QTc prolongation prior to angiography predicts poor outcome and associates significantly with lower left ventricular ejection fractions and higher left ventricular end-diastolic pressures

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Abstract

Background: QT prolongation on the surface ECG is associated with sudden cardiac death. The cause of QT prolongation in ischaemic heart disease (IHD) patients remains unknown, but may be due to a complex interplay between genetic factors and impaired systolic and/or diastolic function through as yet unexplained mechanisms. It was hypothesised that QT prolongation before elective coronary angiography is associated with an increased mortality at six months.

Methods: Complete records of 321 patients who underwent coronary angiography were examined for QT interval corrected for heart rate (QTc), left ventricular ejection fraction (LVEF), left ventricular end-diastolic pressure (LVEDP) and known ischaemic heart disease risk factors. Patients were designated long QTc (LQTc) when they had prolonged QTc intervals or normal QTc (NQTc) when the QTc interval was normal. Patients with atrial fibrillation, bundle branch blocks, no ECG in the 24 hours before angiography, or a creatinin level > 200 μmol/l were excluded. Survival was determined telephonically at six months.

Results: Twenty-eight per cent of the total population had LQTc. During follow up, 15 patients (4.7%) died suddenly, 73% of whom had a LQTc. LQTc was significantly associated with mortality (LQTc 12% vs NQTc 1.7%; p < 0.01), and with lower but normal LVEF (LQTc 52.9 ± 15.4% vs NQTc 61.6 ± 13.6%; p < 0.01), higher LVEDP at LVEF > 45% (LQTc 19.2 ± 9.0 mmHg vs NQTc 15.95 ± 7.5 mmHg; p < 0.05), hypercholesterolaemia and a negative family history of IHD.

Conclusion: In patients with sinus rhythm and normal QRS width, QTc prolongation before coronary angiography predicted increased mortality at six months. QTc also associated strongly with left ventricular systolic and diastolic dysfunction, hypercholesterolaemia and a negative family history of IHD.

Keywords: QT prolongation, sudden death, coronary artery disease

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The QT interval represents ventricular electrical depolarisation and repolarisation on the surface ECG. It increases with age and varies with gender, time of day, season of the year and heart rate.1-3 Bazett’s formula is frequently used to correct the QT interval for heart rate, yielding the QTc interval.4-6

A prolonged QTc interval (LQTc) is a manifestation of a complex interplay between genetic and environmental factors, and is a risk factor for life-threatening dysrhythmias and sudden death. The forme fruste of QT prolongation is congenital long QT syndrome (LQTS), an inherited cardiac ion-channel disease associated with syncope, malignant ventricular tachydysrhythmias and sudden cardiac death. LQTS, by exclusion, occurs in structurally normal hearts.7

Recently, polymorphisms in the gene for NOS1AP, which regulates nitric oxide production and thus coronary perfusion, have been shown to prolong cardiac repolarisation.8,9 Ethnic differences in QT interval have also been reported, LQTc comprising a higher risk among black than white subjects.10

QT prolongation is an independent prognosticator of cardiac and all-cause mortality, especially in the context of cardiovascular disease.11-13 In addition, it is associated with an increased 10-year risk of ischaemic heart disease (IHD) and sudden death in the general population.14

The fact that interventional cardiologists are more interested in the “ST” segment than the ‘QTc’ is underscored by the paucity of QTc studies peri-angiography. In only one study has an LQTc in the period immediately before coronary angiography been directly correlated with outcome, but the authors described QT peak interval instead of QTc.15 LQTc in the presence of coronary artery disease increases the risk of sudden cardiac death by a factor of five.16

IHD is a cause of systolic and diastolic dysfunction of the left ventricle, and both of these are independent predictors of mortality.17,18 QT prolongation is not only inherited, but also linked to cardiac hypertrophy, as frequently observed in hypertensive heart disease.19 However, no reference to an association between left ventricular systolic and diastolic dysfunction and QTc could be identified in the literature. Additionally, the length of the QTc interval appears to be directly related to the number of large coronary arteries that are diseased.20

QT prolongation may also reflect autonomic neuropathy in patients with diabetes mellitus.21,22 It does not, however, provide a reliable measure of the degree of autonomic neuropathy.23 Although smoking has been associated with a LQTc, it has not
been shown to be an independent cause of a LQTc. No clear link is evident in the literature between hypercholesterolaemia and QTc interval.

The purpose of our study was to evaluate LQTc as an independent prognostic indicator with regard to mortality and systolic and diastolic dysfunction in the context of IHD. Furthermore, we endeavoured to assess, in a state hospital setting in the Western Cape, whether LQTc correlated with triple-vessel coronary artery disease (TVCAD), or was significantly associated with hypercholesterolaemia, diabetes mellitus, smoking, hypertension or a family history of IHD.

Methods

The study was approved by the Committee for Human Research, Faculty of Health Sciences, Stellenbosch University. All patients signed informed consent before coronary angiography. All data were collected and recorded as part of routine clinical care.

This was a single-centre, prospective study, enrolling a cohort of patients who were eligible for coronary angiography from 2006 to 2009 at Tygerberg Academic Hospital. Due to the time limit imposed by the authors collecting data, rotating through the coronary care unit, not all eligible patients could be enrolled. Patients with atrial fibrillation, bundle branch blocks, no ECG in the 24 hours before angiography, or renal failure (creatinine ≥ 200 μmol/l) were excluded from the study.5

QTc intervals were recorded on the last ECG taken during the 24 hours before coronary angiography, and designated long QTc (LQTc) or normal QTc (NQTc). The primary outcome was six-month survival. Secondary outcomes included correlation of QTc (LQTc) or normal QTc (NQTc). The primary outcome was the 24 hours before coronary angiography, or renal failure (creatinine ≥ 200 μmol/l) were excluded from the study.5

QTc intervals were recorded on the last ECG taken during the 24 hours before coronary angiography, and designated long QTc (LQTc) or normal QTc (NQTc). The primary outcome was six-month survival. Secondary outcomes included correlation of QTc intervals with left ventricular ejection fraction (LVEF), left ventricular end-diastolic pressure (LVEDP), TVCAD, diabetes mellitus, smoking, hypertension or a family history of IHD.

Statistical analysis

Data were analysed by the Stellenbosch University Centre for Statistical Consultation (CSC) using STATISTICA version 9 (StatSoft Inc, Tulsa, OK, USA, 2009). The Kaplan–Meier method was used to create survival curves for NQTc and LQTc groups and a log-rank test was used to compare the two curves and generate a p-value. NQTc and LQTc groups were compared with regard to LVEF, LVEDP and serum cholesterol with a Mann–Whitney U test. Categorical data (diabetes mellitus, smoking, hypertension and family history of IHD) were tested for an association with LQTc using a chi-square test. Statistical significance was defined as p < 0.05.

Results

Of the 2 023 patients who were catheterised, 321 were enrolled (80.2% Coloured, 18.8% white, 1.0% black) (mean age 56 ± 12 years; range 24–84) (Fig. 1). One hundred and sixteen patients (36%) were female (mean age 57 ± 10 years; range 29–78) and 205 (64%) were male (mean age 57 ± 12 years; range 24–85) (p = 0.168). Ninety patients (28%) had LQTc.

At six months, 15 (4.7%) of the total population had died, 73% of whom had a LQTc. Eleven patients (12%) died in the LQTc group and four (1.7%) in the NQTc group (p < 0.01) (Fig. 2). The hazard ratio was 10.16 (95% CI: 2.91–35.44). LQTc patients had normal LVEF but lower than that of the NQTc cohort (LQTc: 52.9 ± 15.4% vs NQTc: 61.6 ± 13.6%; p < 0.01) (Fig. 3) and higher LVEDP at LVEF > 45% (LQTc: 19.2 ± 9.0 mmHg vs NQTc: 15.9 ± 7.5 mmHg; p < 0.05) (Fig. 4).
LQTc cohort also had significantly higher serum cholesterol levels than the NQTc cohort (Fig. 5). A family history of IHD was significantly less common among those with LQTc \( (p = 0.045) \) (Table 1). No association between LQTc and diabetes mellitus, smoking or hypertension could be detected. No association could be demonstrated between TVCAD and NQTc or LQTc \( (p = 0.96) \).

### Discussion

This study provides further evidence that, regardless of coronary revascularisation, QT prolongation before coronary angiography associated significantly with increased mortality at six months, lower LVEF and higher LVEDP. With regard to IHD risk factors, LQTc patients had higher serum cholesterol values and rarely a family history of IHD.

Traditionally, QT prolongation was seldom regarded by interventional cardiologists to be clinically useful, but it has recently been shown that the risk for coronary stenosis increases by 33 to 41% for every 20-ms QTc interval prolongation.29 The ST segment, on the other hand, which forms an integral part of the QT interval, is considered a better marker of underlying coronary artery disease. Interventional cardiologists rely heavily on ST segment shifts during exercise and recovery to identify those patients who need diagnostic coronary angiography. Little attention is given to the QTc interval, especially if it has to be measured or calculated manually.

Once coronary angiography has been performed, stents have been inserted and dual anti-platelet therapy (DAT) and beta-blockers have been prescribed, patients are often seen only weeks later for follow up at the outpatient clinic, where they are assessed by a junior colleague. The routine ECG is studied for new Q waves and cardiac arrhythmias. The blood pressure is checked, drug compliance with DAT is reiterated, and the patient is given a six-month follow-up appointment. Our data suggest that more than 10% of patients with QTc prolongation prior to coronary angiography will not return for their six-month appointment because they have died suddenly.

The association of LQT with a lower but normal LVEF is interesting. While there is no internationally agreed threshold of a ‘low’ LVEF, it has been characterised in a report of the American Society of Echocardiography and the European Association of Echocardiography by gradation: mild (45–54%), moderate (30–44%) and severe (<30%) left ventricular dysfunction.30 Only one study reported an association between LQTc and impaired LV function.31 The authors also reported that the QTc interval increased significantly from one- to three-vessel disease. We did not find this correlation between TVCAD and LQTc in our study.

The mechanism by which a decreased LVEF results in QT prolongation is unknown, but may involve ion-channel remodelling and/or intracellular calcium transport.32 LVEF is frequently used to prognosticate patients who have suffered a myocardial infarction or who have dilated cardiomyopathy. It is generally accepted that patients with an impaired systolic function have a higher risk for sudden cardiac death, presumably due to malignant ventricular tachydysrhythmias. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), implantable cardioverter-defibrillator (ICD) therapy reduced all-cause mortality by 23% compared with placebo.33 Interestingly, amiodarone, a commonly used anti-arrhythmic agent that also prolongs the QT interval, was ineffective to prevent sudden death in these patients.
The association of LQT with an elevated LVEDP (at a normal LVEF – frequently defined as > 45% , and used for the purpose of this study) is striking. Diastolic dysfunction is a relatively new concept when compared with LVEF. The commonest cause of diastolic dysfunction is hypertensive heart disease. Often these patients have thicker, stiffened left ventricles with good systolic function, but impaired relaxation and compliance. Again, exactly how diastolic dysfunction in IHD patients is associated with QT prolongation remains unknown, but recently an association was found between down-regulation of the hERG gene and QT prolongation in rats with cardiac hypertrophy.34

Ion-channels are embedded in a phospholipid bi-layer primarily composed of cholesterol esters. Both congenital LQTS and familial hypercholesterolaemia are more common in South Africans of European descent. Co-segregation of LQTS and familial hypercholesterolaemia are more common when compared with LVEF. The commonest cause of this study) is striking. Diastolic dysfunction is a relatively new concept when compared with LVEF. The commonest cause of diastolic dysfunction is hypertensive heart disease. Often these patients have thicker, stiffened left ventricles with good systolic function, but impaired relaxation and compliance. Again, exactly how diastolic dysfunction in IHD patients is associated with QT prolongation remains unknown, but recently an association was found between down-regulation of the hERG gene and QT prolongation in rats with cardiac hypertrophy.34

Ion-channels are embedded in a phospholipid bi-layer primarily composed of cholesterol esters. Both congenital LQTS and familial hypercholesterolaemia are more common in South Africans of European descent. Co-segregation of ion-channel disease and hypercholesterolaemia has not yet been described in humans, but in Langendorff-perfused rabbit hearts, hyperlipidaemia led to significant QT prolongation compared with normcholesterolaemia, which can be reversed by administering simvastatin.35

Study limitations
This single-centre study in a state hospital setting may be prone to selection bias due to the fact that patients were enrolled only during rotations of the authors collecting the data through the coronary care unit. However, all eligible patients were enrolled during these intervals, leading us to believe that the cohort was truly representative.

More than 80% of the studied population were of mixed racial ancestry. One should therefore be careful to draw conclusions about race and QT prolongation.

Prescribed medications were not checked and these may well have prolonged the QT interval after discharge. However, this study addressed the relationship between QTc prior to coronary angiography and mortality at six months.

The effects of coronary revascularisation on QTc were also not investigated but it was assumed that significant coronary stenosis would have been treated appropriately by the interventional cardiologist. Mortality in the LQT cohort remained high regardless of coronary revascularisation. Follow up was relatively short owing to the vast extent of the geographical catchment area of the hospital.

Genetic screening was also not performed on the study patients. Diastolic pressure was used as an indicator of diastolic function; however, echocardiographic parameters of diastolic function were not assessed.

Conclusion
This is the first description of LQTc in a cohort of IHD patients in a South African setting. The study confirms that QTc, which can be determined by a simple, non-invasive, inexpensive method, is an index of subsequent sudden death in patients who undergo coronary angiography for suspected IHD.

QTc prolongation before coronary angiography is also a reflection of systolic and diastolic dysfunction (in the context of normal systolic function) of the left ventricle, both of which are independent predictors of mortality rate. Furthermore, LQTc correlates with hypercholesterolaemia and a negative family history of IHD.

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References
1. Reardon M, Malik M. QT interval change with age in an overtly healthy older population. Clin Cardiol 1996; 19: 949–952.
2. Beyerbach DM, Kovacs RJ, Dmitrienko AA. Heart rate-corrected QT interval in men increases during winter months. Heart Rhythm 2007; 4: 277–281.
3. Molnar J, Zhang F, Weiss J, et al. Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. J Am Coll Cardiol 1996; 27: 76–83.
4. Kautzner J. QT interval measurements. Cardiac Electrophysiol Rev 2002; 6: 273–277.
5. Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is “normal”. J Cardiovasc Electrophysiol 2006; 17: 333–336.

| TABLE 1. ASSOCIATION BETWEEN LQTc AND NQTc GROUPS OF PATIENTS WITH REGARD TO MAJOR RISK FACTORS FOR IHD |
| --- |
| Risk factor present | Yes, n (%) | No, n (%) | Total, n | p-value |
| Diabetes mellitus |  |  |  |  |
| NQTc | 62 (29) | 149 (71) | 211 |  |
| LQTc | 29 (33) | 59 (67) | 88 | 0.54 |
| Total n | 91 | 208 | 299 |  |
| Smoking |  |  |  |  |
| NQTc | 116 (56) | 92 (44) | 208 |  |
| LQTc | 55 (64) | 31 (36) | 86 | 0.19 |
| Total n | 171 | 123 | 294 |  |
| Hypertension |  |  |  |  |
| NQTc | 157 (74) | 55 (26) | 212 |  |
| LQTc | 70 (80) | 17 (20) | 87 | 0.23 |
| Total n | 227 | 72 | 299 |  |
| Family history |  |  |  |  |
| NQTc | 74 (36) | 134 (64) | 208 |  |
| LQTc | 21 (24) | 67 (76) | 88 | 0.045* |
| Total n | 95 | 201 | 296 |  |

*Statistically significant association.
20. Krämer B, Brill M, Brühl. A relationship between the degree of coronary artery disease and of left ventricular function and the duration of the QT-interval in ECG. *Europ. Heart J* 1986; 7: 14–24.

21. Pappachan JM, Sebastian J, Bino BC, *et al.* Cardiac autonomic neuropathy in diabetes mellitus: prevalence, risk factors and utility of corrected QT interval in the ECG for its diagnosis. *Postgrad Med J* 2008; 84: 205–210.

22. Klupa T, Mroczeck T, Galicka-Latala D, *et al.* Corrected QT interval and diabetic neuropathy of the cardiovascular system. *Prez. Lek* 1995; 52: 583–587 (abstract).

23. Bravenboer B, Hendriksen PH, Oey LP, *et al.* Is the corrected QT interval a reliable indicator of the severity of diabetic autonomic neuropathy? *Diabetes Care* 1993; 16: 1249–1253.

24. Singh K. Effect of smoking on QT interval, QT dispersion and rate pressure product. *Ind. Heart J* 2004; 56: 140–142.

25. Das G, QT interval and repolarization time in patients with intravenous conduction delay. *J Electrocardiol* 1990; 23: 49–52.

26. Piotrowicz K, Zareba W, McNitt S, Moss AJ. Repolarization duration in patients with conduction disturbances after myocardial infarction. *Am J Cardiol* 2007; 99: 163–168.

27. Resnick HE, Foster GL, Bardlesy J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1992–2002: the National Health and Nutrition Examination Survey. *Diabetes Care* 2006; 29: 531–537.

28. Grundy SM, Cleeman JI, Merz CNB, *et al.* National Cholesterol Education Program (NCEP). Implications of recent clinical trials for chamber quantification. *Europ. J. Echocardiography* 2007, 2 Feb. [Epub ahead of print]

29. Lang RM, Bierig M, Devereux RB, *et al.* Recommendations for chamber quantification. *Europ. J. Echocardiography* 2007; 7: 99–108.

30. Krämer B, Brill M, Brühl A, Köhler W. Relationship between the degree of coronary artery disease and of left ventricular function and the duration of the QT-interval in ECG. *Europ. Heart J* 1986; 7: 14–24.

31. Qi X, Yeh YH, Chartier D, *et al.* The calcium/calmodulin kinase system and arrhythmogenic afterdepolarizations in bradydysrhythmia-related acquired long-QT syndrome. *Circ Arrhythm Electrophysiol* 2009; 2: 295–304.

32. Bandy GH, Lee KL, Mark DB, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352: 225–237.

33. Hu C, Yan C, Lin J, Liu S, Li Y. Down-regulation of the human ether-a-go-go-related gene in rat cardiac hypertrophy. *Am J Med Sci* 2011; 341: 119–125.

34. Lee TM, Lin MS, Chou TF, Chang NC. Effect of simvastatin on left ventricular mass in hypercholesterolemic rabbits. *Am J Physiol Heart Circ Physiol* 2005; 288: H1352–1358.