>0.008</td>
</tr>
<tr>
<td>T-wave loop dispersion</td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.010</td>
<td>NS</td>
</tr>
<tr>
<td>HR</td>
<td>0.056</td>
<td>NS</td>
</tr>
</tbody>
</table>

comparison for the prediction of overall events. In contrast, 2 T-wave morphology variables were strong risk predictors for overall or arrhythmic events, confirmed by the calculation of Kaplan-Meier curves. This strong prognostic value contrasts with the disappointing results with conventional QTD variables. A major aspect of the new variables is the technical improvement over QTD in both reproducibility and measurement objectivity. Importantly, the proposed algorithms do not rely on an accurate T-wave offset measurement, which is the major source of inaccuracy in automatic QTD measurements. In most studies, however, QTD was analyzed manually, which is even less reliable due to subjective variations in waveform assessment between centers. The intraobserver reproducibility is also improved.

Pathophysiological Concept of Novel T-Wave Morphology Descriptors

The prognostic content of abnormal repolarization had been suspected because the early experiments demonstrated the role of ventricular repolarization pathologies in the arrhythmogenesis. Initially, this concept was followed with the use of body surface potential mapping. QTD from 12-lead ECGs was proposed as a more practical surrogate. After the initial enthusiastic reports, meticulous methodological studies cast doubt on the true value of QTD. Finally, the first truly prospective study in a large post-MI population established that none of the conventional QTD variables carried post-MI prognosis. Although this finding is contradicted by recent epidemiological studies, a more sophisticated concept of repolarization analysis for the purpose of risk stratification is clearly required. It was therefore attempted to explore more accurate repolarization qualities from 12-lead ECGs, such as PCA and T-wave loop morphology, or to explore dynamic QT changes on Holter monitoring. None of these newer repolarization markers have been tested in the present study.

Comparison With Other Risk Markers

In testing the independent contribution of T-wave morphology descriptors by means of Cox regression, at least 1 T-wave morphology marker provided independent risk stratification. Importantly, only very weak relationships between the various novel descriptors and conventional variables of QTD were found, demonstrating that the proposed variables assess yet undetected qualities of repolarization and do not reproduce or refine the more conventional measurements. Specifically, we could not confirm the result of the study by Kors et al, which correlated T-wave loop characteristics with QTD in a database of 1220 ECGs.

Study Limitations

Although a large post-MI patient population was studied, the overall number of general end points as well as arrhythmic events was low, which reflects the modern treatment strategies. In particular, the statistics with regard to arrhythmic end points should be viewed with this limitation the number of events in more strictly defined subcategories is not sufficient for further detailed comparisons.
collected ECG data. Consequently, we have used the same algorithmic settings as in the technical report by Acar et al. It is likely that for the purposes of post-MI risk stratification, the original algorithms that quantify T-wave morphology abnormalities should be further refined. It is also possible that the values of the T-wave morphology variables undergo dynamic changes after MI, particularly during the first year. However, such an influence is not expected to yield a false-positive relationship with outcome but rather would weaken the predictive value of the ECG descriptors.

In terms of other risk variables, we restricted our present investigation to the set of risk factors used in the previous report on this population. Other variables, such as recently described factors of heart rate turbulence, were not considered. It is unlikely, however, that heart rate turbulence would be pathophysiologically linked to T-wave morphological abnormalities.

Implications

The present results are important for future risk stratification studies such as those of prophylactic post-MI treatment. The risk stratifiers proposed represent 2 easily accessible measurements available from a single surface ECG recording. Technically, the algorithms can be incorporated into commercially available ECG recorders with digital capabilities. Additional studies are warranted that investigate the usefulness of T-wave morphology descriptors in other populations at risk of sudden cardiac death.

References

6. Perkiomaki JS, Koistinen MJ, Yli-Mayry S, et al. Dispersion of QT action potential durations available from a single surface ECG recording. Consequently, we have used the same algorithmic settings as in the technical report by Acar et al.
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