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Corrected QT interval as a predictor of mortality in elderly patients with syncope

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Abstract

Background: *Prolonged corrected QT interval (QTc) holds independent prognostic importance in predicting mortality in patients with coronary artery disease, diabetes mellitus and congestive heart failure. However, its association with all cause or cardiac mortality in the general population remains unclear. We evaluated the relationship between prolonged QTc and total mortality among patients with syncope.*

Methods: *This was a retrospective study of 348 patients presenting to the emergency department with syncope of any etiology over a period of one year. All patients with atrial fibrillation, left bundle branch block and cardiac devices (pacemaker/defibrillator) were excluded. Prolonged QTc interval was defined as QTc interval ≥ 440 ms. The primary end point for this study was total mortality in patients presenting with syncope.*

Results: *There were 58 (16%) deaths in this population during a mean follow-up of 30 months. Patients with prolonged QTc interval had significantly higher mortality when compared to those with normal QTc interval (22%* vs *11%; p = 0.004). This significance was not retained after adjustment for covariates in the Cox regression model, where we found that age ≥ 65 years (hazard ratio [HR] 7.9; 95% confidence interval [CI] 1.9–32.9; p = 0.004) and QTc interval ≥ 500 ms (HR 3.5; 95% CI 1.56–8.12; p = 0.002) were predictors of increased mortality among patients with syncope.*

Conclusions: *In elderly patients presenting to the emergency department with syncope, QTc interval ≥ 500 ms helps identify patients at higher risk of adverse outcomes.* (Cardiol J 2011; 18, 4: 395–400)

Key words: syncope, prolonged QTc, mortality, older

Introduction

Syncope is a common presenting symptom among patients seen in the emergency department (ED) [1–3]. Among the various etiologic factors, cardiogenic syncope is associated with the highest mortality [3]. Therefore, an electrocardiogram (ECG) is an important diagnostic tool in the initial evaluation of all patients presenting with syncope to rule out potential cardiac causes of syncope such as arrhythmias and acute coronary syndrome. Studies have looked at the possible association and prognosis of QRS morphology in syncope patients [4]. But there have been no studies into the effect of prolonged corrected QT (QTc) in this cohort. QTc holds independent prognostic importance for mor-

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tality in patients with coronary artery disease [5, 6], diabetes mellitus [7] and congestive heart failure (CHF) [8]. However, its association with total mortality in patients with syncope is unclear. Our study aimed to examine the possible association of prolonged QTc with increased mortality in patients with syncope.

Methods

This was a retrospective study of patients presenting to the ED with a diagnosis of syncope at the Unity Health System, Rochester, New York, USA, between January 2007 and January 2008. Patients were identified using the International Classification of Diseases Ninth revision (ICD-9) code (780.2) for syncope. Baseline clinical data, demographics, 12-lead ECG and laboratory findings were collected by reviewing the electronic medical records and paper charts. The mortality data for these patients was collected from the published government death statistics from the National Death Index (NDI).

All patients underwent standard 12-lead ECG acquired using the GE (MAC 5500) recording system, the paper copies of which after scanning in a PDF format were stored in a centralized database. For each cardiac cycle, the individual lead signal was magnified by 800% to occupy a 15.5-inch high-resolution monitor. Electronic calipers (Cardiocaliper V3.3) capable of measuring to within 0.1 mm precision after standard calibration were used to determine the cycle length, QRS duration and QT interval. All intervals were measured by two investigators blinded to the clinical and survival data. QT interval was measured from the beginning of the QRS complex to the visual return of the T wave to the isoelectric line. When the T wave was interrupted by the U wave, the end of the T wave was defined as the nadir between T and U waves. Intervals were measured in two consecutive beats in each chest lead, except in leads where the T wave was isoelectric. All the patients had normal sinus rhythm. Heart rate correction was performed by Bazett's formula and QTc interval was defined as the mean duration of all the QTc measurements. This method is similar to that described in previous studies [9, 10]. Prolonged QTc interval was defined as QTc interval ≥ 440 ms.

The primary end point for this study was total mortality in patients presenting with syncope. Clinical characteristics were compared using the Student's t-test for continuous variables and χ^2 or Fisher exact test for categorical variables. Cox regression model was used to identify clinical factors that predict mortality. The variables evaluated in the Cox regression model were patients' age (≥ 65 years *vs* < 65 years), gender, history of myocardial infarction and QTc interval (≥ 440 ms *vs* < 440 ms), heart rate and QRS duration (> 120 ms *vs* < 120 ms). Separate Cox regression models were created for several categories of QTc interval (450 ms through 500 ms) to find if a cut-off threshold exists beyond which the risk of death increases. Statistical analysis was performed using the SAS 9.2 software package. A p value less than 0.05 was considered statistically significant.

Results

We identified 420 patients who presented to the ED with syncope during the 12 month period in question. Twelve patients were excluded due to missing data. Patients with atrial fibrillation (n = 28), left bundle branch block (n = 10), and implantable devices (n = 22) were also excluded. Medical records of the remaining 348 patients were further reviewed to extract data. Mean age for the study population was 74 ± 17 years, and 199 (57%) were female. Mean QTc was 438 ms and median was 434 ms. One hundred and forty eight (43%) patients had prolonged QTc (≥ 440 ms) interval, while the remaining 200 (57%) had normal QTc (< 440 ms). Mean QTc interval for men was 436 ± 31.0 ms and 439 ± 34.2 ms for women in the study population.

Clinical characteristics of patients by QTc interval are presented in Table 1. Advanced age, incidence of myocardial infarction, hypokalemia and prolonged QRS duration were the preponderant characteristics among the patients with prolonged QTc (≥ 440 ms). Though there was no significant difference in other co-morbid conditions between the two groups, a trend towards a higher number of patients with hypertension was seen in patients with prolonged QTc. There was no difference between the two groups in clinical, laboratory (other than potassium) or pharmacological parameters, which are known to affect the QT interval. During a mean follow-up of 30 months, there were 58 (15.5%) deaths in this study population. Clinical characteristics of patients by survival status (alive and dead) are presented in Table 2.

Deceased patients were older, had significantly prolonged QTc (453 ms *vs* 435 ms; p = 0.001) and a higher incidence of CHF. Resting heart rate was also statistically different among the two

Table 1. Patient demographics and clinical characteristics by QTc interval.

Variables	QTc < 440 (n = 200; 57%)	QTc ≥ 440 (n = 148; 43%)	P
Age (years)	70 ± 18	79 ± 14	< 0.0001
Gender: male/female	89 (44.5%)/111 (55.5%)	60 (40.5%)/88 (59.5%)	0.46
Smoking	76 (38%)	67 (45%)	0.18
Medical conditions:			
Hypertension	133 (67%)	111 (75%)	0.08
Diabetes mellitus	43 (22%)	37 (25%)	0.44
Myocardial infarction	42 (21%)	48 (32%)	0.01
Congestive heart failure	20 (10%)	20 (20%)	0.31
Creatinine	1.18 ± 0.9	1.33 ± 1.7	0.35
Left ventricular ejection fraction (%):			
Mean	57 ± 7	55 ± 9	0.12
Reduced (≤ 40%)	11 (5%)	11 (7%)	0.46
Heart rate:			
Mean	61 ± 23	67 ± 23	0.01
Bradycardia (≤ 50)	65 (32%)	39 (26%)	0.21
Electrolytes:			
Potassium [mg/dL]	4.1 ± 0.5	4.0 ± 0.5	0.03
Magnesium [mg/dL]	1.7 ± 0.27	1.7 ± 0.21	0.11
Calcium [mg/dL]	9.0 ± 0.6	9.0 ± 0.5	0.97
Medications:			
Beta-blockers	82 (41%)	67 (45%)	0.42
Anti-arrhythmics	2 (0.01%)	1 (0.006%)	NA
Quinolone	2 (0.01%)	0 (0%)	NA
QRS duration [ms]	88 ± 14	160 ± 26	< 0.0001
End point: all-cause mortality	21 (11%)	32 (22%)	0.004

Numbers have been rounded to the nearest absolute value; NA — not applicable

Table 2. Patient demographics and clinical characteristics by survival status.

Variables	Alive (n = 295, 85%)	Dead (n = 53, 15%)	P
Age (years)	72 ± 17	84 ± 10	< 0.0001
Gender: male/female	128 (43%)/167 (57%)	21 (40%)/32 (60%)	0.60
Smoking	122 (85%)	21 (15%)	0.79
Medical conditions:			
Hypertension	199 (67%)	45 (85%)	0.01
Diabetes mellitus	65 (22%)	15 (28%)	0.31
Myocardial infarction	71 (24%)	19 (36%)	0.07
Congestive heart failure	26 (9%)	14 (26%)	0.002
Creatinine	1.19 ± 1.3	1.50 ± 1.4	0.36
Left ventricular ejection fraction (%)	57 ± 7.2	54 ± 11.2	0.09
Heart rate [/min]	63 ± 23	71 ± 24	0.01
Electrolytes:			
Potassium [mg/dL]	4.0 ± 0.5	4.1 ± 0.6	0.43
Magnesium [mg/dL]	1.7 ± 0.2	1.7 ± 0.2	0.69
Calcium [mg/dL]	9.0 ± 0.6	8.9 ± 0.5	0.40
Beta-blockers	126 (43%)	23 (43%)	0.92
QRS duration [ms]	93 ± 21	94 ± 23	0.73
QTc duration [ms]	435 ± 31	453 ± 35	0.001

Numbers have been rounded to the nearest absolute value

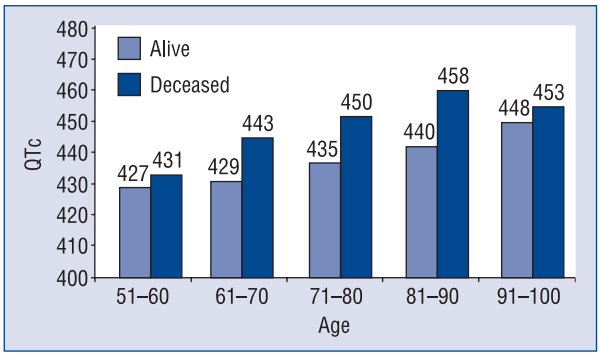

Figure 1. QTc distribution in different age quartiles. For the same given age quartile, patients who died had longer QTc compared to those who survived.

groups. Figure 1 shows that for a given age quartile, patients who died had longer QTc compared to those who survived. In univariate analysis, patients with prolonged QTc had significantly higher mortality compared to those with normal QTc (22% *vs* 11%; p = 0.004).

However, in the Cox regression model, QTc at a cut-off of ≥ 440 ms did not independently predict mortality (hazard ratio [HR] 1.5; 95% confidence interval [CI] 0.86–2.74; p = 0.14) after adjustment for covariates such as age, gender, history of myocardial infarction, heart rate and QRS duration. Age ≥ 65 years was an independent predictor of mortality (HR 6.2; 95% CI 1.4–26; p = 0.01). In separate Cox models including the same variables at different cut-off points for QTc interval, age ≥ 65 and QTc ≥ 500 ms were the most significant predictors of mortality (HR 7.9; 95% CI 1.9–32.9; p = 0.004) and (HR 3.5; 95% CI 1.56–8.12; p = 0.002) respectively (Table 3). Patients with syncope, with a QTc ≥ 500 ms on a 12-lead surface ECG had a greater than three-fold increased risk of death compared to patients with a QTc interval below that value. Figures 2A, B show Kaplan-Meier curves for the relationship of overall mortality to QTc interval. In addition, patients 65 years and older had an almost eight-fold increased risk of death as compared to individuals under 65.

Discussion

In our study, QTc ≥ 440 ms did not predict total mortality independent of other significant covariates. However, age ≥ 65 years and QTc interval ≥ 500 ms were associated with significantly higher total mortality in patients with syncope. There was an almost linear relationship between aging and prolongation of QTc. Patients who died in the study were older, and had a higher incidence of hypertension and CHF.

Syncope is a common disorder, accounting for 1–6% of medical admissions and up to 3% of ED visits [1, 2]. The QTc interval has been associated with increased risk of malignant ventricular arrhythmias and cardiogenic syncope [11]. Even though the patients in our study did not have any objective evidence of arrhythmias as a result of the QTc lengthening, the prolongation of the interval might be viewed as a marker of a potential underlying cardiovascular disease. The heterogeneity in the ventricular repolarization of the different cardiac myocytes accounts for the prolonged QTc interval that accounts for the arrhythmogenicity of abnormal ventricular rhythms such as torsades de pointes [9, 12].

Table 3. Cox regression analysis at different levels of QTc cut-offs.

Cox-regression models	Hazard ratio	95% confidence interval	P
QTc cut off at 450 ms	1.07	0.61–1.90	0.79
Age ≥ 65 years	8.11	1.94–33.84	0.004
QTc cut off at 460 ms	1.36	0.75–2.48	0.30
Age ≥ 65 years	7.99	1.92–33.26	0.004
QTc cut off at 470 ms	1.50	0.79–2.85	0.20
Age ≥ 65 years	7.96	1.91–33.14	0.004
QTc cut off at 480 ms	1.58	0.75–3.33	0.22
Age ≥ 65 years	8.05	1.93–33.51	0.004
QTc cut off at 490 ms	2.01	0.92–4.37	0.076
Age ≥ 65 years	7.82	1.87–32.63	0.004
QTc cut off at 500 ms	3.46	1.50–7.98	0.003
Age ≥ 65 years	7.97	1.87–32.64	0.004

The table shows statistical significance achieved at a QTc cut-off of 500 ms

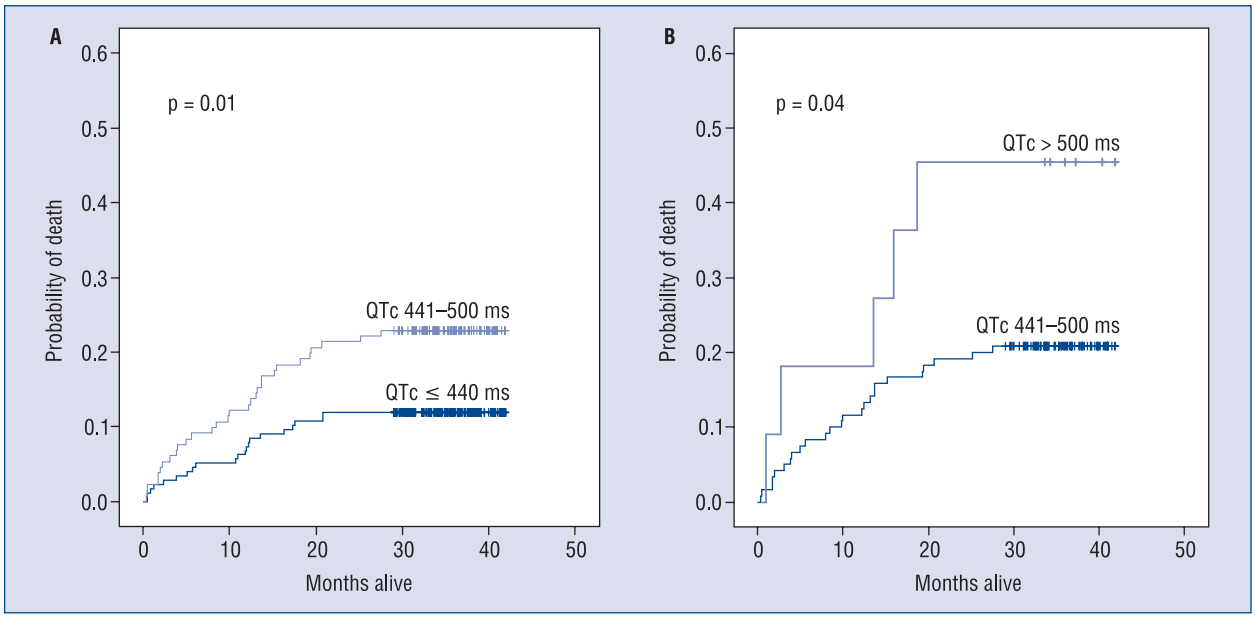

Figure 2. Kaplan-Meier estimates of overall mortality according to QTc quartiles; **A.** Kaplan-Meier estimates of overall mortality at 30 months among patients with QTc ≤ 440 ms and QTc 441–500 ms; **B.** Overall mortality among patients with QTc 441–500 ms and QTc > 500 ms.

QTc interval prolongation potentially has a role as a simply obtained marker of an underlying subclinical cardiovascular disease that might necessitate careful evaluation. QT interval prolongation has been proposed as a risk factor for ventricular arrhythmia and death in an apparently healthy [13], post-myocardial infarction [5, 6] and diabetic population [7]. Results of several large prospective epidemiologic studies evaluating total and cardiovascular mortality in relation to QTc prolongation have yielded conflicting results. In the Zutphen study, QTc prolongation of 420 ms or more was associated with a three-fold increased risk of sudden cardiac death (HR 3.0; 95% CI 1.0–8.9) in elderly men (> 65 years), but not in younger men [5]. The Framingham study however failed to show any association of the QT prolongation with total or cardiovascular mortality or sudden cardiac death [6]. The Rotterdam study evaluated more than 6,500 patients and found that QTc prolongation (> 440 ms) was associated with increased risk of total and cardiovascular mortality [14]. A meta-analysis that looked into these studies failed to show an association between prolonged QTc and mortality or sudden cardiac death [15].

Patients with syncope who are 65 years or older and QTc ≥ 500 ms presenting to the ED have a higher mortality risk beyond the initial hospitalization. This group of patients requires more vigilant follow-up and management of underlying medical and cardiac conditions, particularly any risk factors which may trigger terminal events.

To the best of our knowledge, this is the first study to evaluate the association of prolonged QTc with total mortality among syncope patients. However, it remains to be seen if prolonged QTc can be viewed as an independent marker of mortality above and beyond the current understanding of its arrhythmic potential.

Our study has certain limitations, including the retrospective design and the small study cohort. We also lacked data regarding the etiology of syncope and the exact cause of death (sudden cardiac *vs* non-cardiac death). Further studies involving larger patient populations with detailed information on causes of syncope and mortality are required to elucidate the validity of our clinical findings.

Conclusions

In elderly patients presenting to the emergency department with syncope, measurement of QTc interval is a simple and useful clinical tool for identifying patients at higher risk of adverse clinical outcomes. Prolonged QTc seen on the surface ECG in this patient population, and especially the elderly, warrants careful evaluation and treatment. In future, prolonged QTc interval may emerge as a significant risk stratification tool in patients with syncope.

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