Impact of Infarct-Related Artery Flow on QT Dynamicity in Patients Undergoing Direct Percutaneous Coronary Intervention for Acute Myocardial Infarction

Hendrik Bonnemeier, MD; Uwe K.H. Wiegand, MD; Frank Bode, MD; Franz Hartmann, MD; Volkhard Kurowski, MD; Hugo A. Katus, MD, FESC; Gert Richardt, MD

Background—Complete coronary artery reperfusion in acute myocardial infarction (AMI) has been shown to significantly improve survival. Electrical stability may be the decisive mechanism for this beneficial effect. Because electrical stability is largely dependent on ventricular repolarization, we sought to determine the impact of a modern reperfusion strategy (ie, direct percutaneous coronary intervention [PCI]) on QT dynamicity in AMI and examined its association with infarct-related artery flow.

Methods and Results—We prospectively investigated QT dynamicity in 128 patients undergoing direct PCI for a first AMI. Slopes and correlation coefficients of the linear QT/RR regression were determined in the time interval before reperfusion, within the initial hour after reperfusion, and within the remaining recording period from Holter ECG recordings, which were initiated on admission. Subgroup analysis based on TIMI 3 (n = 100) and TIMI 2 (n = 28) flow after PCI revealed no significant differences in QT/RR slope before PCI (0.145±0.12 versus 0.160±0.19, P=NS). After PCI, QT/RR slopes increased only in the TIMI 2 subgroup (P<0.05). In TIMI 2 patients, QT/RR slopes were significantly steeper in the hour after PCI and in the remaining recording period, respectively (0.155±0.12 versus 0.192±0.15, P<0.05, and 0.159±0.10 versus 0.210±0.17, P<0.01).

Conclusions—Alternations of QT dynamicity in patients with incomplete reperfusion may suggest an altered electrical restitution, potentially providing a substrate for serious ventricular arrhythmias. Thus, our findings offer new insights into mechanisms by which complete reperfusion may affect electrical stability. (Circulation. 2003;108:2979–2986.)

Key Words: myocardial infarction ■ dynamics ■ angioplasty ■ reperfusion

Despite angiographic evidence of an open infarct-related coronary artery, a delayed or sluggish antegrade flow (ie, Thrombolysis In Myocardial Infarction [TIMI] 2 flow) is associated with an increased risk for cardiac mortality in patients with acute myocardial infarction (AMI). A substantial number of these patients are prone to develop life-threatening arrhythmias, obviously facilitated by the interaction of cardiac autonomic imbalance and an abnormal arrhythmic substrate. There is growing evidence that ventricular repolarization, which has been implicated in the development of ventricular arrhythmias, is altered in the acute phase of AMI. It appears likely that more extensive tissue injury with persistent microvascular dysfunction may alter the electrophysiological characteristics of ventricular myocardial cells in the border zone, leading to local differences of ventricular recovery durations. Ventricular repolarization is a complex process that occurs nonuniformly in space and time and is closely coupled with the underlying RR interval. This QT/RR relationship, a major property of ventricular repolarization, is known to be dynamic. QT rate dependence may be altered in the setting of AMI and especially after incomplete reperfusion of the infarct-related artery, which may be associated with an increased susceptibility for malignant ventricular arrhythmias. Recent data strongly suggest an association of abnormal QT rate dependence and ventricular arrhythmogenesis.

Therefore, we hypothesized that incomplete coronary artery reperfusion in AMI, in contrast to complete reperfusion, leads to an abnormal QT/RR relationship due to a sustained transmural “electrical injury.” Using QT dynamicity, we evaluated the impact of a modern reperfusion strategy (ie, direct percutaneous coronary intervention [PCI]) on QT rate dependence in the acute phase of AMI and examined its association with the epicardial infarct-related artery flow.

Methods

Patient Population
A total of 194 consecutive patients with ST-segment elevation AMI, in whom primary PCI for an occluded infarct artery was performed...
at our institution, were prospectively screened for this study. Inclusion criteria were presence of ischemic chest pain for >30 minutes but <24 hours associated with ST-segment elevation ≥0.1 mV in ≥2 leads of the surface ECG. Exclusion criteria were cardiogenic shock, blood pressure <90 mm Hg and clinical signs of heart failure, left bundle-branch block, pacemaker rhythm and rhythm other than sinus, chronotropic incompetence, class I and III antiarrhythmic medication before admission, age >75 years, prior MI or CABG, coronary occlusions unsuitable for PCI, and invalid Holter ECG recordings. β-Blockers and nitrates were given according to current guidelines. All patients gave informed consent for the research protocol, which was by the local ethics committee.

Catheterization
Coronary angioplasty was performed by the percutaneous femoral approach. Calculation of left ventricular ejection fraction (LVEF) was performed offline with a computerized algorithm (QLVA, Medis Medical). Antegrade perfusion of the infarct-related artery was graded according to the classification of the TIMI trial.1 When the study was performed, the primary objective of angioplasty was to achieve an optimal angiographic result by coronary angioplasty alone. Stent implantation was performed if TIMI flow was <2, residual stenosis was >30%, or extensive intimal dissection was present. Arterial plasma concentrations of norepinephrine were investigated before PCI, 60 minutes after PCI, and 6 hours after PCI. Residual stenosis was >30%, or extensive intimal dissection was present. Arterial plasma concentrations of norepinephrine were investigated before PCI, 60 minutes after PCI, and 6 hours after PCI.

Clinical Follow-Up
All patients were seen in our arrhythmia outpatient department at 3, 6, and 12 months after AMI. Major arrhythmic events (MAEs) were assessed after the first 48 hours after AMI and were defined as sudden cardiac death, ventricular fibrillation with consecutive resuscitation, and sustained ventricular tachycardias.

Measurement of QT Dynamicity
The QT interval was analyzed on a Pathfinder 700 analysis system (Reynolds Medical) from 2-lead, 24-hour Holter monitoring (Tracker II, Reynolds Medical), which was started at hospital admission. Immediately after the PCI procedure, a marker was set on the Holter recording (Figure 1). All tapes were edited manually for exclusion of artifacts and premature beats. Beats with a heart rate <30 bpm, >160 bpm, or with a prevailing RR interval <66% or >180%, respectively, were automatically excluded from the analysis. Recordings with longer intervals of severe artifacts or imperceptibility of the T wave were also not suitable for analysis. A minimum of 18 hours of recording time and a minimum of 90% successive QT intervals were required for a tape to be accepted as valid. Twenty-four-hour files of RR and QT intervals were then processed on a personal computer with a special software package (QLT/RR Research Tools version 0.02, Reynolds Medical). Slopes and correlation coefficients of the linear QT/RR regression were computed for the time interval from admission to PCI, the first hour after PCI, and the remaining hours (Figures 1 and 2). Recordings were excluded from further analysis if the pooled QT/RR correlation was <0.5.

Statistical Analysis
Statistical analyses were conducted with a commercially available software package (SPSS version 11.0; SPSS Inc). Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov goodness-of-fit test. Discrete variables were compared by χ2 analysis. Multiple comparisons between groups were done by Bonferroni-corrected ANOVA for repeated measures. Consecutively, an α-corrected paired Student t test was performed for interval-to-interval comparisons. Pearson’s coefficient of correlation was used to assess the association between QT/RR slopes and clinical variables. Stepwise linear multivariate regression analysis was performed with QT/RR slope as a dependent variable to determine the most important predictors of differences in QT/RR slope. QT and RR data are presented as mean±SD. QT and RR data in figures are presented as mean±SEM. A 2-tailed significance level of 0.05 was used for the analyses.

Results

Patient Characteristics
Among the 194 screened patients with a first AMI, a total of 128 fulfilled the clinical and technical inclusion criteria, had valid Holter ECG recordings (median duration 23 hours), and had recanalization of the infarct-related coronary artery. Of the 66 withdrawn patients, a total of 44 had insufficient Holter ECG recordings for analysis of QT dynamicity. Subgroup analysis based on TIMI flow of the target vessel...
after direct PCI revealed no significant differences in baseline and clinical characteristics between patients with TIMI 3 \( (n=100) \) and TIMI 2 \( (n=28) \) flow (Table 1), except the more frequent use of glycoprotein IIb/IIIa antagonists \( (P=0.003) \) in the TIMI 2 subgroup. In the acute phase of MI, almost 40% of patients in both groups received intravenous β-blockade. There were no statistically significant differences in LVEF, left ventricular end-diastolic pressure, peak creatine kinase, or lactate dehydrogenase levels, but there was a trend toward more depressed left ventricular function and higher cardiac enzyme release in patients with TIMI 2 perfusion grade. Serum potassium levels were not significantly different between groups. During the 12-month follow-up, a total of 16 MAEs were documented in 13 patients. The majority of MAEs occurred during the hospitalization period (62.5%). Patients with TIMI 2 flow tended to have a higher incidence of MAEs (TIMI 2 17.8%, \( n=5 \); TIMI 3 8.0%, \( n=8 \); \( P=NS \)).

**Time Course of QT Dynamicity**

QT/RR slopes of the entire population averaged 0.156±0.13 before PCI and tended to increase to 0.166±0.13 in the hour after PCI and to 0.173±0.12 in the remaining recording period \( (P=NS) \). Subgroup analysis based on TIMI flow after PCI revealed no significant differences of QT/RR slope before PCI \( (0.145±0.12 \) versus 0.160±1.19, \( P=NS) \). However, in the TIMI 2 subgroup, QT/RR slopes were significantly steeper in the hour after PCI and in the remaining recording period \( (0.155±0.12 \) versus 0.192±0.15, \( P<0.05 \) and 0.159±0.10 versus 0.210±0.17, \( P<0.01 \), respectively). There was a significant increase in QT/RR slope from baseline levels only in the TIMI 2 subgroup within the observation period (Figure 3). There were no significant differences between TIMI groups regarding QT/RR correlation coefficient and mean RR interval (Figure 3). In both subgroups, mean RR interval remained constant in the hour after PCI (TIMI 2 719.6±103 to 736.4±109 ms, \( P=NS \); TIMI 3 739.4±108 to 740.7±100 ms, \( P=NS \)) and significantly increased within the subsequent recording period (TIMI 2 793.1±150 ms, \( P<0.05 \); TIMI 3 819.5±138 ms, \( P<0.05 \)). Mean QT interval was stable in patients with TIMI 3 flow and only slightly increased in patients with TIMI 2 flow \( (P=NS) \) within the observation period (Figure 3). Patients with TIMI 2 flow exhibited higher mean QT intervals after PCI (before PCI 380.4±51.9 versus 378.5±41.7 ms, \( P=NS \); 60 minutes after PCI 386.8±42.9 versus 378.1±41.9 ms, \( P<0.05 \); remaining recording period 387.4±59.0 versus 377.4±47.2 ms, \( P<0.05 \)).

**QT Dynamicity and Clinical Parameters**

There were no significant correlations between QT/RR slopes measured before PCI and clinical parameters. In the time period after PCI, QT/RR slopes were moderately related to age (Table 2). Furthermore, there was a moderate inverse correlation with LVEF and a weak correlation with left ventricular end-diastolic pressure in the time interval from hour 2 to hour 24 after PCI. No relation was found between QT/RR slopes and either peak enzyme release levels or time of ischemia (Table 2). As previously reported,11 female patients exhibited steeper slopes \( (0.185±0.14 \) versus 0.169±0.11, \( P<0.05 \)). Anterior infarct localization was also associated with a steeper QT/RR slope after PCI \( (0.181±0.13 \) versus 0.162±0.12, \( P<0.05 \)). QT/RR slopes were not signif-
significantly different in patients with single-vessel versus multivessel coronary artery disease, current smokers and non-smokers, and patients with or without diabetes mellitus. Furthermore, there were no significant differences of QT dynamicity in patients with or without β-blockade. Patients with MAEs in the follow-up period exhibited significantly steeper QT/RR slopes after PCI than patients without MAEs (MAEs 0.242±0.09; no MAEs 0.162±0.12; \( P=0.018 \); Figure 5). There were no significant differences in patients with and without MAEs regarding measures of ventricular repolarization on the discharge surface ECG (QT interval: MAE 381±25 ms, no MAE 385±31 ms \( P=\text{NS} \); QTc interval: MAE 409±39 ms, no MAE 401±31 ms \( P=\text{NS} \); QT dispersion: MAE 59.8±24 ms; no MAE 61.9±25 ms \( P=\text{NS} \)). Norepinephrine concentrations tended to be higher \( P=0.13 \), r=0.13, \( P=\text{NS} \); and \( r=0.13, P=\text{NS} \). Stepwise multivariate linear regression analysis with QT/RR slope as the dependent variable revealed that after correction for the covariates, only TIMI flow \( P=0.035 \) and LVEF \( P=0.013 \) were significantly associated with QT/RR slopes, whereas age, gender, infarct site, serum norepinephrine levels, diabetes mellitus, Killip class, and presence of troponin T on hospital admission were not significantly associated with QT/RR slopes.

**Discussion**

Patency of the infarct-related artery in AMI reduces subsequent mortality, and both an improvement of left ventricular function and an increased myocardial electrical stability may contribute to this favorable effect.12,13 Because patency is not perfusion, the optimal outcome after AMI further depends on complete and sustained perfusion of the infarct-related artery.13 Despite angiographic evidence of an open infarct vessel, a number of patients have a mismatch between patency and myocardial perfusion.14,15 Incomplete reperfusion may affect ventricular repolarization, either directly by influencing the electrophysiological milieu or indirectly by interference with cardiac autonomic nervous tone. The data of the present study indicate that, largely independent of left ventricular function, incomplete reperfusion is associated with significant alterations of QT dynamicity in the early

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**TABLE 1. Baseline Clinical Characteristics by TIMI Flow After PCI**

<table>
<thead>
<tr>
<th></th>
<th>Patients With Valid Recordings (( n=128 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIMI 3</strong> (( n=100 ))</td>
<td><strong>TIMI 2</strong> (( n=28 ))</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.4±11.7</td>
</tr>
<tr>
<td>Male/female gender, n</td>
<td>82/18</td>
</tr>
<tr>
<td>Site of infarction (anterior/nonanterior), n</td>
<td>40/60</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54.3±11.1</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>19.3±7.4</td>
</tr>
<tr>
<td>Peak CK, U/L</td>
<td>952±796</td>
</tr>
<tr>
<td>Peak LDH, U/L</td>
<td>643±407</td>
</tr>
<tr>
<td>TIMI grade before reperfusion</td>
<td>0.8±0.9</td>
</tr>
<tr>
<td>Target lesion (LAD/RCA/LCx), n</td>
<td>39/53/8</td>
</tr>
<tr>
<td>One-vessel disease, n (%)</td>
<td>39 (39.0)</td>
</tr>
<tr>
<td>Killip class ≥2, n (%)</td>
<td>24 (24.0)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>16 (16.0)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>56 (56.0)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>58 (58.0)</td>
</tr>
<tr>
<td>Systolic blood pressure on admission, mm Hg</td>
<td>139.4±26.6</td>
</tr>
<tr>
<td>Time from pain onset to reperfusion, min</td>
<td>346±362</td>
</tr>
<tr>
<td>Serum potassium on admission, mmol/L</td>
<td>4.42±0.59</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa antagonists, n (%)</td>
<td>10 (10.0)</td>
</tr>
<tr>
<td>Troponin T &gt;0.1 ng/mL on hospital admission, n (%)</td>
<td>56 (56.0)</td>
</tr>
<tr>
<td>( \beta )-Blockers in acute phase, n (%)</td>
<td>40 (40.0)</td>
</tr>
<tr>
<td>( \beta )-Blockers at hospital discharge, n (%)</td>
<td>92 (92)</td>
</tr>
<tr>
<td>ACE/AT1 inhibitors at hospital discharge, n (%)</td>
<td>90 (90)</td>
</tr>
</tbody>
</table>

LVEDP indicates left ventricular end-diastolic pressure; CK, creatine kinase; LDH, lactate dehydrogenase; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex artery; and AT1, angiotensin II type 1.
postinfarction period, which potentially provides a substrate for serious ventricular arrhythmias. Therefore, the present results suggest that reperfusion of myocardial tissue rather than patency of the infarct-related artery per se is beneficial by improving electrical stability.

Ventricular repolarization is a dynamic process, influenced by changeable variables such as the underlying heart rate, interference with cardiac autonomic nervous tone, and the local ventricular electrophysiological milieu. Therefore, only a dynamic assessment of QT intervals allows an accurate characterization of ventricular repolarization. An abnormal dynamic behavior of ventricular repolarization in relation to heart rate changes has been linked to susceptibility to ventricular arrhythmias; however, QT rate dependence has so far not been studied in the acute phase of AMI.

There are only a few previous studies investigating the QT/RR relationship in post-AMI patients. Savelieva et al observed significantly steeper QT/RR slopes in patients in the chronic phase of AMI than in normal subjects. In the Groupe d’Etude du Prognostic de l’Infarctus du Myocarde (GREPI) trial, diurnal QT/RR slopes independently predicted sudden cardiac death among patients with recent AMI. Extramiana et al, who also investigated patients with a history of AMI, found significantly steeper QT/RR slopes in patients with life-threatening ventricular tachyarrhythmias. Furthermore, their data showed that analysis of heart rate variability and QT rate dependence do not reflect the same components, which suggests that autonomic nervous tone is not the major determinant of the QT/RR relationship. We found that the QT/RR slope significantly increased after PCI in patients with incomplete reperfusion, whereas it remained constant in patients with complete reperfusion. These findings may suggest an ongoing process of microcirculatory malperfusion in TIMI 2 patients, leading to altered electrophysiological properties of the myocytes.

The mechanism by which incomplete reperfusion alters the effects of heart rate changes on ventricular refractory periods remains speculative. It is well recognized that there is a physiological delay in the adaptation of repolarization durations to changing heart rates. It has been shown that the properties and balance of the repolarizing inward sodium and outward potassium channels of ventricular myocardial cell membranes and the metabolic processes surrounding them play an important role in this process. Acute ischemia results in an acidosis- and anoxia-induced depression of membrane excitability and delayed recovery of excitability. There is strong evidence that ischemia-induced delayed conduction is reversible by thrombolytic therapy. In incomplete reperfusion, the ischemia-induced intrinsic myocardial properties may be maintained, resulting in an altered electrical restitution or a loosening of the physiological coupling between repolarization duration and the diastolic interval of...
the preceding beat. Electrical restitution dynamics have been shown to be altered significantly in the infarction border zone. Abrupt changes in the diastolic interval may significantly increase regional dispersion of repolarization because of regional differences in conduction velocity combined with regional differences in electrical recovery. Steeper QT/RR slopes in patients with incomplete reperfusion may therefore indicate an inadequate coupling between the QT interval and the preceding diastolic interval, which is strongly associated with susceptibility to the development of malignant ventricular arrhythmias by facilitating reentry. Using QT-interval variability, we were previously able to demonstrate an abnormal coupling between ventricular repolarization and heart rate in patients with malignant ventricular arrhythmias after AMI. However, QT-interval variability did not discriminate between TIMI 2 and 3 flow. In contrast to the present study, there was a only a trend toward longer QT intervals in TIMI 2 patients, which did not reach statistical significance, probably because of the smaller patient population.

Lecocq et al described that sympathetic stimulation resulted in significant alterations of the QT/RR relationship in healthy subjects. In the present study, serum norepinephrine levels, which reflect efferent sympathetic nervous tone, were slightly higher in patients with TIMI 2 flow. However, the fact that there was almost no relation between norepinephrine concentrations and QT/RR slopes indicates that QT rate dependence is not determined mainly by sympathetic stimulation. Because there were also no significant differences in the underlying mean RR intervals between different perfusion grades, it is likely that steeper QT/RR slopes in patients with incomplete reperfusion are induced mainly by abnormal cellular repolarization due to a persistent electrical injury rather than due to cardiac autonomic nervous interference with or without corresponding heart rate changes. This effect of incomplete reperfusion on the QT/RR slope appears to be largely independent of left ventricular function, time of ischemia, and size and site of the AMI. Therefore, an increase in the QT/RR slope after reperfusion therapy for AMI may provide independent prognostic information and may reflect an “electrical stunning” of the incompletely perfused ventricular myocardium.

**Study Limitations**

There are important factors to be considered in interpreting the results of the present study. First, it has been suggested that the QT/RR relationship in younger healthy subjects...
exhibits a high intrasubject stability, whereas it has a substantial intersubject variability. However, in a sample of 12 healthy subjects (aged 57±18 years) with 5 consecutive 24-hour Holter recordings from our QT-interval database, we were able to show that QT/RR slopes in healthy subjects are intraindividually (coefficient of variance 8.6%) and interindividually (coefficient of variance 12.4%) very reproducible. In the acute phase of AMI, in addition to poor recording quality and artifacts, flat, abnormally shaped, and imperceptible T waves may lead to inaccurate QT-interval measurement, even after manual editing. Almost 26% of the Holter recordings were not suitable for analysis of QT dynamics in the present study.

Second, we cannot definitely rule out that the changes observed are due to the PCI procedure itself. One would have expected a correlation between time of ischemia and QT/RR slopes, because complete reperfusion was able to stop the process of increasing QT/RR slopes. However, there was no relation between QT/RR slopes and time interval from pain onset to reperfusion in the present study. One explanation may be that the accuracy of this parameter is known to be limited by different thresholds of pain perception, episodes of spontaneous reflow, and ischemic preconditioning.

Finally, it is premature to regard the QT/RR slope as an indicator of complete or incomplete reperfusion or even as a risk stratifier in the acute phase of AMI, even though patients with MAEs exhibited significantly steeper QT/RR slopes. The previously unreported alterations of the QT/RR relationship in patients with incomplete reperfusion need further investigation to determine the underlying cellular mechanisms.

Conclusions
Steeper QT/RR slopes in patients with incomplete reperfusion after direct PCI for AMI, which reflect an inadequate shortening of repolarization with increasing heart rate, suggest a distorted electrical restitution that may potentially provide a substrate for serious ventricular arrhythmias by facilitating reentry. Thus, our findings offer new insights into mechanisms by which early complete reperfusion may affect cardiac electrical stability and might explain in part the lower mortality rate in patients with TIMI 3 flow after PCI for AMI.

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