Heart Rhythm Disorders

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

David N. Kenigsberg, MD, Sanjaya Khanal, MD, Marcin Kowalski, MD,
Subramaniam C. Krishnan, MD

Detroit, Michigan

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

Abbreviations and Acronyms

APD = action potential duration

ECG = electrocardiogram

IE = interval editor

LAD = left anterior descending coronary artery

LPC = lysophosphatidylcholine

MUSE = MUSE CV System

STD = ST-segment depression

STE = ST-segment elevation

TWC = T-wave change

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 prepped 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

Table 1	Baseline Characteristics in the 74-Patient Cohort
Variable	**n (%)**
Demographics	
Male	50 (68%)
Age	61 ± 12
History	
Diabetes	24 (32%)
Hypertension	60 (81%)
Prior MI	30 (41%)
CABG	1 (1%)
Medications	
ACEI	38 (51%)
Aspirin	68 (92%)
Beta-blockers	54 (73%)
GP IIb/IIIa inhibitors	43 (58%)
Clopidogrel	35 (47%)
CCB	8 (10%)
Amiodarone	1 (1%)
Vessel	
LAD	24 (32%)
RCA	24 (32%)
LCx	26 (36%)
Ejection fraction % (mean ± SD)	52 ± 9

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

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_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 74 patients analyzed with the MUSE System. The average maximum QTc interval (the longest QTc interval during inflation) prolonged from 423 ± 25 ms at baseline to 455 ± 34 ms (p < 0.001) during balloon occlusion and decreased to 440 ± 33 ms (p < 0.001) after deflation (Fig. 2B). Seven (9%) patients had abnormal QTc intervals at baseline (QTc >460 ms). However, balloon occlusion induced QTc interval prolongation in these patients as well.

The heart rate increased from 66 ± 10 beats/min at baseline to 71 ± 12 beats/min (p < 0.001) during occlusion (Table 2). The average QT interval prolonged from 408 ± 37 ms at baseline to 424 ± 42 ms (p < 0.0001) during balloon occlusion and decreased to 406 ± 58 ms (p = 0.01) after deflation (Table 2). Although the QTc interval prolonged in all patients, the QT interval prolonged in 57 (77%) patients and abbreviated in the remainder (n = 17, 23%). The

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
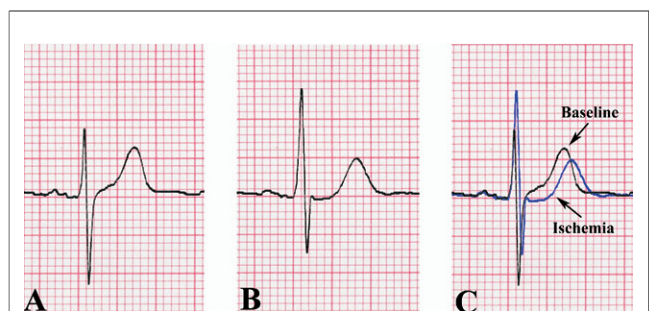

Figure 1	Electrocardiographic Changes Induced by Transmural Ischemia

(A) Single electrocardiographic complex from lead V_2 obtained under baseline conditions, before the start of the angioplasty of the left anterior descending coronary artery (LAD). **(B)** Single electrocardiographic complex from the same lead shown in **A** is displayed 25 s after balloon inflation in the proximal LAD. The QT interval is seen to prolong by 44 ms. **(C)** The 2 complexes seen in **A** and **B** are superimposed to better illustrate ischemia-induced changes showing prolongation of QT interval.
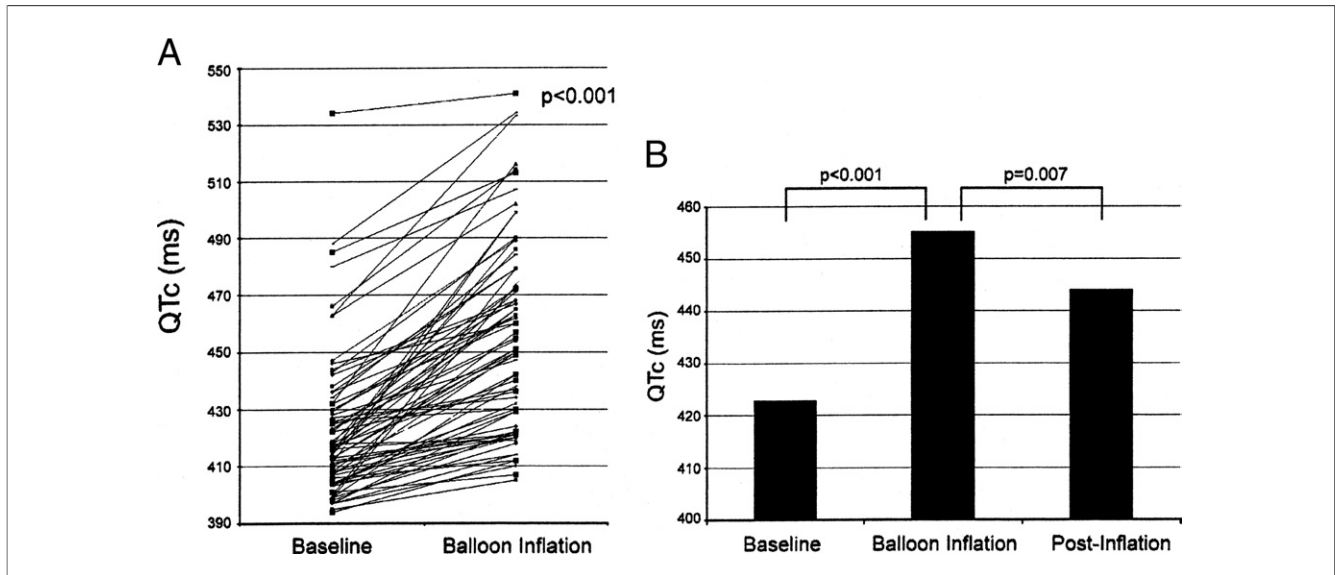
Figure 2   **QTc Interval Prolongation Induced by Brief Episodes of Transmural Ischemia in 74 Patients Analyzed by the MUSE Automated System**

(A) Line graph demonstrating transmural ischemia-induced QTc interval prolongation in all 74 patients. **(B)** Bar graph displaying average QTc interval in 74 patients at baseline, during balloon inflation, and after deflation. The QTc interval is prolonged by 32 ms with balloon inflation and partially returns to baseline upon deflation.

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.
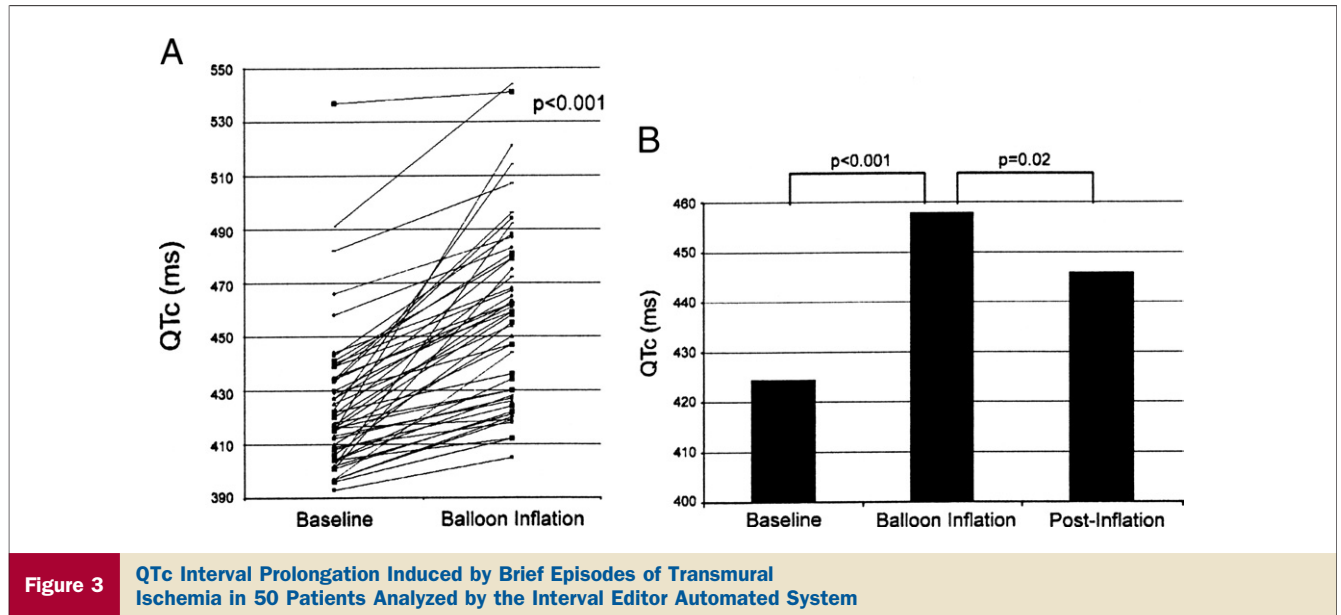
In 20 randomly selected patients, blinded manual measurements revealed that QTc interval prolonged from 431 ± 27 ms to 463 ± 26 ms (p < 0.001) with ischemia and abbreviated to 459 ± 35 ms (p = 0.51) with reperfusion. The changes in QTc interval paralleled those obtained with automated measurements during 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

Table 2	Quantitative Changes in ECG Findings During Brief Episodes of Transmural Ischemia Analyzed by the MUSE Automated System				
	MUSE				
	Baseline	**Balloon Inflation**	**Post Deflation**	**p Value***	**p Value†**
HR	66 ± 10	71 ± 12	70 ± 11	0.01	0.70
QT	408 ± 37	424 ± 42	406 ± 58	0.01	0.04
QTc	423 ± 25	455 ± 34	440 ± 33	<0.001	0.007
QRS	92 ± 17	97 ± 16	95 ± 16	0.03	0.39

*Comparing baseline and balloon inflation. †Comparing balloon inflation to post deflation.
ECG = electrocardiographic; HR = heart rate; QT = QT interval; QTc = QTC interval.

patients (93%); analysis with IE showed QTc interval prolongation from 419.3 ± 26 ms to 446.5 ± 32 ms (p < 0.001) in 48 of 50 patients (96%).

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
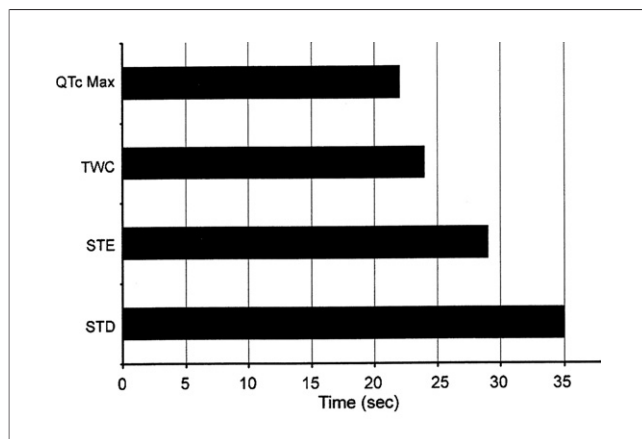

Figure 4 Time Course of Ischemia-Induced Changes in Different Components of the ECG

Analysis performed with the MUSE automated system. Prolongation of the QTc interval occurs earlier than the established criteria for acute ischemia (ST-segment elevation [STE], ST-segment depression [STD] ≥1 mm in 2 contiguous leads). ECG = electrocardiogram; TWC = T-wave change.

Table 3 Quantitative Changes in ECG Findings During Brief Episodes of Transmural Ischemia Analyzed by the Interval Editor Automated System

| | Interval Editor | | | | |
	Baseline	**Balloon Inflation**	**Post Deflation**	**p Value***	**p Value†**
HR	66 ± 10	70 ± 12	70 ± 11	0.06	0.86
QT	409 ± 37	428 ± 43	414 ± 42	0.02	0.11
QTc	424 ± 27	458 ± 33	441 ± 34	<0.001	0.02
QRS	90 ± 16	98 ± 15	95 ± 15	0.02	0.36

*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 arrhythmic 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 inexcitability, 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).

Lysophosphatidylcholine (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 PROLONGATION 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 (≥1 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.

REFERENCES

1. Pardee H. An electrocardiographic sign of coronary artery obstruction. Arch Intern Med 1920;26:244–57.
2. Cook RW, Edwards JE, Popma JJ. Electrocardiographic changes in acute subendocardial infarction. I. Large subendocardial and large nontransmural infarcts. Circulation 1958;18:603–12.
3. Gunnar RM, Pietras RJ, Blackaller J, Dadmun SE, Szanto PB, Tobin JR Jr. Correlation of vectorcardiographic criteria for myocardial infarction with autopsy findings. Circulation 1967;35:158–71.
4. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). J Am Coll Cardiol 2004;44:E1–E211.
5. de Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. J Am Coll Cardiol 2001;38:1283–94.
6. Kleber AG, Janse MJ, van Capelle FJ, Durrer D. Mechanism and time course of S-T and T-Q segment changes during acute regional myocardial ischemia in the pig heart determined by extracellular and intracellular recordings. Circ Res 1978;42:603–13.
7. Janse MJ. Electrophysiology and electrocardiology of acute myocardial ischemia. Can J Cardiol 1986;Suppl A:46A–52A.
8. Shivkumar K, Deutsch NA, Lamp ST, Khuu K, Goldhaber JI, Weiss JN. Mechanism of hypoxic K loss in rabbit ventricle. J Clin Invest 1997;100:1782–8.
9. Kiyosue T, Arita M. Effects of lysophosphatidylcholine on resting potassium conductance of isolated guinea pig ventricular cells. Pflugers Arch 1986;406:296–302.
10. Ito H, Vereecke J, Carmeliet E. Intracellular protons inhibit inward rectifier K+ channel of guinea-pig ventricular cell membrane. Pflugers Arch 1992;422:280–6.
11. Matsuda H. Effects of external and internal K+ ions on magnesium block of inwardly rectifying K+ channels in guinea-pig heart cells. J Physiol 1991;435:83–99.
12. Watanabe I, Kanda A, Engle CL, Gettes LS. Comparison of the effects of regional ischemia and hyperkalemia on the membrane action potentials of the in situ pig heart. Experimental Cardiology Group, University of North Carolina at Chapel Hill. J Cardiovasc Electrophysiol 1997;8:1229–36.
13. Redwood SR, Taggart PI, Sutton PM, et al. Effect of magnesium on the monophasic action potential during early ischemia in the in vivo human heart. J Am Coll Cardiol 1996;28:1765–9.
14. Bethell HW, Vandenberg JI, Smith GA, Grace AA. Changes in ventricular repolarization during acidosis and low-flow ischemia. Am J Physiol 1998;275:H551–61.
15. Bazett HC. An analysis of the time-relations of the electrocardiogram. Heart 1920;7:353–70.
16. Fridericia LS. Die Systolendauer Im Elektrokardiogramm Bei Normalen Menschen Und Bei Herzkranken. Acta Medica Scandinavica 1920;57:469–86.
17. Sagie A, Larson MG, Goldberg RJ, Bengtson JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol 1992;70:797–801.
18. Wagner GS, Marriott HJ. Marriott's Practical Electrocardiography. 9th edition. Baltimore, MD: Williams and Wilkins, 1994.
19. Macfarlane PW. Age, sex, and the ST amplitude in health and disease. J Electrocardiol 2001;34 Suppl:235–41.
20. Surawicz B. Electrophysiologic Basis of ECG and Cardiac Arrhythmias. Baltimore, MD: Lippincott Williams and Wilkins, 1995.
21. Wolf GL, Hirshfeld JW Jr. Changes in QTc interval induced with Renografin-76 and Hypaque-76 during coronary arteriography. J Am Coll Cardiol 1983;1:1489–92.
22. Murdock DK, Euler DE, Kozeny G, Murdock JD, Loeb HS, Scanlon PJ. Ventricular fibrillation during coronary angiography in dogs: the role of calcium-binding additives. Am J Cardiol 1984;54:897–901.
23. Anderson ME, Al Khatib SM, Roden DM, Califf RM. Cardiac repolarization: current knowledge, critical gaps, and new approaches to drug development and patient management. Am Heart J 2002;144:769–81.
24. Lee HC, Mohabir R, Smith N, Franz MR, Clusin WT. Effect of ischemia on calcium-dependent fluorescence transients in rabbit hearts containing indo 1. Correlation with monophasic action potentials and contraction. Circulation 1988;78:1047–59.
25. Downar E, Janse MJ, Durrer D. The effect of acute coronary artery occlusion on subepicardial transmembrane potentials in the intact porcine heart. Circulation 1977;56:217–24.
26. Daniel WG, Svenson RH, Masters TN, Robicsek F. Electrophysiologic effects of partial coronary flow reduction in the exposed canine heart. Effects of ischemia and ischemic-induced regional hypothermia on refractoriness and conduction delay. Circulation 1978;58:670–8.
27. Verkerk AO, Veldkamp MW, van Ginneken AC, Bouman LN. Biphasic response of action potential duration to metabolic inhibition in rabbit and human ventricular myocytes: role of transient outward current and ATP-regulated potassium current. J Mol Cell Cardiol 1996;28:2443–56.
28. Wit AL, Janse MJ. The Ventricular Arrhythmias of Ischemia and Infarction: Electrophysiological Mechanisms. Armonk, NY: Futura Publishing Company, 2005.
29. Cascio W, Yan G, Kleber A. Passive electrical properties, mechanical activity, and extracellular potassium in arterially perfused and ischemic rabbit ventricular muscle. Effects of calcium entry blockade or hypocalcemia. Circ Res 1990;66:1461–73.
30. Kagiyama Y, Hill JL, Gettes LS. Interaction of acidosis and increased extracellular potassium on action potential characteristics and conduction in guinea pig ventricular muscle. Circ Res 1982;51:614–23.
31. Spitzer KW, Hogan PM. The effects of acidosis and bicarbonate on action potential repolarization in canine cardiac Purkinje fibers. J Gen Physiol 1979;73:199–218.
32. Undrovinas AI, Fleidervish IA, Makielski JC. Inward sodium current at resting potentials in single cardiac myocytes induced by the ischemic metabolite lysophosphatidylcholine. Circ Res 1992;71:1231–41.
33. Burnashev NA, Undrovinas AI, Fleidervish IA, Makielski JC, Rosenshtraukh LV. Modulation of cardiac sodium channel gating by lysophosphatidylcholine. J Mol Cell Cardiol 1991;23 Suppl 1:23–30.
34. Ju YK, Saint DA, Gage PW. Hypoxia increases persistent sodium current in rat ventricular myocytes. J Physiol 1996;497:337–47.
35. Hauser AM, Gangadharan V, Ramos RG, Gordon S, Timmis GC. Sequence of mechanical, electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: echocardiographic observations during coronary angioplasty. J Am Coll Cardiol 1985;5:193–7.
36. Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 1987;59:23C–30C.
37. Doroghazi RM, Childers R. Time-related changes in the Q-T interval in acute myocardial infarction: possible relation to local hypocalcemia. Am J Cardiol 1978;41:684–8.
38. Cinca J, Figueras J, Tenorio L, et al. Time course and rate dependence of Q-T interval changes during noncomplicated acute transmural myocardial infarction in human beings. Am J Cardiol 1981;48:1023–8.
39. Halkin A, Roth A, Lurie I, Fish R, Belhassen B, Viskin S. Pause-dependent Torsade de pointes following acute myocardial infarction: a variant of the acquired long QT syndrome. J Am Coll Cardiol 2001;38:1168–74.
40. Viskin S, Rosovski U, Sands AJ, et al. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. Heart Rhythm 2005;2:569–74.
41. Montgomery H, Hunter S, Morris S, Naunton-Morgan R, Marshall RM. Interpretation of electrocardiograms by doctors. BMJ 1994;309:1551–2.