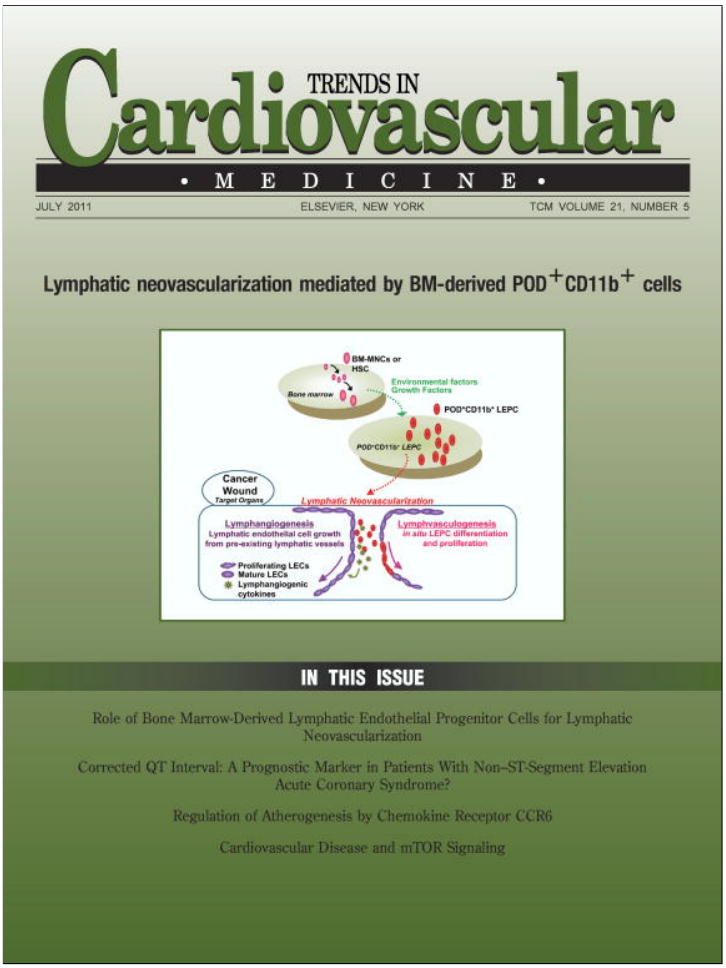

Corrected QT Interval: A Prognostic Marker in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome?

Francisco Gadaleta, Susana Llois, and Juan Carlos Kaski*

Over many decades, the corrected QT (QTc) has become an established clinical tool for the prediction of sudden cardiac death and life-threatening ventricular arrhythmias and for monitoring adverse effects of pharmacological agents capable of triggering serious ventricular arrhythmias mainly associated with QTc prolongation. Recent evidence also suggests that QTc prolongation is a predictor of poor clinical outcome in patients with coronary artery disease, particularly in the setting of the acute coronary syndrome. Indeed, in the past few years, studies assessing the predictive role of QTc measurements have provided important information in this regard and suggest a potential role of the QTc in patient risk stratification. The incorporation of biomarkers of myocardial damage (ie cardiac troponins), clinical risk scores, and other biochemical and angiographic markers in the past two decades has considerably improved the risk stratification of patients presenting with acute coronary syndrome, but further refinement of our prognostic armamentarium is still required. This article reviews the information available regarding the potential role of the QTc as a marker of increased risk in patients with acute presentations of coronary artery disease. (Trends Cardiovasc Med 2011;21:129-135)

• Introduction

The corrected QT interval (QTc) is a useful clinical tool for the identification of subjects who are at a high risk of developing life-threatening ventricular arrhythmias leading to sudden cardiac death. The assessment of the QTc is also useful for monitoring adverse effects of pharmacological agents that cause QTc prolongation and thus place individuals at a high risk for sudden cardiac death. Of interest, however, increasing evidence during the past few years has suggested a prognostic role for the assessment of the QTc in the setting of coronary artery disease. Indeed, studies assessing the possible prognostic role of QTc interval measurements in the setting of acute coronary syndrome (ACS) have provided important information in this regard. Patients presenting with an ACS are at high risk of death and other serious cardiovascular events. However, the accurate identification of patients who are at high, intermediate, and low levels of risk still represents a challenge to the treating physician. The incorporation of biomarkers of myocardial damage (ie cardiac troponins) to our diagnostic and prognostic armamentaria in the past two decades has considerably improved our ability to risk stratify ACS patients, but further refinement is required (Agewall et al. 2011). Several clinical risk scores, as well as biochemical and angiographic markers, have been proposed during the past years that have assisted physicians in their endeavors to identify high-risk subjects presenting with typical chest pain at rest suggestive of ACS. Among these, the GRACE score (Global Registry of Acute Coronary Events; http://www.outcomes-umassmed.org/grace), currently encompassing more than 100,000 patients in 30 countries, has been shown to have a good predictive value during the first 6 months of follow-up in patients presenting with ACS (Granger et al. 2003). The GRACE score includes the following variables: age, heart rate, creatinine levels, arterial blood pressure, Killip class, electrocardiographic (ECG) abnormalities, cardiac biomarkers, left ventricular ejection fraction, cardiac catheterization, cardiac intervention, and drug treatment. The TIMI (Thrombolysis in Myocardial Infarction) risk score is also used for the assessment of patients admitted to the hospital with ACS and, like GRACE, involves the use of clinical, conventional ECG, biochemical, and angiographic variables (Antman et al. 2000). However, despite the relative usefulness of these risk scores and other biomarkers, assessment of risk is far from optimal, and the search for markers that might improve risk assessment continues unabated (Bonaca et al. 2010, National Institute for Health and Clinical Excellence 2010). In the ACS setting, the ECG has important diagnostic and prognostic roles (Birn-

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Table 1. Genes involved in long QT syndrome

Type	*Locus*	*Gene*	*Protein*	*Current*	*Incidence (%)*
LQTS1	11p15.5	KCNQ1/KVLQT1	Main, subunit α I_{ks}	K	30-35
LQTS2	7q35-36	KCNH2/HERG	Main, subunit α I_{kr}	K	25-30
LQTS3	3p21-p24	SCN5A	Main, subunit α I_{Na}	I_{Na}	5-10
LQTS4	4q25-q27	ANKB	Accessory, ankyrin-β	Na/Ca	<1
LQTS5	21q22.1	KCNE1/minK	Accessory, subunit β I_{ks}	K	<1
LQTS6	21q22.1	KCNE2/MiRP1	Accessory, subunit β I_{kr}	K	<1
LQTS7	17q23	KCNJ8	Main, subunit α Kir 2.1	K	<1
LQTS8	12p13.3	CACNA1	Main, subunit α Ca_v 1.2	Ca type L	<1
LQTS9	3p25	CAV3	Accessory, caveolin 3	Na	<1
LQTS10	11q23	SCN4B	Accessory, subunit β 4 I_{Na}	Na	<1
JLN1	11p15.5	KCNQ1/KVLQT1	Main, subunit α I_{ks}	K	>90.5
JLN2	21q22.1	KCNE1/mink	Accessory, subunit β I_{ks}	K	<0.5

baum and Atar 2006, Holmvang et al. 2003). When present, ischemic ST segment changes have been shown in clinical trials to have good prognostic value, superior to that of the T wave (Cannon et al. 1997). However, typical ST segment shifts may not necessarily be present in patients presenting with acute chest pain. For example, in a population of 10,689 patients with symptoms suggestive of ACS, Pope et al. (2000) found that 32% of the subjects had no ST segment changes and 33% had nondiagnostic T wave changes. The QTc may provide useful prognostic information in the setting of acute ischemic heart disease (IHD). We and others have reported that the prolongation of the QTc has both diagnostic and prognostic value in patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) (Gadaleta et al. 2003, Shawl et al. 1990). Moreover, studies have shown a good correlation between circulating cardiac troponin T concentration, a sensitive marker of myocardial necrosis, and QTc prolongation in NSTE-ACS patients (Llois et al. 2008). In fact, a QTc $\geq$ 0.458 s was found to be predictive of major adverse cardiac events (MACE) and increased troponin T, as reported by Llois et al. (2008). This review focuses on the potential role of QTc prolongation as a marker of risk of subsequent serious events in patients with NSTE-ACS.

• QTc Segment Prolongation and Cardiac Disease

Since 1921, when Katz described changes in the QT interval associated with electrolyte disturbances, QT interval prolongation has been the subject of intensive research (Katz 1921). A large number of publications have focused on the intriguing relationship between QTc interval prolongation and both cardiac arrhythmias and sudden cardiac death. The role of QTc prolongation in myocardial ischemia, however, has been less well studied. Congenital QTc prolongation has been shown to be associated with sudden cardiac death and ventricular arrhythmias. This association was first reported in 1957 by Jervell and Lange-Nielsen. The Jervell–Lange-Nielsen syndrome, characterized by congenital deafness, syncope, high risk of sudden death, and abnormal prolongation of the QT interval, thus constitutes the first reported association between QT interval prolongation and cardiac death. Following this seminal observation, many subsequent publications have focused on the association between an inherited abnormal prolongation of the QT interval and cardiac death (Romano et al. 1963) (Table 1). The Romano–Ward syndrome, for example, is another relatively frequent condition (incidence of approximately 1 in 3000 individuals) in which a congenital prolongation of the QT interval has been shown to be associated with sudden cardiac death (Romano et al. 1963). The International Congenital Long QT Syndrome Registry (LQTS), which was created in 1979, has allowed the characterization of the genotype in more than 70% of patients with the syndrome (Moss and Schwartz 2005).

Life-threatening arrhythmias can also result from drug-induced prolongations of the QTc interval**:** This is a topic of major concern to the treating physician, the pharmaceutical industry, and regulatory agencies. Most of the pharmacological agents that alter ventricular repolarization are also potentially able to trigger life-threatening ventricular arrhythmias such as torsade de pointes, often a predictor for ventricular fibrillation and sudden death (Malik 2004).

Neither congenital abnormalities of the QTc interval nor their associated channelopathies or other proarrhythmogenic entities are considered in this review, which, as mentioned previously, focuses on the predictive value of QTc changes in patients with ischemic heart disease.

• Measuring the QTc in Everyday Practice

Despite the clinical importance of QTc prolongation and the relatively easy technique proposed for its measurement, few clinicians actually assess the QTc routinely, particularly in the context of IHD. Proper measurements of the QTc are required if one is to draw meaningful clinical conclusions from the assessment of this ECG marker. Often, 12-lead ECGs are reported as "normal" in the clinical setting, despite the presence of a prolonged QTc (Figure 1). One of the most common reasons for this common error is that physicians tend to look at the absolute value of QT interval rather than calculating the QTc. Of some concern is the finding by Viskin et al. (2005) that one-third of arrhythmia specialists and more than 70% of cardiologists measure the QTc incorrectly in everyday practice.

For the accurate measurement of the QTc, several basic concepts have to be applied. One of these critical points is the accurate identification of the end of the T wave, and there are two well-

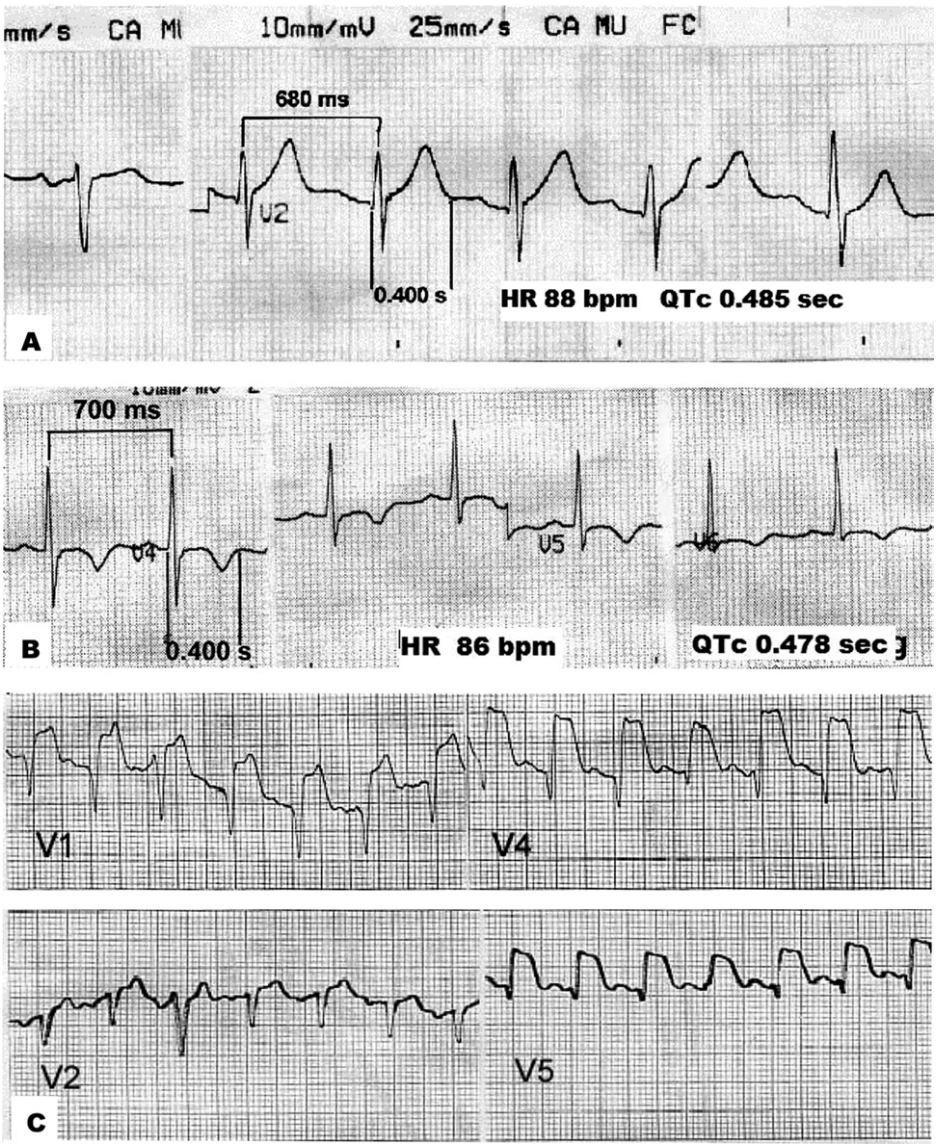

Figure 1. (**A**) ECG tracing in a 64-year-old male patient presenting with acute chest pain showing normal T waves and QTc prolongation (0.485 s) in the absence of ST segment or T wave changes. (**B**) ECG taken 16 h later, during recurrent angina. The tracing shows negative T waves and the QTc continues to be prolonged (0.478 s). (**C**) ECG during a prolonged episode of chest pain while the patient is being transported to a tertiary referral center for PCI.

known methods to identify this important landmark. One of these is known as the "tangent" technique, in which the end of the T wave is defined by the intersection, in lead II or V5, of a tangent to the steepest slope of the last limb of the T wave and the baseline (Postema et al. 2008). The other method is based on the detection of the nadir that exists between the T wave and the U wave to identify the end of the T wave. Both methods are useful and provide comparable data. The application of one of these as opposed to the other depends mainly on the characteristics of the T waves in the individual patient (Lepeschkin and Surawicz 1952, Postema et al. 2008). Chest leads V2 to V3 are usually recommended for the assessment of the QTc because it is in these leads that the T and U waves are most often clearly apparent (Kautzner and Malik 1997).

There are also automated techniques that provide rapid measurements of the QTc, but some publications have questioned the usefulness of these automated methods (Malik 2004). However, more recent studies have reported improved accuracy of automatic algorithms for QT measurement (Hnatkova et al. 2006). Of interest, the traditional method that involves the use of a magnifying glass offers similar or even better accuracy than automated techniques, according to some authors (Kautzner and Malik 1997, Malik 2004, Rossenbacker and Priori 2007). In 2004, Malik stated that "unfortunately, even the most modern ECG equipment uses rather simple and imprecise algorithms for interval measurement. Consequently, although the results are approximately accurate, more frequently than not, substantial errors are not rare." Along the same lines, Rossenbacker and Priori suggested that "when approaching the diagnosis of one of these diseases (LQTS, VT, etc.) the cardiologist has to leave fancy computer screens and go back to the 'ruler and caliper' to measure the duration of an 'interval.'" Unfortunately, we still lack an automated method than can provide accurate standards to make the use of manual methods unnecessary (Rossenbacker and Priori 2007).

In Gadaleta et al.'s (2003) series, QTc measurements were carried out manually in chest leads V2, V3, and V4 by two experienced observers. In reporting our findings, we used the averaged results of the two observers. The detection of the beginning of the QT interval, in general, poses no major difficulties because Q and R waves are usually good landmarks. Both manual—particularly with the use of manual calipers on digital ECG recordings—and automated methods provide reasonably accurate measurements that can be useful in everyday clinical practice. However, both techniques have limitations; that is, the manual method is time-consuming and highly dependent on the expertise of the operator, whereas the automated methods have problems regarding the identification of the true beginning and end of the QT interval. Automated measurement with manual overriding, making feasible corrections by the observer, particularly for the identification of accurate landmarks, is likely to provide more reliable measurements than purely automated systems.

- **Heart Rate Corrected QT and QTc Prolongation**

Most automated and semiautomated systems use the Bazett formula for the calculation of the QTc; that is, (QTc = QT interval/$\sqrt{}$RR (s)), where RR is the duration of the cardiac cycle (length) expressed in seconds. Bazett's correction of the QT interval duration in accor-

dance with the heart rate has represented an important contribution to QT measurement, but the true accuracy of the correction remains a matter of debate (Toivonen 2002). For example, when the heart rate changes, there is no "instantaneous" change in the duration of the QTc interval. This temporal delay is known as "heart rate hysteresis" (Malik 2004) and may affect QTc interval measurement. For everyday clinical electrocardiography, the QT/RR hysteresis means that ideally one should calculate the QTc interval only after the heart rate has been stable (eg with ±3 beats/min) for at least 1 or 2 min (Fenichel et al. 2004). On the other hand, when reading a previously recorded standard 10-s ECG, it is not appropriate to correct the QT interval only for the immediately preceding RR interval. A simple way to achieve more accurate and meaningful results is to correct the QT interval for the average heart rate recorded over the whole 10-s recording, which most likely will include several respiratory cycles, thus encompassing periods when the heart rate increases and decreases.

The major limitation of the Bazett's formula is the overcorrection of the QT interval duration that results from its use. As such, it renders artificially long QTc intervals with heart rate considerably higher than 60 and artificially short QTc intervals when the heart rate is very low (Viskin 2009). In prospective studies in cardiac patients, those with adverse outcomes are more likely to have had higher heart rates than those with better clinical outcomes (the heart rate is also an independent predictor of adverse outcome in various patient populations). Hence, if in such a study patients with adverse outcomes also have longer QTc (Bazett) intervals, it is possible that at least to some extent this could have been due to the higher heart rates in those individuals. Despite this limitation, however, the Bazett formula remains widely used in the clinical setting.

Consensus exists that the cut-off point that defines QTc prolongation is ≥0.450 s in men and ≥0.460 s in women (Rautaharju et al. 2009). A value >0.440 s should be considered to be borderline abnormal, and this value has been shown to have 81% sensitivity and 90% specificity for prediction of cardiovascular abnormalities (Rossenbacker and Priori 2007). Of importance, individuals with QTc values ≥0.500 s should be considered to be at high risk of developing recurrent syncope or sudden cardiac death (Priori et al. 2003).

• QT Dispersion and Its Association with Myocardial Ischemia

In 1990, Day et al. published data indicating that the ECG lead with the shortest QT interval accounted for an area in the left ventricle with earlier myocardial repolarization, whereas the ECG lead with the longest QT interval represented the region that repolarized the latest. They called the difference between these two leads "QT dispersion" (QTd). QTd had been the subject of extensive research since its initial description in 1990, and it has been shown by some investigators to be a predictor of both myocardial electrical instability and life-threatening arrhythmias. It was shown in many trials that QTd increases as a result of myocardial ischemia (Zareba et al. 1994). Okishige et al. (1996) assessed 47 coronary artery disease patients undergoing percutaneous coronary intervention (PCI) and observed a significant decrease in QTd values when the first and fifth balloon inflations and deflations were compared ($P < .01$), a finding indicating that reductions in QTd were the result of ischemic preconditioning associated with the multiple balloon inflations. Zimarino et al. (2011) assessed 612 IHD patients in whom a 12-lead ECG had been obtained prior to PCI and repeated 6 and 18 h after the procedure. The authors aimed at assessing mortality rates in relation to QTd values during a follow-up period of 4 years. The study showed that patients with the highest QTd and greater increases in creatine kinase–MB (CK-MB) levels post-PCI had a higher mortality rate than patients with lesser degrees of QTd and normal CK-MB concentrations (14.6% vs 2.4%, $P < .001$). Despite these findings, measurements of QTd have not been routinely used in clinical practice for several reasons, including the need for relatively expensive equipment and the technical complexities of the assessment. Thus, QTd does not currently represent a useful predictive variable in the clinical setting.

• QTc Prolongation and Ischemic Heart Disease

It has been shown that in more than 80% of patients who experience sudden cardiac death, atheromatous coronary artery disease is the underlying anatomic substrate (Sporton et al. 1997). Krasnoff (1950) was the first to report the occurrence of QTc prolongation in patients with ST elevation myocardial infarction (STEMI) compared to subjects with normal ECGs, selected at random from files in the Cardiac Station at the Jewish Hospital in Philadelphia (0.448 vs 0.397 s). In 1981, Taylor et al. (1981) found a close correlation between QTc values and the presence of myocardial ischemia in 32 patients with acute chest pain. The duration of the QT interval varies depending on whether subjects are in the hyperacute phase of the event or in later stages; that is, Surawicz and Knoebel (1984) observed a shortening of the QTc interval in patients with acute myocardial ischemia and, subsequently, a prolongation of the QTc interval in the subacute phase of the disease. Of importance, the increased duration of the QTc in the acute phase was found to be a predictor of ventricular tachycardia and so was the persistent prolongation of the QTc (documented in 57% of the patients in Taylor et al.'s study). Clayton et al. (2005), in the ACTION (A Coronary Disease Trial Investigating Outcome with Nifedipine GITS–Gastro-Intestinal Therapeutic System) trial, showed that in more than 7000 patients a prolonged QTc ≥ 430 ms (OR =3.05) was a predictor of mortality in stable coronary patients and, as a result, included the measurement of the QTc as a new variable in their risk assessment score.

Myocardial ischemia increases extracellular potassium, a mechanism that is time dependent and could explain the ECG changes observed a few minutes after the onset of myocardial ischemia (Kléber et al. 1978). Kenigsberg et al. (2007) published an observation that appears to challenge established concepts regarding the sequence of events taking place in the myocardial ischemia "cascade." They found that prolongation of the QTc was the earliest ischemic event in the cascade, and this appears to have been found in all their patients. In their study, QTc prolongation occurred well before any other ECG changes (ie ST

Table 2. Comparison of QTc measurements in patients with ischemic heart disease

Year	Reference	IHD	N	QTc interval (average)		P
				Ischemic group	Non-ischemic group	
1950	Krasnoff	STEMI	117	0.448 s	0.397 s	ND
1990	Shawl et al.	UA	76	0.490 s	0.416 s	ND
2002	Rukshin et al.	NSTE-ACS	52	0.475 s	0.439 s	<0.0001
2003	Gadaleta et al.	UA	102	0.460 s	0.440 s	0.015
2007	Jiménez-Candil J et al.	NSTEACS	427	0.497 s	0.443 s	<0.001
2007	Kenigsberg et al.	CAD	74	0.455 s	0.423 s	<0.001
2008a	Gadaleta et al.	NSTEACS	55	0.487 s	0.440 s	<0.001
2008b	Gadaleta et al.	NSTEACS	211	0.466 s	0.406 s	<0.0001

CAD, coronary artery disease; IHD, ischemic heart disease; ND, not done; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; STEMI, ST elevation myocardial infarction; UA, unstable angina.

segment depression or elevation) were detected. This finding is in agreement with observations reported three decades earlier by Taylor et al. (1981). The molecular basis for these findings is likely to lie in changes affecting the late sodium ion current, which occur early during myocardial ischemia and are responsible for the prolongation of the action potential. For example, ranolazine inhibits the late sodium current and thus has an anti-ischemic effect that should, in turn, shorten the QT interval (Belardinelli et al. 2004).

QTc Prolongation and the Risk of ACS

Whereas prolongation of the QTc in STEMI has been investigated, little is known about its behavior in the setting of NSTE-ACS. Shawl et al. reported in 1990 that in patients with unstable angina (UA) and left anterior descending coronary artery stenoses, successful PCI resulted in the normalization of repolarization changes and the duration of the QTc (0.490 s before PCI vs 0.416 s post PCI). Later, Rukshin et al. (2002) observed that patients with elevated biomarkers of necrosis showed a prolongation of the QTc compared to those with normal troponin values (QTc 0.450 vs 0.417 s). They compared findings in 52 patients with NSTE-ACS vs 52 patients with UA and observed a greater QTc prolongation in NSTE-ACS cases ($P <$ .0001) (Table 2). These authors also found that the maximum prolongation of the QTc occurred within 36 h of the onset of the acute symptoms and normalized within 96 h.

Studies from our group and others have shown the presence of QTc prolongation in patients with symptoms suggestive of ACS and those with recurrent angina, with or without typical diagnostic ECG changes (Gadaleta et al. 2003, Schamroth 1984). In 2003, we reported for the first time that QTc prolongation represented an independent prognostic variable in 102 patients with ACS (Gadaleta et al. 2003). In the subset of patients with QTc ≥0.460 s during the first hours after admission, we observed that the risk of a MACE increased threefold, for up to 30 days after discharge, compared with patients without QTc changes (Table 3). In a study published in 2007, patients with a QTc ≥0.450 s at admission had MACE such as death, recurrent ischemia, or need for urgent revascularization at 17 months of follow-up (Jiménez-Candil et al. 2007). In a subsequent study, the same group of investigators showed that a QTc ≥ 0.450 s measured at admission had independent prognostic value in addition to abnormalities of ST segment and troponin I values (Jiménez-Candil et al. 2008).

Regarding the possible mechanisms responsible for the prolongation of the QTc in ACS patients, the presence of micronecrosis, a common finding in NSTE-ACS as suggested by increased troponin concentrations, features prominently (Kaul et al. 2003). This pathogenic association is of clinical interest. Recently, a study of 106 patients with NSTE-ACS showed a positive correlation between the prolongation of the QTc and the evidence of micronecrosis, as assessed by the increase in troponin T (Llois et al. 2008). Similarly, Rushkin et al. (2002) observed that a QTc ≥ 0.460 s was associated with the presence of myocardial necrosis. Moreover, in a series of 55 patients, a QTc ≥ 0.458 s was an independent risk predictor of the combined end point of death, nonfatal myocardial infarction, or need for revascularization ($P <$ .001) (Gadaleta et al. 2008a). Again, this study showed a positive correlation between a prolonged QTc and troponin T concentrations ($P <$ .001).

Gadaleta et al. (2008b) prospectively studied 211 coronary artery disease patients to assess the potential added value of measuring the QTc in patients with T wave abnormalities—that is, negative diagnostic T wave (≥2 mm) and negative nondiagnostic T wave (<2 mm, flat or normal). The results indicate that the QTc adds prognostic value to T wave abnormalities present on the admission ECG ($P \leq$ .0001). In the study, it was found that the QTc was significantly

Table 3. Clinical events distribution and its correlation with QTc prolongation

Events	Patients, n (%)	QTc (s), average ± SD
Revascularization	17 (30.9)	0.473 ± 0.043
AMI	2 (3.6)	0.570 ± 0.089
Death	2 (3.6)	0.529 ± 0.034

From Gadaleta et al (2008a).

prolonged in patients with clinical evidence of acute myocardial ischemia. This was confirmed by comparing the 211 patients admitted for NSTE-ACS against 152 normal controls, with QTc values of 0.466 and 0.406 s, respectively ($P \leq .0001$) (Table 2). Patients in this series who continued to experience recurrent angina underwent coronary artery bypass grafting or PCI. In this group of patients, we observed that the sustained prolongation of the QTc was a predictor of recurrent angina, whereas the normalization of the QTc following the administration of anti-ischemic medication was a predictor of good clinical outcome and the absence of recurrent angina.

• Conclusion

Accumulating evidence during the past few decades strongly suggests that the assessment of the QTc at hospital admission and within 24 h of admission has a predictive role in patients with ACS. Studies are now required to establish whether these measurements improve risk stratification in comparison with more established markers of risk and help in the reclassification of patients presenting with ACS.

References

Agewall S, Giannitsis E, Jernberg T, & Katus H: 2011. Troponin elevation in coronary vs. non-coronary disease. Eur Heart J 32:404–411.

Antman EM, Cohen M, Bernink PJLM, et al: 2000. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 284:835–842.

Belardinelli L, Antzelevitch C, & Fraser H: 2004. Inhibition of late (sustained/persistent) sodium current: A potential drug target to reduce intracellular sodium-dependent calcium overload and its detrimental effects on cardiomyocyte function. Eur Heart J 6:13–17.

Birnbaum Y & Atar S: 2006. Electrocardiogram risk stratification of non–ST-elevation acute coronary syndromes. J Electrocardiol 39:S57–S61.

Bonaca M, Scirica B, Sabatine M, et al: 2010. Prospective evaluation of the prognostic implications of improved assay performance with a sensitive assay for cardiac troponin I. J Am Coll Cardiol 55:2118–2124.

Cannon CP, McCabe CH, Stone PH, et al: 1997. The electrocardiogram predicts one-year outcome of patients with unstable angina and non–Q wave myocardial infarction: Results of the TIMI III Registry ECG Ancillary Study. J Am Coll Cardiol 30:133–140.

Clayton TC, Lubsen J, Pocock SJ, et al: 2005. Risk score for predicting death, myocardial infarction, and stroke in patients with stable angina, based on a large randomized trial cohort of patients. BMJ 331:869–872.

Day CP, McComb JM, & Campbell RW: 1990. QT dispersion: An indication of arrhythmia risk in patients with long QT intervals. Br Heart J 63:342–344.

Fenichel RR, Malik M, Antzelevitch C, et al: 2004. Drug-induced torsades de pointes and implications for drug development. J Cardiovasc Electrophysiol 15:475–495.

Gadaleta FL, Llois SC, Sinisi VA, et al: 2008a. Corrected QT interval prolongation: A new predictor of cardiovascular risk in patients with non–ST-elevation acute coronary syndrome. Rev Esp Cardiol 61:572–578.

Gadaleta FL, Llois SC, Avanzas P, et al: 2008b. Corrected QT interval measurement in patients with non–ST elevation acute coronary syndrome and T-wave abnormalities: Any additional clinical value? Circulation 118:e173.

Gadaleta FL, Llois SC, Lapuente AR, et al: 2003. Prognostic value of corrected QT-interval prolongation in patients with unstable angina pectoris. Am J Cardiol 92: 203–205.

Granger CB, Goldberg RJ, Dabbous O, et al: 2003. For the Global Registry of Acute Coronary Events Investigators: Predictors of hospital mortality in the Global Registry of Acute Coronary Events. Arch Intern Med 163:2345–2353.

Hnatkova K, Yi Gang, Batchvarov VN, & Malik M: 2006. Precision of QT interval measurement by advanced electrocardiographic equipment. Pacing Clin Electrophysiol 29:1277–1284.

Holmvang L, Clemmensen P, Lindahl B, et al: 2003. Quantitative analysis of the admission electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. J Am Coll Cardiol 41:905–915.

Jervell A & Lange-Nielsen FP: 1957. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J 54:59–68.

Jiménez-Candil J, Diego M, Cruz González IC, et al: 2008. Relationship between the QTc interval at hospital admission and the severity of the underlying ischaemia in low and intermediate risk people studied for acute chest pain. Int J Cardiol 126:84–91.

Jiménez-Candil J, González IC, González Matas JM, et al: 2007. Short- and long-term prognostic value of the corrected QT interval in the non–ST-elevation acute coronary syndrome. J Electrocardiol 40:180–187.

Katz LN: 1921. Factors modifying the duration of ventricular systole. J Lab Clin Med 6:291.

Kaul P, Newby LK, Fu Y, et al: 2003. Troponin T and quantitative ST-segment depression offer complementary prognostic information in the risk stratification of acute coronary syndrome patients. J Am Coll Cardiol 41:371–380.

Kautzner J & Malik M: 1997. QT interval dispersion and its clinical utility. Pacing Clin Electrophysiol 20:2625–2640.

Kenigsberg DN, Khanal S, Kowalski M, & Krishnan SC: 2007. Prolongation of the QTc interval is seen uniformly during early transmural ischemia. J Am Coll Cardiol 49:1299–1305.

Kléber AG, Janse MJ, van Capelle FJ, & Durrer D: 1978. 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 42:603–613.

Krasnoff SO: 1950. The duration of the Q-T interval in myocardial infarction. Am Heart J 39:523–531.

Lepeschkin E & Surawicz B: 1952. The measurement of the Q-T interval of the electrocardiogram. Circulation 6:378–388.

Llois SC, Gadaleta FL, Avanzas P, et al: 2008. Prognostic value of corrected QT interval and its correlation with cardiac troponin T in non–ST-elevation acute coronary syndrome. Circulation 118:e172.

Malik M: 2004. Errors and misconceptions in ECG measurement used for the detection of drug induced QT interval prolongation. J Electrocardiol 37:25–33.

Moss AJ & Schwartz PJ: 2005. 25th anniversary of the International Long-QT Syndrome Registry. Circulation 111:1199–1201.

National Institute for Health and Clinical Excellence: 2010. Unstable angina and NSTEMI: The early management of unstable angina and non–ST-segment-elevation myocardial infarction, Clinical Guideline 94. London: National Clinical Guidelines Centre at The Royal College of Physicians. Available at: http://guidance.nice.org.uk/CG94.

Okishige K, Yamashita K, Toshinaga H, et al: 1996. Electrophysiologic effects of ischemic preconditioning on QT dispersion during coronary angioplasty. J Am Coll Cardiol 28:70–73.

Pope JH, Aufderheide TP, Ruthazer R, et al: 2000. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 342:1163–1170.

Postema PG, De Jong JS, Van der Bilt IA, & Wilde AA: 2008. Accurate electrocardiographic assessment of the QT interval: Teach the tangent. Heart Rhythm 5:1015–1018.

Priori SG, Schwartz PJ, Napolitano C, et al: 2003. Risk stratification in the long-QT syndrome. N Engl J Med 348:1866–1874.

Rautaharju PM, Surawicz B, Gettes LS, et al: 2009. AHA/ACC/HRS recommendations for the standardization and interpretation of the electrocadiogram part IV: The ST segment, T and U waves, and the QT interval. A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 53:982–991.

Romano C, Gemme G, & Pongiglione R: 1963. Rare cardiac arrhythmias of the pediatric age: I. Repetitive paroxysmal tachycardia. Minerva Pediatr 15:1155–1164.

Rossenbacker T & Priori SG: 2007. Clinical diagnosis of long QT syndrome: Back to the caliper. Eur Heart J 28:527–528.

Rukshin V, Monakier D, Olshtain-Pops K, et al: 2002. QT interval in patients with unstable angina and non-Q wave myocardial infarction. Ann Noninvasive Electrocardiol 7:343–348.

Schamroth L: 1984. The electrocardiology of coronary disease. Oxford, Blackwell.

Shawl FA, Velasco CE, Goldbaum TS, & Forman MB: 1990. Effect of coronary angioplasty on electrocardiographic changes in patients with unstable angina secondary to left anterior descending coronary artery disease. J Am Coll Cardiol 16:325–331.

Sporton SC, Taggart P, Sutton PM, et al: 1997. Acute ischaemia: A dynamic influence on QT dispersion. Lancet 349:306–309.

Surawicz B & Knoebel SB: 1984. Long QT: Good, bad or indifferent? J Am Coll Cardiol 4:398–413.

Taylor GJ, Crampton RS, Gibson RS, et al: 1981. Prolonged QT interval at onset of acute myocardial infarction in predicting early phase ventricular tachycardia. Am Heart J 102:16–24.

Toivonen L: 2002. More light on QT interval measurement. Heart 87:193–194.

Viskin S: 2009. The QT interval: Too long, too short or just right. Heart Rhythm 6:711–715.

Viskin S, Rosovski U, Sands AJ, et al: 2005. Inaccurate electrocardiographic interpretation of long QT: The majority of physicians cannot recognize a long QT when they see one. Heart Rhythm 2:569–574.

Zareba W, Moss AJ, & Le Cessie S: 1994. Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease. Am J Cardiol 74:550–553.

Zimarino M, Corazzini A, Tatasciore A, et al: 2011. Defective recovery of QT dispersion predicts late cardiac mortality after percutaneous coronary intervention. Heart 97: 466–472.

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Role of Bone Marrow-Derived Lymphatic Endothelial Progenitor Cells for Lymphatic Neovascularization

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The lymphatic vasculature plays a pivotal role in maintaining tissue fluid homeostasis, immune surveillance, and lipid uptake in the gastrointestinal organs. Therefore, impaired function of the lymphatic vessels caused by genetic defects, infection, trauma, or surgery leads to the abnormal accrual of lymph fluid in the tissue and culminates in the swelling of affected tissues, known as lymphedema. Lymphedema causes impaired wound healing, compromised immune defense, and, in rare case, lymphangiosarcoma. Although millions of people suffer from lymphedema worldwide, no effective therapy is currently available. In addition, recent advances in cancer biology have disclosed an indispensable function of the lymphatic vessel in tumor growth and metastasis. Therefore, understanding the detailed mechanisms governing lymphatic vessel formation and function in pathophysiologic conditions is essential to prevent or treat these diseases. We review the developmental processes of the lymphatic vessels and postnatal lymphatic neovascularization, focusing on the role of recently identified bone marrow-derived podoplanin-expressing (podoplanin$^+$) cells as lymphatic endothelial progenitor cells. (Trends Cardiovasc Med 2011;21:135-140) © *2011 Elsevier Inc. All rights reserved.*

• Introduction

The vasculature, which includes the blood vessels and the lymphatic vessels, is indispensable for the development and the survival of mammals. Extensive efforts have been made to study the biology of blood vessels; however, recent investigations of the molecular mechanisms controlling the development of the lymphatic vessels during embryogenesis and the diseases related to lymphatic dysfunctions have gained much attention. In the adult, the lymphatic vasculature is composed of three distinct but interconnected parts: lymphatic capillaries, precollectors, and lymphatic collecting vessels. The lymphatic capillaries are single-layered vessels consisting of staggered lymphatic endothelial cells (LECs), which lack mural cells and are surrounded by few basement membranes. The LECs of the lymphatic capillaries are anchored to extracellular matrix by anchoring filaments. These features allow the lymphatic capillaries to have a high permeability to macromolecules as well as interstitial fluids. In contrast to the LECs in the capillaries,

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