American Journal of Emergency Medicine 37 (2019) 685–689

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

QTc prolongation as a marker of 30-day serious outcomes in older patients with syncope presenting to the ED

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ARTICLE INFO

Article history:
Received 12 May 2018
Received in revised form 7 July 2018
Accepted 10 July 2018

ABSTRACT

Background: Syncope is a common chief complaint in the ED, and the electrocardiogram (ECG) is a routine diagnostic tool in the evaluation of syncope. We assessed whether increasingly prolonged QTc intervals are associated with composite 30-day serious outcomes in older adults presenting to the ED with syncope.
Methods: This is a secondary analysis of a prospective, observational study at 11 EDs in adults 60 years or older who presented with syncope or near syncope. We excluded patients presenting without an ECG, measurement of QTc, non-sinus rhythm, bundle branch block or those without 30-day follow-up. We categorized QTc cutoffs into values of <451; 451–470; 471–500, and >500 ms. We determined the rate of composite 30-day serious outcomes including ED serious outcomes and 30-day arrhythmias not identified in ED.
Results: The study cohort included 2609 patients. There were 1678 patients (64.3%) that had QTc intervals <451 ms; 544 (20.8%) were 451–470 ms; 302 (11.6%) were 471–500 ms, and 85 (3.3%) had intervals >500 ms. Composite 30-day serious outcomes was associated with increasingly prolonged QTc intervals (13.0%, 15.3%, 18.2%, 22.4%, $p = 0.01$), but this association did not persist in multivariate analysis.
Conclusions: In a cohort of older patients presenting with syncope, increased QTc interval was a marker of but was not independently predictive of composite 30-day serious outcomes.

1. Introduction

1.1. Background

Syncope is common occurrence, as 1 in 4 people will experience an episode in their lifetime [1-3]. It is responsible for 1–3% of all visits to an Emergency Department (ED) in the United States [4]. Syncope may

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https://doi.org/10.1016/j.ajem.2018.07.022
0735-6757/

be due to a benign cause such as vasovagal syncope, a cardiac cause such as arrhythmia, or non-cardiac condition such as gastro-intestinal bleed [5-7]. The current guidelines recommend obtaining an electrocardiogram (ECG) on all patients presenting to the ED with syncope [8-10].

1.2. Importance

QTc prolongation on the presenting ECG is a simple, almost uniformly obtained data point that is determined shortly after arrival in most patients with syncope. Although generally thought to be associated with increased risk of cardiac arrhythmias, syncope is associated with cardiac and non-cardiac causes of morbidity and mortality in patients with heart failure, obesity, surgery, electrolyte abnormalities, kidney failure and coronary artery disease [11-20].

1.3. Goals of investigation

We hypothesized that longer QTc intervals incrementally predict composite 30-day serious outcomes. Our main objective was to identify whether incrementally prolonged QTc intervals are predictive of composite 30-day serious outcomes in older adults presenting to the ED with syncope.

2. Material and methods

2.1. Study design

We conducted a secondary analysis of a multicenter, prospective cohort study (ClinicalTrials.gov identifier NCT01802398) to determine whether increasingly prolonged QTc intervals are predictive of composite 30-day serious outcomes in older adults presenting to the ED with syncope. The study was approved by the institutional review boards at all sites and written informed consent was obtained from all participating subjects.

2.2. Setting and patient population

Eligible patients were ≥60 years old with a complaint of syncope or near-syncope at 11 academic EDs across the United States. Exclusion criteria were as follows: intoxication, medical or electrical intervention to restore consciousness, inability or unwillingness to provide informed consent or follow-up information. Patients with a presumptive cause of loss of consciousness due to seizure, stroke or transient ischemic attack, or hypoglycemia were also excluded. For this analysis, we also excluded patients that did not have an ECG, or were missing QTc values. Patients with bundle branch blocks or (QRS >120 ms) and non-sinus rhythms on initial ECG were excluded because a prolonged QRS will result in a falsely prolonged QTc and the computer generated QTc for non-sinus rhythms will not be accurate due to irregular R-R intervals.

2.3. Study protocol

All patients underwent standardized history, physical examination, laboratory testing, and 12-lead ECG testing. Additional testing and patient disposition were directed by the treating clinical providers. We conducted 30-day patient follow-up through review of the electronic medical records by local research personnel to evaluate for serious outcomes within 30-days from the index ED evaluation [21]. Additionally, we called patients at 30-days to identify out-of-hospital deaths, ED visits, and hospitalizations that occurred outside of the study sites. If a patient or their authorized representative reported an ED or hospital visit outside of the study site, then medical charts associated with those visits were reviewed. All potential serious outcomes identified by research staff were reviewed and adjudicated by a study physician.

3. Theory/calculation

Data collected were consistent with reporting guidelines for ED based syncope research [22]. ECG interpretations were based on the first ECG obtained in the ED and were abstracted by one of five research study physicians who were blinded to all clinical data. The QTc was computer generated. QTc was classified into increments categorized as follows: normal (<451 ms), mildly prolonged but still under the 99th percentile (451–470 ms), greater than 99th percentile (471–500 ms) and markedly prolonged >500 ms [23]. These intervals were chosen based upon consensus of the authors after a review of the literature.

3.1. Outcome

Our primary outcome was a composite endpoint of 30-day serious events including any of the following: a significant arrhythmia (ventricular fibrillation, symptomatic ventricular tachycardia longer than 30 s, sick sinus syndrome, sinus pause longer than 30 s, Mobitz II heart block, complete heart block, symptomatic supraventricular tachycardia, or symptomatic bradycardia <40 beats per minute), myocardial infarction, cardiac intervention including pacemaker, automated implantable cardio-defibrillator (AICD), coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), new diagnosis of structural heart disease, stroke, pulmonary embolism, aortic dissection, subarachnoid hemorrhage, cardiopulmonary resuscitation, internal hemorrhage/anemia requiring transfusion, recurrent syncope/fall resulting in major traumatic injury, and death within 30-days. The primary outcome included events identified both during and after the ED evaluation.

3.2. Analysis

Data are presented as cross-classified counts or means with standard deviations within categories of QTc and analyzed with chi-square or Fisher's exact tests for counts or analysis of variance for continuous variables. We calculated odds ratios for each QTc increment compared to the reference value of <451 ms for composite 30-day serious outcomes.

We fit logistic models of QTc predicting the outcomes with QTc as a categorical variable (<451, 451–470, 471–500, >500 ms), with and without gender and a QTc ∗ gender interaction (due to the known difference in QTc between genders) and then adjusted for additional variables: gender, history of congestive heart failure, history of coronary artery disease, history of arrhythmia, dyspnea, physician risk assessment and hypotension. These variables were chosen as they are either known to effect baseline QTc or are clinically important. Variables were selected for multivariate analysis based on $p < 0.05$. Statistical analyses were performed using the R package (Vienna, Austria) [24]. All p-values are two-sided and considered significant at the 5% level.

4. Results

There were 6930 subjects that met eligibility criteria, of which 2609 (37.6%) subjects consented and met all inclusion criteria (Fig. 1). Subjects had a mean age of 71.7 years, 1351 (51.8%) female (Table 1). There were 2051 (79.7%) admitted to the hospital or observation and 524 (20.3%) discharged home. Of the 2609 enrolled subjects, there were 1678 patients (64.3%) with QTc intervals <451 ms; 544 (20.8%) were 451–470 ms; 302 (11.5%) were 471–500 ms, and 85 (3.3%) were > 500 ms. Female gender, history of congestive heart failure, history of coronary artery disease, dyspnea, history of arrhythmia, and physician risk assessment were associated with increasing QTc intervals (Table 1).

Overall, 375 (14.4%) people had a composite 30-day serious outcome. Increasing QTc intervals were associated with increasing composite 30-day serious outcomes (Table 1). Compared to the reference group (<451 ms), the odds ratio for prolonged QTc for 30-day composite serious outcomes in the univariate analysis was 1.21 (0.91, 1.58) for

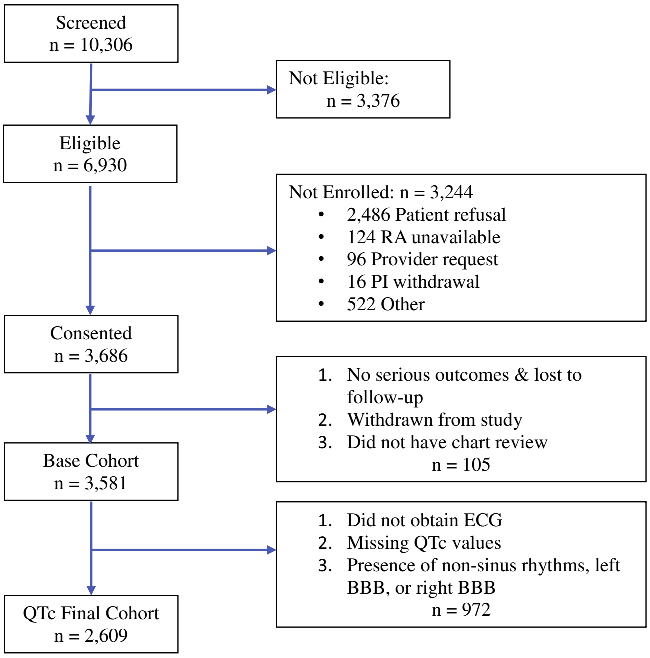

Fig. 1. Flow diagram of study cohort.

QTc 451–470; 1.49 (95% CI 1.07, 2.05) for QTc 471–500; and 1.93 (95% CI 1.11, 3.21) for QTc >500 ms (Table 2).

In a multivariate analysis, the adjusted OR for increasing QTc predicting composite 30-day serious outcomes was not statistically significant (Table 3). History of congestive heart failure, history of arrhythmia, dyspnea, physician risk assessment and hypotension are predictive of composite 30-day serious outcomes in the adjusted analysis.

Table 2
Univariate logistic regression model predicting composite 30-day serious outcomes.

Variables	OR	95% CI	*p*-Value
QTc (<451 ms)	Reference		*
451–470 ms	1.21	(0.91, 1.58)	0.18
471–500 ms	1.49	(1.07, 2.05)	0.016
>500 ms	1.93	(1.11, 3.21)	0.015
Male	1.35	(1.09, 1.69)	0.007
History of Congestive Heart Failure	2.24	(1.61, 3.09)	<0.001
History of Coronary Artery Disease	1.57	(1.23, 1.99)	<0.001
History of Arrhythmia	2.10	(1.59, 2.74)	<0.001
Dyspnea	1.81	(1.41, 2.32)	<0.001
Physician Risk Assessment	1.03	(1.02, 1.04)	<0.001
Hypotension	2.07	(1.51, 2.81)	<0.001

* Overall *p*-value is 0.016.

5. Discussion

In this large, multicenter cohort of older adults with syncope, we found that increasing QTc was associated with composite 30-day serious outcomes in a dose dependent fashion. To the best of our knowledge, this is the first study to specifically evaluate QTc as a function of increasing intervals, after exclusion of underlying ECG abnormalities that are known to be associated with adverse cardiovascular events. We found that longer QTc predicted adverse outcomes as a univariate variable, but when adjusted for variables known to predict adverse outcomes, the effect disappeared. Thus, longer QTc intervals should be considered a marker for adverse outcomes rather than an independent

Table 1
Study cohort characteristics.

Variable[a]	Overall Cohort (n = 2609)	<451 ms (n = 1678)	451–470 ms (n = 544)	471–500 ms (n = 302)	>500 ms (n = 85)	*p*-Value
	N (%)	N (%)	N (%)	N (%)	N (%)	
Demographics						
Age, mean (SD)	71.7 (8.6)	71.7 (8.5)	71.9 (8.9)	71.1 (7.9)	71.6 (8.9)	0.55
Age						0.52
60 to <70	1243 (47.6)	798 (47.6)	260 (47.8)	143 (47.4)	42 (49.4)	
70 to <80	835 (32.0)	540 (32.2)	163 (30.0)	107 (35.4)	25 (29.4)	
80 to <90	454 (17.4)	289 (17.2)	100 (18.4)	48 (15.9)	17 (20.0)	
90+	77 (3.0)	51 (3.0)	21 (3.9)	4 (1.3)	1 (1.2)	
Gender						0.012
Male	1258 (48.2)	845 (50.4)	232 (42.6)	145 (48.0)	36 (42.4)	
Female	1351 (51.8)	833 (49.6)	312 (57.4)	157 (52.0)	49 (57.6)	
Race (n = 2593)						0.37
White or Caucasian	2116 (81.6)	1364 (81.8)	454 (83.9)	233 (77.7)	65 (76.5)	
Black or African American	392 (15.1)	243 (14.6)	74 (13.7)	57 (19.0)	18 (21.2)	
Asian	33 (1.3)	24 (1.4)	4 (0.7)	4 (1.3)	1 (1.2)	
Other	52 (2.0)	36 (2.2)	9 (1.7)	6 (2.0)	1 (1.2)	
Race (n = 2593)						0.087
White or Caucasian	2116 (81.6)	1364 (81.8)	454 (83.9)	233 (77.7)	65 (76.5)	
Other	477 (18.4)	303 (18.2)	87 (16.1)	67 (22.3)	20 (23.5)	
History of						
Congestive Heart Failure (n = 2608)	218 (8.4)	94 (5.6)	51 (9.4)	50 (16.6)	23 (27.1)	<0.001
Coronary Artery Disease (n = 2608)	607 (23.3)	343 (20.5)	135 (24.8)	96 (31.8)	33 (38.8)	<0.001
Arrhythmia (n = 2608)	368 (14.1)	218 (13.0)	85 (15.6)	53 (17.5)	12 (14.1)	0.13
Disposition (n = 2575)						0.32
Hospitalized	2051 (79.7)	1303 (78.7)	438 (81.1)	239 (80.5)	71 (85.5)	
Discharged	524 (20.3)	352 (21.3)	102 (18.9)	58 (19.5)	12 (14.5)	
Dyspnea (n = 2552)	523 (20.5)	317 (19.3)	108 (20.4)	74 (25.2)	24 (28.6)	0.032
Hypotension	257 (9.9)	154 (9.2)	53 (9.7)	30 (9.9)	20 (23.5)	<0.001
Physician Risk Assessment, mean (SD)	8.3 (11.8)	7.7 (11.0)	9.2 (13.1)	10.2 (13.4)	8.3 (12.0)	0.001
Composite 30 Day Serious Outcomes	375 (14.4)	218 (13.0)	83 (15.3)	55 (18.2)	19 (22.4)	0.012
Serious Outcomes Identified after ED Discharge	212 (8.1)	126 (7.5)	48 (8.8)	26 (8.6)	12 (14.1)	0.15

[a] Counts of subjects do not add up to the total number of subjects because of missing values.

Table 3
Multivariate logistic regression model predicting composite 30-day serious outcomes.

Variables	OR	95% CI	p-Value
QTc (<451 ms)	Reference		*
451–470 ms	1.13	(0.84, 1.51)	0.41
471–500 ms	1.19	(0.83, 1.68)	0.33
>500 ms	1.48	(0.81, 2.59)	0.18
Male	1.21	(0.96, 1.53)	0.12
History of Congestive Heart Failure	1.62	(1.11, 2.33)	0.010
History of Coronary Artery Disease	1.15	(0.87, 1.51)	0.33
History of Arrhythmia	1.83	(1.36, 2.43)	<0.001
Dyspnea	1.70	(1.31, 2.20)	<0.001
Physician Risk Assessment	1.03	(1.02, 1.04)	<0.001
Hypotension	1.93	(1.38, 2.67)	<0.001

* Overall p-value is 0.46.

predictor of them. The most likely explanation for this is that other clinical factors that contribute to serious outcomes are also related to QTc interval length. In the ED, where clinicians cannot calculate the relative contribution each independent risk factor toward serious outcomes, the QTc can be useful to serve as that marker. It is a marker of composite 30-day adverse outcomes because it effectively integrates the independent predictor variables into one easy to apply clinical variable.

Our findings are consistent with prior studies and have biological plausibility. Two mechanisms of adverse events can be ascribed to a prolonged QT interval – first is that a prolonged QTc is associated with increased torsades de pointes and second that the QT interval is reacting to the physiologic stressor. QTc is longer in many conditions that predispose patients to adverse outcomes in syncope such as heart failure, coronary artery disease, renal disease, age, therefore the effect of QTc alone on an elderly cohort disappears as these things are controlled for, however, patients with longer QTc have more adverse outcomes regardless of underlying condition than those with shorter QTc. Previous studies have demonstrated that a QTc >500 ms is associated with ED, in hospital and 30-day all-cause mortality [11,29]. This finding appears to be true in all age groups and in different disease processes [25]. While the association of a prolonged QTc with torsades de pointes has been well established, there is also an association with adverse outcomes from other cardiac and non-cardiac causes with prolongation of the QT interval [12,26,27]. For example, QTc is a predictor of mortality in subarachnoid hemorrhage. This association may be due to QTc lengthening in response to the catecholaminergic surge following intracranial catastrophe that indicates a more severe brain injury as compared to a predisposition to ventricular instability and cardiac arrhythmias [28]. Another example is pulmonary embolism, where QT prolongation also occurs. This might be because pulmonary embolism leads to some right heart strain (even subclinically), that results in abnormal repolarization and a prolonged QTc [29]. This suggests that the QT interval is a surrogate marker and/or result of other non-cardiac events [14].

The utility of the 12-lead ECG in predicting adverse events in the setting of syncope in older adults is not disputed [30]. Previous studies have demonstrated the association of various ECG abnormalities and syncope associated morbidity and mortality [5,30-34]. These include new or previously unknown left bundle branch block, bifascicular block plus first degree AV block, Brugada ECG pattern, ECG changes consistent with acute ischemia, non-sinus rhythm and QTc >451 ms [32]. Our study is unique in that we excluded many baseline ECG abnormalities associated with prolonged QT (for example, bundle branch blocks) and looked at the primary outcome segregated into increasing QTc intervals: normal, mildly prolonged, prolonged and markedly prolonged. Prior studies looked only at QTc >500 ms without excluding baseline ECG abnormalities which are known to be predictive of higher all-cause mortality [11]. Our study demonstrates that incremental increases in QTc is still a marker of adverse events as described above.

There are several potential limitations. Although we screened consecutive patients while study coordinators were available, we did not enroll 24/7, therefore we might have had a sampling bias, if off-hour presentations are different from weekday-daytime presentations. Patients with intrinsic conduction delays were excluded, which would be expected to have biased the study toward the null, as these patients have more structural heart disease and higher likelihood of short term adverse outcomes. Despite these biases toward the null we demonstrated a difference. We did not use a gold standard central core measurement for determination of QTc intervals, but rather used the computerized reading; however, this mirrors what is done in clinical practice. Thus, this might be seen as a methodological weakness or as enhancing generalizability.

In conclusion, we found that a prolonged QTc on the ED electrocardiogram in older patients with syncope serves as a marker of composite 30-day serious events. Patients with syncope and QTc prolongation should be considered higher risk than patients without QTc prolongation; however, this study did not address how to manage them to mitigate this increased risk. As the ECG is obtained early in the ED course for virtually all syncope patients, this simple computer obtained marker can be useful to predict 30-day cardiac and noncardiac outcomes shorty after ED arrival.

Conflicts of interest

JLW has no conflicts to report.

AMC has received research funding from Abbott, Akers, Alere, Nanomix, Siemens, Roche, Ortho Diagnostics, Portola and Trinity.

JEH has received research funding from Alere, Siemens, Roche, Portola and Trinity.

ES has no conflicts to report.

REW has no conflicts to report.

ANY has no conflicts to report.

SEM has no conflicts to report.

DHA has received research funding from Roche.

AB has received research funding from Radiometer and Portola and has been a consultant for Portola.

CWB has received advisory board and speaker's fees from Roche, research funding from Janssen and Boehringer Ingelheim and consulting and advisory board fees from Janssen.

JMC has received funding from Aztra Zeneca.

CLC has received research funding from Astra Zeneca, Radiometer, Ortho clinical trials, Janssen, Pfizer, NIH, Portola, Biocryst, Glaxo Smith Klein, Hospital Quality Foundation, and Abbott. She is a consultant for Portola, Janssen, and Hospital Quality Foundation.

DBD is a consultant for Janssen and Roche, has received institutional research support from Novartis, ortho Scientific, and Roche and is on the editorial board for AEM and circulation.

DKN has received honorarium for Pfizer.

BAN has no conflicts to report.

MNS has no conflicts to report.

KAS has no conflicts to report.

ABS is a consultant for Quidel, Siemens, and MCM Education.

STW has no conflicts to report.

BCS is a consultant for Medtronic.

Funding sources and support

Research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number R01HL111033. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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