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

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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<0.0002, 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 n death, sudden n risk factors n waves n 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, 1–3 QT dispersion (QTD), 4–8 QT interval alternans 9,10 have shown promise for VT risk stratification 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. 11 The total cosine R-to-T (TCRT) reflects the spatial angle between depolarization and repolarization, akin to the venerable concept of the ventricular gradient. 12 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 13 and arrhythmogenic right ventricular dysplasia. 14

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. 15 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. Complexity 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 to express spatial and temporal variations of T-wave morphology and repolarization wavefront direction (Figure 1). (1) The so-called T-wave loop 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 TCRT measures the vector deviation between the depolarization and repolarization waves by calculating cosine values between the 3-dimensional R- and T-wave loop vectors within the optimized decomposition space. This variable is unitless. (4) The so-called T-wave morphology dispersion expresses the dissimilarities between the T-wave shapes in individual leads, based on the differences between reconstruction vectors of individual ECG leads created from the 3-dimensional T-wave loop. It is calculated as the average of angles between all possible pairs of reconstruction vectors. A small value indicates that reconstruction vectors are close to each other, indicating similar T-wave morphology between leads.

The fully automatic processing ensures 100% reproducibility of all variables for any given ECG. For serial ECGs in the same subject, a high reproducibility, of up to 99.7%, was previously reported.

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.

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, LVEF), and for clinical variables (age, reperfusion therapy, β-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 analyses 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. Kaplan-Meier event probability curves were computed, with patient groups stratified according to the median value of the respective variable. The cumulative probability of events of 2 patient groups was compared by the log-rank test. The independent correlation of multiple variables with the timing of events during follow-up as the dependent variable was determined by Cox regression analysis. Because of the strong correlation of left bundle-branch block
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>Complexity ratio</td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>T-wave morphology dispersion, °</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>TCRT</td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>Normalized T-wave loop area</td>
<td></td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>T-wave loop dispersion</td>
<td></td>
<td>&lt;0.0004</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, β-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 end points 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 ECG11 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, ≥ 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 2o of the proposed T-wave morphology descriptors were superior. At best, PCA yielded borderline significance in the univariate

| TABLE 4. 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 Primary End Points as the Dependent Variable |
|-----------------|-----------------|-----------------|
| Risk Stratifier  | P (all patients, n = 261) | P (patients without LBBB, n = 252) |
| Reperefusion therapy | 0.014 | 0.013 |
| LVEF | 0.016 | NS |
| HR | 0.017 | 0.012 |
| TCRT | 0.025 | NS |
| T-wave loop dispersion | 0.064 | 0.024 |

Values are given for patient groups including (n = 261) and excluding (n = 252) LBBB.
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 QT variables\(^\text{13}\) from the same ECGs. 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.\(^\text{16–18}\) In most studies, however, QTd was analyzed manually, which is even less reliable due to subjective variations in waveform assessment between centers. The intra-subject reproducibility is also improved.\(^\text{11}\)

### 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.\(^\text{1,19–21}\) Initially, this concept was followed with the use of body surface potential mapping.\(^\text{21–24}\) QTd from 12-lead ECGs was proposed as a more practical surrogate.\(^\text{25}\) After the initial enthusiastic reports,\(^\text{5,6,25–27}\) meticulous methodological studies\(^\text{16,28}\) and reviews\(^\text{28–30}\) 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 QT variables\(^\text{13}\) from the same ECGs. 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.\(^\text{16–18}\) In most studies, however, QTd was analyzed manually, which is even less reliable due to subjective variations in waveform assessment between centers. The intra-subject reproducibility is also improved.\(^\text{11}\)

### Comparison With Other Risk Markers

In testing the independent contribution of T-wave morphologic descriptors by means of Cox regression, at least 1 T-wave morphology variable carried post-MI prognosis.\(^\text{15}\) Although this finding is contradicted by recent epidemiological studies,\(^\text{7,8}\) a more sophisticated concept of repolarization analysis for the purpose of risk stratification is clearly required.\(^\text{31}\) It was therefore attempted to explore more accurate repolarization markers from body surface ECGs, such as PCA\(^\text{13,14}\) and T-wave loop morphology,\(^\text{32}\) or to explore dynamic QT changes on Holter monitoring.\(^\text{4,33,34}\) None of these newer repolarization markers have been tested in a post-MI population. Although PCA had been shown to be predictive in long QT syndrome\(^\text{13}\) and in patients with arrhythmogenic right ventricular dysplasia,\(^\text{14}\) it was not found to be very useful in the present study. Beyond the approach of PCA, Acar et al\(^\text{3}\) developed a set of novel T-wave morphology descriptors to quantify various abnormal temporospatial repolarization indices. With an analysis of these novel T-wave descriptors in a strictly blinded manner, the predictive usefulness of TCRT and T-wave loop dispersion was established in this study.

TCRT reflects a 3-dimensional comparison between repolarization and depolarization wavefronts and therefore is akin to the ventricular gradient introduced by Wilson et al\(^\text{15}\) in 1934 and later expanded with QRST area distributions\(^\text{20–24}\) from body surface mapping. Importantly, with TCRT, the amplitude of depolarization and repolarization processes is not considered, but rather only the difference in their direction is considered and thus represents a modification of the earlier concepts. The variable was found to be associated with LBBB but not with a prolonged QRS duration alone. With or without consideration of LBBB, it proved to be a powerful risk predictor in the present study.

When values for the present post-MI population are compared with the reported normal values,\(^\text{11}\) increased T-wave morphology dispersion and lowered values for TCRT, T-wave loop dispersion, and normalized T-wave area are pathological as such and differentiate event from nonevent patients. Although a low TCRT relates to a large deviation between the QRS and T-wave loops, a large T-wave morphology dispersion is associated with increased dissimilarities among the T waves in ECG leads, and a low value of normalized T-wave area as well as T-wave loop dispersion may be explained as arrhythmogenic with a pathologically compressed and narrowed T-wave loop. Furthermore, irregularity of the loop and deviation from an ellipsoid would also result in a decreased normalized T-wave area. Beyond these considerations and due to the novelty of the algorithms used in the present study, they lack a more detailed experimental basis of the electrophysiological mechanisms involved. Although basic research is under way, other approaches to noninvasive risk stratification of arrhythmia substrates, such as PCA, T-wave alternans, or QT variability, likewise fell short of a precise pathophysiological explanation during their clinical evaluation.

Importantly, only very weak relationships between the various novel descriptors and conventional variables of QTd were found, demonstrating that the proposed variables assess as 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,\(^\text{36}\) 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.

The present study was the first attempt to apply detailed T-wave morphology descriptors in a set of prospectively

### 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=232)</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>
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 underlie 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

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