Assessment of QT Dispersion for Prediction of Mortality or Arrhythmic Events After Myocardial Infarction
Results of a Prospective, Long-term Follow-up Study

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**Background**—Risk stratification by means of analysis of QT dispersion (QTD) in the 12-lead surface ECG is under intense investigation in various patient populations. The aim of the present prospective study was to evaluate the prognostic value of QTD and other ECG variables reflecting dispersion of ventricular repolarization in comparison with established risk stratifiers during long-term follow-up in a large cohort of post–myocardial infarction patients treated according to contemporary therapeutic guidelines.

**Methods and Results**—In 280 consecutive infarct survivors, the 12-lead ECG was optically scanned and digitized for analysis of QTD ($QT_{max} - QT_{min}$) and 25 other repolarization variables, including recently developed and validated parameters such as the T peak–to–T end interval and the area under the T wave. In addition, a variety of established risk stratifiers were assessed. After a mean follow-up period of 32±10 months, 30 patients reached one of the prospectively defined study end points (death, ventricular tachycardia, or resuscitated ventricular fibrillation). Comparisons between event and nonevent patients by means of Kaplan-Meier event probability analyses revealed that none of the ECG dispersion variables were of discriminative value. In contrast, variables such as left ventricular ejection fraction ($P = 0.007$), mean 24-hour heart rate ($P = 0.022$), or heart rate variability ($P = 0.007$) proved to be potentially useful risk stratifiers in this patient population. On multivariate analysis, only LVEF, heart rate variability, and a history of thrombolysis were independent predictors of outcome.

**Conclusions**—Determination of QTD from the surface ECG even when performed with the best available methodology failed to predict subsequent risk in this large series of infarct survivors. (Circulation. 1998;97:2543-2550.)

**Key Words:** infarction ■ death, sudden ■ risk factors ■ electrophysiology

The QT interval has long been known to vary significantly between the individual 12 leads of the surface ECG. A potential clinical application of this interlead difference was proposed in 1990 by Day and coworkers, who suggested that the interlead difference in QT interval may provide a measure of repolarization inhomogeneity, which they called “QT dispersion.” The method subsequently gained popularity owing to its simplicity and a widely perceived need for new markers of ventricular arrhythmogenicity. For instance, in a retrospective analysis of patients with the congenital long-QT syndrome, QTD was demonstrated to predict efficacy of antiadrenergic therapy. Other investigators described an association between increased QTD during therapy with class Ia antiarrhythmic drugs and the occurrence of drug-induced torsades de pointes. Subsequently, the potential value of QTD for risk stratification was examined in populations vulnerable to sudden cardiac death, such as patients with congestive heart failure or post–myocardial infarction patients. All of these studies, however, were retrospective in nature, and most followed a case-control design. Moreover, several investigators reported conflicting results in similar patient populations, for example, those with congestive heart failure. In the only available retrospective case-control study comparing postinfarction patients who died during follow-up with matched survivors, assessment of QTD yielded only borderline predictive value for subsequent death.

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Some of these as yet unexplained discrepancies may be related to methodological problems inherent with the manual determination of QTD from the surface ECG, for instance, those due to difficulties in determination of the T-wave offset in individual leads. To overcome such methodological limitations, a new software program for improved accuracy in the analysis of QTD was recently developed in our laboratory and validated in an experimental study. This methodology
was used in the present prospective study to examine the potential value of QTD and several newly established parameters of dispersion of ventricular repolarization for risk stratification in comparison with other well-established risk parameters such as LVEF or HRV during long-term follow-up in consecutive postinfarction patients.

Methods

Patient Population
The present prospective study enrolled all patients who presented to our institution with acute myocardial infarction during the time period 1992 to 1996. Patients were eligible for participation if the following inclusion criteria were met: (1) confirmed diagnosis of myocardial infarction based on clinical presentation (typical chest pain for $>30$ minutes, unresponsive to nitrates), elevation of CK with CK-MB isoenzyme $>8\%$, and typical ECG changes; and (2) availability of a high-quality standard 12-lead ECG recorded before hospital discharge.

Follow-up
Patients were seen in the arrhythmia outpatient clinic at 4, 8, and 12 months after myocardial infarction and at 6-month intervals thereafter. All episodes of nonfatal arrhythmic events, reinfarction, and revascularization procedures were carefully recorded. Information about deceased patients was obtained from family members, their general practitioners, and the hospitals they had been admitted to. Particular attention was given to the circumstances of each death.

The primary end point of the study was prospectively defined as a composite end point of all-cause mortality, documented sustained VT, and resuscitated ventricular fibrillation. Secondary end points of the study were (1) all-cause mortality and (2) arrhythmic events (defined as sudden cardiac death, documented sustained VT, and resuscitated ventricular fibrillation). Sudden death was defined as instantaneous, unexpected death or death within 1 hour of symptom onset not related to circulatory failure. Sustained VT was defined as a documented tachycardia of ventricular origin at a rate of $>100$ bpm and lasting for $>30$ seconds or resulting in hemodynamic collapse.

ECG Analysis
Standard 12-lead ECG recordings were obtained at the time of hospital discharge at a paper speed 50 mm/s. For ECG analysis, a newly developed method was used that has been described in detail previously. In brief, all RR intervals were measured on the limb lead and precordial lead tracings to ensure that the variation of RR intervals was within 5% of the average value, which was also taken for determination of heart rate. Then, one steady-state beat was selected in each lead set, and the respective RR interval before the beat was considered for rate correction of the ECG variables according to Bazett’s formula. The paper recordings were then scanned to an image file at high resolution (300 dpi), edited, and converted to a digital ECG recording that was interactively analyzed by means of a custom-written ECG analysis program. In case of U waves, the tangent of the T wave was extended to the baseline to define the end of the T wave. In case of a biphasic T wave, the initial T peak was used to determine some repolarization parameters. All measurements were performed by a single experienced investigator who was completely unaware of the clinical course of the patients (M.Z.).

A total of 26 repolarization parameters were determined for each ECG recording. JT, JT<sub>c</sub>, QT, and QT<sub>c</sub> intervals were averaged among all analyzable leads. Conventional QT, JT, QT<sub>c</sub>, and JT<sub>c</sub> dispersion were calculated as the maximum minus the minimum duration of all analyzable ECG leads. As proposed by others, adjusted and relative dispersions as well as the SD of QTD were also determined. As newly defined variables of dispersion of repolarization, the area under the T wave (total T wave area defined from J point to T end, late T wave area from T peak to T end) and the TPE interval were measured. Finally, all variables were recalculated on the basis of the precordial leads only, as suggested previously. To compare our results with those of previous studies, 50 randomly selected ECGs were also evaluated by manual determination of the QT intervals by means of a digitizing tablet equipped with a magnifying cursor. The correlation coefficient was $0.84$ for the results obtained with both methods. R values for reproducibility of QT-interval measurements were $0.99$ for both interobserver and intraobserver variation. The respective values for determination of QTD, TPE, and T-wave area ranged between 0.95 and 0.99.

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Figure 1. Top, Kaplan-Meier event probability curves for patient groups stratified by LVEF $>50\%$ and $<50\%$. Bottom, Kaplan-Meier event probability curves for patient groups stratified by a mean RR interval determined from the 12-lead surface ECG above and below the median value of 895 ms.
TABLE 1A. ECG Parameters in Patients With and Without Events During Follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients</th>
<th>Patients Without Events</th>
<th>Patients With Events</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>280</td>
<td>250</td>
<td>30</td>
<td>...</td>
</tr>
<tr>
<td>Mean RR, ms</td>
<td>904±164</td>
<td>913±160</td>
<td>823±171</td>
<td>0.004</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>98±14</td>
<td>97±14</td>
<td>103±20</td>
<td>0.04</td>
</tr>
<tr>
<td>QT, ms</td>
<td>407±44</td>
<td>408±44</td>
<td>399±45</td>
<td>NS</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>431±39</td>
<td>429±39</td>
<td>444±43</td>
<td>NS</td>
</tr>
<tr>
<td>QTD, ms</td>
<td>64±28</td>
<td>65±29</td>
<td>61±21</td>
<td>NS</td>
</tr>
<tr>
<td>JT, ms</td>
<td>68±30</td>
<td>68±30</td>
<td>69±26</td>
<td>NS</td>
</tr>
<tr>
<td>JTc, ms</td>
<td>309±42</td>
<td>311±42</td>
<td>296±43</td>
<td>NS</td>
</tr>
<tr>
<td>JTcD, ms</td>
<td>323±36</td>
<td>327±36</td>
<td>329±41</td>
<td>NS</td>
</tr>
<tr>
<td>JTD, ms</td>
<td>63±28</td>
<td>64±29</td>
<td>58±20</td>
<td>NS</td>
</tr>
<tr>
<td>JTcD, ms</td>
<td>67±30</td>
<td>67±30</td>
<td>64±28</td>
<td>NS</td>
</tr>
<tr>
<td>TPE interval, ms</td>
<td>96±20</td>
<td>95±19</td>
<td>100±20</td>
<td>NS</td>
</tr>
<tr>
<td>T area, ms×mV</td>
<td>31±14</td>
<td>34±17</td>
<td>NS</td>
<td>31±14</td>
</tr>
</tbody>
</table>

D indicates dispersion.

Holter Monitoring and Analysis of HRV

Before hospital discharge and in stable clinical conditions, 250 patients underwent 24-hour ambulatory monitoring by two-channel bipolar Marquette 8500 Holter recorders. The tapes were subsequently analyzed by the Marquette 8000 laser scanner run with its arrhythmia analysis program to identify and label each QRS complex. HRV analysis was performed as previously reported. The data file was overread and corrected when appropriate by one of the investigators who was unaware of the clinical course of the patients (T.K.). For the purpose of this study, the SDNN was used prospectively as a measure of cardiac autonomic tone.16

Statistical Methods

Continuous values are reported as mean±SD. All data were analyzed with the Statistical Package for the Social Sciences.17 Comparisons between patients with and without events during follow-up were performed by means of the unpaired Student’s t test for normally distributed continuous variables (two-sided) or the χ² test for categorical data. For comparison of various repolarization parameters, Bonferroni’s correction was applied. The independent correlation of various risk stratifiers to events during follow-up was determined by means of logistic regression analysis with the occurrence of events as the dependent variable. Kaplan-Meier event probability curves18 were computed with patient groups stratified by use of the median value for each repolarization variable, because no commonly accepted normal ranges for various dispersion parameters exist,19 and were repeated for patient quartiles. The cumulative probability of events of two patient groups was compared by means of a log-rank test. Significance was considered at a value of P≤0.05.

Results

Patient Characteristics

The study group comprised 280 patients (51 women, 229 men) at a mean age of 58±11 years (range, 25 to 78 years). These patients were taken from a consecutive series of 296 infarct survivors; 15 patients were not considered for the present analysis because fewer than 8 surface ECG leads were analysable for QT interval determination. One additional patient was excluded because of the presence of continuous VVI pacing. On admission, ECG signs of acute anterior wall infarction were present in 135 patients (48%). In 145 patients (52%), the inferior wall was involved. Peak CK averaged 855±707 U/L. The study ECG before discharge showed new Q waves in 215 patients (77%). Thrombolytic therapy had been administered to 116 patients (41%). Thirty-three patients (12%) were treated by means of acute PTCA and 3 other patients (1%) by both PTCA and thrombolytic therapy. During their initial hospital stay, a total of 156 patients (56%) underwent PTCA or CABG. β-Blockers were administered to 231 patients (83%) at hospital discharge. LVEF averaged 47±11%.

Events During Follow-up

During an average follow-up duration of 32±21 months, 21 patients died, 10 (48%) of sudden cardiac death and 6 (29%) of pump failure. In 5 cases (23%), death from extracardiac causes was documented. Sustained VT occurred in 7 patients, whereas 2 patients could be resuscitated from documented

TABLE 1B. ECG Parameters Compared Between Alive and Deceased Patients and Patients With and Without Arrhythmic Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients Alive</th>
<th>Patients Deceased</th>
<th>P</th>
<th>Patients Without Arrhythmic Events</th>
<th>Patients With Arrhythmic Events</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>259</td>
<td>21</td>
<td>...</td>
<td>261</td>
<td>19</td>
<td>...</td>
</tr>
<tr>
<td>Mean RR, ms</td>
<td>912±161</td>
<td>802±162</td>
<td>0.003</td>
<td>908±163</td>
<td>845±171</td>
<td>NS</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>98±14</td>
<td>101±23</td>
<td>NS</td>
<td>97±14</td>
<td>104±18</td>
<td>0.05</td>
</tr>
<tr>
<td>QT, ms</td>
<td>408±44</td>
<td>390±34</td>
<td>NS</td>
<td>407±44</td>
<td>404±49</td>
<td>NS</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>430±38</td>
<td>441±48</td>
<td>NS</td>
<td>430±40</td>
<td>442±27</td>
<td>NS</td>
</tr>
<tr>
<td>QTD, ms</td>
<td>65±29</td>
<td>61±22</td>
<td>NS</td>
<td>65±29</td>
<td>58±20</td>
<td>NS</td>
</tr>
<tr>
<td>JT, ms</td>
<td>311±42</td>
<td>289±32</td>
<td>NS</td>
<td>310±42</td>
<td>300±47</td>
<td>NS</td>
</tr>
<tr>
<td>JTc, ms</td>
<td>327±36</td>
<td>327±42</td>
<td>NS</td>
<td>327±36</td>
<td>327±32</td>
<td>NS</td>
</tr>
<tr>
<td>JTD, ms</td>
<td>64±29</td>
<td>58±23</td>
<td>NS</td>
<td>64±29</td>
<td>56±18</td>
<td>NS</td>
</tr>
<tr>
<td>JTcD, ms</td>
<td>67±30</td>
<td>65±32</td>
<td>NS</td>
<td>67±30</td>
<td>59±22</td>
<td>NS</td>
</tr>
<tr>
<td>TPE interval, ms</td>
<td>96±20</td>
<td>100±20</td>
<td>NS</td>
<td>95±20</td>
<td>101±22</td>
<td>NS</td>
</tr>
<tr>
<td>T area, ms×mV</td>
<td>31±14</td>
<td>34±17</td>
<td>NS</td>
<td>31±14</td>
<td>37±17</td>
<td>NS</td>
</tr>
</tbody>
</table>

D indicates dispersion.
ventricular fibrillation. One patient was censored at the time of cardiac transplantation. Accordingly, 30 patients reached a prospectively defined study end point.

Prediction of Clinical Events: Clinical Parameters
Seven clinical parameters (sex, age, infarct location, peak CK levels, thrombolysis, acute PTCA, and LVEF) were included in the statistical analysis. On univariate analysis, 3 parameters were significantly different for event-free survivors and patients reaching a study end point. Patient age averaged 58±11 years in event-free survivors compared with 63±14 years in patients who died or suffered arrhythmic events (P=0.03). Considering total mortality, the difference was even more pronounced (58±11 versus 67±5 years, P=0.0008). Thrombolytic therapy was administered less frequently to patients with events during follow-up (17%) than to patients without events (44%, P=0.007). Similarly, deceased patients received thrombolysis less frequently (10%) than long-term survivors (44%, P=0.004). LVEF also separated event-free individuals (48±11%) from those with events (40±13%, P=0.0001). A similar difference was observed with respect to all-cause mortality (survivors, 48±11%; deceased patients, 42±13%; P=0.02). Calculation of Kaplan-Meier curves for event-free survival revealed a significant difference for patient groups stratified by an LVEF of 50% (Figure 1, top). LVEF remained an important risk predictor when only patients with LVEF <40% were considered (P=0.01).

Prediction of Clinical Events: Holter-Derived Parameters
Analysis of mean 24-hour RR interval revealed significant differences between event and nonevent patients (830±163 versus 893±129 ms, P=0.02). This difference was even more pronounced for all-cause mortality only (survivors, 892±132 ms; deceased patients, 807±140 ms; P=0.007). The difference remained significant when only arrhythmic events were considered (P=0.02).

Holter-derived HRV was depressed in event-positive patients compared with event-free survivors (SDNN, 76±26 versus 99±42 ms, P=0.007). Similar results were obtained with respect to all-cause mortality (75±30 versus 98±42 ms, P=0.02) or arrhythmic events (70±21 versus 98±42 ms, P=0.008).

Prediction of Clinical Events: ECG-Derived Parameters
As in the findings obtained from Holter analysis, there was a significant difference in mean RR interval derived from the 12-lead ECG (survivors, 913±160 ms; event patients, 823±171 ms; P=0.004) (Figure 1, bottom). The mean RR interval derived from the 12-lead surface ECG and the average mean RR interval from the 24-hour Holter recording were correlated to each other (r=0.75, P<0.0001). The mean RR interval remained significantly different when total mortality was considered (911±161 versus 802±162 ms; P=0.003).

In Table 1, the average values for the different parameters of ventricular repolarization are summarized. All parameters analyzed showed no significant difference between patients with and without primary (Table 1A) or secondary (Table 1B) study end points. This applied to conventional parameters, such as QT or JT dispersion, as well as to new variables, such as TPE interval or the area under the T wave. Moreover, normalization of QTd according to the number of ECG leads analyzable or use of only precordial leads for determination of various dispersion parameters revealed no significant differences. In Figure 2, Kaplan-Meier event probability curves are shown for patients stratified according to the median QTd (61 ms) and the median TPE (92 ms) intervals, respectively. For 31 patients exhibiting U waves in their ECGs, the analysis was repeated including and excluding these U waves. However, this did not impact on predictive value.

Subgroup Analysis
Finally, subgroups known to be at particularly high risk after MI were analyzed with respect to various repolarization
parameters. Data for event-free survivors and individuals with end points during follow-up were compared separately for patients with an anterior myocardial infarction only (n=135), for patients with a QTc interval duration of ≥440 ms at the time of hospital discharge (n=110), and for patients with an LVEF of ≤40% (n=87). As shown in Table 2, analysis of the above-described repolarization and ECG parameters did not reveal a significant difference between event-free and event-positive patients in any patient group.

Multivariate Analysis of Risk Factors
To determine independent risk parameters, a stepwise regression analysis incorporating a total of 10 different clinical and ECG-derived variables was performed. As indicated in Table 3, only LVEF, a history of thrombolysis and/or acute PTCA, and SDNN were found to be independent risk stratifiers.

Discussion

Main Study Findings
This prospective study in 280 consecutive infarct survivors demonstrates that noninvasive assessment of dispersion of ventricular repolarization by use of QT dispersion or additional newly developed parameters as determined from the 12-lead surface ECG fails to identify patients at risk for future death or arrhythmic complications. Conversely, the study confirms the predictive value of other ECG-derived parameters, such as mean heart rate or heart rate variability, in the era of acute coronary revascularization of myocardial infarction.

Pathophysiological Considerations Underlying the Concept of QTD
Experimental data have provided a strong link between the vulnerability of the ventricular myocardium to serious tachyarrhythmias and increased spatial dispersion of ventricular repolarization.19–21 Recent clinical studies have indicated that the interlead variability of the QT interval in the surface ECG may reflect regional differences in ventricular recovery time,22 a hypothesis that was confirmed by an experimental validation study from our laboratory.11 In this study, additional new parameters reflecting inhomogeneous ventricular repolarization, such as the TPE interval and T area, were validated and were found to correlate better with the dispersion of simultaneously obtained monophasic action potentials from different regions of the myocardium.11 The concept of considering the TPE interval as a measure of ventricular dispersion of repolarization was recently put forward by Antzelevitch and coworkers.23,24 Their experiments provided evidence that delayed repolarization of M cells residing in the midmyocardium contributes significantly to dispersion of ventricular repolarization.24,25 Specifically, it was demonstrated that the time interval between the peak and the end of the T wave represents the transmural dispersion of repolarization,24 indicating the potential usefulness of the TPE interval as an additional ECG index. The transmural gradient has been shown to be involved not only in the genesis of the peak and the end of the T wave but also in the genesis of U waves.23,24 Accordingly, this experimental evidence questions the convention of excluding U waves from the measurement of QTc.2,5,7,8 These considerations apply particularly for situations in which ventricular repolarization is grossly altered, as in the case of the congenital or acquired long-QT syndrome, in which an increased dispersion of repolarization in addition to other initiating factors, such as early afterdepolarizations, has been convincingly shown to be present.26,27

In contrast, the available studies demonstrating the facilitation of reentrant arrhythmias based on a global increase in dispersion of ventricular repolarization—for instance, due to regional hypothermia28—may not pertain to patients with a myocardial scar or infarct. Notably, animal models in the subacute infarction period focus on the formation of a functional arc of block and very localized dispersion of

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**TABLE 2. ECG Analysis in Patients With and Without Events During Follow-up in Three Selected Patient Subgroups**

<table>
<thead>
<tr>
<th>Event Status</th>
<th>QTc (ms)</th>
<th>QTc dispersion (ms)</th>
<th>QTdisp (ms)</th>
<th>QTd (ms)</th>
<th>JT (ms)</th>
<th>JTdisp (ms)</th>
<th>JTd (ms)</th>
<th>TPE interval (ms)</th>
<th>T area (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anterior myocardial infarction (n=135)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event-free (n=122)</td>
<td>407±48</td>
<td>430±44</td>
<td>68±31</td>
<td>73±32</td>
<td>309±46</td>
<td>325±41</td>
<td>68±32</td>
<td>72±32</td>
<td>97±22</td>
</tr>
<tr>
<td>Event-positive (n=13)</td>
<td>392±38</td>
<td>456±53</td>
<td>65±29</td>
<td>75±34</td>
<td>286±42</td>
<td>332±51</td>
<td>61±26</td>
<td>68±37</td>
<td>107±26</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
</tr>
<tr>
<td>QTc &gt;440 ms (n=110)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Event-free (n=93)</td>
<td>429±39</td>
<td>466±22</td>
<td>68±31</td>
<td>75±32</td>
<td>328±40</td>
<td>356±28</td>
<td>68±32</td>
<td>73±33</td>
<td>104±21</td>
</tr>
<tr>
<td>Event-positive (n=17)</td>
<td>413±46</td>
<td>467±46</td>
<td>70±22</td>
<td>80±26</td>
<td>310±43</td>
<td>350±41</td>
<td>64±22</td>
<td>73±30</td>
<td>106±18</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<td></td>
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<tr>
<td>Event-free (n=70)</td>
<td>401±44</td>
<td>439±35</td>
<td>67±35</td>
<td>74±38</td>
<td>301±44</td>
<td>329±27</td>
<td>66±35</td>
<td>73±37</td>
<td>95±17</td>
</tr>
<tr>
<td>Event-positive (n=17)</td>
<td>398±46</td>
<td>451±47</td>
<td>65±26</td>
<td>74±31</td>
<td>290±46</td>
<td>327±48</td>
<td>61±23</td>
<td>67±33</td>
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</tbody>
</table>

D indicates dispersion.
refractoriness. Furthermore, arcs of functional or both fixed and functional conduction block also have been demonstrated by high-density intraoperative mapping of VT in patients with previous myocardial infarction. Thus, it is conceivable that these functional arcs of block giving rise to localized dispersion of refractoriness may not be susceptible to a global measure, such as QTD determined from the surface ECG. Indeed, a more localized measurement of activation and recovery forces, for instance, using precordial mapping techniques, has been demonstrated to differentiate between patients with and without susceptibility to malignant ventricular arrhythmias. These techniques are able to detect subtle patterns of repolarization, which explains their superior diagnostic capability compared with QTD. However, multilead mapping requires sophisticated recording techniques and is therefore not widely applicable in the clinical setting.

### Potential Reasons for Opposing Results Observed in Previous Studies on QTD

To the best of our knowledge, this is the first prospectively designed study assessing the predictive value of QTD and a variety of other repolarization parameters in a large number of consecutive infarct survivors treated according to contemporary therapeutic guidelines. Data on the predictive value of QTD available at present stem almost exclusively from retrospective analysis of trials such as the LIMIT-2 trial. Even more importantly, most of these studies followed a case-control design, ie, retrospectively analyzed data from patients who died during follow-up were compared with those obtained in survivors matched for clinical characteristics. In the report by Glancy and coworkers, for example, QTD assessed from ECG recordings at day 3 after infarction failed to predict future deaths. Only when ECGs obtained at 4 weeks were evaluated was the lack of decrease in QTD associated with a higher death rate. It is important, however, to point out that 4-week ECG tracings were available in only 53 of 162 patients in the event group, because this particular ECG had been recorded only if patients were readmitted to the hospital for a specific cause, such as angina or heart failure. Despite attempts to avoid selection bias, the described recruitment pattern could have resulted in selection of patients overrepresenting individuals with recurrent myocardial ischemia. Similarly, many of the event patients in the study by Zareba et al had unstable angina rather than acute myocardial infarction. Even if those patients subsequently suffered sudden cardiac death, ischemia is conceivable as the decisive trigger of at least a considerable proportion of patients. Because it has been well described that acute ischemia leads to a significant increase in QTD, the selection bias discussed could well explain why event patients in these and possibly other studies had increased QTD. In our study, the influence of ischemia was minimized by the extensive use of β-blocker treatment and revascularization procedures.

Conflicting results concerning the predictive value of QTD have also been reported for other patient populations. In patients with congestive heart failure, for example, some investigators have found QTD to yield predictive value, whereas others failed to do so. Undoubtedly, a variety of methodological difficulties inherent in the method of QTD are in part responsible for the described contradictory findings. Most commonly, the digitizing pad method with magnifying glasses has been used for QTD assessment. The intraobserver and interobserver reproducibility of this method has been shown to vary and the results may therefore not be fully comparable between studies and centers.

As yet, no clinical study has evaluated other parameters than the traditionally proposed QTD (QT max − QT min) and related variables. The present study, therefore, is the first to extend QTD measurements to additional parameters of dispersion of ventricular repolarization previously validated in an experimental model. Despite the reasonable electrophysiological basis, for instance, of the interval from the peak to the end of the T wave or the area under the T wave, determination of these new parameters did not increase the predictive value of analysis of inhomogeneous repolarization. Similarly, inclusion or exclusion of U waves in the analysis of dispersion of ventricular recovery did not affect its prognostic value. Although it is beyond the design of this clinical study, the most likely explanation for this lack of predictive power is the too imprecise resolution of regional discrepancies of ventricular repolarization by analyzing parameters derived from a conventional 12-lead surface ECG.

### Comparison of QTD With Other Risk Parameters

The results of the present study confirm those of previous studies concerning the predictive value of other clinical parameters. A history of thrombolysis during the acute course of myocardial infarction was associated with a better prognosis during follow-up, supporting the concept of the open infarct artery. LVEF was significantly lower in patients with events during follow-up, which confirmed numerous studies indicating that LVEF remains the most important risk factor after myocardial infarction. An interesting new finding was related to mean heart rate. As recently reported by Copie and coworkers, increased heart rate assessed from 24-hour Holter recordings was a strong predictor of mortality after myocardial infarction. In this study, however, only 6% of the patients were on antiadrenergic therapy at the time of Holter monitoring. Despite the high incidence of β-blocker treatment at the time of testing in the present study, average heart rate was higher in patients who subsequently died or suffered an arrhythmic event. Given the good correlation between mean heart rate determined from the short standard ECG tracing and from that assessed from Holter monitoring, this easily obtainable parameter might be a valuable bedside risk stratifier, particularly if assessed before initiation of β-blocker therapy. Preliminary data from the EMIAT trial support this notion.

Furthermore, findings reported by Nul et al from the GESICA study can be interpreted along the same lines. These authors found that patients with a mean heart rate of ≥90 bpm before the start of amiodarone therapy benefited from this therapy with respect to total mortality, whereas patients with a mean heart rate of <90 bpm did not.
In agreement with previous findings obtained before \textsuperscript{16} or after \textsuperscript{15,26} the widespread use of thrombolytic therapy, HRV was an independent risk predictor for both all-cause mortality and arrhythmic events. Concerning the value of markers of autonomic tone versus that of QTD, preliminary results of a recent study in patients with congestive heart failure are of particular interest. Mortara et al.,\textsuperscript{41} examining 165 such patients, demonstrated that both baroreflex sensitivity and HRV identified subjects at high risk for subsequent arrhythmic events or death, whereas assessment of QTD failed to do so. Thus, that study is in agreement with the observations of our study.

Limitations of the Study

Although this study is at present the largest to prospectively evaluate the prognostic value of QTD, the sample size studied is still relatively small. However, there was no indication that any of the examined ECG variables of repolarization would achieve statistical significance on increasing the sample size. Because we did not measure changes in QT duration over time (eg, over 24 hours), we cannot exclude the possibility that assessment of changes in temporal dispersion of the QT interval might provide prognostic information.

Implications for Future Research

The results of the present prospective study demonstrate that determination of QTD from the surface ECG lacks predictive value for subsequent arrhythmic events or death in survivors of myocardial infarction. Nevertheless, it is still conceivable that more sophisticated techniques for evaluation of ventricular repolarization from the surface ECG will yield prognostic value. For instance, taking into account morphological features of the ST-T segment may be a valuable approach for future studies. Determination of microvolt level T-wave alternans is another promising approach of assessing repolarization abnormalities.\textsuperscript{49,50} Thus, the concept of using ECG indices of ventricular repolarization to assess arrhythmogenic risk of individual patients remains an important research objective. According to the present data, however, simple determination of QTD, even when pursued with the best technology available for this purpose, does not permit such risk stratification.

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