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Utility of the QT interval in Predicting Outcomes in Patients Presenting to the Emergency Department with Chest Pain

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ABSTRACT

OBJECTIVES: To investigate whether prolongation of the heart rate-corrected QT interval (QTc) is an independent risk factor for predicting future acute coronary syndrome (ACS) occurrence or mortality in patients with at least one cardiac risk factor presenting with chest pain to the Emergency Department (ED).

BACKGROUND: QTc prolongation is associated with ventricular arrhythmias and increased mortality in patients with ACS or known coronary artery disease (CAD). In contrast, population-based studies have shown no consistent association between QTc prolongation and ACS or mortality in a population with no known CAD. The prognostic implications of QTc prolongation on clinical outcomes in patients who present to the ED with chest pain is not known.

METHODS: Single center, retrospective study in patients presenting with chest pain to the Einstein Medical Center Philadelphia ED between 2011 and 2012. Proportional hazards models were used to calculate hazard ratios for occurrence of ACS or death within 1 year. Kaplan Meier Curves were used to determine time to event for QTc low (<460 ms) versus QTc high ($\geq$460 ms) groups.

RESULTS: Five hundred ninety five patients met criteria. Older age, hypertension, diabetes mellitus and hyperlipidemia were more common in the QTc high group. Patients in the QTc high group were more likely to experience subsequent ACS or death (HR 8.12 95% CI 4.00-16.72), even after adjusting for traditional cardiac risk factors (HR 7.68 95% CI 3.57-16.61).

Conclusion: QTc prolongation at ED presentation with chest pain and at least one cardiac risk factor predicts subsequent ACS and death.

Introduction

The International Long QT Syndrome Registry found that the risk of developing malignant arrhythmias in patients with QT prolongation is exponentially related to the length of the QT interval.[1] However, the role of the heart rate-corrected QT interval (QTc) for prognostication in a population with no known coronary artery disease (CAD), versus those with CAD, is not known.[2,3,4,5,6,7] The availability and widespread use of digitized electrocardiographic recordings for patients presenting with chest pain to the ED provides readily accessible data in determining the QTc interval.

Retrospective studies found that QTc prolongation is associated with a higher risk of morbidity and mortality in patients with known CAD.[1] QTc prolongation has been associated with ventricular arrhythmias and increased mortality in ACS patients.[11,12] In contrast, population-based studies have shown no consistent association between QTc prolongation and occurrence of ACS or mortality in a healthy asymptomatic population.[2,3,4,5,6,7,13] Further, the effect of QTc prolongation on clinical outcomes of patients who present to the ED with chest pain is not known. The objective of this study was to investigate whether QTc prolongation is an independent risk factor for predicting ACS occurrence or mortality in patients, with at least one cardiac risk factor, presenting to the ED with chest pain. .

Methods

This was a retrospective review of medical records including all patients 18 years or older presenting to the Einstein Medical Center Philadelphia ED between June 2011 and June 2012 with chest pain, who had known cardiac risk factors, but no prior CAD history. Cardiac risk factors included hypertension, dyslipidemia, family history of CAD, diabetes mellitus, smoking and obesity (body mass index [BMI$\geq$26]). This study was approved by the Einstein Medical Center Institutional Review Board (IRB).

Patients taking medications that prolong the QT interval (e.g. methadone, specific antiarrhythmics, antihistamines, antibiotics and psychotropics), had electrolyte abnormalities (hypokalemia, hypocalcemia), had central nervous system injury, known CAD and those with baseline atrial fibrillation or bundle branch block were excluded.

Demographic data including age, gender, BMI, hypertension, hyperlipidemia, diabetes mellitus, family history of premature CAD and smoking status were collected from patient charts (Table 1). QTc intervals were collected from the index electrocardiogram and were classified as high or low based on a cut point set of 460 msec (cut off used in majority of prior studies) [9,11,12]. The QT interval was corrected for heart rate in surface ECG using Bazett's formula. Electronic medical records of Einstein Medical Center Philadelphia were used to access subsequent ACS diagnoses. Patients were followed for a mean of 1 year for subsequent ACS diagnosis or death (Social Security Death Index), whichever happened first. Social security death index was used to assess occurrence of death within 1 year after presentation to the ED.

Data analysis: Patient groups were compared with and without QT prolongation with regards to each of the demographic variables using Student t-tests for quantitative variables and chi squared tests for categorical variables. Hazards ratio were calculated for death or ACS within one year. Proportional hazards model/cox model was constructed to adjust for the effect of demographics on mortality and ACS within one year, and to calculate the adjusted hazards ratios. Kaplan Meier curve was used to estimate time to event for the QTc low and high groups. Log rank p values were used to compare curves. JMP 10 (SAS, Cary, NC) was used for all statistics. A p value of 0.05 or less was considered statistically significant.

Results

Of 700 charts reviewed, 105 charts were excluded: fifty eight due to absence of any cardiac risk factor, 20 due to absence of a baseline ECG at the ED visit, 12 had atrial fibrillation or bundle branch block, and 13 had electrolyte abnormalities or use of drugs known to prolong QTc. Mean follow up was 1 year from index ED visit. Demographic variables were compared between groups with and without QT prolongation (Table IA). Fifty nine of 595 (10%) patients studied experienced an ACS event during the index hospitalization and were not included in outcome measures. Patients with QTc > 460 had a higher incidence of older age (>60 years old), hypertension, diabetes mellitus and hyperlipidemia. Multivariate analysis for the composite of ACS and mortality was performed to account for these significant demographic differences (Table IB). Multivariate analysis demonstrated that a prolonged QTc was associated with a marked increase in risk of having ACS or death within 1 year after ED presentation. As shown in Figure. 1, the Kaplan Meier survival plot shows that ACS and mortality occurrence appears to increase at 4 months after index presentation with chest pain in the ED.

Discussion

The major finding of this study was that a prolonged QTc interval was associated with a more than seven-fold increased risk of ACS or death within 1 year of ED presentation for chest pain in patients with at least one cardiac risk factor. This was independent of other cardiac risk factors.

Epidemiological studies evaluating total and cardiovascular mortality associated with QTc prolongation have yielded conflicting results. The Framingham study failed to show an association of baseline QTc prolongation with total mortality, sudden death, or coronary mortality in a healthy population.[8] In contrast, the Cardiovascular Health Study, showed an association between a QTc >450 ms and total mortality in a healthy population. In the Strong Heart Study, a QTc >460 ms was associated with a two-fold increased risk of cardiac and total mortality in a healthy population.[9] In the Rotterdam Study, QTc prolongation >440 ms was associated with an increased risk of total and cardiovascular mortality, this time with an elderly population.[2] A recent study of Beinart et al, found that QTc of >460 or each 10 ms increase in the QTc with patients not known to have CAD was associated with increased risk for future rate of strokes, cardiovascular events and heart failure readmissions.[12] In studies by Gadelata et al and Jiménez-Candil et al, prolongation of QTc interval (>458 msec) in patients with ACS on admission ECG was an independent predictor of cardiovascular risk, defined as recurrence of ACS within 30 days and at 1 year of follow up.[10, 11] In their studies they

found a positive correlation between prolonged QTc intervals and cTnT levels. To date, no study has examined the prognostic value of the QTc interval in patients presenting to the ED with chest pain. Thus, the present study extends the findings summarized above, in that patients presenting with chest pain to the ED with at least one cardiac risk factor are at increased risk for ACS events and all cause death within one year if their QTc is greater than 460 ms.

This is the first study to address a population of patients presenting to the ED symptomatic of chest pain and having at least one cardiac risk factor, but with no known CAD or past ACS. Factors that may affect QTc prolongation such as drugs, and electrolyte abnormalities which were not accounted for in most prior studies were excluded in the present study. Also important to note, is the interesting finding that BMI defined in our study as BMI>26 was also an independent risk factor for ACS and all cause mortality within 1 year for patients presenting with chest pain and at least one cardiac risk factor. Further studies are needed to explore this finding.

This study was limited to a single center and was retrospective. We could not control for patients who may have gone to other medical centers for occurrence of subsequent ACS within 1 year of follow up. Also QTc was not manually calculated but rather was obtained from the computer reported ECG on index ED visit. However, this does reflect real world care and offers an easy quick look predictor of future ACS and death risk for patients presenting to the ED with chest pain.

In conclusion, QTc prolongation at ED presentation in patients with chest pain with at least one cardiac risk factor is an independent risk factor for occurrence of ACS or all-cause mortality within 1 year. Whether this finding can be a potential add on feature to risk scores, such as TIMI GRACE or PURSUIT will require prospective studies to confirm and compare the predictive value of QTc interval prolongation in patients presenting to the ED with chest pain.[13, 14, 15]

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Figure Legends

Figure 1: Kaplan-Meier log survival plot of heart rate corrected QT (QTc) interval prolongation and composite outcome of ACS and all cause mortality within 1 year , p<.001
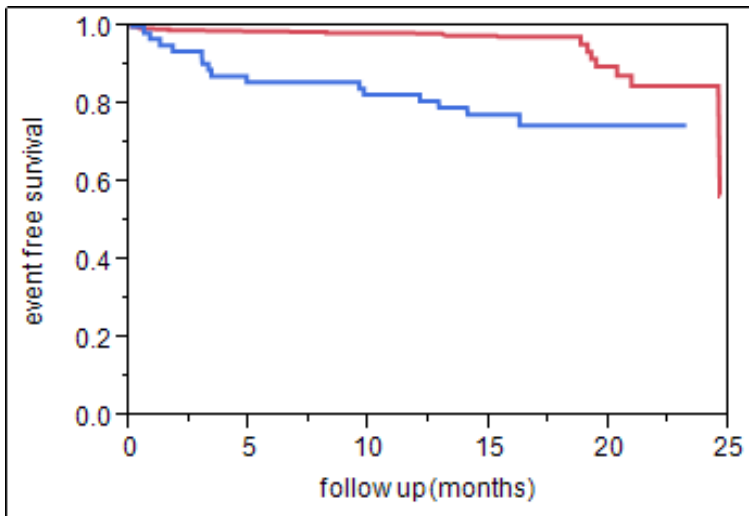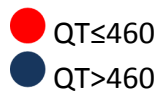
Figure 1

🔴 QT≤460
🔵 QT>460

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Table 1a. Baseline characteristics of the study population stratified by the QTc prolongation at baseline

	QTc≤460 msec	QTc>460 msec	p
n	445	64	
Male Gender %	49	40.6	0.21
Age>60 %	28.5	46.9	0.003
Hypertension %	59.3	81.2	0.0007
Diabetes Mellitus %	34.4	46.9	0.05
Hyperlipidemia %	30.2	45.3	0.015
Family History of CAD %	8.3	9.4	0.77
Overweight BMI >26 %	68.8	67.2	0.78
Smoking %	60.1	57.8	0.72

*Values are percentages as they are dichotomous variables. QTc = heart rate corrected QT interval

Table 1b. Survival Analysis (ACS or mortality within one year), Hazard Ratios with 95% confidence intervals

	Univariate analysis	Multivariate analysis
Age>60	2.14 (1.10-4.15)	1.03 (0.47-2.21)
Hypertension	2.01 (1.01-4.27)	1.48 (0.65-3.70)
Diabetes Mellitus	2.22 (1.14-4.30)	1.35 (0.63-2.90)
Hyperlipidemia	3.12 (1.61-6.13)	2.26 (1.08-4.88)
Family History of CAD	1.58 (0.46-4.06)	1.38 (0.40-3.61)
BMI>26	2.03 (0.99-4.58)	2.55 (1.08-7.05)
QTc>460	8.12 (4.00-16.72)	7.68 (3.57-16.61)[†]

†Adjusted for age>60, presence of hypertension, diabetes mellitus, hyperlipidemia family history of CAD, BMI>26