Prolongation of the QTc Interval Is Seen Uniformly During Early Transmural Ischemia

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Objectives
In order to more clearly understand the electrocardiographic manifestations of early transmural ischemia, we studied electrocardiograms (ECGs) in patients undergoing balloon angioplasty.

Background
Decisions regarding reperfusion strategies in patients with acute myocardial infarction rely largely on the presence of ST-segment elevation (STE) in the ECG, consequently with significant limitations. Studies of the “ischemic cascade” show that ST-segment changes occur well after the onset of wall motion abnormalities.

Methods
We prospectively analyzed ECGs obtained at 20-s intervals in 74 patients undergoing elective balloon angioplasty. The ECGs were analyzed using 3 methodologies. In 74 patients, the ST-segment, the T-wave, and the QT-interval were analyzed using the MUSE (General Electric HC, Menomonee Falls, Wisconsin) automated system (MUSE). Fifty patients were also analyzed using the Interval Editor automated system (IE; General Electric HC). In 20 patients, measurements were made manually.

Results
Transmural ischemia prolonged the QTc interval (using the Bazett’s formula) in 100% of patients. In all 74 patients analyzed with MUSE, QTc interval prolonged from 423 ± 25 ms to 455 ± 34 ms (p < 0.001). In the 50 patients analyzed with IE, QTc interval prolonged in 50 of 50 (100%) patients (from 424 ± 27 ms to 458 ± 33 ms [p < 0.001]). Mean time to maximal QTc interval prolongation, changes in T-wave polarity, ≥1 mm STE, and ST-segment depression (STD) were 22, 24, 29, and 35 s, respectively. Although QTc interval prolonged in 100% of patients, T-wave changes, STE, and STD (>1 mm) occurred in 7%, 15%, and 7%, respectively.

Conclusions
The QTc interval prolongs in 100% of patients with early transmural ischemia. When compared with clinically accepted indexes of transmural ischemia (i.e., STD and STE >1 mm) it is the earliest ECG abnormality. (J Am Coll Cardiol 2007;49:1299–305) © 2007 by the American College of Cardiology Foundation

The classical electrocardiographic (ECG) abnormality used to diagnose transmural ischemia and infarction is ST-segment elevation (STE) >1 mm in 2 contiguous leads followed by the development of Q waves (1–3). Decisions regarding emergent reperfusion strategies in patients with acute myocardial infarction rely largely on the presence of STE (4). In addition, resolution of STE indicates reperfusion at epicardial and tissue levels with excellent prognosis. Conversely, persistent STE suggests either an occluded infarct-related artery or poor myocardial tissue perfusion (5).

The critical importance of ST-segment changes in the recognition of ischemic syndromes and the high incidence of lethal arrhythmias in these patients have led to investigations of the electrophysiological mechanisms underlying the ECG changes and arrhythmias seen during ischemia. These ECG changes are thought to be due to changes in the local milieu of ischemic myocardium, especially an increase in the extracellular potassium concentration (6). Increased extracellular potassium is thought to induce a decrease in the resting membrane potential (i.e., a depolarization), an abbreviation of the action potential duration (APD), and myocyte inexcitability. Depolarization or a decrease in the resting membrane potential results in depression of the QT-segment, whereas an abbreviation of the APD and myocyte inexcitability results in true STE on the ECG (6,7).

The increase in extracellular potassium concentration in ischemic myocardium is time-dependent and possibly explains why potassium-induced changes on the ECG are apparent only after a few minutes of ischemia rather than instantaneously. Other changes occur in the local milieu that precede the increase in local potassium and might serve to
prolong the local APD (8–11). In fact, numerous animal and human studies show an increase in APD occurring in the initial portions of transmural ischemia. This biphasic change in the APD (i.e., initial prolongation followed by abbreviation) after coronary artery occlusion raises the possibility that early transmural ischemia might not initially manifest itself by STE but by prolongation of the QT interval (12–14). We tested the hypothesis that early transmural ischemia might manifest as QT prolongation in humans.

Methods

Between August 2003 and April 2005, patients with epicardial atherosclerotic coronary artery disease who presented to our cardiac catheterization laboratory for elective coronary intervention were prospectively enrolled. Patients with left bundle branch block and ventricular pacing were excluded. After signing informed consent for the procedure as well as a separate consent form approved by the hospital institutional review board, patients were prepared and draped for elective percutaneous coronary intervention in standard fashion. Twelve-lead ECGs were recorded with the MAC 8 Marquette ECG Cart (GE Medical Systems, Milwaukee, Wisconsin) with electrodes placed in standard fashion by 1 of the 2 investigators (D.N.K. and M.K.).

A baseline ECG was obtained before the procedure and the administration of conscious sedation. Sedation consisted of midazolam and/or opioid analgesic drugs (dilaudid, morphine, or fentanyl), administered by the intravenous route, in all patients. The procedure was performed with non-ionic (Optiray 350 [ioversol], Mallinckrodt, St. Louis, Missouri) contrast in all patients.

The duration and pressure of balloon inflation, the number of inflations, and the choice of interventional equipment, including the balloon and stent, was left to the discretion of the operator performing the procedure. Non-perfusion standard balloon angioplasty catheters were used for all procedures (including Sprinter [Medtronic, Minneapolis, Minnesota], Stormer [Medtronic], and Raptor [Cordis, Miami Lakes, Florida]).

The ECGs were obtained during balloon inflation at 19-s intervals until deflation. This was typically the minimum time interval required to record an ECG, including the 10 s of data recorded on a standard 12 lead. The ECG data from the initial balloon inflation were analyzed. Tracings were also obtained after balloon deflation. In 10 patients who underwent coronary angiography and were subsequently noted to have normal coronary arteries, the QT intervals were analyzed.

Three different methods of ECG analysis were employed. Seventy-four patients were analyzed with the original QT interval measurements calculated from General Electric 12-lead interpretation algorithm 12SL and then stored in MUSE CV System (MUSE; General Electric HC, Menomonee Falls, Wisconsin). The 12SL algorithm performs an automated analysis of QT interval that combines ECG complexes from 12 standard leads into 1 waveform beat and measures a global QT interval from the onset of the Q-wave to the end of the T-wave of the combined waveform. To verify the findings from the 12SL algorithm, 50 of these patients were also analyzed with the ECG Interval Editor (IE; version 005D.02, General Electric HC). The IE measures the Q-onset and T-offset of each lead and then computes the final QT interval with the latest T offset subtracting the earliest Q onset. In 20 randomly selected patients, the data was also studied with manual measurement with calipers by 1 of the investigators (S.C.K.) blinded to the sequence of the ECGs. In these 20 patients the QTc interval was calculated with the Bazett’s formula (15).

Each ECG was analyzed for STE or ST-segment depression (STD), T-wave change (TWC), QRS complex prolongation or shortening, and QT interval prolongation or abbreviation. The STE was defined as new ≥1 mm elevation in 2 anatomically contiguous leads. The STD was defined as new ≥1-mm depression in 2 anatomically contiguous leads. The TWC was defined as a change in the polarity of the T-wave in 2 anatomically contiguous leads. Prolongation of the QT interval was corrected for the heart rate with the Bazett’s QT interval correction formula (QT interval/square root [R-R interval]) (15) for all 3 methodologies of analysis. Although our primary focus was on QT interval corrected with Bazett’s formula, we also report the results with the Fridericia (16) (QT interval/cubed root [R-R interval]) and the Framingham (17) (QT interval+0.154[1−R-R interval]) formulas for heart rate correction of the QT intervals. These were calculated manually.

In the patients analyzed by MUSE, automated measurements of the QRS duration and the QT interval were obtained, whereas STE, STD, and TWC were determined visually. In the 50 patients analyzed by IE, all measurements were automated.

Statistical analysis. Continuous variables were expressed as mean ± SD and analyzed with 2-tailed paired Student t tests. Categorical variables were summarized as percentage. The SPSS Version 10.0 (SPSS Inc., Chicago, Illinois) computer software was used for statistical analysis.

Results

The baseline characteristics of the study population are presented in Table 1. Amiodarone was used in 1 patient for 2 days before the procedure (total dose 600 mg) for suppression of nonsustained ventricular tachycardia; his
baseline QTc interval was not prolonged. No other patient was taking a medication known to prolong the QT interval. The left anterior descending (LAD), right coronary, and circumflex arteries were equally represented (Table 1).

A representative ECG complex from lead V\textsubscript{2} in a patient undergoing occlusion of the LAD is shown in Figure 1: panel A shows a baseline tracing; panel B shows the complex during occlusion (25 s); and panel C shows the 2 complexes superimposed over each other.

Transmural ischemia induced by balloon occlusion prolonged QTc interval (as measured by Bazett’s formula) in 100% of patients. Figure 2A shows a line graph demonstrating a prolongation of the QTc interval with transmural ischemia in each of the 50 patients analyzed with IE. The QTc interval prolonged from 424.0 ± 27 ms at baseline to 458 ± 33 ms (p < 0.001) during the occlusion and abbreviated to 441 ± 34 ms (p < 0.001) with reperfusion (Fig. 3B). Although the QTc interval prolonged in all patients, the QT interval prolonged in 40 (80%) patients (404 ± 35 ms to 430 ± 41 ms, p = 0.002) and abbreviated in the remainder (n = 10, 20%) (423 ± 44 ms to 416 ± 43 ms, p = 0.02) (Table 3). Similar to the group of patients analyzed by MUSE, the patients exhibiting ischemia-induced QT interval abbreviation had a significantly greater increase in heart rate with balloon occlusion (64 ± 9 beats/min to 76 ± 11 beats/min; average change of 11.2 ± 5 beats/min, p = 0.02). In contrast, in the patients in whom QT interval prolonged, the rise in heart rate was not significant (63 ± 10 beats/min to 69 ± 12 beats/min; p = 0.32).

The QTc interval prolongation was noticed in each of the coronary vessels studied. The average increase measured by MUSE in the LAD (n = 24) distribution was 430.8 ± 34 ms to 464.9 ± 36 ms (p = 0.002); in the circumflex

### Table 1 Baseline Characteristics in the 74-Patient Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (68%)</td>
</tr>
<tr>
<td>Age</td>
<td>61 ± 12</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>24 (32%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 (81%)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>30 (41%)</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>38 (51%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>68 (92%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>54 (73%)</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitors</td>
<td>43 (58%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>35 (47%)</td>
</tr>
<tr>
<td>CCB</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Vessel</strong></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>24 (32%)</td>
</tr>
<tr>
<td>RCA</td>
<td>24 (32%)</td>
</tr>
<tr>
<td>LCx</td>
<td>26 (36%)</td>
</tr>
<tr>
<td><strong>Ejection fraction % (mean ± SD)</strong></td>
<td>52 ± 9</td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitors; CCB = calcium channel blockers; GP = glycoprotein; LAD = left anterior descending artery; LCx = left circumflex artery; MI = myocardial infarction; RCA = right coronary artery.

average QT interval in these 57 patients was 404 ± 34 ms at baseline and 430 ± 41 ms during occlusion (p < 0.001). The average QT interval in the 17 patients in whom it abbreviated was 419 ± 44 ms at baseline and 402 ± 40 ms during occlusion (p < 0.001). The increase in heart rate during balloon inflation was substantially greater in these patients (62 ± 11 beats/min to 73 ± 12 beats/min [p = 0.008]). The magnitude of increase in heart rate (11.0 ± 5 beats/min) was almost 4 times that seen in the other 57 patients (2.8 ± 5 beats/min) and likely accounts for the prolongation of the QTc interval in the cohort, despite a decrease in QT interval.

We also verified the results in 50 patients with IE, another automated system. The QTc interval prolonged in 100% of patients when analyzed by IE. Figure 3A shows a line graph demonstrating a prolongation of the QTc interval with transmural ischemia in each of the 50 patients analyzed with IE. The QTc interval prolonged from 424.0 ± 27 ms at baseline to 458 ± 33 ms (p < 0.001) during the occlusion and abbreviated to 441 ± 34 ms (p < 0.001) with reperfusion (Fig. 3B). Although the QTc interval prolonged in all patients, the QT interval prolonged in 40 (80%) patients (404 ± 35 ms to 430 ± 41 ms, p = 0.002) and abbreviated in the remainder (n = 10, 20%) (423 ± 44 ms to 416 ± 43 ms, p = 0.02) (Table 3). Similar to the group of patients analyzed by MUSE, the patients exhibiting ischemia-induced QT interval abbreviation had a significantly greater increase in heart rate with balloon occlusion (64 ± 9 beats/min to 76 ± 11 beats/min; average change of 11.2 ± 5 beats/min, p = 0.02). In contrast, in the patients in whom QT interval prolonged, the rise in heart rate was not significant (63 ± 10 beats/min to 69 ± 12 beats/min; p = 0.32).

The QTc interval prolongation was noticed in each of the coronary vessels studied. The average increase measured by MUSE in the LAD (n = 24) distribution was 430.8 ± 34 ms to 464.9 ± 36 ms (p = 0.002); in the circumflex
coronary artery (n = 26) distribution was 421.4 ± 16 ms to 452.4 ± 29 ms (p < 0.001); and in the right coronary artery (n = 24) distribution was 416.4 ± 19 ms to 448.4 ± 34 ms (p < 0.001). The average increase in QTc interval as measured by the IE in the LAD (n = 19) distribution was 436.1 ± 37 ms to 470.6 ± 36 ms (p = 0.006); in the circumflex coronary artery (n = 16) distribution was 418.8 ± 14 ms to 444.4 ± 22 ms (p = 0.001); and in the right coronary artery (n = 15) distribution was 415.7 ± 14 ms to 455.9 ± 37 ms (p < 0.001).

The average total occlusion time for the inflation in our patients was 40 ± 19 s. During balloon occlusion, maximum QTc interval prolongation was seen to occur before clinically accepted criteria for diagnosing acute ischemia (STE, STD ≥ 1 mm or change in T-wave polarity) (4, 18, 19) (Fig. 4). The average time to maximal QTc interval prolongation was 22 s. The QTc interval prolongation was followed by TWCs at 24 s, STE at 29 s, and STD at 35 s. Although the QTc interval prolonged in 100% of patients, TWCs, STE, and STD occurred in 7%, 15%, and 7% of patients, respectively, during brief episodes of transmural ischemia.

Balloon occlusion produced a statistically significant prolongation of QRS duration when measured with MUSE and IE (Tables 2 and 3). It is noteworthy that the magnitude of ischemia-induced QRS prolongation is only marginal compared with prolongation of the QTc interval.

In 20 randomly selected patients, blinded manual measurements revealed that QTc interval prolonged from 431 ± 27 ms to 463 ± 26 ms (p < 0.001) with ischemia and abbreviated to 459 ± 35 ms (p = 0.51) with reperfusion. The changes in QTc interval paralleled those obtained with automated measurements during occlusion and after reperfusion. Non-ionic contrast infusion, in 10 patients with normal coronary arteries, produced no significant changes in QT or QTc interval. In these patients, the average QT interval changed from 413.4 ± 27 ms at baseline to 416.4 ± 37 ms during the injection (p = 0.8), whereas the Bazett’s QTc interval decreased from 429.3 ± 14 ms at baseline to 423.6 ± 18 ms (p = 0.4).

Although not the primary focus of our analysis, we also calculated the changes in the QTc interval as determined by the Fridericia and Framingham methods. With the Fridericia method, MUSE analysis showed that ischemia prolonged QTc interval from 417.8 ± 26 ms to 444.6 ± 33 ms (p < 0.001) in 69 of 74 patients (93%); analysis with the IE automated system showed QTc interval prolongation from 419.1 ± 27 ms to 447.7 ± 33 ms (p < 0.001) in 46 of 50 patients (92%). With the Framingham method, MUSE analysis showed that ischemia prolonged QTc interval from 417.8 ± 24 ms to 443.6 ± 31 ms (p < 0.001) in 69 of 74
Discussion

Summary of findings. We show for the first time that early transmural ischemia in humans consistently prolongs the Bazett's QTc interval. Our observation withstood the test of 2 different ECG automated QT interval measurement systems (IE and MUSE). Although the change in QTc interval was modest (mean prolongation by MUSE was 32.3 ± 21; and by IE, 33.4 ± 23), it is noteworthy that it occurred in 100% of patients.

It is important to point out that the most consistent ECG abnormality seen with early transmural ischemia was a prolongation of the QTc interval and not the QT interval. The QT interval actually abbreviated in 20% of patients as analyzed by IE and in 23% of patients as analyzed by MUSE. However, these patients exhibited QTc interval prolongation as well. Patients who displayed ischemia-induced QT interval abbreviation had a significantly greater rise in heart rate during balloon inflation. This observation suggests that the magnitude of QT interval abbreviation is significantly less than what would be expected for the change in heart rate in these patients, accounting for a prolongation of the QTc interval. The failure of prior studies, assessing ECG abnormalities during ischemia, to demonstrate early QT interval lengthening is most likely due to surface ECG not being recorded early enough. This early QT interval lengthening described in this report might not be similar in mechanism or significance to the QT prolongation recorded within hours or days of the ischemic event.

The post-reperfusion ECG did not entirely return to baseline in our study. This possibly reflects the short time interval between occlusion and reperfusion ECGs or other unexplored mechanisms. During balloon inflation, maximal QTc interval prolongation occurred before clinically accepted parameters of acute ischemia (≥1 mm). The small

Table 3

<table>
<thead>
<tr>
<th>Interval Editor</th>
<th>Baseline</th>
<th>Balloon Inflation</th>
<th>Post Deflation</th>
<th>p Value*</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>66 ± 10</td>
<td>70 ± 12</td>
<td>70 ± 11</td>
<td>0.06</td>
<td>0.86</td>
</tr>
<tr>
<td>QT</td>
<td>409 ± 37</td>
<td>428 ± 43</td>
<td>414 ± 42</td>
<td>0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>QTc</td>
<td>424 ± 27</td>
<td>458 ± 33</td>
<td>441 ± 34</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>QRS</td>
<td>90 ± 16</td>
<td>98 ± 15</td>
<td>95 ± 15</td>
<td>0.02</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*Comparing baseline and balloon inflation. †Comparing balloon inflation to post deflation.

Abbreviations as in Table 2.
percentage of STE, STD, and TWCs seen is possibly due to the short duration of balloon inflation (average inflation time was 40 ± 19 s) or to the discrete partition used for detecting ST-segment changes.

Injection of ionic contrast into coronary arteries is known to prolong the QT interval. These have been attributed to APD prolongation caused by the calcium binding additives sodium citrate and sodium ethylenediaminetetraacetic acid (EDTA) found in the medium, or to its high sodium concentration (20–22). Nonionic contrast, used in our study, is not known to prolong QT. To confirm the absence of any effect on myocardial repolarization, we recorded ECGs in 10 patients with normal coronary arteries during non-ionic contrast infusion. No changes in QT or QTc intervals were noted.

We focused on Bazett’s formula for QTc interval calculations for the following reasons: 1) it is the oldest and most widely recognized formula in clinical practice and has been used in many studies to evaluate arrhythmia risk from QT prolongation; 2) the ECG machines (MAC 8 Marquette ECG Cart [GE Medical Systems]) used in our study routinely report Bazett’s QTc interval; and 3) the limitations of the Bazett’s formula is seen only at extreme of heart rates (23). The heart rates ranged between 46 and 98 beats/min in our study, and extremes of rates were not encountered. Although ischemia-induced QTc interval prolongation with the Fridericia and Framingham formulas did not occur 100% of the time, it was still the most consistent ECG abnormality seen with transmural ischemia.

Underlying physiological explanation. Our findings, although novel, are not entirely unexpected. Numerous prior human, animal, and tissue investigations studying the electrophysiology of ischemia describe a biphasic change in the APD of ischemic myocardium. Although the dominant effect of ischemia on the cellular electrophysiology is abbreviation of APD, conduction slowing, and eventually excitability, the first minute of ischemia actually results in temporary prolongation of APD (12–14,20,24–28). This transient APD prolongation has been attributed to decrease in epicardial temperature (28), changes in impedance (29), acidosis (14,30,31), and the observation that sodium influx might precede potassium efflux during ischemia (8). During early ischemia, the activation of an inward current prolonging APD could underlie the sodium gain that triggers the onset of net potassium loss (8).

Lyso phosphatidylcholine (LPC), a product of ischemia-induced phospholipid catabolism has been shown to alter the sodium channel kinetics, resulting in a noninactivated component of the sodium current and thus prolonging repolarization (9,32,33). In addition to LPC, hypoxia has also been shown to modulate the sodium channel and the sodium inward current. In rat ventricular myocytes, hypoxia greatly increased the activity and open probability of inactivation resistant sodium channels (34). The dominant factor responsible for the initial APD and QTc interval prolongation in early ischemia merits further investigation.

Physiological and clinical implications. QTc INTERVAL PROLON GATION AND ISCHEMIC CASCADE. During early stages of myocardial ischemia, the ischemic cascade represents a pathophysiologic continuum that begins with manifestations of diastolic dysfunction, systolic dysfunction followed by ECG changes, and angina pectoris (35,36). Our observation that ischemia-induced QTc interval prolongation is seen early during myocardial ischemia suggests that prolongation of repolarization might figure prominently in the ischemic cascade. The time course of where this fits in the cascade relative to the other ischemia-induced changes remains a subject for future investigation.

ECG diagnosis of ischemia and infarction. The diagnosis of acute transmural myocardial infarction for purposes of delivering emergent therapy is based almost exclusively on the presence of STE (4). However our findings suggest a possible role for QTc interval prolongation in the detection of early or intermittent transmural ischemia. QT and QTc interval prolongation has been described to occur 12 h to 24 h after the onset of infarction but has not been shown to occur during the early phases of transmural ischemia (37,38). The QTc interval prolongation seen later during myocardial infarction has significant clinical and arrhythmic relevance, especially in the development of ventricular arrhythmias and Torsades de pointes (39).

Study limitations. Our ECGs were recorded at 19- to 20-s intervals. The 9-s interruptions in recording each ECG prevent detection of beat-to-beat changes in repolarization. This also limits our ability to compare the time course of ischemic changes in QTc interval with more conventional ischemic parameters such as changes in ST-segment and T waves. A more reliable assessment of changes in the time course of ischemia-induced ECG parameters will need technology that allows a more frequent or continuous recording with automated beat-to-beat measurements of parameters including the ST-segment. We used a discrete partition for defining ST-segment changes on the basis of the well established clinical criteria for diagnosing acute ischemia (2 mm in 2 contiguous leads). Our comparison of ischemia-induced QTc interval prolongation (a global measurement) with changes in the ST-segment and T waves (both local measurements with a vectorial component) necessitated the use of different yardsticks for making the measurements.

In some of our patients, the small magnitude of increase in QTc interval seen makes it likely that manual measurements will not discern these changes and automated techniques will be necessary (40,41). Although manual measurements correlated with our overall findings, we believe that automated techniques will be more accurate and reliable in detecting changes in the QT interval especially when they are small in magnitude. Our data are strengthened by the fact that 2 automated systems with different methodologies verified the findings.
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REFERENCES