Title
Prevalence and Prognostic Significance of Long QT Interval among Patients with Chest Pain: Selecting an Optimum QT Rate Correction Formula

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Prevalence and Prognostic Significance of Long QT Interval among Patients with Chest Pain: Selecting an Optimum QT Rate Correction Formula

by

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DISSERTATION

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Acknowledgement

In the name of God (Allah) the entirely merciful the especially merciful. Praise be to Allah, Lord of the worlds, and peace and blessings be upon his prophet and servant Muhammad, peace be upon him.

'Indeed, Allah orders justice and good conduct and giving [help] to relatives and forbids immorality and bad conduct and oppression. He admonishes you that perhaps you will be reminded.' (An-Annahl; 90). 'O you who have believed, bow and prostrate and worship your Lord and do good - that you may succeed' (Al-Hajj; 77). Toward achieving these goals, my Lord, I was doing this. Thank you for everything, I love you. All success is from Allah and all praise is due to him.

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Chapter 2, *Prevalence and Prognostic Significance of Long QT Interval in Patients with Acute Coronary Syndrome: Review of the Literature*, is a reprint of the material as it appears in the Journal of Cardiovascular Nursing. The coauthor listed in this publication directed and supervised the research that form the basis for the dissertation.

Chapter 3, *Prevalence and Prognostic Significance of Long QT Interval among Patients with Chest Pain: Selecting an Optimum QT Rate Correction Formula*, is a reprint of the material as it appears in the Journal of Electrocardiology. The coauthor listed in this publication directed and supervised the research that form the basis for the dissertation.

Prevalence and Prognostic Significance of Long QT Interval among Patients with Chest Pain: Selecting an Optimum QT Rate Correction Formula

By

Amer A. Hasanien

Abstract

Background. Little is known about the prevalence and prognostic significance of long QT interval (QTi) among patients with chest pain during the acute phase of suspected cardiovascular injury. Previous attempts to research similar questions resulted in conflicting conclusions. This is primarily because of the inappropriate expression of the QT/RR relation when calculating the QTi corrected for heart rate (HR).

Aims. The author aims to (1) determine the prevalence and time duration of long QTi , (2) investigate whether a long QTi is associated with mortality and other adverse cardiovascular events at 1 year follow-up, and (3) determine whether the QT/RR slope is different among different HR zones (bradycardia, normal, and tachycardia).

Methods. This is a secondary analysis of data obtained from the IMMEDIATE AIM trial. Data included 24-hour 12-lead Holter electrocardiographic recordings. The sample of the present analysis consisted of patients who presented to the emergency department with chest pain (N, 145). The QTi was measured automatically and rate corrected using seven QTc formulas including subject specific correction. The formula with the closer to zero absolute mean QTc/RR correlation was considered the most accurate. The QT/RR slope was compared among different HR zones applying steady (with minimal fluctuation) beat selection technique.

Results. Subject specific QT rate correction outperformed other QTc formulas and resulted in the closest to zero absolute mean QTc/RR correlation. Using linear subject specific correction, the prevalence of long QTc interval was 14.5%. The QTc interval did not predict mortality or hospital admission at short and long term follow-up. The QT/RR slope was significantly less

under the bradycardia zone (0.074 ± 0.07) compared to the normal (0.114 ± 0.1, $p < 0.01$) or the tachycardia zones (0.147 ± 0.1, $p < 0.001$). There was no difference between the normal and the tachycardia zone.

Conclusion. Adequate QT rate correction can only be performed using subject specific correction. Long QTi is not uncommon among patients presenting to the emergency department with chest pain. The QT/RR slope is different among different HR zones. These differences can be used in resetting the limits defining different HR zones boundaries.

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Chapter 1

Introduction

The QT interval is the measured distance in seconds (or milliseconds) from the beginning of the QRS complex to the end of the T wave on the body surface electrocardiogram (ECG). This time interval reflects the ventricular action potential (AP) duration and corresponds to the ventricular repolarization time (1). The ventricular AP duration and consequently the QT interval becomes long when positive ions are trapped inside the cell. This occurs either because of an increased activity of depolarizing ion channels that allow more positive ions to get inside the cell (Na^+, Ca^{+2}), or because of decreased activity of repolarizing ion channels that allow less positive ions to get outside the cell (K^+) (2). Ion channels are small pores in the cell membrane that regulate ion movement inside and outside the cell. Function of these ions and consequently the ventricular AP duration are regulated primarily by the sympathetic nervous system because of its greater role in regulating repolarizing ion channels compared to the parasympathetic nervous system (3, 4). Repolarizing ion channels control the largest portion of the ventricular AP duration, which consists mostly of repolarization duration, and consequently have the greatest role in determining its duration.

Abnormal ion channels regulation leading to long QT interval is either genetic or acquired. Acquired long QT interval is primarily the result of administering one or more of the drug compounds known to abnormally affect ion channels (http://www.azcert.org). Nevertheless, when long, the QT interval favors the development of early afterdepolarizations which are secondary depolarizations occurring after the initial depolarization, usually during phase 3(5). Early after depolarizations when sufficient conditions exist are capable of inducing (triggering) ventricular arrhythmias. These conditions are increased transmural dispersion of repolarization accompanied by premature ventricular contractions (6). *Transmural dispersion of repolarization* or the *inhomogenous repolarization of the ventricular muscle wall* is the difference in repolarization duration (AP duration) among different myocardial cell types (epicardial, endocardial, and M cells). Ventricular arrhythmia occurs when the repolarization duration of the M cells is preferentially longer than other myocardial cell types and thus increasing the

transmural dispersion of repolarization (7). Preferentially longer repolarization duration of the M cells compared to other myocardial cell types open a gate for a *reentry* current. Reentry is the arrhythmic mechanism responsible for sustaining ventricular arrhythmias associated with long QT interval (8).

Problem Statement

Acute coronary syndrome (ACS) is the most common cause of death among adults (9) and accounts for approximately one fifth of deaths among all age groups (10). It is estimated that three-quarters of sudden cardiac death events are attributed to ACS (11). In addition to mortality, patients with ACS are at increased risk of suffering other adverse cardiovascular events (ACEs) both at short and long term follow up. ACEs include ventricular arrhythmias (12), recurrent ischemic events (13), re-hospitalization (14), and heart failure (15). Being able to predict which patients with ACS are more likely to suffer an ACE is critically important. It allows these patients to receive early drug therapy and revascularization interventions which have proved to be successful. In addition, it allows health care providers to anticipate risk and choose among the more aggressive therapeutic approaches. The need to introduce new risk assessment tools to stratify patients with ACS according to the possibility of risk occurrence has never been greater.

Sympathetic hyperactivity early in the process of ischemia is believed to be responsible for the occurrence of several ACEs. Ischemia and sympathetic hyperactivity interact synergistically with each one potentiating the effect of the other (16). In the ischemic zone, increased sympathetic activity is manifested by β receptors up regulation and catecholamine overexposure (17) which both are thought to be responsible for the electromechanical instability and ventricular arrhythmias induced by ischemia (18). Sympathetic hyperactivity also produces hypokalemia which adds to the proarrhythmic potential of ischemia and sympathetic hyperactivity (16). The keen association between ischemia and sympathetic hyperactivity is best illustrated by the high success rate of reducing mortality and morbidity following the introduction

of β blocker therapy and several other sympathetic inhibition modalities in patients with ACS (19) (20) (21) (22) (23).

Finding an index that reflects sympathetic hyperactivity at the cellular level might constitute a useful tool or add to our existing risk stratification repertoire to improve prediction of ACEs at short and long term follow-up. The QT interval on the surface ECG is largely determined by the sympathetic division of the autonomic nervous system. Sympathetic hyperactivity associated with an underlying structural damage affecting repolarizing ion channels is likely to make the QT interval longer (24). Using the QT interval for risk prediction is attractive because of its ease of measurement, ease of interpretation, being non invasive, dynamic, and almost instantaneous requiring only a couple of minutes to reflect the adaptability to sympathetic activity.

Sympathetic hyperactivity with the resultant electrical instability triggered by ischemia is likely to be greater during the acute phase of ACS and early thereafter. During this time, the alterations in ventricular repolarization as measured by the QT interval are expected to be more pronounced and more compatible with the damage occurring in the ventricular myocardium. Little is known about the prevalence and duration of long QT interval in these patients during this critical time. Furthermore, it is intriguing to question whether a long QT interval measured during this time is associated with mortality and other ACEs. Previous attempts to research similar questions resulted in conflicting conclusions. This is primarily because of the inappropriate expression of the QT/RR relation when calculating the HR corrected QT interval. Revisiting the QT/RR relation as the HR shifts from one zone to another (bradycardia, normal, and tachycardia) and introducing a novel method to express this relation will be highly required. This will help bring a more accurate HR corrected QT interval for risk prediction.

Research Questions

In a sample of patients who presented to the emergency department with chest pain and who underwent continuous 12-lead electrocardiographic monitoring over 24 hours, the author want to answer the following questions:

1. What is the prevalence and time duration of long QT interval?
2. Is long QT interval associated with mortality and other adverse cardiovascular events at 1 year follow-up?
3. Does the QT/RR slope depend upon HR zone (bradycardia, normal, tachycardia)?

The hypotheses for the second and third questions are,

$H_0$2: there is no association between long QT interval and mortality as well as other adverse cardiovascular events at 1 year follow-up.

$H_0$3, the QT/RR slope does not differ by HR zone (bradycardia, normal, tachycardia).

Conceptual Model

The conceptual model is based on the molecular and cellular influences of the sympathetic nervous system on ventricular repolarization duration, reflected as the QT interval on the body surface ECG, during ischemia. At the molecular level, sympathetic imbalance is thought to affect ion channels in a way that increases potassium ion retention and thus prolonging the QT interval. At the cellular level, long QT interval is likely to result in increased heterogeneity of ventricular repolarization among different myocardial cells (subepicardial, subendocardial, and M cells) by preferentially prolonging the AP of the M cells and thus inducing ventricular arrhythmias with other ACEs.

Background

Several investigators have reported a prolongation in the QT interval after an ACS event (25) (26) (27) (28). In one study (29), prolongation of the QT interval after elective balloon angioplasty was found to be the earliest abnormality to show up on surface ECG, earlier than the T wave and the ST segment abnormalities. Evidence suggests that the maximum peak in the QT

interval occurs between day 2 and day 11 after an ACS event which might explain the exact occurrence of torsade de pointes during this time (25) (26). After several days, the QT interval starts to decrease (30) but never to the pre-ischemic values.

The prevalence of long QT interval during the acute phase of ACS in the emergency department where repolarization abnormalities are expected to be greater and more pronounced has never been investigated. However, few studies have investigated the prevalence of long QT interval later during hospital stay and provided varying estimations ranging between 19 and 60% (26) (28) (31) (32) (33). Differences are primarily because of different ACS patients' types, different measurement points, and no agreed upon cut points to define the limits of what constitutes a normal QT interval.

Nevertheless, when long, the QT interval predicts several ACEs among patients with ACS. According to several studies, long QT interval predicts ventricular arrhythmias (34) (35) (study 1) including torsade de pointes (30), extent of myocardial damage (31), recurrent ischemia (36) (37) (38), sudden cardiac death at long term follow-up (39), and mortality at short (37) and long term follow-up (35) (study 2). Long QT interval predictive and prognostic effect possibly manifests through three primary pathways. First, long QT interval reflects sympathetic imbalance which is known to be linked with several ACEs (16) (40). Second, there is an intimate relation between long QT interval and ejection fraction (27) (28) (31) (41), left ventricular dysfunction (42), and extent of coronary artery disease (43) which all are well known prognostic predictors (44). Third, long QT interval is itself arrhythmogenic (45).

In contrast, several researchers have reported a negative association between long QT interval and ACEs in patients with ACS (26) (35) (41) (46) (47) (48) (49). These researchers maintain that the predictive power of long QT interval was only possible before the thrombolytic era but after the advent of thrombolytics, ST segment depression in the lateral leads and atrial abnormalities became the factors that predict ACEs. Furthermore, some of these researchers are more convinced that, at the cellular level, failing to decrease AP upstroke following ischemia is

the most critical factor in determining the occurrence of ACEs rather than the prolongation of the AP duration (49). Long AP duration is reflected on the body surface ECG as a long QT interval which represents delayed ventricular repolarization time. According to this perspective, excluding reperfusion arrhythmias, there is no evidence that early after depolarizations and delayed after depolarizations resulting from delayed repolarization have a role in acute ischemia. Early and delayed after depolarizations are the cellular mechanisms thought to induce ventricular arrhythmias when the repolarization duration is long.

However, with the current available evidence, it is difficult to reach a conclusion about the association between long QT interval and ACEs in patients with ACS. Despite the serious possible negative consequences of long QT interval in patients with ACS on mortality and morbidity, it has not been properly investigated. The majority of the information available comes from observational studies that carried out univariate analysis with a small sample size (25) (26) (27) (38). Most of these studies measured the QT interval manually from a single lead with a 10 second 12-lead ECG during rest (26) (43) (46) (47). Recent QT interval measurement techniques are automatic and capable of measuring the QT interval continuously during real time using a root mean square signal that gathers ECG information from the 12 ECG leads simultaneously (50) (51).

In addition, one of the most challenging issues with the currently available evidence, and probably in the whole science of electrocardiology, is QT rate correction. Inaccurate correction of the QT interval for HR is most likely the result of an inappropriate evaluation of the QT/RR relation in different HR zones. The QT/RR interaction is primarily manipulated by the autonomic nervous system which is different at different HR zones. Unfortunately, the differences in the QT/RR relation as the HR shifts from one zone to another have never been investigated. Accordingly, currently available QT rate correction formulas do not take this into account but rather assumes a fixed QT/RR association, thus ignoring much of the available autonomic nervous system signal.

Until reliable and accurate data about the relation between long QT interval and ACEs following ischemic changes is available, it is difficult to know how much attention needs to be given to the QT interval during the acute phase as well as on ongoing follow-up.

Dissertation Organizing Sections

The aim of the following dissertation chapters is to answer the dissertation research questions within a theoretical framework derived from the literature. In chapter 2 of this dissertation, *Prevalence and Prognostic Significance of Long QT Interval in Patients with Acute Coronary Syndrome: Review of the Literature*, the author reviews the clinical and physiological underpinnings for using the QT interval to predict risk in patients with ACS. Furthermore, the author critically reviews and critiques the existing literature pertinent to this matter. Chapter 3, *Prevalence and Prognostic Significance of Long QT Interval among Patients with Chest Pain: Selecting an Optimum QT Rate Correction Formula*, is a research study that addresses the first two dissertation questions. The third dissertation question is answered in chapter 4, *QT/RR Dynamicity among Different Heart Rate Zones: Introducing a Physiological Evidence for Setting the Limits Defining Heart Rate Zones Boundaries*.

Undoubtedly, the reader will enjoy moving from one chapter to another in this dissertation while exploring the amazing science of ventricular repolarization as manifested by the QT interval on the body surface ECG and its potential power as a risk prediction tool.

References

1. Franz MR, Bargheer K, Rafflenbeul W, Haverich A, Lichtlen PR. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. Circulation. 1987 Feb;75(2):379-86.

2. Hedley PL, Jorgensen P, Schlamowitz S, et al. The genetic basis of long QT and short QT syndromes: a mutation update. Hum Mutat. 2009 Nov;30(11):1486-511.

3. Marx SO, Kurokawa J, Reiken S, et al. Requirement of a macromolecular signaling complex for beta adrenergic receptor modulation of the KCNQ1-KCNE1 potassium channel. Science. 2002 Jan 18;295(5554):496-9.

4. Terrenoire C, Clancy CE, Cormier JW, Sampson KJ, Kass RS. Autonomic control of cardiac action potentials: role of potassium channel kinetics in response to sympathetic stimulation. Circ Res. 2005 Mar 18;96(5):e25-34.

5. Antzelevitch C. Role of transmural dispersion of repolarization in the genesis of drug-induced torsades de pointes. Heart Rhythm. 2005 Nov;2(2 Suppl):S9-15.

6. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings. Circulation. 2010;121(8):1047-60.

7. Antzelevitch C. M cells in the human heart. Circ Res. 2010 Mar 19;106(5):815-7.

8. Akar FG, Yan GX, Antzelevitch C, Rosenbaum DS. Unique topographical distribution of M cells underlies reentrant mechanism of torsade de pointes in the long-QT syndrome. Circulation. 2002 Mar 12;105(10):1247-53.

9. Ruff CT, Braunwald E. The evolving epidemiology of acute coronary syndromes. Nat Rev Cardiol. 2011 Mar;8(3):140-7.

10. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013 Jan 1;127(1):143-52.

11. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death). J Am Coll Cardiol. 2006;48(5):e247.

12. de Luna AB, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J. 1989;117(1):151-9.

13. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2012 Aug 14;126(7):875-910.

14. Mandelzweig L, Battler A, Boyko V, et al. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. Eur Heart J. 2006;27(19):2285.

15. Weir RP, McMurray JV, Velazquez EJ. Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical characteristics, and prognostic importance. Am J Cardiol. 2006;97(10):13-25.

16. Podrid P, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. Circulation. 1990;82(2 Suppl):I103-13.

17. Schwaiger M, Guibourg H, Rosenspire K, et al. Effect of regional myocardial ischemia on sympathetic nervous system as assessed by fluorine-18-metaraminol. J Nucl Med. 1990 August 1, 1990;31(8):1352-7.

18. Sasano T, Abraham MR, Chang KC, et al. Abnormal sympathetic innervation of viable myocardium and the substrate of ventricular tachycardia after myocardial infarction. J Am Coll Cardiol. 2008;51(23):2266-75.

19. Schömig A, Haass M, Richardt G. Catecholamine release and arrhythmias in acute myocardial ischaemia. Eur Heart J. 1991;12(suppl F):38.

20. O'Connor RE, Brady W, Brooks SC, et al. Part 10: acute coronary syndromes: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122(18_suppl_3):S787.

21. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis. 1985;27(5):335.

22. Hjalmarson Å, Herlitz J, Malek I, et al. Effect on mortality of metoprolol in acute myocardial infarction: a double-blind randomised trial. Lancet. 1981;318(8251):823-7.

23. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. Lancet. 1986 Jul 12;2(8498):57-66.

24. Zipes DP, Rubart M. Neural modulation of cardiac arrhythmias and sudden cardiac death. Heart Rhythm. 2006 Jan;3(1):108-13.

25. Obayashi T, Tokunaga T, Liizumi T, Shiigai T, Hiroe M, Marumo F. Transient QT interval prolongation with inverted T waves indicates myocardial salvage on dual radionuclide single-photon emission computed tomography in acute anterior myocardial infarction. Jpn Circ J. 2001;65(1):7.

26. Rukshin V, Monakier D, Olshtain Pops K, Balkin J, Tzivoni D. QT interval in patients with unstable angina and non Q wave myocardial infarction. Ann Noninvasive Electrocardiol. 2002;7(4):343-8.

27. Bonnemeier H, Hartmann F, Wiegand UKH, Bode F, Katus HA, Richardt G. Course and prognostic implications of QT interval and QT interval variability after primary coronary angioplasty in acute myocardial infarction. J Am Coll Cardiol. 2001;37(1):44.

28. Shawl FA, Velasco CE, Goldbaum TS, Forman MB. Effect of coronary angioplasty on electrocardiographic changes in patients with unstable angina secondary to left anterior descending coronary artery disease. J Am Coll Cardiol. 1990;16(2):325-31.

29. Kenigsberg DN, Khanal S, Kowalski M, Krishnan SC. Prolongation of the QTc interval is seen uniformly during early transmural ischemia. J Am Coll Cardiol. 2007;49(12):1299-305.

30. 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(4):1168-74.

31. Raev D. Relationship between rate-corrected QT interval and wall motion abnormalities in the setting of acute myocardial infarction. Int J Cardiol. 1997;61(1):15-20.

32. Pohjola-Sintonen S, Siltanen P, Haapakoski J. Usefulness of QTc interval on the discharge electrocardiogram for predicting survival after acute myocardial infarction. Am J Cardiol. 1986;57(13):1066-8.

33. Doroghazi RM, Childers R. Time-related changes in the QT interval in acute myocardial infarction: possible relation to local hypocalcemia. Am J Cardiol. 1978;41(4):684-8.

34. Taylor GJ, Crampton RS, Gibson RS, Stebbins PT, Waldman MTG, Beller GA. Prolonged QT interval at onset of acute myocardial infarction in predicting early phase ventricular tachycardia. Am Heart J. 1981;102(1):16-24.

35. Ahnve S. QT interval prolongation in acute myocardial infarction. Eur Heart J. 1985;6(suppl D):85.

36. Jiménez-Candil J, González IC, González Matas JM, et al. Short-and long-term prognostic value of the corrected QT interval in the non-ST-elevation acute coronary syndrome. J Electrocardiol. 2007;40(2):180-7.

37. Jiménez-Candil J, González Matas JM, González IC, et al. In-hospital prognosis in non-ST-segment elevation acute coronary syndrome derived using a new risk score based on electrocardiographic parameters obtained at admission. Rev Esp Cardiol. 2010;63(7):851-5.

38. Gadaleta FL, Llois SC, Lapuente AR, Batchvarov VN, Kaski JC. Prognostic value of corrected QT-interval prolongation in patients with unstable angina pectoris. Am J Cardiol. 2003;92(2):203-5.

39. Yi G, Guo X-H, Reardon M, et al. Circadian variation of the QT interval in patients with sudden cardiac death after myocardial infarction. Am J Cardiol. 1998;81(8):950-6.

40. Kapa S, Venkatachalam K, Asirvatham SJ. The autonomic nervous system in cardiac electrophysiology: an elegant interaction and emerging concepts. Cardiol Rev. 2010;18(6):275.

41. Juul-Möller S. Corrected QT-interval during one year follow-up after an acute myocardial infarction. Eur Heart J. 1986;7(4):299.

42. Davey P. QT interval and mortality from coronary artery disease. Prog Cardiovasc Dis. 2000;42(5):359-84.

43. Locati E, Schwartz P. Prognostic value of QT interval prolongation in post myocardial infarction patients. Eur Heart J. 1987;8(suppl A):121.

44. Krämer B, Brill M, Brühn A, Kübler W. Relationship between the degree of coronary artery disease and of left ventricular function and the duration of the QT-interval in ECG. Eur Heart J. 1986;7(1):14.

45. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation endorsed by the American Association of Critical-Care Nurses and the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2010;55(9):934.

46. Wolfe CL, Nibley C, Bhandari A, Chatterjee K, Scheinman M. Polymorphous ventricular tachycardia associated with acute myocardial infarction. Circulation. 1991;84(4):1543.

47. Choi WS, Lee JH, Park SH, et al. Prognostic value of standard electrocardiographic parameters for predicting major adverse cardiac events after acute myocardial infarction. Ann Noninvasive Electrocardiol. 2011;16(1):56-63.

48. Wheelan K, Mukharji J, Rude RE, et al. Sudden death and its relation to QT-interval prolongation after acute myocardial infarction: two-year follow-up. Am J Cardiol. 1986;57(10):745-50.

49. Kleber AG, Janse M. Ischemia-related changes in repolarization. Cardiac repolarization: bridging basic and clinical science. 2003:153.

50. Zhou SH, Helfenbein ED, Lindauer JM, Gregg RE, Feild DQ. Philips QT interval measurement algorithms for diagnostic, ambulatory, and patient monitoring ECG applications. Ann Noninvasive Electrocardiol. 2009;14:S3-S8.

51. Mortara DW. Automated QT measurement and application to detection of moxifloxacin-induced changes. Ann Noninvasive Electrocardiol. 2009 Jan;14 Suppl 1:S30-4.

Chapter 2

Prevalence and Prognostic Significance of Long QT Interval in Patients with Acute Coronary Syndrome: Review of the Literature

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Abstract

Background: Sympathetic hyperactivity is linked with several adverse cardiovascular events in patients with acute coronary syndrome (ACS). Sympathetic activity increases early in the process of ischemia through two mechanisms. One originates from the central nervous system and leads to enhanced sympathetic activity. The other mechanism originates at the infarct zone and leads to B receptors up-regulation and catecholamine overexposure. Nevertheless, sympathetic hyperactivity accompanied by an underlying myocardial structural damage is likely to increase the ventricular repolarization duration measured as QT interval on the body surface electrocardiogram.

Purpose: The aims of the current review of the literature are to examine the physiological processes underlying the use of long QT interval as a risk prediction tool in patients with ACS and to critically review and critique the existing evidence related to this matter.

Conclusion: The available evidence is contradictory and includes serious limitations in design and QT measurement and correction. Until accurate and reliable data are available, it is difficult to determine the additional clinical value and prognostic significance of long QT interval in patients with ACS beyond that in other patients.

Clinical implications: Long QT interval is not uncommon among patients with ACS. Automated continuous QT interval monitoring is superior to manual QT interval measurement with the standard 10-second ECG. Optimum care for patients with ACS requires nurses to keep monitoring the QT interval several days after the initial event.

Introduction

Acute coronary syndrome (ACS) includes the diagnoses of ST elevation myocardial infarction (STEMI), non ST elevation myocardial infarction (NSTEMI), and unstable angina (UA). ACS is the most common cause of death among adults (1) and accounts for 16.7% of deaths among all age groups (2). Approximately three quarters of sudden cardiac death (SCD) events are attributed to ACS (3). In addition to mortality, patients with ACS are at increased risk for suffering other adverse cardiovascular events (ACEs) during hospitalization and consequent follow up. These events include re-hospitalization (4), recurrent ACS events (ischemia or infarction) (5), heart failure (6), and arrhythmias (7).

Increased sympathetic activity is thought to be responsible for and associated with several ACEs following ACS especially ventricular arrhythmias and SCD (8). Increased sympathetic activity accompanied by ischemic myocardial structural damage affecting ion channels is likely to result in long QT interval (QTi) (9). Accordingly, the QTi on the surface electrocardiogram (ECG) might constitute a useful tool or add to our existing risk stratification repertoire to improve prediction of short and long term ACEs. Other features that make the QTi an attractive tool are its ease of measurement, ease of interpretation, being non invasive, dynamic, and almost instantaneous requiring only a couple of minutes to reflect adaptability to sympathetic activity.

Sympathetic nervous system imbalance and associated electrical instability induced by ischemia are likely to be greater during the acute phase of ACS and early thereafter (10). Moreover, during this time the changes in ventricular repolarization as measured by the QTi are likely to be more pronounced and more compatible with the damage occurring in the ventricular myocardium. The purpose of this paper is twofold: (1) to review the clinical and physiological underpinnings for using the QTi to predict risk in patients with ACS, and (2) to critically review and critique the existing literature pertinent to this matter.

Why the QT Interval?

Sympathetic hyperactivity predisposes patients to life threatening arrhythmias and SCD. The risk is greater during myocardial ischemia. Ischemia and sympathetic activity interacts in such a way that each one potentiates the effect of the other (8). Sympathetic hyperactivity also produces hypokalemia which adds to the proarrhythmic potential of sympathetic hyperactivity and ischemia (11) (12).

During ischemia there are two mechanisms primarily responsible for increasing sympathetic activity. The first one is enhanced sympathetic stimulation originating from the central nervous system (8). This occurs for several reasons including systemic cardiovascular reflexes reacting to depressed myocardial oxygen supply, activation of the afferent nerve fibers at the ischemic zone by damaged myocardium, pain, and anxiety (13). The second mechanism is the non-uniform denervation at the infarct zone (8). Sympathetic nerve terminals in the myocardium are more prone to damage from ischemia than regular myocytes. At the infarct zone minutes after ischemia (30 minutes) it is possible to find damaged sympathetic nerve terminals side by side with viable myocytes (14). This non uniform denervation results in two important events that are directly linked to increased sympathetic activity proarrhythmic potential, β receptors up regulation (15, 16) and catecholamine super-sensitivity (17, 18).

Evidence suggests that 15 minutes following ischemia there is a 100 fold increase in extracellular catecholamines within the ischemic zone (19). This increase accompanied by impaired catecholamine reuptake because of sympathetic denervation results in catecholamine accumulation in the synaptic cleft, a phenomenon called catecholamine super-sensitivity or catecholamine overexposure. Catecholamine super-sensitivity is responsible for electromechanical instability and ventricular arrhythmia (10). Also contributing to this phenomenon is the concurrent increase in adrenoreceptors. During ischemia there is a two fold increase in α receptors and a 30% increase in β receptors (19).

Within the first 10 minutes following ischemia, extracellular potassium accumulation, acidosis, and adenosine protect the myocardium from catecholamine overexposure. Several minutes later, catecholamine activity becomes unopposed and the arrhythmic risk increases substantially (19).

Further evidence on the association between sympathetic activity upsurge and ventricular arrhythmia has been established from high success rates in eliminating this risk and consequent SCD in patients who have undergone sympathetic denervation (19). Additionally, the use of β blocker therapy in patients with ACS has greatly decreased morbidity and mortality (20-23).

Ventricular repolarization duration measured by the QTi on the surface ECG is largely determined by the sympathetic division of the autonomic nervous system (24). Most likely this is because of the preferential distribution of the sympathetic nerve fibers in the ventricles (25, 26). Investigators examining the association between long QTi and ACEs in patients with ACS implicitly assume that the QTi is sensitive enough to capture the imbalance in the sympathetic nervous system discharge during ischemia. From an autonomic and molecular perspective, prolongation of the QTi is rarely normal (27, 28).

Methods

A search of the literature was conducted for studies that examined the association between long QTi measured during the acute phase or early thereafter and ACEs (short and long term) in patients with ACS. The acute phase and early thereafter was defined as within 60 days following an ACS event onset. This definition was used because beyond 60 days, the difference between the pre and post ACS event QTi is expected to be small and unlikely to reflect the magnitude of the structural and electrophysiological alterations encountered. The following search terms were used in searching the literature; QT interval, long QT, ACS, coronary syndrome, MI, STEMI, NSTEMI, and UA. After reviewing the abstracts, we excluded case reports and studies that primarily included patients with the congenital form of long QTi. This search resulted in 30 articles. After careful examination of each article, we excluded another

seven articles. Four studies were excluded because the QTi was measured more than 60 days following the ACS event. Two studies were excluded because their samples consisted primarily of patients with chronic coronary artery disease. The seventh study was excluded because it did not specifically assess the association between the QTi and ACEs. As a result, the final review consisted of 23 articles including 26 studies published between 1981 and 2011 (Table 1). One of these articles included the results from 5 studies (29). Four of them are relevant and consequently were individually included. These four studies are referred to as Ahnve 1985, Study 1, Study 2, Study 3, and Study 5.

The published studies report on two QT measurements: the *QTi* and the *QTc interval*. There is an inverse relation between the QTi and heart rate (HR). Therefore, a value that is less dependent on HR is usually calculated using different mathematical equations (formulas). This value is called the HR corrected QTi, or shortly the QTc interval (30).

Long QT Interval in Patients with Acute Coronary Syndrome

Several investigators have reported an increase in the QTi following an ACS event (31, 32). Investigators in one study reported a statistically significant increase in the QTc interval from baseline after transmural ischemia associated with ST elevation in 100% of patients undergoing elective balloon angioplasty (from 423 ± 25 to 455 ± 34 ms, $p < 0.001$) (33). In this investigation, a long QTc interval was the earliest ECG abnormality to change (within 2 minutes of coronary artery balloon occlusion) compared to T wave (24 s after QTc), ST elevation (29 s after QTc), and ST depression (35 s after QTc).

Evidence suggests that the maximal increase in the QTi is reached between day 2 and day 11 of an ACS event which might explain the exact occurrence of torsade de pointes (TdP) during this time (31, 32, 34). In one study (34), TdP occurred between days 3 and 11 following acute MI. In this study, the QTc interval started to prolong by day 2 in patients who did and did not develop TdP, but the prolongation was statistically greater in patients who developed TdP (from 470 ± 46

to 492 ± 57 ms [p <0.05] vs. from 445 ± 58 to 558 ± 84 ms, respectively [p < 0.01]). The incidence of TdP in acute MI patients was 1.8% (95% CI, 0.8% to 3.6%).

After reaching maximum values within a few days of an ACS event, the QTi begins to decrease. Usually, it takes another several days for the QTi to return to the initial values recorded upon admission (31, 32, 34, 35) but they never return to the pre-infarction value. There is not yet sufficient evidence to suggest exactly when the reduction in the QTi stops which probably signals the end of electrophysiological adaptation to an ACS event. In one report (36), the QTc interval measured at 6 months following acute MI (436 ± 3 ms) was still statistically different from the initial QTc interval measured within 1 month of acute MI (450 ± 3 ms, p < 0.001).

Prevalence of Long QT Interval in Patients with Acute Coronary Syndrome

The prevalence of long QTi depends largely on the cut point used to define the upper limit of normal with higher cut points associated with lower prevalence. Prevalence also depends on the time interval between QTi measurement and onset of an ACS event with longer time intervals associated with lower prevalence. Unfortunately, neither of these two factors was the same in the reviewed studies which confounds finding an exact number to define prevalence. However, Table 1 presents the studies and the values they reported for the prevalence of long QTi among patients with ACS. In summary, the prevalence was between 19 and 60%.

Does Long QT Interval Predict Adverse Cardiovascular Events in Patients with Acute Coronary Syndrome

Seventeen studies out of 26 reported a positive association between long QTi and one or more ACEs. In contrast, nine studies reported a negative association (Table 1).

Long QT in Patients with Q Wave Myocardial Infarction

We found no studies that included only patients with STEMI and examined the association between long QTi and the occurrence of one or more ACEs. However, there is a single prospective study that examined this risk in patients with QWMI (37). In this study, there was a statistically significant association between left ventricular dysfunction as determined by

wall motion index (the higher the value the worse the function) and the QTc interval ($r = 0.83$, $n = 108$, $p < 0.001$), both measured on the fourth day following infarction. The correlation was higher in patients with anterior and anterio-inferior MI ($r = 0.91$, $n = 67$, $p < 0.001$) compared to patients with inferior MI ($r = 0.68$, $n = 41$, $p < 0.001$). According to the authors, the QTi might be used to predict the extent of myocardial damage in this group of patients with more accurate prediction in patients with anterior and anterio-inferior MI.

Long QT Interval in Patients with Non ST Elevation Myocardial Infarction

There was only one study that involved patients with NSTEMI (38). In this prospective study that included only patients with sinus rhythm ($n = 427$), three ECG criteria predicted death or recurrent ischemia: (1) a QTc $\geq$ 450 ms (odds ratio (OR) 4.2, $p < 0.001$), (2) ST segment depression < 0.5 mm (OR 2.7, $p < 0.001$), and (3) left atrial enlargement (OR 1.8, $p < 0.005$). According to this study, 49% of patients with a QTc $\geq$ 450 ms suffered an adverse event, death or recurrent ischemia.

Long QT Interval in Patients with Acute Myocardial Infarction Including Both ST Elevation and Non ST Elevation

For a long time researchers hypothesized an association between long QTi, autonomic dysfunction, and the risk for ventricular tachyarrhythmias during the early phase of acute MI and attempted to establish this link with clinical evidence. An early investigation (35) that examined patients with acute MI ($n = 32$) within hours of infarction onset (2 ± 1.8 hours) found a statistically longer QTi in patients who developed ventricular tachycardia within the first 48 hours ($n = 14$, QTc = 520 ± 70 ms) compared to patients with frequent ventricular premature beats ($n = 8$, QTc = 470 ± 30 ms) and patients without ventricular premature beats ($n = 10$, QTc = 460 ± 30), $p < 0.001$. By the fifth day, the QTc interval became statistically shorter compared to initial values only in patients who developed ventricular tachycardia (470 ± 60 ms, $p < 0.05$). This finding is in agreement with our previous discussion that the QTc interval is longer in high risk patients for a few days post MI before resolving to near-baseline levels (but never reaching the

pre-infarction baseline level). In addition, these investigators found a 69% incidence of early ventricular tachycardia in patients with a long QTc interval (≥ 480 ms) compared to an only 19% incidence in patients with a normal QTc interval (< 480 ms), $p < 0.01$.

A long QTi also predicts ACEs far beyond the acute phase of MI. In a retrospective analysis of patients with acute MI undergoing 24 hour Holter monitoring before hospital discharge, the QTc interval was longer among SCD victims compared to acute MI survivors at 1 year follow up (424 ± 25 vs. 404 ± 32 ms, $p < 0.05$) (39). The significant difference between the two groups was only possible when considering the mean QTc value of the total 24 hour recording. The authors concluded that more than 10 seconds of ECG recording may be needed to achieve statistically significant results.

In contrast, there were several studies that reported a negative association between a long QTi and an ACE. Eight of the nine negative studies in this review are of patients with acute MI. According to one investigation (40), regardless of the class Ia antiarrhythmic drug used to treat polymorphic VT, there was no difference in QT and QTc length between patients who responded to drug therapy (n=1, QT = 380, QTc = 400) and patients who did not respond to drug therapy (n=5, QT = 382, QTc = 434). Response to drug therapy was determined by the drug ability to completely terminate polymorphic VT within 30 to 60 minutes. In a more recent study (41), the QTc interval was able to predict ACEs at 1 year follow up only when using univariate analysis (no ACEs QTc = 433.2 ± 43 ms vs. 454.3 ± 63 ms in patients with ACEs). However, after controlling for other ECG and non ECG variables, the QTc interval was no longer able to predict ACEs (hazard ratio, 1.006; 95% CI, 0.994 to 1.018; $p = 0.325$). ECG variables were: left ventricular hypertrophy (voltage SV1+RV5), lateral ST depression, pathological Q wave, ST elevation, and T wave inversion. Non ECG variables were: age > 65, body mass index, Killip class > 1, diabetes mellitus, PCI, hemoglobin, serum creatinine, triglyceride, and B-type natriuretic peptide.

Long QT Interval in Patients with Unstable Angina

The two studies in this review that included only patients with UA were positive for a link between a long QTi and an ACE (42, 43). In one study (42) the QTc interval was statistically longer in patients who suffered an ACE (n = 62, 470 ± 60 ms) compared to patients without an ACE (n = 40, 440 ± 50 ms), $p < 0.05$. In this study, a greater percentage of patients with an ACE had a long QTc interval (58% vs. 30%, $p < 0.01$). Using logistic regression, the QTc was found to predict ACEs significantly during hospitalization and 30 days follow up (OR, 2.81; 95% CI, 1.01 to 7.82; $p = 0.047$) after controlling for age, gender, previous MI, negative T wave, ST deviation, and 3 vessel coronary artery disease. Moreover, the QTc interval was found to be longer in patients who died compared to patients who survived at 30 days follow up (498 ± 70 vs. 452 ± 50 ms, $p < 0.01$).

Investigations that included both patients with UA and non-STEMI/NQWMI reported conflicting results regarding the link between a long QTi and an ACE (32, 44). In one study (44) that included patients with UA and NSTEMI, the QTc interval ≥ 450 ms was able to predict ACEs (OR, 3; 95% CI: 1.5 to 5.8; $p = 0.001$) after controlling for age > 65, diabetes mellitus, hypertension, prior by-pass surgery, ST depression ≥ 0.5 mm, ≥ 2 inverted T waves, QRS complex ≥ 120 ms, left ventricular ejection fraction ≤ 40%, peripheral vascular disease, serum elevation of cardiac injury markers, and multi-vessel disease. In this study, patients with a QTc ≥ 450 ms had a higher frequency of in-hospital death (8.8% vs. 1.2%, $p = 0.001$) and a higher frequency of an ACE (72% vs. 25%, $p < 0.00.1$). Following hospital discharge, there were three predictors of cardiovascular mortality: QTc ≥ 450 ms (14.7% vs. 2.1%, $p < 0.0001$), age > 65, and left ventricular ejection fraction < 40%.

The negative study in this category included patients with UA and NQWMI (32). According to the authors, a long QTi was not associated with increased frequency of ventricular or atrial arrhythmias. Furthermore, patients with a long QTi did not require more antiarrhythmic therapy during hospitalization.

Characteristics of Long QT Interval that Modify Prognosis in Patients with Acute Coronary Syndrome

Several researchers who reported positive findings concluded that it is not the long QTi per se that predicts an ACE but rather a persistent long QTi that does not return to initial pre-ACS values (31, 34, 45). In one study (34), the authors emphasized the importance of patient follow-up for several days following acute MI or after hospital discharge to evaluate whether the QTi has returned to initial values or not. According to this study, a persistent or progressively lengthening QTc interval increases the risk of ACEs especially TdP. Another study (45) that examined patients with a first time acute MI who underwent successful PTCA found that failing to shorten QTc interval was associated with increased risk for 1 year ACEs. ACEs included SCD, ventricular fibrillation, and sustained ventricular tachycardia.

In contrast to a persistent long QTi which is associated with an unfavorable outcome, a transient long QTi might be used to predict a better short term prognosis. According to one study (31), transient prolongation of the QTc interval following a reperfusion intervention is a good sign. In this study, maximal QTc interval prolongation in the first 36 to 48 hours following acute MI indicated the presence of a viable myocardium, early reperfusion as demonstrated by dual scintigraphy, and improved left ventricular ejection fraction measured 4 weeks following acute MI.

To evaluate the dynamic aspects of QTi prolongation after ACS, continuous QTi monitoring or at least QTi measurement on several occasions becomes a necessity. According to this viewpoint, a single QTi measurement obtained from a resting 12 lead ECG is not adequate to predict risk of ACEs following ACS (46).

Sensitivity and Specificity

In this review only 3 studies reported the sensitivity and specificity of a long QTc interval in predicting ACEs (Table 2). Sensitivity ranged from 58% to 92% while specificity ranged from 40% to 84%. This wide range can be explained primarily by the differences among different

studies in defining a long QTi, QTi measurement technique, QTc correction formulae, ACE definitions, ACS patient types, and follow up duration.

How long QT Interval Alters Prognosis in Patients with Acute Coronary Syndrome

A long QTi possibly modifies prognosis in ACS through several pathways. First, a long QTi is associated with autonomic nervous system imbalance, primarily sympathetic, which is known to be linked with several ACEs (8, 47). Second, there is a close relation between long QTi and decreased ventricular ejection fraction (36, 37, 43, 45), left ventricular dysfunction (48), and extent of coronary artery disease (46) which all are well known prognostic predictors (49). Third, a long QTi is by itself arrhythmogenic (50).

Limitations of Existing Studies

Despite the serious possible negative consequences of a long QTi on mortality and morbidity in patients with ACS, it has not been satisfactorily investigated. All existing studies have substantial limitations related to at least three of the following;

1. Study design and sample. Approximately half of the reviewed studies are retrospective. Retrospective studies have a great deal of missing data, confounders, and confusion about the chronological order of events. The other half of existing studies is prospective with the majority of them not carrying out multivariate analysis in an attempt to statistically control for extraneous variables. Approximately two thirds of existing studies have a small sample and in almost all studies the sample was selected conveniently.
2. QTi measurement. Findings from existing studies are complicated by the fact that all studies, except three (38, 45, 51), measured the QTi manually (17 studies) or did not report explicitly how the QTi was measured (6 studies). Manual measurement is not accurate (30, 52). The Majority of existing studies measured the QTi from a single lead or a couple of leads. This is considered inaccurate when compared to recent advanced automated techniques which measure the QTi from the 12 ECG leads simultaneously (53). Furthermore, more than half of existing studies did not report clearly how the end of

the T wave was determined or used inappropriate methods (54) compared to the more recently developed techniques (55).

3. QTi monitoring. In majority of existing studies (23 studies), the QTi was monitored non-continuously using 10 second ECG recordings. Non-continuous monitoring does not allow accounting for circadian variation and as importantly does not allow for QT hysteresis correction (see next point). Non-continuous monitoring also does not allow differentiation between persistent and transient QTi changes.
4. QTi correction. In majority of existing studies (22 studies) the QTi was corrected for heart rate using Bazett's formula ($QTc = QT / \sqrt{RR}$, QTi and RRi are measured in seconds). Bazett's formula is the most commonly used formula but the least accurate (56). Furthermore, all existing studies did not correct the QTi for hysteresis. QT hysteresis is the delayed and gradual adaptation of the QTi to sudden alterations in heart rate.

Critical Evaluation of Positive and Negative Studies of an Association between Long QT Interval and Adverse Cardiovascular Events

In this review, negative and positive studies were compared from different aspects. Initially, studies were compared in terms of type of ACS patients. Almost all negative studies were of patients with acute MI (8 out of 9). Acute MI studies with negative findings constituted one third of the studies that included patients with acute MI. This does not necessarily suggest an association between type of ACS patients and study outcome because the majority of existing studies are of patients with acute MI (22 studies). As a consequence, one would expect to find more negative results in this category. When patients from each type of acute MI (STEMI and NSTEMI) were considered separately in a single study, the results of the two studies were positive. An assumption here is that QWMI is comparable to STEMI. This indicates that inferring a study outcome based on the presence or absence of ST elevation is also not legitimate. The

single negative study that included patients other than acute MI was of patients with NSTEACS. But, as previously described, there was another study that included patients with NSTEACS and the findings were positive.

Negative and positive studies were also compared in terms of study design and there was no difference between them. Also, there was no difference in terms of using multivariate analysis, that is to say controlling or not controlling for other variables in predicting ACEs. Among the six studies that carried out multivariate analysis, there were two negative studies and four positive studies. In regard to sampling issues such as sample size and selection there was no difference.

Positive and negative studies also did not differ in the way they measured and corrected the QTi, the year the study was carried out, follow up duration, or in the number and type of ACEs they set as outcomes. The only difference between positive and negative studies was that negative studies tended to set lower limits for defining a long QTi (QTc not longer than 460 ms) or to avoid defining it altogether (4 out of 9). In general, the higher the cut point used to define a long QTi, the more likely it was to predict an ACE. We also examined existing studies to see if the selection of a specific cut point to define a long QTi is influenced by type of ACS patients and there was no difference.

Conclusion

Our review revealed 26 studies that evaluated the association between long QTi measured during the acute phase and early thereafter following an ACS event and ACEs at short and long term follow up. The findings from previous studies are conflicting with 17 studies providing supporting evidence and 9 studies providing opposing evidence. The majority of existing studies have considerable limitations related to study design, sample, QTi measurement and correction, as well as duration of QTi monitoring. Future research needs to address these limitations.

Cardiovascular nurses caring for patients with ACS in hospital settings should understand that it is not uncommon for these patients to exhibit an increase in QTi, especially 2-11 days post event. Continuous ECG monitoring that shows an increase in the QTi may predict risk for

malignant ventricular arrhythmias. Until future research provides reliable and accurate data about the relation between long QTi and ACEs in patients with ACS, it is unclear how much additional attention needs to be given to QTi monitoring in these patients.

What's New

- Long QT interval is not uncommon among patients with acute coronary syndrome. Long QT interval increases the risk of ventricular arrhythmias.
- Maximal increase in the QT interval after an acute coronary syndrome event occurs between day 2 and 11. This explains the exact occurrence of TdP during this time. Nurses taking care of patients with acute coronary syndrome should carefully monitor the QT interval during this time.
- Existing studies that examined the association between long QT interval and several adverse cardiovascular events in patients with acute coronary syndrome have serious limitations. Future research needs to address these limitations.

References

1. Ruff CT, Braunwald E. The evolving epidemiology of acute coronary syndromes. Nat Rev Cardiol. 2011 Mar;8(3):140-7.

2. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013 Jan 1;127(1):143-52.

3. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death). J Am Coll Cardiol. 2006;48(5):e247.

4. Mandelzweig L, Battler A, Boyko V, et al. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. Eur Heart J. 2006;27(19):2285.

5. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2012 Aug 14;126(7):875-910.

6. Weir RP, McMurray JV, Velazquez EJ. Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical characteristics, and prognostic importance. Am J Cardiol. 2006;97(10):13-25.

7. de Luna AB, Coumel P, Leclercq JF. Ambulatory sudden cardiac death: mechanisms of production of fatal arrhythmia on the basis of data from 157 cases. Am Heart J. 1989;117(1):151-9.

8. Podrid P, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. Circulation. 1990;82(2 Suppl):I103-13.

9. Zipes DP, Rubart M. Neural modulation of cardiac arrhythmias and sudden cardiac death. Heart Rhythm. 2006 Jan;3(1):108-13.

10. Sasano T, Abraham MR, Chang KC, et al. Abnormal sympathetic innervation of viable myocardium and the substrate of ventricular tachycardia after myocardial infarction. J Am Coll Cardiol. 2008;51(23):2266-75.

11. Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta2-receptor stimulation by circulating epinephrine. N Engl J Med. 1983 Dec 8;309(23):1414-9.

12. Surawicz B. Ventricular fibrillation. J Am Coll Cardiol. 1985 Jun;5(6 Suppl):43B-54B.

13. Malliani A, Schwartz P, Zanchetti A. A sympathetic reflex elicited by experimental coronary occlusion. Am J Physiol. 1969 September 1, 1969;217(3):703-9.

14. Schwaiger M, Guibourg H, Rosenspire K, et al. Effect of regional myocardial ischemia on sympathetic nervous system as assessed by fluorine-18-metaraminol. J Nucl Med. 1990 August 1, 1990;31(8):1352-7.

15. Mukherjee A, Wong TM, Buja LM, Lefkowitz RJ, Willerson JT. Beta adrenergic and muscarinic cholinergic receptors in canine myocardium. Effects of ischemia. J Clin Invest. 1979 Nov;64(5):1423-8.

16. Kajiyama H, Obara K, Nomura Y, Segawa T. The increase of cardiac beta 1-subtype of beta-adrenergic receptors in adult rats following neonatal 6-hydroxydopa treatment. Eur J Pharmacol. 1982 Jan 8;77(1):75-7.

17. Miyazaki T, Zipes DP. Protection against autonomic denervation following acute myocardial infarction by preconditioning ischemia. Circ Res. 1989 Mar;64(3):437-48.

18. Sasano T, Abraham MR, Chang KC, et al. Abnormal sympathetic innervation of viable myocardium and the substrate of ventricular tachycardia after myocardial infarction. J Am Coll Cardiol. 2008 Jun 10;51(23):2266-75.

19. Schömig A, Haass M, Richardt G. Catecholamine release and arrhythmias in acute myocardial ischaemia. Eur Heart J. 1991;12(suppl F):38.

20. O'Connor RE, Brady W, Brooks SC, et al. Part 10: acute coronary syndromes: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122(18_suppl_3):S787.

21. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis. 1985;27(5):335.

22. Hjalmarson Å, Herlitz J, Malek I, et al. Effect on mortality of metoprolol in acute myocardial infarction: a double-blind randomised trial. Lancet. 1981;318(8251):823-7.

23. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. Lancet. 1986 Jul 12;2(8498):57-66.

24. Davidowski TA, Wolf S. The QT interval during reflex cardiovascular adaptation. Circulation. 1984 Jan;69(1):22-5.

25. Kawano H, Okada R, Yano K. Histological study on the distribution of autonomic nerves in the human heart. Heart Vessels. 2003 Mar;18(1):32-9.

26. Zipes DP. Heart-brain interactions in cardiac arrhythmias: role of the autonomic nervous system. Cleve Clin J Med. 2008 Mar;75 Suppl 2:S94-6.

27. Kleber AG, Janse M. Ischemia-related changes in repolarization. Contemporary cardiology: cardiac repolarization: bridging basic and clinical science. 2003:153-67.

28. Napolitano C, Priori S. The long QT syndrome: molecular and genetic aspects: cardiac repolarization: bridging basic and clinical science. 2003:169-85.

29. Ahnve S. QT interval prolongation in acute myocardial infarction. Eur Heart J. 1985;6(suppl D):85.

30. Pickham D, Hasanien AA. Measurement and rate correction of the QT interval. AACN Adv Crit Care. 2013 Jan-Mar;24(1):90-6.

31. Obayashi T, Tokunaga T, Liizumi T, Shiigai T, Hiroe M, Marumo F. Transient QT interval prolongation with inverted T waves indicates myocardial salvage on dual radionuclide single-photon emission computed tomography in acute anterior myocardial infarction. Jpn Circ J. 2001;65(1):7.

32. Rukshin V, Monakier D, Olshtain Pops K, Balkin J, Tzivoni D. QT interval in patients with unstable angina and non Q wave myocardial infarction. Ann Noninvasive Electrocardiol. 2002;7(4):343-8.

33. Kenigsberg DN, Khanal S, Kowalski M, Krishnan SC. Prolongation of the QTc interval is seen uniformly during early transmural ischemia. J Am Coll Cardiol. 2007;49(12):1299-305.

34. 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(4):1168-74.

35. Taylor GJ, Crampton RS, Gibson RS, Stebbins PT, Waldman MG, Beller GA. Prolonged QT interval at onset of acute myocardial infarction in predicting early phase ventricular tachycardia. Am Heart J. 1981;102(1):16-24.

36. Juul-Möller S. Corrected QT-interval during one year follow-up after an acute myocardial infarction. Eur Heart J. 1986;7(4):299.

37. Raev D. Relationship between rate-corrected QT interval and wall motion abnormalities in the setting of acute myocardial infarction. Int J Cardiol. 1997;61(1):15-20.

38. Jiménez-Candil J, González Matas JM, González IC, et al. In-hospital prognosis in non-ST-segment elevation acute coronary syndrome derived using a new risk score based on electrocardiographic parameters obtained at admission. Rev Esp Cardiol. 2010;63(7):851-5.

39. Yi G, Guo X-H, Reardon M, et al. Circadian variation of the QT interval in patients with sudden cardiac death after myocardial infarction. Am J Cardiol. 1998;81(8):950-6.

40. Wolfe CL, Nibley C, Bhandari A, Chatterjee K, Scheinman M. Polymorphous ventricular tachycardia associated with acute myocardial infarction. Circulation. 1991;84(4):1543.

41. Choi WS, Lee JH, Park SH, et al. Prognostic value of standard electrocardiographic parameters for predicting major adverse cardiac events after acute myocardial infarction. Ann Noninvasive Electrocardiol. 2011;16(1):56-63.

42. Gadaleta FL, Llois SC, Lapuente AR, Batchvarov VN, Kaski JC. Prognostic value of corrected QT-interval prolongation in patients with unstable angina pectoris. Am J Cardiol. 2003;92(2):203-5.

43. Shawl FA, Velasco CE, Goldbaum TS, Forman MB. Effect of coronary angioplasty on electrocardiographic changes in patients with unstable angina secondary to left anterior descending coronary artery disease. J Am Coll Cardiol. 1990;16(2):325-31.

44. Jiménez-Candil J, González IC, González Matas JM, et al. Short-and long-term prognostic value of the corrected QT interval in the non-ST-elevation acute coronary syndrome. J Electrocardiol. 2007;40(2):180-7.

45. Bonnemeier H, Hartmann F, Wiegand UH, Bode F, Katus HA, Richardt G. Course and prognostic implications of QT interval and QT interval variability after primary coronary angioplasty in acute myocardial infarction. J Am Coll Cardiol. 2001;37(1):44.

46. Locati E, Schwartz P. Prognostic value of QT interval prolongation in post myocardial infarction patients. Eur Heart J. 1987;8(suppl A):121.

47. Kapa S, Venkatachalam K, Asirvatham SJ. The autonomic nervous system in cardiac electrophysiology: an elegant interaction and emerging concepts. Cardiol Rev. 2010;18(6):275.

48. Davey P. QT interval and mortality from coronary artery disease. Prog Cardiovasc Dis. 2000;42(5):359-84.

49. Krämer B, Brill M, Brühn A, Kübler W. Relationship between the degree of coronary artery disease and of left ventricular function and the duration of the QT-interval in ECG. Eur Heart J. 1986;7(1):14.

50. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings. Circulation. 2010;121(8):1047-60.

51. Järvenpää J, Oikarinen L, Korhonen P, Väänänen H, Toivonen L, Viitasalo M. Changing capacity of electrocardiographic ventricular repolarization in post-myocardial infarction patients with and without nonfatal cardiac arrest. Am J Cardiol. 2007;99(3):295-9.

52. Murray A, McLaughlin NB, Bourke JP, Doig JC, Furniss SS, Campbell R. Errors in manual measurement of QT intervals. Br Heart J. 1994;71(4):386.

53. Zhou SH, Helfenbein ED, Lindauer JM, Gregg RE, Feild DQ. Philips QT interval measurement algorithms for diagnostic, ambulatory, and patient monitoring ECG applications. Ann Noninvasive Electrocardiol. 2009;14:S3-S8.

54. Zhou X, Wei D. A multidifferentiator-based approach to the reliable determination of T-wave offset in electrocardiograms. J Electrocardiol. 2011 May-Jun;44(3):330-9.

55. Helfenbein ED, Zhou SH, Lindauer JM, et al. An algorithm for continuous real-time QT interval monitoring. J Electrocardiol. 2006 Oct;39(4 Suppl):S123-7.

56. Aytemir K, Maarouf N, Gallagher MM, Yap YG, Waktare JEP, Malik M. Comparison of formulae for heart rate correction of QT interval in exercise electrocardiograms. Pacing Clin Electrophysiol. 1999;22(9):1397-401.

57. Piotrowicz K, Zareba W, McNitt S, Moss AJ. Repolarization duration in patients with conduction disturbances after myocardial infarction. Am J Cardiol. 2007;99(2):163-8.

58. Brendorp B, Elming H, Jun L, Køber L, Torp Pedersen C. The prognostic value of QTc interval and QT dispersion following myocardial infarction in patients treated with or without dofetilide. Clin Cardiol. 2003;26(5):219-25.

59. Tapanainen JM, Still A, Airaksinen KEJ, Huikuri HV. Prognostic significance of risk stratifiers of mortality, including T wave alternans, after acute myocardial infarction: results of a prospective follow up study. J Cardiovasc Electrophysiol. 2001;12(6):645-52.

60. Yi G, Crook R, Guo XH, Staunton A, Camm AJ, Malik M. Exercise-induced changes in the QT interval duration and dispersion in patients with sudden cardiac death after myocardial infarction. Int J Cardiol. 1998;63(3):271-9.

61. Wheelan K, Mukharji J, Rude RE, et al. Sudden death and its relation to QT-interval prolongation after acute myocardial infarction: two-year follow-up. Am J Cardiol. 1986;57(10):745-50.

62. Pohjola-Sintonen S, Siltanen P, Haapakoski J. Usefulness of QTc interval on the discharge electrocardiogram for predicting survival after acute myocardial infarction. Am J Cardiol. 1986;57(13):1066-8.

Table 1.
Association between long QT interval and adverse cardiovascular events in existing studies (26 studies).

Study (REF)	Year	N (M:F)	ACS patients	Design, methods	Long QT [a] (Prevalence)	Follow-up duration	ACEs [b]	Association with ACEs
Choi et al. (41)	2011	497 (2.5:1)	AMI	Retrospective. ECG on hospital discharge.	…	1 y ± 119 day.	1,2,3	-
Jiménez-Can et al. (38)	2010	427 (2.1:1)	NSTEMI	Prospective. ECG on admission.	≥450	5 d ± 3 IQR	1,2	+
Piotrowicz et al. (57)	2007	3282 (3.9:1)	MI	Retrospective. ECG before hospital discharge	>490	…	1	+
Järvenpää et al. (51)	2007	56 (8.3:1)	AMI	Prospective. 24 hour Holter recording	…	…	4	-
Jiménez-Can et al. (44)	2007	427 (2.1:1)	NSTEACS	Prospective. ECG on admission.	≥450	17 month (median)	1,2,3	+
Gadaleta et al. (42)	2003	102 (2:1)	UA	Prospective. ECG on admission and daily thereafter.	≥450 males, ≥470 females	30 day	1, 2,3	+
Brendorp et al. (58)	2003	894 (2.9:1)	MI	Double blind randomized controlled. ECG 3-7 day following MI.	>429	14 month (median)	1	-
Rukshin et al. (32)	2002	104 (2.2:1)	NQWMI + UA	Retrospective. ECG on admission and every day thereafter for 4 day.	>460 (33.7%)	Hospital stay	4	-
Tapanainen et al. (59)	2001	379 (2.5:1)	AMI	Prospective. ECG between day 2 and 20 of admission.	>440	14 ± 8 month	1	-
Obayashi et al. (31)	2001	34 (2.8:1)	AMI	Prospective. Serial ECG every 6 (2 day), 12 (next 2day), and 24 hour (next 3 d).	…	4 weeks	5	-
Halkin et al. (34)	2001	434 (3.1:1)	AMI	Case-control. ECG on admission, after 24-48 hour, and on discharge.	…	Hospital discharge	4	+
Bonnemeier et al. (45)	2001	97 (3.6:1)	AMI	Prospective. 24 hour Holter during and after PTCA.	…	3,6, and 12 month	1,4	+
Yi et al. (60)	1998	39 (5.5:1)	AMI	Prospective. ECG before discharge	>440	39 ± 6 month	1	+
Yi et al. (39)	1998	30 (5:1)	AMI	Retrospective. 24 hour Holter before hospital discharge.	>450	1 year	1	+
Raev (37)	1997	108 (2:1)	QWMI	Prospective. ECG 4 days after infarction.	≥440 (>30%)	…	5	+
Wolfe et al. (40)	1991	11 (4.5:1)	AMI	Retrospective. ECG 1 to 14 hour before polymorphic VT onset	>460	2.9 year	4	-
Shawl et al. (43)	1990	76 (2:1)	UA	Retrospective. ECG within 24 hour of admission.	… (8%)	23 ± 10 month	2,5	+
Locati et al. (46)	1987	55 (…)	AMI	Case-control design. ECG every 2 months for 7 years.	>440	7 year	1	+
Juul-Möller (36)	1986	101 (6.8:1)	AMI	Prospective. ECG 1, 6, and 12 months of MI	>480	1 year	1	+
Wheelan et al. (61)	1986	533 (…)	AMI	Secondary analysis. ECG before hospital discharge	…	18 ± 8 month	1	-
Pohjola-Sint et al. (62)	1986	457 (2.3:1)	AMI	Retrospective. ECG 8 to 14 days of infarction.	>440 (60%)	4 year	1	-
Ahnve, STUDY 1 (29)	1985	81 (…)	AMI	Retrospective. ECG on admission.	…	CCU stay	4	+
Ahnve, STUDY 2	1985	463 (…)	AMI	Retrospective. ECG at hospital discharge.	…	3-6 year	1,4	+
Ahnve, STUDY 3	1985	160 (3.8:1)	AMI	Retrospective. ECG during and after CCU stay, and at 1, 3, 6, and 12 months after discharge.	…	1 year	1,4	+
Ahnve, STUDY 5	1985	865 (…)	AMI	Prospective. ECG at hospital discharge	>440	30 day	1	+
Taylor et al. (35)	1981	32 (…)	AMI	Prospective. ECG on admission and daily until discharge.	≥480	8-18 day	4	+

Studies on bold are multivariate studies; examined the association between long QT interval and ACEs controlling for other confounding variables.
[a] How long QT interval was defined, values are for QTc interval in milliseconds.
[b] ACEs are (1) death including sudden cardiac death, (2) a recurrent ACS event including ischemia or infarction, (3) coronary revascularization including repeated PCI or CABG, (4) arrhythmia including ventricular fibrillation, ventricular tachycardia, and/or torsade de pointes, and (5) decreased left ventricular function measured by left ventricular ejection fraction or wall motion index.

…, information unavailable; ±, Mean ± standard deviation unless stated otherwise; ACEs, adverse cardiovascular events; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; ECG, electrocardiogram; IQR, interquartile range; MI, myocardial infarction; M:F, male female ratio; NSTEACS, non ST elevation ACS (this includes NSTEMI and UA); NSTEMI, non ST elevation MI; PTCA, percutaneous transluminal coronary angioplasty; QT, QT interval; QTc, heart rate corrected QT interval; QWMI, Q wave MI; UA, unstable angina, VT, ventricular tachycardia.

Table 2.

Early measured QTc interval sensitivity and specificity in predicting adverse cardiovascular events in patients with acute coronary syndrome.

Study	QTc	Sensitivity	Specificity	Criterion
Jiménez-Candil et al. 2007	QTc ≥ 450	92%	40%	Death at 17 months follow up
	QTc ≥ 450	80%	64%	Death, recurrent ischemia, or urgent coronary revascularization at 17 month follow up.
Gadaleta et al. 2003	QTc > 460	58%	70%	Mortality, new acute MI, newly established indication for emergency PTCA or CABG during CCU stay and ≤ 30 days after hospital discharge at 30 days follow up.
Ahnve 1985 (STUDY 5)	QTc > 440	77%	84%	Death at 1-year follow up.

CABG, coronary artery bypass graft; CCU, cardiac care unit; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

Chapter 3

Prevalence and Prognostic Significance of Long QT Interval among Patients with Chest Pain: Selecting an Optimum QT Rate Correction Formula

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Abstract

Background: Little is known about the prevalence and prognostic significance of long QT interval among patients with chest pain during the acute phase of suspected cardiovascular injury.

Objectives: Our aim was to investigate the prevalence and prognostic significance of long QT interval among patients presenting to the emergency department (ED) with chest pain using an optimum QT rate correction formula.

Methods: We performed secondary analysis on data obtained from the IMMEDIATE AIM trial (N, 145). Data included 24-hour 12-lead Holter electrocardiographic recordings that were stored for offline computer analysis. The QT interval was measured automatically and rate corrected using seven QTc formulas including subject specific correction. The formula with the closer to zero absolute mean QTc/RR correlation was considered the most accurate.

Results: Linear and logarithmic subject specific QT rate correction outperformed other QTc formulas and resulted in the closest to zero absolute mean QTc/RR correlations (mean ± SD; 0.003 ± 0.002; 0.017 ± 0.016; respectively). These two formulas produced adequate correction in 100% of study participants. Other formulas (Bazett's, Fridericia's, Framingham, and Study specific) resulted in inadequate correction in 47.6 to 95.2% of study participants. Using the optimum QTc formula, linear subject specific, the prevalence of long QTc interval was 14.5%. The QTc interval did not predict mortality or hospital admission at short and long term follow-up. Only the QT/RR slope predicted mortality at 7 year follow-up (odds ratio, 2.01; 95% CI, 1.02 to 3.96; $p < 0.05$).

Conclusions: Adequate QT rate correction can only be performed using subject specific correction. Long QT interval is not uncommon among patients presenting to the ED with chest pain.

Introduction

Ventricular repolarization duration is reflected on the body surface electrocardiogram (ECG) as the QT interval. When delayed, it is likely to increase heterogeneity of ventricular repolarization among different myocardial cells and to produce early afterdepolarizations (1). These conditions combined and accompanied by premature ventricular contractions place sufficient conditions for triggering the life threatening ventricular arrhythmia, torsade de pointes. Delayed repolarization has also been found to predict the occurrence of several adverse cardiovascular (CV) events especially in patients with acute coronary syndrome (ACS). These events include recurrent ischemia (2), ventricular arrhythmias (3), and death (2). Long QT interval in patients with ACS probably results from increased sympathetic activity when accompanied by underlying cellular damage because of ischemia (4, 5).

Despite the serious negative consequences of long QT interval, it has not been properly investigated. The majority of information comes from studies that measured the QT interval manually from a single lead with 10 second ECG during rest (3, 6-8). Recent techniques are automatic and capable of measuring the QT interval continuously using a root mean square signal that gathers ECG information from the 12 ECG leads simultaneously (9). Furthermore, almost all previous studies calculated the heart rate (HR) corrected QT interval using a single population derived formula such as Bazett's or Fridericia's. This type of QT rate correction produces misleading and random findings (10).

In a sample of patients who presented to the emergency department with chest pain and underwent 12 lead ECG monitoring over 24 hours, we aimed to determine the prevalence and prognostic significance of long QT interval using an optimum QT rate correction formula.

Methods

This was a secondary analysis of data obtained from the Ischemia Monitoring and Management in the Emergency Department in Analysis and Treatment of Acute Ischemic Myocardium (IMMEDIATE AIM) trial funded by the National Institutes of Health (RO1HL69753) (11). Data included 24-hour, 12-lead Holter with high resolution ECG acquisition signal (1000 sample/second/channel) (N, 187). Excluded from the present analysis were patients with right (n, 16) or left (n, 10) bundle branch block, atrial fibrillation (n, 8), atrial flutter (n, 1), artificial pacemakers (n, 3), or a combination of these conditions (n, 4). The total sample size for the final analysis was 145.

The QT and RR intervals were measured automatically using the software, Super ECG (Mortara Instruments, Milwaukee, WI) (9). Briefly, this software gathers information from the 12 ECG leads simultaneously to generate one root mean square ECG signal. The measured QT interval with this method will be from the earliest onset of the QRS complex in any lead to the latest T wave offset in any lead. Each measured QT interval is then matched with the preceding RR interval, the average preceding RR interval, or an RR interval that is corrected for unsteadiness in the underlying HR called the RRc. In this study, only beats within the RR range of 400 to 1500 ms were analyzed to eliminate extremes of HR and get rid of outliers.

There is an inverse relation between the QT interval and HR. This is especially evident when the QT interval is monitored over extended periods of time such as with 24 hour Holter monitoring. In such a circumstance, HR can vary considerably. Therefore, a QT value that is less dependent on the HR is usually calculated using one of several mathematical formulas. The resultant value is called the rate corrected QT interval or QTc. Currently there is no perfect formula that can completely eliminate the effect of HR. For maximum precision we calculated the QTc interval using three types of QT rate correction formulas,

1. Population derived QTc formulas. The QTc interval was calculated using three existing formulas of this type; Bazett's ($QTc = QT / \sqrt{RR}$), Fridericia's ($QTc = QT / \sqrt[3]{RR}$), and Framingham's ($QTc = QT + 0.154\ (1\text{-}RR)$). Bazett's and Fridericia's belong to the mathematical expression that has the general logarithmic format, $QTc = QT/RR^{b}$, where *b* is the LnQT/LnRR regression line slope. On the other hand, Framingham's belongs to the mathematical expression that has the general linear format, $QTc = QT + b\ (1\text{-}RR)$, where *b* is the QT/RR regression line slope. Logarithmic expressions assume a non linear QT/RR pattern while linear expressions assume a linear pattern.
2. Study specific QTc formulas. The QTc interval was calculated using two formulas of this type, one belongs to the general logarithmic format and another belongs to the general linear format. The value of the slope (*b*) in both expressions was the average slope value derived from all study participants.
3. Subject Specific QTc formulas. As with study specific correction, the QTc interval was calculated using the general logarithmic format and the general linear format. The value of the slope (*b*) this time was made unique to each participant; it was derived from each participant's own data. Using this type of QT rate correction, each participant has his own unique logarithmic and linear QTc formulas.

Different QTc formulas were solved using the QT interval and the RR interval from the preceding beat so that each participant has a continuous recording for each formula (7 formulas). Both intervals were measured in seconds. The formula with the closest to zero absolute QTc/RR correlation average among all participants was selected to perform further analyses. This formula was called the optimum QTc formula. Closer to zero QTc/RR correlation suggests that this particular formula was more successful in eliminating the effect of the RR interval. This is the underlying assumption of QT rate correction. The performance of a particular QTc formula was

considered adequate when the QTc/RR correlation was small (< 0.3). However, when the correlation was medium or large (≥ 0.3), the performance was considered inadequate.

The QT interval was considered long when either of the following was met:

1- The mean QTc interval calculated using the optimum QTc formula for each participant over the entire Holter recording time exceeded the upper limit of normal recommended by the American Heart Association and the American College of Cardiology (12). The upper limit of normal corresponds to values greater than the 99^{th} percentile QTc values in males (470 ms) and in females (480 ms).

2- At least one episode of long QTc interval greater than 500 ms lasting for at least 15 minutes. This was determined by examining the QTc/Time scatter plot where QTc interval was plotted on the Y axis and Time on the X axis. Time on the X axis was divided into segments of 15 minutes corresponding to 900,000 ms. An episode of long QTc interval was identified whenever the QTc interval consistently exceeded 500 ms throughout the 15 minutes time period. However, this does not necessarily mean that all beats were greater than 500 ms.

We also calculated the QTc > 500 ms burden for the 24-hour Holter recording [(QTc > 500 ms beat count X 100) / total beat count] using only the optimum QTc formula. Adverse CV events were defined as hospital admission or seeking medical attention because of coronary artery disease, heart failure, CV thrombotic event, or arrhythmia. Adverse events also included death of any cause during hospitalization, at 1 year follow-up, and up to 7 years of follow-up. Death was confirmed by public death records including internet accessible obituaries and the Social Security Death Index (ancestry.com, July, 2012).

Statistical analysis

The data were analyzed using SPSS for Windows version 17 (SPSS, Inc., Chicago). A $p \leq 0.05$ was considered statistically significant. Pearson's correlation was used to examine the association between two continuous variables. Binary logistic regression with the method 'enter' (all variables entered at the same time in the model) was used to examine predictors influencing the likelihood of observing adverse CV events and long mean QTc interval.

Results

Sample descriptive statistics are summarized in Table 1. Total time of Holter monitoring was 24 hours (median; interquartile range, 21 to 24).

Table 2 presents the mean QTc/RR correlation of all study participants for different QTc formulas. This value emphasizes the direction of the QTc/RR relation, that is, over or under estimation of the QT interval. A positive sign indicates under estimation of the QT interval with increasing HR (↓ RR) while a negative sign indicates over estimation of the QT interval with increasing HR. Nevertheless, using the mean QTc/RR correlation for estimating the true magnitude, on average, of this correlation is not accurate. This is because positive and negative values tend to cancel each other when calculating the mean value. Importantly, the magnitude of the correlation should not be affected by the sign. Therefore, we are also reporting in the same table the mean value of the absolute QTc/RR correlation. It is this value that was used to judge the adequacy of QT rate correction by different formulas.

Table 2 shows large mean absolute QTc/RR correlation when Bazett's formula was used for QT rate correction. The mean absolute correlation was medium using Fridericia's, Framingham's, and study specific QT rate correction. However, subject specific QTc correction resulted in almost zero mean absolute QTc/RR correlations. Therefore, among these formulas only subject specific correction resulted in adequate QT rate correction. In fact, subject specific

correction completely eliminated the RR interval effect on the QT interval. Linear subject specific correction outperformed logarithmic subject specific correction. Nevertheless, the difference in mean absolute QTc/RR correlation was small, approximately 0.01. To the contrary, with study specific correction, the logarithmic expression outperformed the linear expression but again the difference was small, approximately 0.03. In this study, the QT/RR regression line pattern was linear in 91% of the study participants.

The difference in QT rate correction between study specific formulas and population derived formulas (Fridericia's and Framingham's), excluding Bazett's, was not enormous as one would expect (Table 2). The maximum difference in mean absolute QTc/RR correlation between using either one was 0.112, which is the difference between using logarithmic study specific correction and Framingham's. Referring to the same table, subject specific correction resulted in adequate correction among all study participants, 100% of the time. Other formulas, excluding Bazett's, resulted in adequate correction in 32.4 to 52.4% of study participants. Bazett's formula produced adequate correction in less than 5% of study participants.

Comparing different QTc formulas to the optimal formula (linear subject specific) resulted in a QTc difference of less than 17 ms on average (Table 3). This difference was less than 8 ms excluding Bazett's formula which resulted in the maximum QTc difference. The QTc difference between using linear subject specific correction and Bazett's formula exceeded 20 ms in 42 participants (29%). A QTc difference greater than 20 ms occurred in less than 12 participants using other formulas, excluding the logarithmic subject specific correction. Logarithmic subject specific correction resulted in zero participants with a QTc difference exceeding 20 ms. A QTc difference greater than 20 ms is of concern because a difference of this magnitude increases substantially the proarrhythmic risk associated with long QTc interval (13).

The time duration, prevalence of long mean QTc interval, and QTc > 500 ms burden were different based on the QTc formula being used (Table 4). Other QTc indices calculated only using the linear subject specific formula were prevalence of mean QTc > 500 ms (8, 5.5%) and

number of participants who had at least one episode of long QTc interval greater than 500 ms lasting for at least 15 minutes (19, 13.1%). None of these indices (regardless of the QTc formula being used) predicted any of the adverse CV events reported in Table 1. Only the QT/RR slope predicted mortality at 7 year follow-up. The odds ratio (OR) for mortality at 7 year follow-up for each 0.1 unit increase in the QT/RR slope was 2.01 (95% CI, 1.02 to 3.96, $p < 0.05$). The overall prevalence of long QT interval using either definition (mean or episode) was 14.5% (21 participants).

Univariate predictors of long mean QTc interval calculated using linear subject specific correction are presented in Table 5. With multivariate analysis, however, only the QT/RR slope and having a history of old MI predicted long mean QTc interval. The overall multivariate model was statistically significant (Χ, 35.07; df, 5; $p < 0.0001$) and showed a god fit (Hosmer and Lemeshow Χ, 6.06; df, 8; p, 0.64). The model explained between 22.4 (Cox and Snell R squared) and 43.8% (Nagelkerke R square) of the total variance and correctly classified 91.3% of cases.

Discussion

This is the first study to examine the prevalence and time duration of long QT interval among patients presenting to the emergency department with chest pain. For maximum precision, the prevalence of long QT interval was calculated using the optimum QT rate correction formula, linear subject specific. This formula was selected after statistically comparing seven different QTc formulas. In this study, we monitored the QT interval continuously for 24 hours. Twenty-four hour continuous monitoring is likely to be more reliable and accurate compared with a single 10-second ECG recording.

Subject specific correction almost completely eliminated the RR effect on the QT interval and resulted in adequate correction in 100% of the study participants. In contrast, Bazett's formula exerted only minimal control on the RR interval and resulted in inadequate correction in more than 95% of the study participants. Interestingly, the difference in correction adequacy

between population derived and study specific formulas was not large as one would expect. However, this difference is considerable given that slight changes in the QTc interval can make a difference between low risk and substantial risk of developing life threatening ventricular arrhythmias (13).

These findings indicate that subject specific correction is the only type of correction that adequately corrects the QT interval for rate. This is consistent with previous research (14). The QT/RR relation is highly individualized and thus only an individualized correction approach can mathematically express it (15). Our findings also showed inadequate correction using the other types of QT rate correction on average. Current practice standards (12, 16) and regulatory guidelines (13) still advocate the use of some of these formulas, specifically Framingham's and Fridericia's. Giving the mounting evidence against their use, it might be appropriate now to revise these guidelines.

More than being inaccurate, using the other formulas compared to subject specific correction resulted in a QTc difference greater than 20 ms in 6 to 29% of the study participants. This indicates that further caution is needed when the concern is a QTc difference less than 20 ms or when the underlying HR is unsteady. HR unsteadiness will likely increase the QTc difference (17, 18).

The use of subject specific QT rate correction in hospital settings would be feasible with a software upgrade in patient monitoring equipment. The technology and equipment necessary for continuous monitoring are already in place. Calculating the QTc interval using subject specific correction would require computer measurement of an adequate number of QT-RR beat history for at least 2 minutes. To deal with the resultant delay during this initial measurement period, the monitoring device could in the meanwhile calculate the QTc interval using one of the population derived formulas, preferably Fridericia's, and display the message 'Processing… preliminary QTc = 420 ms,' for example. Two minutes of QT-RR beat history are adequate for the average individual and are likely to produce a QT/RR slope (*b*) value with a high level of statistical

confidence (two tailed type 1 error < 0.05 and statistical power ≥ 0.8). However, when the QT/RR slope is extremely low, an extended period of monitoring is required. The required monitoring time might be as long as 25 minutes when the QT/RR slope is ≤ 0.02. This is likely to occur in some individuals (see the range values for the QT/RR slope reported in Table 1). In addition to the absolute QT/RR slope value, the required monitoring time is affected by the QT and RR intervals variability (standard deviation), shape of the QT/RR regression line (linear vs. non-linear), underlying HR, and whether the HR is steady or unsteady. All these factors would need to be accounted for in the upgraded software.

The prevalence of long QTc interval was 14.5% calculated using the optimum QT rate correction formula, linear subject specific. This includes participants with long mean QTc values and participants with at least one episode of long QTc interval consistently exceeding 500 ms for at least 15 minutes. Nearly 6% of the study participants had a mean QTc longer than 500 ms. On average, the QTc > 500 ms burden was approximately 5%. These findings indicate that long QTc interval is not uncommon among patients presenting to the emergency department with chest pain. This was the first study to examine these indices during the acute phase of suspected CV injury where repolarization abnormalities are expected to be greater and more pronounced. Previous research in patients with ACS carried out later during hospital stay reported varying estimations of long QTc interval ranging between 19% and 60% (6, 19, 20). In addition to other limitations, however, almost all these studies used inaccurate formulas to calculate the QTc interval such as Bazett's and Fridericia's.

Regardless of the QT rate correction formula, QTc indices did not predict any of the adverse events reported in this study. Only the QT/RR slope predicted mortality at 7 year follow-up. This indicates that using the QTc interval as a prediction tool primarily for mortality and hospital admission at short and long term follow-up might not be appropriate. Evidence on the prediction power of long QTc interval is confusing with some studies providing supporting

evidence (2, 21) and others providing opposing evidence (3, 6). All these studies are with serious limitations related to QT measurement and rate correction.

The factors we found to predict long mean QTc interval can all be linked to structural changes in the myocardium. The clearest example is having a history of old MI which increases the odds of having a long mean QTc interval by almost 12 folds, controlling for other variables in the model. This finding is congruent with the existing notion that long QTc interval is unlikely to occur without an underlying structural damage affecting ion channels. Sympathetic hyperactivity, for example, cannot by itself make the QTc interval longer (4). This finding indicates that the QT interval needs to be carefully monitored in such patients.

To acknowledge some of the limitations in this study, there were fewer males than females. Males have shorter QT interval than females. Furthermore, long QTc interval calculated with subject specific correction was defined using the same cut points used to define long QTc interval calculated using Bazett's formula. We do not know if this was accurate. We think that new limits need to be specifically set to define long QTc interval calculated with subject specific correction. One more limitation is that there were 14.5% of the study participants taking beta blocker therapy. Beta blockers affect the QT interval tending to underestimate its prediction power and prevalence of long QT interval. However, we analyzed the data excluding participants taking beta blockers and the sample estimates were similar. There were only one major difference; heart size on X ray no longer predicted long mean QTc interval with univariate analysis.

Another possible limitation is not accounting for QT hysteresis. QT hysteresis or the delayed QT interval adaptation to sudden alterations in the RR interval makes matching the QT interval to its theoretical RR interval predecessor a challenge. This is always a concern when the underlying HR is unsteady. In such a circumstance, the coming QT interval might not be a good match with the immediately preceding RR interval and therefore render the calculated QTc interval inaccurate. On average, full adaptation of the QT interval requires more than 112 seconds

(22). However, this is very unlikely affected our findings giving that the prevalence of long QT interval was determined using a mean QTc value over 24 hours in addition to an episode of consistently long QTc interval for at least 15 minutes. Furthermore, the QTc interval for the further analyses we carried out was calculated using subject specific correction. Subject specific correction resulted in almost zero QTc/RR correlation which necessarily means that the effect of the underlying HR regardless of how much it was variable on the QTc interval was also almost zero.

References

1. Antzelevitch C, Sicouri S. Clinical relevance of cardiac arrhythmias generated by afterdepolarizations: role of M cells in the generation of U waves, triggered activity and torsade de pointes. J Am Coll Cardiol. 1994;23(1):259-77.

2. Jiménez-Candil J, González Matas JM, González IC, et al. In-hospital prognosis in non-ST-segment elevation acute coronary syndrome derived using a new risk score based on electrocardiographic parameters obtained at admission. Rev Esp Cardiol. 2010;63(7):851-5.

3. Wolfe CL, Nibley C, Bhandari A, Chatterjee K, Scheinman M. Polymorphous ventricular tachycardia associated with acute myocardial infarction. Circulation. 1991;84(4):1543.

4. Zipes DP, Rubart M. Neural modulation of cardiac arrhythmias and sudden cardiac death. Heart Rhythm. 2006 Jan;3(1):108-13.

5. Davey P. QT interval and mortality from coronary artery disease. Prog Cardiovasc Dis. 2000 Mar-Apr;42(5):359-84.

6. Rukshin V, Monakier D, Olshtain-Pops K, Balkin J, Tzivoni D. QT interval in patients with unstable angina and non-Q wave myocardial infarction. Ann Noninvasive Electrocardiol. 2002 Oct;7(4):343-8.

7. Locati E, Schwartz P. Prognostic value of QT interval prolongation in post myocardial infarction patients. Eur Heart J. 1987;8(suppl A):121.

8. Choi WS, Lee JH, Park SH, et al. Prognostic value of standard electrocardiographic parameters for predicting major adverse cardiac events after acute myocardial infarction. Ann Noninvasive Electrocardiol. 2011;16(1):56-63.

9. Mortara DW. Automated QT measurement and application to detection of moxifloxacin-induced changes. Ann Noninvasive Electrocardiol. 2009 Jan;14 Suppl 1:S30-4.

10. Malik M. Problems of heart rate correction in assessment of drug-induced QT interval prolongation. J Cardiovasc Electrophysiol. 2001;12(4):411-20.

11. Drew BJ, Schindler DM, Zegre JK, Fleischmann KE, Lux RL. Estimated body surface potential maps in emergency department patients with unrecognized transient myocardial ischemia. J Electrocardiol. 2007 Nov-Dec;40(6 Suppl):S15-20.

12. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation endorsed by the American Association of Critical-Care Nurses and the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2010;55(9):934.

13. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. FDA. 2005.

14. Malik M, Hnatkova K, Batchvarov V. Differences between study-specific and subject-specific heart rate corrections of the QT interval in investigations of drug induced QTc prolongation. Pacing Clin Electrophysiol. 2004 Jun;27(6 Pt 1):791-800.

15. Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart. 2002 Mar;87(3):220-8.

16. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: 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. 2009 Mar 17;53(11):982-91.

17. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is" normal". J Cardiovasc Electrophysiol. 2006;17(3):333-6.

18. Sundaram S, Carnethon M, Polito K, Kadish AH, Goldberger JJ. Autonomic effects on QT-RR interval dynamics after exercise. Am J Physiol Heart Circ Physiol. 2008;294(1):H490.

19. Raev D. Relationship between rate-corrected QT interval and wall motion abnormalities in the setting of acute myocardial infarction. Int J Cardiol. 1997;61(1):15-20.

20. Pohjola-Sintonen S, Siltanen P, Haapakoski J. Usefulness of QTc interval on the discharge electrocardiogram for predicting survival after acute myocardial infarction. Am J Cardiol. 1986;57(13):1066-8.

21. Piotrowicz K, Zareba W, McNitt S, Moss AJ. Repolarization duration in patients with conduction disturbances after myocardial infarction. Am J Cardiol. 2007;99(2):163-8.

22. Malik M, Hnatkova K, Novotny T, Schmidt G. Subject-specific profiles of QT/RR hysteresis. Am J Physiol Heart Circ Physiol. 2008 Dec;295(6):H2356-63.

Table 1.
Sample descriptive statistics (N, 145).

	Mean ± SD (Range)
Age (years)	62.92 ± 13.94 (30 to 93)
Mean RR (ms)	899.52 ± 148.20 (595.59 to 1328.88)
Mean QT (ms)	422.26 ± 39.88 (325.23 to 542.77)
QT/RR slope (linear)	0.121 ± 0.056 (0.019 to 0.349)
QT/RR slope (log)	0.244 ± 0.10 (0.041 to 0.57)
	n (%)
Gender	
Male	61 (42.1%)
Female	84 (57.9%)
ACS	41 (28.3%)
ST elevation MI	5 (3.4%)
Non ST elevation MI	7 (4.8%)
Unstable angina	29 (20%)
History	
MI	40 (27.6%)
Angina	36 (24.8%)
CABG	15 (10.3%)
PCI	26 (17.9%)
Beta blockers	21 (14.5%)
Adverse Cardiovascular Events	
Hospital admission	111 (76.6%)
Mortality during hospital admission	4 (2.8%)
Hospital admission at 1 year follow-up	45 (40.5%)
Mortality at 1 year follow-up	10 (8.6%)
Mortality at 7 year follow-up	32 (22.1%)
Any adverse cardiovascular event	121 (83.4%)

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; linear, linear QT/RR regression line pattern; log, logarithmic QT/RR regression line pattern; MI, myocardial infarction; ms, millisecond; PCI, percutaneous coronary intervention; QTc, QT interval corrected for heart rate.

Table 2.
Adequacy of QT rate correction by different QTc formulas (N, 145).

	QTc/RR correlation			Absolute QTc/RR correlation			
QTc formula	Mean	SD	Range	Mean	SD	Range	Adequate correction, n (%)
Bazett	-0.714	0.205	-0.962 to 0.233	0.720	0.183	0.070 to 0.962	7 (4.8%)
Fridericia	-0.344	0.356	-0.945 to 0.659	0.432	0.242	0.014 to 0.945	47 (32.4%)
Framingham	-0.295	0.417	-0.962 to 0.753	0.442	0.254	0.001 to 0.962	49 (33.8%)
Study specific (log)	-0.023	0.401	-0.912 to 0.789	0.330	0.227	0.000 to 0.912	76 (52.4%)
Study specific (linear)	-0.058	0.433	-0.936 to 0.808	0.362	0.244	0.006 to 0.936	64 (44.1%)
Subject specific (log)	0.004	0.023	-0.055 to 0.072	0.017	0.016	0.000 to 0.072	145 (100%)
Subject specific (linear)	0.000	0.003	-0.008 to 0.010	0.003	0.002	0.000 to 0.010	145 (100%)

linear, linear QT/RR regression line pattern; log, logarithmic QT/RR regression line pattern; QT, QT interval; QTc, QT interval corrected for heart rate; RR, RR interval; SD, standard deviation.

Table 3.
Absolute mean QTc difference between using linear subject specific (LSS) QT rate correction and other QTc formulas.

Comparison	Mean difference (ms)	SD	Range	QTc difference > 20 ms, n (%)
Mean LSS vs. mean Bazett's	16.38	13.30	0.02 to 63.07	42 (29%)
Mean LSS vs. mean Fridericia's	7.32	7.70	0.00 to 37.54	11 (7.6%)
Mean LSS vs. mean Framingham's	7.52	7.89	0.00 to 45.88	9 (6.2%)
Mean LSS vs. mean Study specific (log)	6.51	8.97	0.00 to 49.95	9 (6.2%)
Mean LSS vs. mean Study specific (linear)	6.66	8.89	0.00 to 53.65	9 (6.2%)
Mean LSS vs. mean Subject specific (log)	1.64	2.05	0.02 to 12.27	0 (0.0%)

linear, linear QT/RR regression line pattern; log, logarithmic QT/RR regression line pattern; ms, millisecond; QTc, QT interval corrected for heart rate; SD, standard deviation.

Table 4.
Time duration, prevalence of long mean QTc interval, and QTc > 500 ms burden using different QTc formulas.

QTc formula	**Mean QTc (ms)**	**Long Mean QTc [Male / Female]**	**QTc > 500 ms Burden (%)**
	Mean ± SD (range)	n, %	Mean ± SD (range)
Bazett	447.31 ± 30.26 (381.56 to 550.98)	19 (13.1%) [7 (4.8%) / 12 (8.3%)]	8.22 ± 20.66 (0.00 to 99.80)
Fridericia	438.23 ± 29.37 (386.79 to 548.08)	14 (9.7%) [6 (4.1%) / 8 (5.5%)]	4.77 ± 16.92 (0.00 to 99.80)
Framingham	436.50 ± 28.37 (384.42 to 547.00)	13 (9%) [5 (3.4%) / 8 (5.5%)]	4.08 ± 16.11 (0.00 to 99.80)
Study specific (log)	433.69 ± 30.90 (369.25 to 546.60)	14 (9.7%) [6 (4.1%) / 8 (5.5%)]	4.28 ± 16.21 (0.00 to 99.60)
Study specific (linear)	433.45 ± 29.72 (374.19 to 546.10)	13 (9%) [5 (3.4%) / 8 (5.5%)]	3.83 ± 15.60 (0.00 to 99.40)
Subject specific (log)	435.66 ± 33.74 (373.10 to 553.26)	17 (11.7%) [8 (5.5%) / 9 (6.2%)]	5.16 ± 19.12 (0.00 to 99.80)
Subject specific (linear)	436.61 ± 33.33 (372.02 to 555.83)	17 (11.7%) [8 (5.5%) / 9 (6.2%)]	5.09 ± 19.11 (0.00 to 99.7)

linear, linear QT/RR regression line pattern; log, logarithmic QT/RR regression line pattern; ms, millisecond; QTc, QT interval corrected for heart rate; SD, standard deviation.

Table 5.
Predictors of long mean QTc (n, 138).

Predictors	Univariate			Multivariate		
	B	**S.E.**	**OR (95% CI)**	**B**	**S.E.**	**OR (95% CI)**
Acute MI (yes, no)	1.529	0.678	4.62 (1.22 to 17.45)*	1.291	1.013	3.64 (0.50 to 26.50)
Old MI (yes, no)	1.824	0.550	6.20 (2.12 to 18.20)***	2.464	0.819	11.75 (2.36 to 58.49)**
QT/RR slope [a]	1.675	0.466	5.34 (2.14 to 13.31)***	1.790	0.630	5.99 (1.74 to 20.58)**
Heart size on X ray (normal , enlarged)	1.723	0.574	5.60 (1.82 to 17.26)**	0.824	0.770	2.28 (0.50 to 10.31)
T wave inversion (yes, no)	1.979	0.562	7.24 (2.40 to 21.80)***	0.801	0.834	2.23 (0.43 to 11.43)

*p < 0.05, **p < 0.01, ***p < 0.001.

[a] QT/RR slope multiplied by 10 so that ORs are interpreted for each 0.1 unit increase in the QT/RR slope.

B, b- weight of multiple regression (logistic); CI, confidence interval; MI, myocardial infarction; OR, odds ratio; QT, QT interval; QTc, QT interval corrected for heart rate; RR, RR interval; S.E., standard error.

Chapter 4

QT/RR Dynamicity among Different Heart Rate Zones: Introducing a Physiological Evidence for Setting the Limits Defining Heart Rate Zones Boundaries

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Abstract

Background. The autonomic nervous system signal and balance is different among different heart rate (HR) zones (bradycardia, normal, and tachycardia). These differences might be reflected on the steepness of the QT-RR intervals regression line (QT/RR slope) and might be useful in resetting the limits defining different HR zones boundaries. The aims of this study were to investigate whether the QT/RR slope is different among different HR zones and whether this difference is associated with the level of steadiness (minimal fluctuation) in the underlying HR.

Methods. This is a secondary analysis of data obtained from 145 participants from the prospective clinical trial, the IMMEDIATE AIM. The data included 24-hour, 12-lead Holter electrocardiogram recordings (1000 samples/second/lead) that were stored for offline computer analysis. In the study, the QT/RR slope among different HR zones was examined and then compared for statistical significance. Beats selected for building the QT/RR slope were steady to account for the delayed and gradual adaptation of the QT interval to alterations in the RR interval (QT hysteresis). HR zones boundaries were defined based on change in the QT/RR slope as the HR shifted from one zone to another.

Results. The QT/RR slope was significantly less under the bradycardia zone (Mean ± SD, 0.074 ± 0.07) compared to the normal (0.114 ± 0.1, $p < 0.01$) or the tachycardia zones (0.147 ± 0.1, $p < 0.001$). There was no difference between the normal and the tachycardia zone ($p = 0.22$). This was explained by the finding that QT interval steadiness was significantly less under the bradycardia zone (estimated marginal mean, 13.92) compared to the normal (22.05, $p < 0.0001$) or the tachycardia zones (24.72, $p < 0.0001$).

Conclusions. The QT/RR slope is different among different HR zones. These differences should be accounted for in QT rate correction formulas and can be used in resetting the limits defining different HR zones boundaries.

Keywords: QT dynamicity, QT-RR slope, QT Interval, QT variability, heart rate zones.

There is an inverse relation between the QT interval (QTi) and heart rate (HR). To account for this, a QT value that is less dependent on HR is calculated using one of different mathematical equations. This value is called the HR corrected QTi or the QTc. Adequate QT rate correction is of prime importance in drug development trials (1) and in taking care of patients at risk for developing life threatening arrhythmias (2). Such patients include patients with acute coronary syndrome especially during the first 24 to 48 hours of vascular injury (3).

QT rate correction is one of the most challenging issues in electrocardiology (4). Up to date, there is no QTc formula that can adequately correct the QTi for HR (5). Inadequate QT rate correction explains much of the confusion in existing literature concerning the usefulness and the prediction power of long QTi (6, 7). The challenge of developing an optimum QTc formula primarily results from the complex QT/HR interaction that is manipulated by the autonomic nervous system (ANS) (8). This interaction is best expressed using the steepness of the QT-RR intervals regression line (QT/RR slope) obtained from examining their scatter plot. The complexity of the QT/HR interaction manifests in part by the delayed and gradual adaptation of the QTi to alterations in HR, a phenomenon known as QT hysteresis (9). QT hysteresis makes matching the QTi with its theoretical RR interval (RRi) associate difficult.

The complexity of the QT/HR interaction also manifests by the variability and instability of the ANS discharge and balance as HR shifts from one zone to another (bradycardia, normal, and tachycardia). The effect of HR zone on QT/HR dynamics has never been investigated. Consequently, much of the underlying ANS signal that might affect QT rate correction has been ignored. Ignoring the effect of HR zone might explain in part why the majority of QTc formulas currently available perform optimally only under a particular HR zone (10).

In a secondary analysis of data obtained from the IMMEDIATE AIM trial (Ischemia Monitoring and Mapping in the Emergency Department in Appropriate Triage and Evaluation of Acute Ischemic Myocardium), the aims of this study were to evaluate whether the QT/RR slope is

different among different HR zones and whether this difference, if any, is associated with the level of steadiness (minimal fluctuation) in the underlying HR.

Methods

The IMMEDIATE AIM trial funded by the National Institute of Health (RO1HL69753) enrolled patients presenting to the emergency department with chest pain between 2002 and 2004. Data obtained included 24-hour, 12-lead Holter electrocardiogram (ECG) recordings that were stored for offline computer analysis. Further details about this trial can be found elsewhere (11).

For precise measurement of the QTi, only participants with high resolution ECG detection signal (1000 sample/second/channel) were included in the analysis (n, 187). ECG data from these participants was acquired using H12+ Holter recorders (Mortara Instruments, Milwaukee, WI). Excluded from the analysis were patients with right (n, 16) or left (n, 10) bundle branch block, atrial fibrillation (n, 8), atrial flutter (n, 1), artificial pacemakers (n, 3), or a combination of these conditions (n, 4). The remaining sample for the present analysis was 145.

The QTi was measured automatically using the software, Super ECG (Mortara Instruments) (12). The software measures the QTi from the earliest onset of the QRS complex in any lead to the latest offset of the T wave in any lead.

In this study, the QT/RR slope was defined as the steepness of the best line of fit (regression line) defining the rate of change in the QTi as the RRi changes. The best line of fit was drawn after examining the QT/RR scatter plot. HR zone is the HR range defining bradycardia, normal HR, or tachycardia. Currently, HR zones are defined using arbitrary cut points such as using the 60 beat per minute (bpm) cut point to define the limit separating the normal HR from bradycardia. In this study, the limits defining each HR zone boundaries were set based on observing a change in the QT/RR slope as it shifts from one HR zone to another (Figure 1). HR zones' boundaries based on these observations were close but not exactly the same as conventionally defined HR zones' boundaries. Although there were substantial inter-individual

differences, HR zones' boundaries in this study were defined the same among all study participants based on the prevailing theme.

Regardless of HR zone, all beats used for the analysis were within the RR range of 400 to 1500 ms. This filtering was applied to reduce the amount of waveform deformity resulting primarily from muscular artifact and accidental electrode detachment because of extended monitoring time.

To investigate whether the QT/RR slope varies by HR zone, an adequate number of representative beats from each HR zone from each participant was selected and then compared. A beat consisted of a QTi matched with an RRi from the preceding beat. The beats selected from each HR zone met the following criteria:

1. They were consequent one to another.
2. They were steady (i.e., with minimal fluctuation). Assessing the QT/RR slope while the underlying rhythm is unsteady is challenging (8) and is a great source of error (10). Steadiness was defined as no fluctuation in the underlying rhythm (RRi) by more than a specific amount of milliseconds per minute. This amount was made subject specific and corresponded to the minimum count of milliseconds that resulted in the selection of an adequate number of beats for building the QT/RR slope (Table 1). Steadiness was not allowed to be less than 5 milliseconds whatsoever thinking that a minimum amount of fluctuation in the underlying rhythm is needed to make the ANS direct effect (RR independent) on the QT interval more pronounced and consequently easier to be captured. QT interval variability rarely occurs when the underlying rhythm is held extremely constant.
3. They were within clusters. This is to assure adequate variability in the underlying rhythm and sufficient representation of that particular HR zone. The total count of beats within these clusters when added together was HR zone specific (Table 1). Within each cluster, selected beats were preceded by steady consecutive beats to account for QT hysteresis.

The count of preceding beats was also HR zone specific, corresponding to approximately 2 minutes of steady RR history (Table 1). The amount of RR steadiness in the preceding beats was the same as the selected beats.

For the purpose of comparing different QT/RR slopes among different HR zones, the shape (pattern) of the slope was assumed linear all the time.

Statistical Analysis

Data were analyzed using SPSS for Windows version 17 (SPSS, Inc., Chicago). A $p \leq 0.05$ was considered statistically significant. All tests were two tailed. All pair-wise comparisons were carried out using Bonferroni adjustment. Hierarchical linear modeling (HLM) with full maximum likelihood method was used to run repeated measures analyses throughout the study. HLM was used instead of repeated measures ANOVA primarily to maximize the sample size available. Repeated measures ANOVA requires that all participants have a complete set of measurement occasions at different levels of the independent variable.

Results

Sample Characteristics and the QT/RR Slope among Different Heart Rate Zones

Total time of Holter monitoring was 24 hours (median). This corresponded to approximately one hundred thousand beats from where beats were selected for building the QT/RR slope under the three HR zones. Sample characteristics are described in Table 2.

HLM modeling revealed a statistically significant overall difference in the QT/RR slope among the three HR zones ($F(2, 79.95) = 12.2$, $p < 0.001$). The QT/RR slope under the bradycardia zone was significantly lower than the normal ($p < 0.01$) and the tachycardia zones ($p < 0.001$). There was no statistically significant difference in the QT/RR slope between the normal and the tachycardia zones ($p = 0.22$), Table 3.

Steadiness between Intervals and among Different Heart Rate Zones

HLM modeling revealed a statistically significant difference in steadiness between the RRi and the QTi ($F(1, 283.95) = 202.23$, $p < 0.0001$), controlling for HR zone. There was also an overall statistically significant difference in steadiness among different HR zones, controlling for the interval ($F(2, 98.15) = 31.01$, $p < 0.0001$). The level of steadiness was significantly less under the bradycardia zone compared to the normal or the tachycardia zones. There was no statistically significant difference between the normal zone and the tachycardia zone. Table 4 model A, presents the estimated marginal means (EMMs) differences for these comparisons. EMMs estimate predicted means for the dependent variable adjusting for any covariate (or factor) in the HLM model.

In model B of HLM modeling (Table 4), an interaction term between HR zone and interval was added. This resulted in a better model fit as demonstrated by a lower AIC (Akaike's Information Criterion). The interaction term contributed significantly to the model ($F(2, 85.88) = 7.66$, $p < 0.01$), controlling for HR zone and interval. However, steadiness was no longer statistically different among different HR zones ($F(2, 89.88) = 0.33$, $p = 0.72$). With regard to the difference between the RRi and the QTi controlling for HR zone and the interaction term, it remained statistically significant ($F(1, 91.72) = 108.58$, $p < 0.0001$). A statistically significant interaction between HR zone and interval indicates that the difference in steadiness between the QTi and the RRi depends on HR zone. According to this model (B), the difference in steadiness between the QTi and the RRi under the bradycardia zone was significantly different from the difference in steadiness between the QTi and the RRi under the normal zone and under the tachycardia zone. The difference in steadiness between the QTi and the RRi under the normal zone was not statistically significant from the difference in steadiness between the QTi and the RRi under the tachycardia zone, Figure 2.

To further understand the differences in steadiness between intervals and among different HR zones, the level of steadiness in the RRi and the QTi was compared, each separately, as they shift from one HR zone to another. HLM modeling was used again to run this comparison. RRi steadiness was not statistically different among different HR zones ($F(2, 60.68) = 1.69$, $p = 0.19$). The EMMs for RR steadiness were 48.72, 43.00, and 42.36 under the bradycardia, normal, and tachycardia zones, respectively. However, QTi steadiness was statistically different among different HR zones ($F(2, 82.88) = 36.62$, $p < 0.0001$). QTi steadiness was significantly less under the bradycardia zone compared to the normal (EMMs, 13.92 vs. 22.05; $p < 0.0001$) or the tachycardia zones (EMMs, 13.92 vs. 24.72; $p < 0.0001$). There was no statistically significant difference between the normal and the tachycardia zones (EMMs, 22.05 vs. 24.72; $p = 0.16$), Figure 3.

Discussion

The QT/RR slope among different heart rate zones

This is the first study to compare the QT/RR slope among different HR zones. The QT/RR slope is less under the bradycardia zone accounting for QT hysteresis. Different QT/RR slope under the bradycardia zone casts doubt in currently available QTc formulas. Currently available formulas assume the same QT/RR slope among different HR zones and thus produce misleading QTc values. The finding presented here is consistent with previous research that shows a steeper QT/RR slope with sympathetic activity and a shallower slope with parasympathetic activity (8, 13-15). Therefore, it is reasonable to find a shallower QT/RR slope under the bradycardia zone where parasympathetic activity is increased and sympathetic activity is decreased. However, there was no difference in the QT/RR slope between the normal zone and the tachycardia zone.

Based on this finding, using a single QTc formula under different HR zones appears to be not optimal. A single formula will result in an optimum rate correction only at one HR zone at

best and in an under or over correction at other zones. This is explained by the variability of the ANS signal and balance among different HR zones. For proper QT rate correction at least two linear formulas should be used, one under the bradycardia zone and another for the normal and the tachycardia zones. In a previous study (16), researchers warned against using a single QTc formula. They found the QT/RR relation best expressed using three QT/RR slopes, one for each HR zone. In a more recent study (17), authors recommended using two different QTc formulas, one under the bradycardia zone and another for the other two HR zones.

According to this study and in similar cohorts to the one presented here the QT/RR slope (*b*) might be set around 0.074 when the HR is within the bradycardia zone and anywhere between 0.114 and 0.147 when the HR is within the normal or the tachycardia zones. This is certainly assuming a linear QT/RR pattern and using a linear QTc formula (QTc = QT + *b* (1-RR), where *b* is the QT/RR slope). Using these values eliminate the need for QT hysteresis correction, even if the HR is unsteady. This is because these values already explain the QT/RR relation accounting for QT hysteresis. What is primarily still needed for adequate QT rate correction is proper QT/RR matching which is best accomplished by matching the QTi with the preceding RRi average for 60 seconds.

However, when the underlying HR is variable around more than a single HR zone including the bradycardia zone, then it might be more appropriate to consider the QT/RR relation non- linear and adopt a non-linear expression for QT rate correction such as the logarithmic expression ($QTc = QT \times RR^{b}$). This is likely to occur with continuous ECG monitoring for extended periods of time.

The change in the QT/RR slope as the HR shifts from one zone to another might be used to set the limits defining different HR zones boundaries for the first time based on physiological evidence. Previously these limits were set arbitrarily such as using the 100 bpm cut point to define the limit separating the normal zone from the tachycardia zone. Setting these limits will be accomplished if one is able to determine exactly at what HR point the QT/RR slope starts to

differ substantially as the HR shifts from one zone to another. This physiological definition relies on the principle that it is possible to use other ANS indicators in addition to HR to determine HR zones boundaries. One of these indicators is the HR zone dependent change in ANS signal and balance reflected on the QT/RR slope. This is clearly will help bring more accurate definition of HR zones boundaries.

Steadiness between intervals and among different heart rate zones

QT steadiness was substantially less under the bradycardia zone while RR steadiness was not different among different HR zones. This explains the previous finding that the QT/RR slope was less under this particular zone. One should recall that, QT/RR slope = $r_{QT,RR}$ X (SD_{QT}/SD_{RR}) where r is the correlation coefficient and SD is the standard deviation. Accordingly, it is the QTi but not the RRi that affects the QT/RR slope under steady HR conditions.

Existing literature supports an association between increased sympathetic activity beyond that existing during the resting state and increased variability (less steadiness) in the QTi only in certain pathophysiological conditions (18). These conditions are classically known to be associated with increased levels of sympathetic activity such as exercise (19), congestive heart failure (20), acute ischemia (21), and certain types of long QT syndrome (22). In a recent study (23), variability in the QTi was found to correlate positively only with high levels of cardiac norepinephrine release (> 20 ng/min) but not with low levels. According to the authors, there might be a certain threshold for cardiac sympathetic activity only beyond which sympathetic activity is capable of inducing change and correlate positively with variability in the QTi.

Accordingly, the finding of minimal QT steadiness under the bradycardia zone might be explained by minimal sympathetic activity under this zone. Once sympathetic activity reach a certain threshold such as that required to shift the HR from the bradycardia zone to the normal zone, it can substantially increase the level of QT steadiness. Levels of QT steadiness were not different between the normal zone and the tachycardia zone. Probably because the level of sympathetic activity required to shift the HR from the normal zone to the tachycardia zone is not

large enough as that required to shift the HR from the bradycardia zone to the normal zone and consequently did not reach changing QT steadiness threshold. One can think of this by appreciating that shifting the HR from the bradycardia zone to the normal zone might require an amount of sympathetic activity that is greater than that only needed to shift the HR from one zone to another. The additional amount is needed to overcome the enormous parasympathetic activity dominating the bradycardia zone. No difference in QT steadiness between the normal zone and the tachycardia zone explains the finding previously reported that there was no difference in the QT/RR slope between these two HR zones.

In this study, QT steadiness was each time lower than RR steadiness under the three HR zones. The QTi reflects the action potential duration (24) and the ventricular mechanical contraction time (25) which directly affect the cardiac output. Consequently lower levels of QT steadiness might be a protective mechanism mediated by the ANS, primarily the sympathetic division, to make the ventricular contraction time less affected by fluctuations in the cycle length (HR). Further support to this supposition is the finding that QT steadiness was the lowest under the bradycardia zone. Under this zone, reductions in the cardiac output is the most likely compared to other zones primarily because of the reductions in HR (CO = HR X SV, where CO is cardiac output and SV is the stroke volume). Thus, maximum control of ventricular contraction time is most needed under this zone. Additional supporting evidence is the challenge associated with understanding the phenomenon of QT hysteresis, why the ANS would make the QT adaptation to sudden alterations in the RRi gradual and delayed? The most plausible explanation one can think of is preventing sudden changes in the ventricular contraction time and thus contributing to a more steady cardiac output.

Limitations

There were more females than males in this study. However, despite the well known effect of gender on the QTi, the evidence on its effect on the QT/RR slope is still inconclusive (13, 15). In this study, circadian variation was not accounted for. The QT/RR slope is different in the day compared to night (13, 15).Thus, care should be taken in interpreting the findings presented here.

Around 15% of study participants were taking beta blockers. Beta blockers decrease variability in the QTi (26) and reduce the QT/RR slope (27). The author of this study compared the QT/RR slope under the three HR zones among participants including and excluding patients taking beta blocker therapy and there was no difference. The study investigator also found no difference in the QT/RR slope under the three HR zones among participants taking and not taking beta blocker therapy. One explanation for the unnoticeable effect of beta blocker therapy might be that the majority of participants taking beta blocker therapy were with chronic ischemia compared to participants with acute ischemia. Only acute ischemia is known to be associated with increased variability in the QTi.

References

1. FDA. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. 2005.

2. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation endorsed by the American Association of Critical-Care Nurses and the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2010;55(9):934.

3. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death). J Am Coll Cardiol. 2006;48(5):e247-e346.

4. Rautaharju PM, Surawicz B, Gettes LS. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: 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. 2009;53(11):982.

5. Malik M. Problems of heart rate correction in assessment of drug-induced QT interval prolongation. J Cardiovasc Electrophysiol. 2001;12(4):411-20.

6. Choi WS, Lee JH, Park SH, et al. Prognostic value of standard electrocardiographic parameters for predicting major adverse cardiac events after acute myocardial infarction. Ann Noninvasive Electrocardiol. 2011;16(1):56-63.

7. Jiménez-Candil J, González Matas JM, González IC, et al. In-hospital prognosis in non-ST-segment elevation acute coronary syndrome derived using a new risk score based on electrocardiographic parameters obtained at admission. Rev Esp Cardiol. 2010;63(7):851-5.

8. Sundaram S, Carnethon M, Polito K, Kadish AH, Goldberger JJ. Autonomic effects on QT-RR interval dynamics after exercise. Am J Physiol Heart Circ Physiol. 2008;294(1):H490.

9. Franz MR, Swerdlow CD, Liem LB, Schaefer J. Cycle length dependence of human action potential duration in vivo. Effects of single extrastimuli, sudden sustained rate acceleration and deceleration, and different steady-state frequencies. J Clin Invest. 1988;82(3):972.

10. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is" normal". J Cardiovasc Electrophysiol. 2006;17(3):333-6.

11. Drew BJ, Schindler DM, Zegre JK, Fleischmann KE, Lux RL. Estimated body surface potential maps in emergency department patients with unrecognized transient myocardial ischemia. J Electrocardiol. 2007 Nov-Dec;40(6 Suppl):S15-20.

12. Mortara DW. Automated QT measurement and application to detection of moxifloxacin-induced changes. Ann Noninvasive Electrocardiol. 2009 Jan;14 Suppl 1:S30-4.

13. Extramiana F, Maison-Blanche P, Badilini F, Pinoteau J, Deseo T, Coumel P. Circadian modulation of QT rate dependence in healthy volunteers: gender and age differences. J Electrocardiol. 1999;32(1):33-43.

14. Cappato R, Alboni P, Pedroni P, Gilli G, Antonioli GE. Sympathetic and vagal influences on rate-dependent changes of QT interval in healthy subjects. Am J Cardiol. 1991 Nov 1;68(11):1188-93.

15. Jensen BT, Larroude CE, Rasmussen LP, et al. Beat-to-beat QT dynamics in healthy subjects. Ann Noninvasive Electrocardiol. 2004 Jan;9(1):3-11.

16. Karjalainen J, Viitasalo M, Manttari M, Manninen V. Relation between QT intervals and heart rates from 40 to 120 beats/min in rest electrocardiograms of men and a simple method to adjust QT interval values. J Am Coll Cardiol. 1994 Jun;23(7):1547-53.

17. Luo S, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. J Electrocardiol. 2004;37 Suppl:81-90.

18. Berger RD. QT interval variability is it a measure of autonomic activity? J Am Coll Cardiol. 2009 Aug 25;54(9):851-2.

19. Boettger S, Puta C, Yeragani VK, et al. Heart rate variability, QT variability, and electrodermal activity during exercise. Med Sci Sports Exerc. 2010 Mar;42(3):443-8.

20. Piccirillo G, Magnanti M, Matera S, et al. Age and QT variability index during free breathing, controlled breathing and tilt in patients with chronic heart failure and healthy control subjects. Transl Res. 2006 Aug;148(2):72-8.

21. Murabayashi T, Fetics B, Kass D, Nevo E, Gramatikov B, Berger RD. Beat-to-beat QT interval variability associated with acute myocardial ischemia. J Electrocardiol. 2002 Jan;35(1):19-25.

22. Bilchick K, Viitasalo M, Oikarinen L, et al. Temporal repolarization lability differences among genotyped patients with the long QT syndrome. Am J Cardiol. 2004 Nov 15;94(10):1312-6.

23. Baumert M, Lambert GW, Dawood T, et al. QT interval variability and cardiac norepinephrine spillover in patients with depression and panic disorder. Am J Physiol Heart Circ Physiol. 2008 Sep;295(3):H962-H8.

24. Franz MR, Bargheer K, Rafflenbeul W, Haverich A, Lichtlen PR. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. Circulation. 1987 Feb;75(2):379-86.

25. Seed WA, Noble MI, Oldershaw P, et al. Relation of human cardiac action potential duration to the interval between beats: implications for the validity of rate corrected QT interval (QTc). Br Heart J. 1987 Jan;57(1):32-7.

26. Furukawa Y, Shimizu H, Hiromoto K, Kanemori T, Masuyama T, Ohyanagi M. Circadian variation of beat-to-beat QT interval variability in patients with prior myocardial infarction and the effect of beta-blocker therapy. Pacing Clin Electrophysiol. 2006 May;29(5):479-86.

27. Hintze U, Wüpper F, Mickley H, Mφller M. Effects of beta-blockers on the relation between QT interval and heart rate in survivors of acute myocardial infarction. Ann Noninvasive Electrocardiol. 1998;3(4):319-26.

Table 1.

Descriptive statistics, Mean ± SD (Range), for the selected beats used for building the QT/RR slope and for the preceding beats used to account for QT hysteresis (N, 145[a]**).**

	Bradycardia zone (n, 110)	Normal zone (n, 116)	Tachycardia zone (n, 39)
Selected beats count	496.32 ± 326.21 (160 to 2068)	752.67 ± 943.64 (142 to 6669)	799.90 ± 880.61 (191 to 4835)
RRi steadiness (ms)[b]	48.45 ± 25.95	42.67 ± 33.28	41.28 ± 34.94
Clusters count	10.02 ± 4.93	8.83 ± 6.06	7.21 ± 4.74
RRi (ms)	1022.97 ± 120.53 (correspond to, 59 bpm)	760.71 ± 49.77 (correspond to, 79 bpm)	581.44 ± 40.39 (correspond to, 103 bpm)
Preceding beats count [c]	105.94 ± 11.71 (1 minute and 48 second)	143.71 ± 33.53 (1 minute and 48 second)	197.69 ± 38.21 (1 minute and 55 second)
QTi steadiness (ms)	14.05 ± 9.62	22.01 ± 10.43	24.31 ± 6.51
QTi (ms)	443.26 ± 33.45	397.86 ± 27.44	359.23 ± 24.06

[a] 21 participants provided a complete set of measurement occasions under the three heart rate zones.

[b] These levels of RR interval steadiness corresponded to fluctuations in the underlying heart rate by approximately ± 3, ± 4, and ± 7 beats per minute, under the bradycardia, normal, and tachycardia zones, respectively. These values are calculated based on the average RR value reported in this table under each specific HR zone.

[c] Preceding steady beat history in minutes was HR zone specific. It was calculated based on the average RR interval value reported under each specific HR zone in this table using the following formula, (RR interval X Preceding beats count) ÷ 60000.

HR, heart rate; ms, millisecond; QTi, QT interval; RRi, RR interval; SD, standard deviation.

Table 2.
Sample characteristics (N, 145).

Mean ± SD (Range)	
Age (years)	62.92 ± 13.94 (30 to 93)
BMI (Kg/m^2)	28.20 ± 7.88 (15.04 to 58.56)
Median (IQR)	
Total time of Holter monitoring in hours	24 (21 to 24)
n (%)	
Gender	
Male	61 (42.1%)
Female	84 (57.9%)
Race	
While	61 (42.1%)
Black	37 (25.5%)
Asian	29 (20%)
Other	18 (12.4%)
ACS	41 (28.2%)
STEMI	5 (3.4%)
NSTEMI	7 (4.8%)
Unstable angina	29 (20%)
History	
Beta blockers	21 (14.5%)
Hypercholesteremia	67 (46.2%)
Hypertension	91 (62.8%)
Smoking	21 (14.5%)
Diabetes mellitus	27 (18.6%)
MI	40 (27.6%)
Angina	36 (24.8%)
CABG	15 (10.3%)
PCI	26 (17.9%)

ACS, acute coronary syndrome; BMI, Body Mass Index; CABG, Coronary artery bypass graft; IQR, interquartile range; Kg/m^2, kilogram per square meter; MI, Myocardial infarction; NSTEMI, non ST elevation MI; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST elevation MI.

Table 3.
Descriptive statistics for the QT/RR slope under the three heart rate zones.

HR zone	n	Mean	SD
Bradycardia	110	0.074	0.071
Normal	116	0.114	0.099
Tachycardia	39	0.147	0.102

HR, heart rate; SD, standard deviation.

Table 4.
Hierarchical linear modeling comparing steadiness, the dependent variable, between intervals (RR vs. QT) and among different heart rate zones.

	Model A	Model B
Comparison	**EMMs Difference (95% CI)[a]**	
Normal vs. Bradycardia	35.30 – 28.40 = 6.9**	32.40 – 31.13 = 1.27
	(3.99 to 9.8)	(-3.69 to 6.23)
Tachycardia vs. Bradycardia	38.24 – 28.40 = 9.84**	33.26 – 31.13 = 2.13
	(6.61 to 13.08)	(-5.53 to 9.79)
Tachycardia vs. Normal	38.24 – 35.30 = 2.94	33.26 – 32.40 = 0.86
	(-0.29 to 6.18)	(-7.06 to 8.79)
RRi vs. QTi	47.74 – 20.22 = 27.52**	44.27 – 20.25 = 24.02**
	(23.73 to 31.34)	(19.44 to 28.59)
Interaction Term (HR zone*Interval)		
(Brady) RRi vs. QTi compared to, (Norm) RRi vs. QTi		48.33 – 13.93 = 34.4 compared to, 42.73 – 22.06 = 20.67*
(Brady) RRi vs. QTi compared to, (Tachy) RRi vs. QTi		48.33 – 13.93 = 34.4 compared to, 41.75 – 24.77 = 16.98*
(Norm) RRi vs. QTi compared to, (Tachy) RRi vs. QTi		42.73 – 22.06 = 20.67 compared to, 41.75 – 24.77 = 16.98

*p < 0.05 , **p < 0.0001

[a] 95% CI is not shown for the interaction term.

Brady, bradycardia; CI, confidence interval; EMMs, estimated marginal means; QTi, QT interval; RRi, RR interval; Tachy, tachycardia.

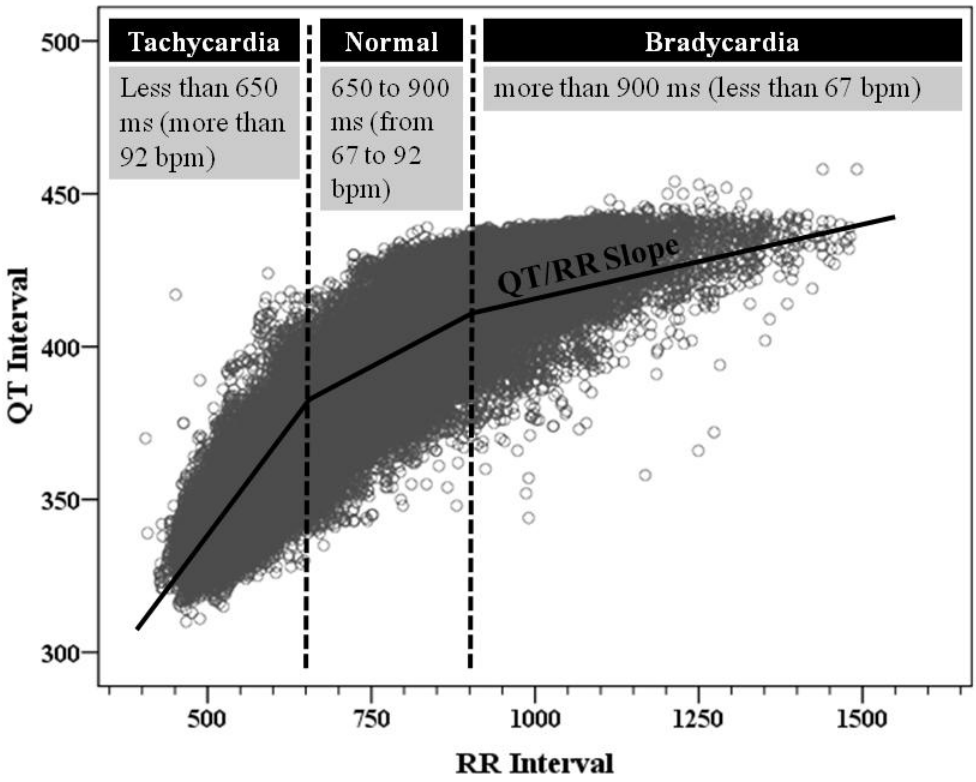

Figure 1. The QT/RR scatter plot for a single typical participant. Note the change in the QT/RR slope as the HR shifts from one zone to another. HR zones' boundaries as determined by the QT/RR slope are different from HR zones' boundaries that are conventionally defined (60 and 100 beat per minute).

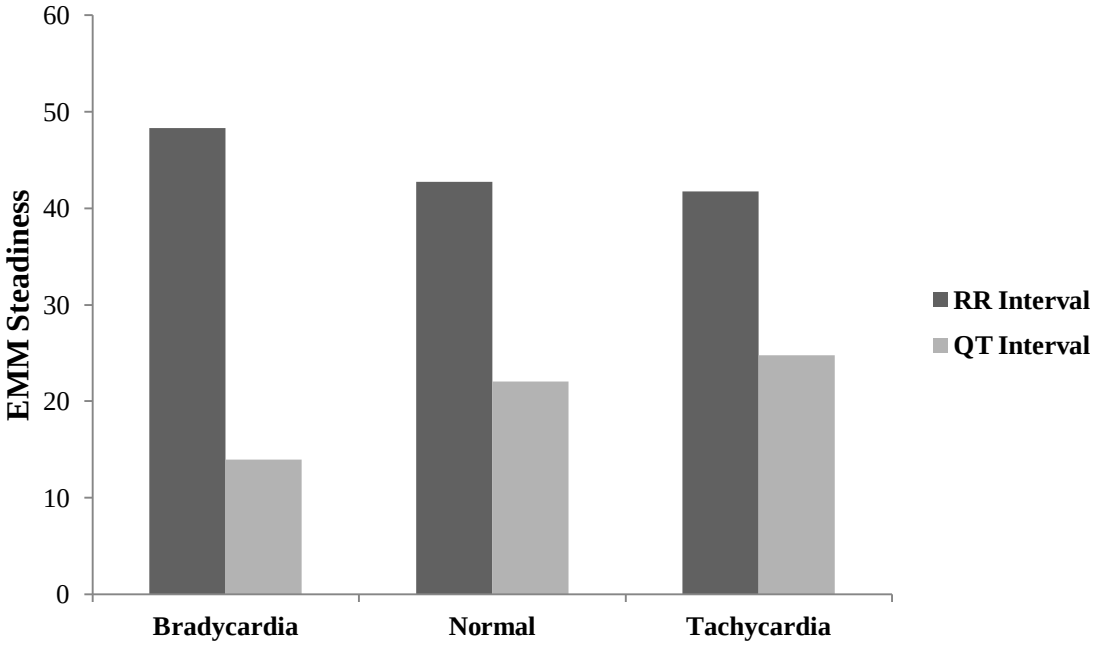

Figure 2. The difference in steadiness (milliseconds) between the QT interval and the RR interval under the bradycardia zone was greater than under the normal zone or the tachycardia zone. (EMM, estimated marginal mean).

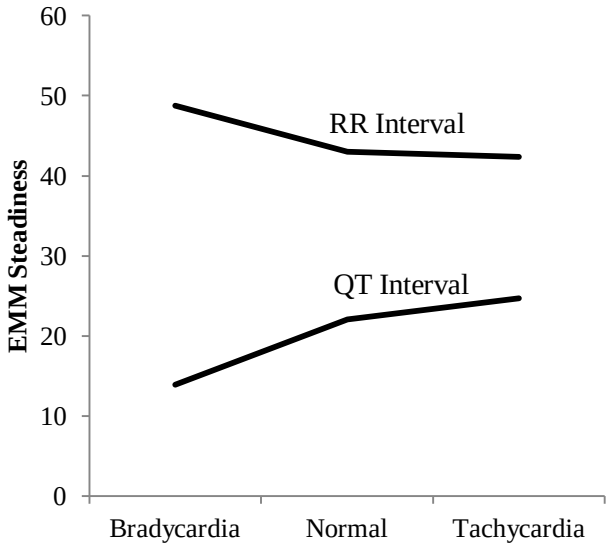

Figure 3. Steadiness and the pattern of change in steadiness as the heart rate shifts from one zone to another appear to be different in the QT interval compared to the RR interval. While QT interval steadiness tended to increase (Statistically significant only between the bradycardia zone and the other zones), RR interval steadiness tended to decrease (not statistically significant). (EMM, estimated marginal mean).

Chapter 5

Summary and Conclusion

Nurse scientists conduct research with the ultimate goal of advancing knowledge related to nursing practice, education, research, and administration. Nurse scientists are interested in any phenomenon as long as it is relevant to at least one of the nursing main defining concepts as a profession. These concepts, which are classically termed "metaparadigms," are the person, environment, health, and nursing (1). In brief, the person is the recipient of nursing care whether an individual or a group of individuals. The environment is the setting where this care is provided and the surrounding factors that influence it. Health is the subject of nursing care. Nursing are the nurses' actions that are carried out to deliver care. For a full discussion of the relation between investigating a phenomenon related to the electrocardiogram and nursing metaparadigms, the reader is advised to refer to the following reference (2).

Nurses carry out their responsibilities with the intent of protecting patients, promoting health, and preventing illness and injury. These goals are accomplished through the diagnosis and treatment of human responses (3). One of these duties is ECG monitoring. Nurses, especially those working in critical care settings, are required to monitor patients' ECGs continuously to assure their safety and to anticipate possible risks (4, 5). Large amounts of information can be obtained from the ECG about the patient's current and ongoing health status. The ECG reflects the adequacy of blood flow to the myocardium, certain drug effectiveness, electrolyte balance, as well as metabolic and hemodynamic abnormalities. The ECG is the standard for the diagnosis of cardiac arrhythmias (6).

With regard to the QT interval, as discussed in previous chapters, it reflects the activity of the ANS and the ventricular ion channels and the outcome of their interaction. The QT interval is also an index of homogeneity of ventricular repolarization. These two properties allow the QT interval to predict ventricular arrhythmias and according to some researchers to predict other adverse cardiovascular events (ACEs) (7, 8). Therefore, nurses monitoring the QT interval are likely to anticipate and consequently to prevent the occurrence of these ACEs.

The aims of this dissertation were (1) to determine the prevalence and prognostic significance of long QT interval among patients presenting to the emergency department with chest pain, (2) to investigate the association between long QT interval and several ACEs at 1 year follow-up among this group of patients, and (3) to evaluate the QT/RR dynamics as the heart rate (HR) shifts from one zone to another (Bradycardia, normal, and tachycardia). Toward achieving these aims, a secondary analysis of data obtained from the IMMEDIATE AIM trail was carried out.

In chapter 2, *Prevalence and Prognostic Significance of Long QT Interval in Patients with Acute Coronary Syndrome: Review of the Literature*, we reviewed pertinent literature related to the first two aims. The authors reviewed 26 studies published between 1981 and 2011. In the literature search we found no studies that have investigated the prevalence of long QT interval among patients with acute coronary syndrome (ACS) during the early acute phase. Instead, there were several studies that have examined the prevalence of long QT interval later during hospital stay. In these studies, the prevalence ranged between 19 and 60%. After careful review of existing studies, we concluded that the available evidence that examined the association between long QT interval and the occurrence of ACEs is contradictory. The majority of existing studies used inappropriate methods for QT measurement and correction. For example, most of these studies measured the QT interval from a single lead manually and calculated the HR corrected QT interval using Bazett's formula. We also concluded that nurses taking care of patients with ACS need to monitor the QT interval carefully especially between day 2 and 11 of hospital admission.

In chapter 3, *Prevalence and Prognostic Significance of Long QT Interval among Patients with Chest Pain: Selecting an Optimum QT Rate Correction Formula*, we determined for the first time the prevalence of long QT interval among patients presenting to the emergency department with chest pain. The prevalence was 14.5%. This was calculated using the optimum QT rate correction formula, linear subject specific correction, obtained after comparing seven different QTc formulas. Subject specific correction in this study resulted in almost zero absolute

mean QTc/RR correlation which indicates almost perfect correction. In this study, long QT interval did not predict mortality or hospital admission at short and long term follow-up. Only, the QT/RR slope predicted mortality at 7 year follow-up. Authors also reported in this study a 12 fold increase in the odds of having a long QT interval in patients with a history of old myocardial infarction (MI), controlling for other variables in the model.

Much of the confusion in the QT interval prediction power is resulting primarily from the inappropriate correction of the QT interval for HR. In Chapter 4, *QT/RR Dynamicity among Different Heart Rate Zones: Introducing a Physiological Evidence for Setting the Limits Defining Heart Rate Zones Boundaries*, the author reported a steeper QT/RR slope under the bradycardia zone. This finding cast doubt in currently available QTc formulas which assume the same QT/RR slope among different HR zones. In contrast, there was no difference in the QT/RR slope between the normal HR zone and the tachycardia zone. This was explained by the smaller change in the sympathetic activity required to shift the HR from the normal zone to the tachycardia zone compared to the larger sympathetic activity required to shift the HR from the bradycardia zone to the normal zone. The additional amount of sympathetic activity is required in the latter case to overcome the dominating parasympathetic activity under the bradycardia zone.

Innovation

The study reported in chapter 3 is the first to examine the prevalence of long QT interval among patients presenting to the emergency department with ACS. This study is among few that have monitored the QT interval continuously for 24 hours. With non continuous monitoring, the QT interval might be measured at a time where full adaptation to HR changes has not yet occurred, a phenomenon known as QT hysteresis, thus rendering the measurement inaccurate. For extra precision, seven different formulas have been used to calculate the HR corrected QT interval. Subject specific rate correction was among them. This type of correction has rarely been used and is considered the most accurate so far.

The study reported in chapter 4 is the first to examine the change in the QT/RR slope as the HR shifts from one zone to another. This comparison was carried out employing a steady heart beat selection technique. With this technique, only beats with a stable RR history were used for building the QT/RR slope under each HR zone which eliminated the need for QT hysteresis correction. This study is also the first to suggest setting new limits for defining different HR zones boundaries based on physiological evidence.

Implications

Implications for Practice

Long QT interval is not uncommon among patients presenting to the emergency department with chest pain. Long QT interval is associated with the polymorphic ventricular arrhythmia, torsade de pointes (9). If not treated, torsade de pointes almost half of the time degenerates into ventricular fibrillation and result in cardiac death (10). Long QT interval has also been reported by several investigators to be associated with other ACEs including mortality and hospital readmission at short and long term follow-up. Nurses taking care of patients in critical care units need to monitor the QT interval carefully especially between day 2 and 11 of hospital admission. During this time, the QT interval is more likely to be longer following acute vascular injury and consequently the risk of ACEs might be greater.

Prolongation of the QT interval may persist for several months following an ACS event. Optimum care of these patients requires ongoing follow-up until the QT interval returns to near pre-ACS values. In some patients, the QT interval might not return to pre-ACS values.
In chapter 3, one of the findings reported was that having a history of old MI increases the odds of having a long QT interval by 12 folds. This indicates that the electrophysiological alterations associated with an ACS event might persist and consequently monitoring these patients for ACEs needs to be continuously taken into account.

Accounting for the delayed adaptation of the QT interval to sudden alterations in HR (QT hysteresis) requires continuous monitoring. Using 10 second ECG recording for QT measurement

is not accurate especially when the HR is unsteady (fluctuating). A single point in time measurement might measure the QT interval at a time when full QT interval adaptation has not yet occurred and thus producing a QT-RR intervals mismatch. QT-RR intervals mismatch render the calculated QT interval corrected for HR (QTc) inaccurate. Non-continuous monitoring also does not allow differentiating between persistent and transient changes, does not allow calculating the QTc burden [(long QT beat count X 100) / total beat count] which might be an important predictor of ACEs, and more importantly does not allow timely intervention in emergency situations, for example when more than a single QT prolonging drug is administered in a high risk individual.

Only subject specific QT rate correction for HR produces adequate correction. Despite being inaccurate, other types of QT rate correction are still useful in the clinical setting for several reasons. First, they are easy to use, such as Bazett's formula. Second, they usually result in QTc values that are not much different from subject specific QT correction, on average 16 ms. These QTc differences are most of the time of no clinical significance and do not change treatment decisions. Third, the software upgrade necessary for subject specific QT rate correction has not yet been developed and installed in monitoring devices. Health care providers should be aware that using accurate QT rate correction becomes increasingly important when the underlying HR is unsteady (fluctuating) and when the HR is at extreme, outside the 55 to 120 bpm range.

Implications for Research

Patients with most likely ACS events should be classified to either STEMI or NSTEMI/UA within 10 minutes of hospital arrival based on ECG findings (11). Classifying ACS patients to these two groups is meaningful even after hospital admission giving the differences in the treatment options (12, 13). Researchers examining the association between long QT interval and ACEs in patients with ACS need to take these differences into account and preferably investigate each of these two groups separately. Researchers need also to carefully consider the time interval between symptom onset and initiation of QT interval monitoring. This time interval

greatly affects the length of the QT interval and consequently the prevalence as well as the sensitivity and specificity of the QT interval for predicting ACEs.

Researchers are advised to measure the QT interval automatically, preferably in addition to using semiautomatic techniques to verify measurement for a number of selected beats. In majority of previous studies the QT interval was measured manually. Manual measurement is not accurate. On average, the difference in QT interval measurement between one cardiologist and another could be as high as 20.2 ms (14), large enough to make a difference between low risk and substantial risk of developing ventricular arrhythmias (15). In addition, most of the previous studies did not use another investigator to verify or over-read the measured QT interval.

In the previous studies reviewed there were 8 different methods described to select the lead or the set of leads from where to measure the QT interval. The most common method was selecting the lead with the longest QT interval. Regardless of the method applied in lead selection, most of previous studies measured the QT interval from a single lead. Using only a single lead or a couple of leads to measure the QT interval is considered inaccurate especially when compared to more recent advanced techniques (16). Recent techniques combine information gathered from all available leads taken simultaneously to generate one root mean square ECG signal. The computed QT interval with this technique is from the earliest onset of the QRS complex in any lead to the latest offset of the T wave in any lead. The resultant QT interval will be longer than any other QT interval measured from any single lead. This measurement technique is the most accurate so far because it accounts for the total repolarization duration without being affected by the lead orientation relative to the cardiac vector (17).

Using a single lead for QT interval measurement add other challenges. For example comparing findings from different studies, accounting for the normal inter-lead variation in the QT interval (QT dispersion) which could be as high as 50 ms (18), and accounting for the ischemia or infarction repolarization changes when its anatomical location does not correspond to the lead being monitored. With regard to the last issue, most investigators chose to measure the

QT interval from the lead with the longest QT interval, usually the anterior leads, V3 or V4 (7, 8, 19). The challenge in using the anterior leads arises when the myocardial damage is occurring in the inferior wall. Damage in the inferior wall is best viewed with leads II, III, or aVF. The same issue arises in the studies that used one of these leads and reported a statistically longer QTc interval in anterior MI compared to inferior MI (20) (21) (22) (study 2). Again, is this a true difference or merely a difference because of the proximity in physical location between the anterior infarction and the recording ECG electrodes, as one author argued (20).

Researchers are advised to refrain from using Bazett's formula for QT rate correction. Bazett's formula is the most commonly used formula and the least accurate (23). Being the least accurate principally means that it will leave the greatest HR residual in the calculated QTc interval. Although not yet conclusive, the HR can also modify the prognosis following ACS (24) (25) (26) (27) (28). Thus, the prognostic effect of the QTc interval in the majority of existing studies might be in fact the prognostic effect of both the QTc interval and the HR. Researchers instead should use subject specific correction which is likely to produce complete control for HR.

Researchers are also advised to take into account QT interval circadian variation. Only few researchers pay attention to this phenomenon. In the previous studies reviewed, the QT interval was measured at different times during the day in different patients and then compared together. The clearest example is when admission QTc intervals from different patients were compared to each other without acknowledging that patients were admitted at different times of the day.

Because there are several researchers who believe that it is not a long QT interval per se that predicts ACEs but rather a persistent long QT interval (19, 29, 30), future research needs to adopt a longitudinal design. In one study (30), the authors emphasized how important it is to follow patients for several days following acute MI or after hospital discharge to evaluate whether the QTc interval has returned to initial values or not. According to this study, a persistent or progressively lengthening QTc interval increases the risk of ACEs especially torsade de pointes.

Another study (29) that examined patients with a first time acute MI who underwent successful percutaneous transluminal coronary angioplasty found that failing to shorten QTc interval was associated with increased risk for 1 year ACEs. ACEs included sudden cardiac death, ventricular fibrillation, and sustained ventricular tachycardia.

Conducting high quality QT research requires continuous monitoring. Continuous monitoring allows accounting for QT hysteresis, circadian variation, and proper QT rate correction.

Future research needs to focus more on the dynamic QT-RR interaction through studying the QT/RR slope. In the study reported in chapter 3, the QT/RR slope predicted mortality at 7 year follow-up (odds ratio, 2.01; 95% CI, 1.02 to 3.96; $p < 0.05$). The advantages of using the QT/RR slope are that it appears to be more sensitive to autonomic nervous system (ANS) influences than the QT interval itself and that using it eliminates the need for QT rate correction. In chapter 4 using steady beat selection we showed that the QT/RR slope is sensitive enough to capture even small variations in the ANS when the HR shifts from one zone to another. In discussing the findings, we suggested using the QT/RR slope for resetting the limits defining different HR zones' boundaries (bradycardia, normal, and tachycardia). This work can be the core for future research that leads to the development of advanced bedside cardiac monitors being able to display the QT/RR slope as an indicator of ANS activity and use this information to calculate subject specific HR zones' boundaries. For example, the monitor might be able to display a tachycardia alarm when the HR for a particular subject reaches 85 bpm. The alarm signals reaching the tachycardia threshold specific for that subject developed based on his own ANS profile. Using this technology, the patient's life could be saved by initiating appropriate therapy early before waiting until HR reaches the currently defined tachycardia threshold (100 bpm) which might be too dangerous for that particular patient. A similar scenario is when undue therapy is introduced by initiating unnecessary or harmful therapy for patients that their

tachycardia threshold has not yet been reached, for example when it is higher than 100 bpm, may be at 130.

It might be too early to recommend using HR zone specific QT rate correction. In fact, this might be unnecessary most of the time giving that subject specific correction can accomplish QT rate correction adequately using a single QT/RR coefficient under different HR zones. The only scenario where HR zone specific correction might be needed is in drug development trials where even small errors in QT rate correction are of substantial importance.

Implications for Education

Nurses and physicians working in critical care environments and taking care of patients with ACS need to be educated about QT interval measurement and rate correction.

References

1. Fawcett J. On the requirements for a metaparadigm: an invitation to dialogue. Nurs Sci Q. 1996 Fall;9(3):94-7; discussion 8-106.

2. Drew BJ. Value of MCL(1), MCL(6), and selected leads in the diagnosis of wide QRS complex tachycardia. Chapter two: conceptual framework and literature review. Ph.D. dissertation. San Francisco: University of California San Francisco; 1990: 14-27.

3. ANA. Nursing's social policy statement: the essence of the profession: Amer Nurses Assn; 2010: 1.

4. Drew BJ, Califf RM, Funk M, et al. Practice standards for electrocardiographic monitoring in hospital settings: an American Heart Association scientific statement from the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young: endorsed by the International Society of Computerized Electrocardiology and the American Association of Critical-Care Nurses. Circulation. 2004;110(17):2721.

5. Hebra JD. The nurse's role in continuous dysrhythmia monitoring. AACN Clin Issues Crit Care Nurs. 1994 May;5(2):178-85.

6. Charles F. Evolution of the clinical electrocardiogram. J Am Coll Cardiol. 1989;14(5):1127-38.

7. Gadaleta FL, Llois SC, Lapuente AR, Batchvarov VN, Kaski JC. Prognostic value of corrected QT-interval prolongation in patients with unstable angina pectoris. Am J Cardiol. 2003;92(2):203-5.

8. Jiménez-Candil J, González IC, González Matas JM, et al. Short-and long-term prognostic value of the corrected QT interval in the non-ST-elevation acute coronary syndrome. J Electrocardiol. 2007;40(2):180-7.

9. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings. Circulation. 2010;121(8):1047-60.

10. Costa A, Chalvidan T, Belounas A, et al. Predictive factors of ventricular fibrillation triggered by pause dependent torsades de pointes associated with acquired long QT interval. J Cardiovasc Electrophysiol. 2000;11(9):990-7.

11. O'Connor RE, Brady W, Brooks SC, et al. Part 10: acute coronary syndromes: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122(18_suppl_3):S787.

12. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2012 Aug 14;126(7):875-910.

13. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Jan 29;127(4):e362-425.

14. Murray A, McLaughlin NB, Bourke JP, Doig JC, Furniss SS, Campbell RW. Errors in manual measurement of QT intervals. Br Heart J. 1994 Apr;71(4):386-90.

15. FDA. Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. 2005.

16. Zhou SH, Helfenbein ED, Lindauer JM, Gregg RE, Feild DQ. Philips QT interval measurement algorithms for diagnostic, ambulatory, and patient monitoring ECG applications. Ann Noninvasive Electrocardiol. 2009;14:S3-S8.

17. Pickham D, Hasanien AA. Measurement and rate correction of the QT interval. AACN Adv Crit Care. 2013 Jan-Mar;24(1):90-6.

18. Statters DJ, Malik M, Ward DE, Camm AJ. QT dispersion: problems of methodology and clinical significance. J Cardiovasc Electrophysiol. 1994 Aug;5(8):672-85.

19. Obayashi T, Tokunaga T, Liizumi T, Shiigai T, Hiroe M, Marumo F. Transient QT interval prolongation with inverted T waves indicates myocardial salvage on dual radionuclide single-photon emission computed tomography in acute anterior myocardial infarction. Jpn Circ J. 2001;65(1):7.

20. Ahnve S. QT interval prolongation in acute myocardial infarction. Eur Heart J. 1985;6(suppl D):85.

21. Raev D. Relationship between rate-corrected QT interval and wall motion abnormalities in the setting of acute myocardial infarction. Int J Cardiol. 1997;61(1):15-20.

22. Juul-Möller S. Corrected QT-interval during one year follow-up after an acute myocardial infarction. Eur Heart J. 1986;7(4):299.

23. Aytemir K, Maarouf N, Gallagher MM, Yap YG, Waktare JEP, Malik M. Comparison of formulae for heart rate correction of QT interval in exercise electrocardiograms. Pacing Clin Electrophysiol. 1999;22(9):1397-401.

24. Yi G, Guo X-H, Reardon M, et al. Circadian variation of the QT interval in patients with sudden cardiac death after myocardial infarction. Am J Cardiol. 1998;81(8):950-6.

25. Bangalore S, Messerli FH, Ou FS, et al. The association of admission heart rate and in-hospital cardiovascular events in patients with non-ST-segment elevation acute coronary syndromes: results from 135 164 patients in the CRUSADE quality improvement initiative. Eur Heart J. 2010;31(5):552.

26. Dyer AR, Persky V, Stamler J, et al. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. Am J Epidemiol. 1980;112(6):736.

27. Risk stratification and survival after myocardial infarction. N Engl J Med. 1983;309(6):331-6.

28. Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction : results from an international trial of 41 021 patients. Circulation. 1995 March 15, 1995;91(6):1659-68.

29. Bonnemeier H, Hartmann F, Wiegand UH, Bode F, Katus HA, Richardt G. Course and prognostic implications of QT interval and QT interval variability after primary coronary angioplasty in acute myocardial infarction. J Am Coll Cardiol. 2001;37(1):44.

30. 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(4):1168-74.

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