Title

Hyperglycemia Is Associated With Corrected QT Prolongation and Mortality in Acutely Ill Patients

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HYPERGLYCEMIA IS ASSOCIATED WITH QTc PROLONGATION AND MORTALITY IN THE ACUTELY ILL

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Keywords

Long QT Syndrome; Hyperglycemia; Physiologic Monitoring

INTRODUCTION

The QT interval on an electrocardiogram, measured from the onset of the QRS complex to the end of the T wave, represents ventricular repolarization time. The QTc interval is the corrected QT interval after adjusting for heart rate. Lengthening of the QTc interval can be a precursor to Torsade de Pointes, a potentially life-threatening ventricular dysrhythmia.[1] Further, prolonged QTc is associated with sudden cardiac death, all-cause mortality, and adverse cardiovascular events,[2–7] which led to the publication of practice guidelines recommending QTc interval monitoring in at-risk patients[8,9]. QTc interval prolongation is caused by both heri and acquired factors. Currently, there are 13 known genes associated with the heritable form of the disease (Long QT Syndrome), accounting for 70–80% of all cases.[10] The majority of these gene abnormalities affect the function of ion channels in cardiomyocytes. Contributing to the acquired form of Long QT Syndrome are factors commonly experienced by patients that are critically ill. Contributing factors are pharmacologic agents, electrolyte levels such as hypokalemia and hypomagnesia, sex, age, and comorbidities.[11]

Patients that are critically ill are also susceptible to developing hyperglycemia induced by illness-related physiologic phenomenon, primarily hormones and cytokines.[12] Hyperglycemia can occur in both diabetic and non-diabetic patients and is well known to be associated with poorer outcomes.[12] Trauma patients experiencing stress-induced hyperglycemia have greater than two-fold increased risk for mortality[13], orthopedic patients have increased risk for surgical site infection[14], and hyperglycemia causes four- to ten-fold

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increased risk for mortality in sepsis patients[15]. Studies in surgical patients show that prevention of hyperglycemia through glucose control protocols leads to decreased mortality[16] and morbidity[17], and therefore standard practice is to maintain tight control of glucose (<150 mg/dL) in critically ill patients. However, a randomized control study of 6,104 patients from multiple intensive care units found that maintaining blood glucose between 81 and 108 mg/dL *increased* the risk of mortality compared to conventional blood glucose parameters of <180mg/dL, possibly resulting from episodes of hypoglycemia.[18] With evidence suggesting both hyper- and hypoglycemia are associated with adverse events in hospitalized patients, it is clear that glucose control in the critical care setting needs to be optimized.

Whether an association exists between QTc prolongation, hyperglycemia, and mortality in critically ill patients is not known. The sole study in a critically ill population reported a positive correlation with hyperglycemia and QTc interval prolongation.[19] However, that study was limited by a single QT interval measurement and a borderline threshold for QTc interval prolongation (QTc > 440 msec). The purpose of this study is to determine whether there is an association between hyperglycemia and QTc interval prolongation in critically ill patients, and whether combined QTc interval prolongation and hyperglycemia are associated with increased mortality.

METHODS

Setting and Sample

Data for this study was obtained from the QT In Practice (QTIP)[20] study cohort. This study includes consecutive patients admitted to an adult unit providing cardiac monitoring over a two-month period. Patients admitted to these units included medical, surgical, trauma, neurosurgical, vascular surgery, and cardiothoracic surgery patients. In our study we excluded patients with unknown diabetes status and inaccurate QT interval measurements (i.e. grossly irregular cardiac rhythms (e.g. atrial fibrillation), abnormal conduction delays (e.g. QRS duration > 120 msec), QTc interval measures that were unable to be manually verified, and inaccurate automated QTc interval measurements). All data reported here were obtained under approval from the Institutional Review Board.

Clinical Data

Demographic and clinical conditions associated with QTc interval prolongation and blood glucose (i.e. type-2 diabetes, renal disease, thyroid disease, liver disease, and heart failure), as well as proarrhythmic drug administration, were abstracted from the medical record. Glucose was defined as peak blood glucose during the patients' length of stay.[20] We trichotomized glucose: <140 mg/dl, 140–180 mg/dL, or >180 mg/dL. Continuous QTc interval estimates were derived from the bedside cardiac monitoring system using limb leads and a single chest lead (Philips Healthcare IntelliVue Patient Monitoring System). QTc interval prolongation was defined as a being an episode of QTc interval > 500 msec lasting 15 minutes or more.[21] All episodes of QTc interval prolongation were manually reviewed by the investigator, and ambiguous measurements were confirmed with expert consultation.

Statistical Analysis

Descriptive statistics were used to provide means, ranges, standard deviations, and proportions for demographic and clinical variables. Student's t-test, Welch t-test, Analysis of Variance (equal variances), and Kruskall Wallis Chi-square (unequal variances) were used to assess for differences between peak glucose and QTc interval. A Pearsons test was used to assess for a linear correlation between serum glucose and QTc interval. We performed univariate logistic regression with QTc interval prolongation greater than 500 msec as the outcome variable and an ordinal peak glucose predictor variable (<140 mg/dL, 140–180 mg/dL, >180 mg/dL), and multivariate logistic regression to control for age, sex, and relevant clinical factors. To determine the relationship between hyperglycemia, QTc interval prolongation, and mortality, chi square test of independence was performed. All statistical tests were performed using STATA version 11 (College Station, TX).

RESULTS

Data were obtained on 940 patients. Approximately half (54%) were male, with a mean age of 60 ± 19 years. The mean length of stay was 7 ± 11 days. Overall mean glucose was 158 ± 65 mg/dL. Normal peak glucose (<140mg/dL) was observed in 440 patients (47%), moderately elevated (140–180 mg/dL) in 269 patients (29%), and highly elevated (>180 mg/dL) in 231 patients (25%). We found no difference in peak glucose with age, sex, race, or body surface area (Table 1). With the exception of heart failure and thyroid disease, higher peak glucose was associated with a higher prevalence of potentially confounding illnesses ($p < 0.05$). Similarly, there was an increase in proarrhythmic drug use, abnormal laboratory values, mean heart rate, and length of stay associated with higher peak glucose ($p < 0.05$).

Patient characteristics of those with and without QTc interval prolongation are shown (Table 2). Overall mean QTc interval was 432 ± 28 msec and was expectedly longer in women (435 ± 30 msec) than men (428 ± 27msec, $p < 0.05$). More women (14%) than men (11%, $p < 0.05$) developed QTc interval prolongation. Overall, 233 (25%) of patients developed QTc interval prolongation (>500msec for ≥ 15 min) during hospitalization. Like glucose, QTc interval prolongation was associated with a higher prevalence of potentially confounding disease ($p < 0.05$), with the exception of heart failure and thyroid disease. Proarrhythmic drugs and drugs with class III antiarrhythmic action were more common in individuals with prolonged QTc interval ($p < 0.05$); however there was no difference in mean heart rate between QTc interval groups.

The proportion of patients with QTc interval prolongation increased significantly by peak glucose group (Figure 1). There was no significant linear correlation between peak blood glucose and mean QTc interval ($r = 0.02$, $p > 0.05$). In univariate testing, hyperglycemia during hospitalization was highly associated with QTc interval prolongation (Table 3). Compared to the group with a peak glucose <140 mg/dL, those with moderately elevated glucose (140–180 mg/dL) had 2.1 (95% CI 1.5, 3.1) higher odds of QTc interval prolongation during hospitalization, and the highly elevated glucose group (>180 mg/dL) had 3.8 (95% CI 2.6, 5.5) higher odds of QTc interval prolongation during hospitalization. In a multivariate model (Table 3), after adjusting for age and sex, the odds of QTc interval

prolongation were 2.1 (95% CI 1.5, 3.1) for the moderate glucose group, and 3.7 (95% CI 2.5, 5.4) for the highly elevated glucose group, compared to those with peak glucose <140 mg/dL. When we included factors known to be associated with QTc interval prolongation and hyperglycemia (renal disease, liver disease, type 2 diabetes), the odds of QTc interval prolongation remained consistently higher for the moderately elevated group (2.1, 95% CI 1.4, 3.0), and highly elevated group (3.3, 95% CI 2.2, 4.8).

During the study period, 39 (4%) patients died. Mortality was unevenly distributed between those with and without QTc interval prolongation (8.2% vs 2.8%, respectively), and by peak glucose groups: normal, moderately elevated, and highly elevated (1.8%, 4.5%, and 8.2%, respectively). Those with QTc interval prolongation and hyperglycemia (>180 mg/dL) had the highest proportion of mortality (16%). Patients with a normal QTc interval and normal peak glucose levels had the lowest mortality (0.7%) (Table 4).

DISCUSSION

Joint guidelines from the American Heart Association and the American College of Cardiology recommend providing QTc interval monitoring to hospitalized patients who are receiving QT-prolonging drugs, having electrolyte disturbances, or experience bradycardia.[9] Numerous studies have linked prolongation of the QTc interval to adverse outcomes: all-cause mortality, sudden cardiac death, time to first cardiac event (myocardial infarction/stroke), and length of hospitalization.[2–6,22–24] In critically ill patients, the prevalence of QT interval prolongation is estimated to be 24%. [21] The association of this risk for mortality is highly prevalent in the critically ill patient population.

Recently, a major shift in how glucose is managed in the critical care setting has occurred. For the past decade, the standard of practice has been to maintain tight glucose control (<150mg/dL); however a randomized control study of 6,104 patients from multiple intensive care units demonstrated that maintaining blood glucose between 81 and 108 mg/dL increased the risk for mortality compared to conventional blood glucose parameters, possibly resulting from a significant increase in episodes of hypoglycemia.[18] Consequently, the ideal parameters for glucose control within the critical care setting, balancing the hazards of hypoglycemic episodes with the risks associated with hyperglycemia, require further investigation.

A relationship between glucose levels and QTc interval prolongation has been observed in ambulatory populations. There is a positive correlation between blood glucose and QTc interval duration in non-diabetics, independent of cardiovascular risk factors, including dyslipidemia and obesity.[25] Similarly, individuals with type-2 diabetes have been shown to have longer QTc intervals than non-diabetics, possibly due to abnormalities in glucose, but not insulin metabolism.[26] Importantly, it has also been shown that a prolonged QTc interval is associated with increased risk for sudden cardiac death in these ambulatory populations.[27] A postulated mechanism underlying the glucose-QTc interval relationship is parasympathetic tone, namely heart rate variability.[26]

In non-critically ill patients, hyperglycemia is most commonly a sign of impaired glucose metabolism or type-2 diabetes. van Noord, et. al., found an association between impaired fasting glucose (> 6 mmol/L), impaired fasting insulin (>100 pmol/L or 14uIU/dL), and increased QTc interval estimates and decreased RR intervals.[27] In contrast, other studies have found a positive association with glucose and QTc interval, but no association between insulin and QTc interval estimates. In a 2-hour glucose infusion study of 20 healthy patients, Marfella et. al.,[28] observed a significant increase in QTc interval durations. However the addition of octreotide, which blocks release of endogenous insulin, did not change the observed effects of glucose on QTc interval duration. Similarly, in 30 obese patients, Iacobellis, et. al.,[29] found that insulin infusion did not significantly modify the QTc interval (401 msec vs. 413 msec), and concluded that acute hyperinsulinemia does not appear to affect ventricular repolarization. Consequently, it appears that glucose, but not insulin, is responsible for ventricular repolarization abnormalities associated with type-2 diabetes. Though we were unable to obtain fasting insulin estimates, our results are similar to those of van Noord et. al, finding a difference in mean heart rate (decreased mean RR intervals) between glucose groups, with patients with hyperglycemia (>180 mg/dL) having faster mean heart rates.

There are two primary plausible mechanisms by which glucose has an effect on the QTc interval (cardiac repolarization). Previous studies using a whole patch clamp method to determine cellular ion channel activity found QTc interval prolongation can result from both hypo- and hyperglycemia conditions, possibly through overproduction of reactive oxygen species targeting the I_{Kr} ion channel (the primary contributing ion channel to potassium extrusion and therefore repolarization).[30] In animal studies, intracellular glucose levels modified the effects of dofetilide (a potent proarrhythmic agent), acting directly on the I_{Kr} ion channel.[31] Reactive oxygen species also appears to impair the function of P-glycoprotein efflux protein, an efflux channel responsible for lowering intracellular concentrations of proarrhythmic drugs.[32]

I_{Kr} ion channel and P-glycoprotein suppression by glucose-mediated reactive oxygen species has been demonstrated in animal models and appears to be a mechanism for glucose-induced changes to the QTc interval. Though these mechanisms are plausibly at play in humans as well, hyperglycemia-related QTc prolongation is undoubtedly multi-factorial. To explain how single verse multiple insults produce varying degrees of QT interval prolongation, Roden [11] postulated a theory of *repolarization reserve*. Applying this theory, metabolic insults such as hyperglycemia, in conjunction with a patient's medical history, genetic profile, proarrhythmic drug use, and electrolyte levels, all contribute to impaired ventricular repolarization. Each factor alone may not be significant enough to produce QT prolongation, as the blockage in one ion channel may produce up-regulation and compensation by another. However, as risk factors accumulate, repolarization reserve is depleted and QT interval prolongation results. This theory may explain why a high percentage of critical care patients develop QT interval prolongation.

Our study is the largest study to date describing the relationship between elevated blood glucose and continuously monitored QTc interval prolongation, two substantial risk factors for increased morbidity and mortality, in acute and critically ill patients. We find peak

glucose during hospitalization to be strongly associated with QTc interval prolongation and increased mortality. We show that critically ill patients developing QTc prolongation, have a greater prevalence clinical history, proarrhythmic drug administration, and electrolyte and metabolic abnormalities. The only other study of hyperglycemia and QTc interval prolongation in critical care patients (n=197),[19] reported a small (r = 0.3) correlation between time-matched serum glucose level and QTc interval derived from 12 lead electrocardiogram. They also found that patients with QTc interval prolongation had higher blood glucose levels, greater illness severity, and higher rates of mortality compared to patients without QTc interval prolongation.[19] Our study supports these findings. We confirm a relationship between QTc interval prolongation, hyperglycemia, and mortality, and show that patients experiencing both QTc interval prolongation and hyperglycemia (>180 mg/dL) during hospitalization have a higher incidence of mortality (16%) then patients with normal QTc interval estimates and normal blood glucose levels (0.7%).

Limitations

As we analyzed data obtained from a prior study, we did not have control of the collected data. As such we could not examine additional pertinent factors such as fasting glucose levels or adjust our multivariate model for patient severity using standardized scoring systems such as APACHE score. As such, further research is needed to determine whether there is a direct relationship between hyperglycemia, QTc interval duration, and mortality, or whether hyperglycemia and QT interval duration are both independent markers for illness severity and consequently mortality.

CONCLUSION

Our data demonstrate an association between hyperglycemia, QT interval prolongation, and mortality. Mortality was highest (16%) in patients with both hyperglycemia and QT prolongation. Incidence of mortality in those with normal QT interval and normal glucose was less (0.7%). Further studies are needed to extrapolate the relationship between glucose and ventricular repolarization, as well as appropriate glucose control parameters and QTc interval monitoring in critical care units.

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What's New

- Elevated blood glucose during hospitalization is associated with increased odds for developing QTc interval prolongation, a precursor to the potentially fatal dysrrhythmia, Torsades de Pointes
- Patients with elevated blood glucose and prolonged QTc have higher odds of death during hospitalization than patients with one or neither of these conditions.

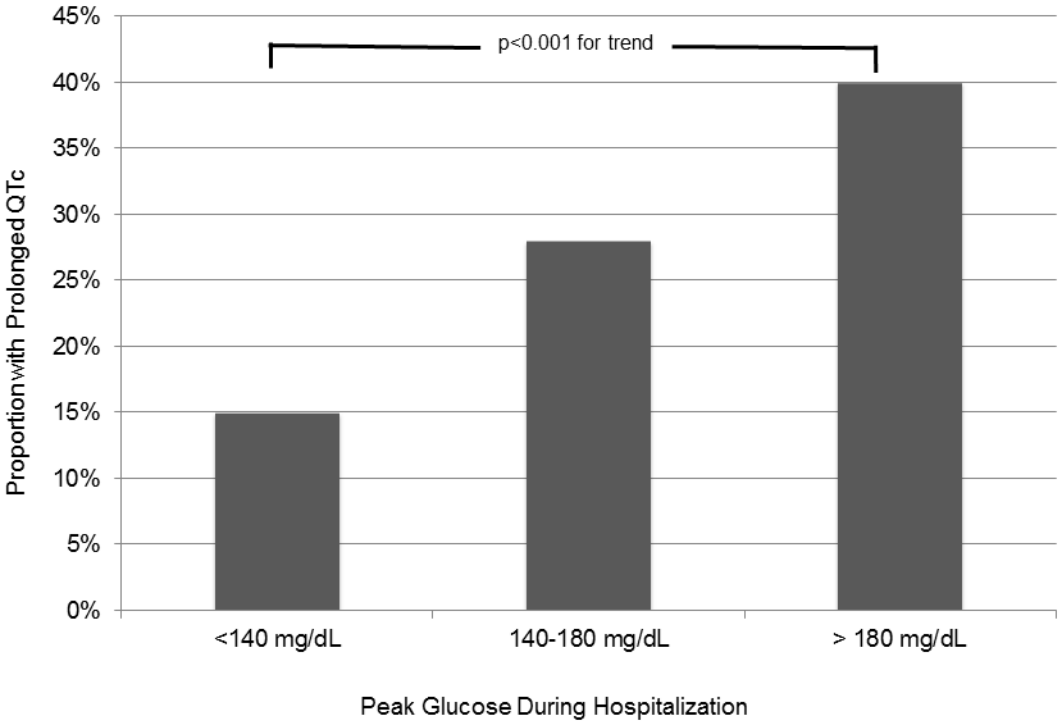

Figure 1.

Table 1

Demographic and clinical variables by glucose group

Characteristics	Overall *n* = 940 *n* (%) or mean ± sd	Low Glucose *n* = 440 *n* (%) or mean ± sd	Target Glucose *n* = 269 *n* (%) or mean ± sd	Elevated Glucose *n* = 231 *n* (%) or mean ± sd	p-value
Age (years)	60 ± 19	60 ± 20	59 ± 19	61 ± 17	0.7*
Sex (male)	503 (54)	251 (57)	141 (52)	111 (48)	0.08
Race					0.2
Caucasian	597 (64)	296 (50)	169 (28)	132 (22)	
Latino	134 (14)	50 (37)	41 (31)	43 (32)	
Asian	117 (12)	54 (12)	29 (11)	34 (29)	
African American	57 (6)	26 (46)	18 (32)	13 (23)	
Other	35 (4)	14 (31)	12 (34)	9 (26)	
Heart Failure	100 (11)	44 (10)	34 (13)	22 (10)	0.4
Diabetes	156 (17)	35 (8)	36 (13)	85 (37)	<0.001
Renal Disease	100 (11)	39 (9)	26 (10)	35 (15)	0.04
Hepatic Disease	57 (6)	20 (5)	15 (6)	22 (10)	0.03
Thyroid Disease	97 (10)	46 (10)	28 (10)	23 (10)	0.9
Proarrhythmic Drugs	545 (58)	189 (43)	191 (71)	165 (71)	<0.001
Class III Antiarrhythmic Action¥	67 (7)	13 (3)	27 (10)	27 (12)	<0.001
Body Surface Area (m^2)	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.3	0.2
Potassium (mEq/L)	3.6 ± 0.5	3.7 ± 0.4	3.6 ± 0.5	3.5 ± 0.5	<0.001*
Chloride (mg/dL)	100 ± 9	102 ± 11	99 ± 5	99 ± 5	<0.001*
Sodium (mg/dL)	135 ± 4	136 ± 4	134 ± 4	134 ± 5	<0.001*
Calcium (mmol/dL)	8.1 ± 0.7	8.4 ± 0.7	8.0 ± 0.7	8 ± 0.8	<0.001*
Magnesium (mg/dL)	1.8 ± 0.4	1.9 ± 0.4	1.7 ± 0.3	1.7 ± 0.4	<0.001*
Glucose (mg/dL)	158 ± 65	114 ± 16	159 ± 11	243 ± 74	<0.001*
Creatinine (mg/dL)	1.4 ± 1.5	1.3 ± 1.5	1.4 ± 1.5	1.7 ± 1.5	0.02
Blood Urea Nitrogen (mg/dL)	23 ± 18	20 ± 14	23 ± 17	29 ± 24	<0.001*
Mean Heart Rate (bpm)	80 ± 14	78 ± 14	84 ± 14	83 ± 14	<0.001
Mean QTc Interval (msec)	432 ± 28	430 ± 27	430 ± 27	437 ± 33	0.004*

Characteristics	Overall *n* = 940 *n* (%) or mean ± sd	Low Glucose *n* = 440 *n* (%) or mean ± sd	Target Glucose *n* = 269 *n* (%) or mean ± sd	Elevated Glucose *n* = 231 *n* (%) or mean ± sd	p-value
QTc prolongation (>500msec)	233 (25)	66 (15)	74 (28)	93 (40)	<0.001
Length of Stay (days)	7 ± 11	4 ± 10	9 ± 10	10 ± 13	<0.001*

All laboratory values, including the glucose level used to stratify the sample, were defined as the peak level during hospitalization.

¥ dofetilide, sotalol, ibutilide, amiodarone, quinidine

* Kruskal Wallis rank test (unequal variance between groups)

Table 2

Characteristics of Individuals With and Without Prolonged QTc (*n* = 940)

Characteristics	Normal QTc *n* = 707 *n* (%) or mean ± sd	Prolonged QTc *n* = 233 *n* (%) or mean ± sd	p-value
Age (years)	60 ± 19	62 ± 17	0.2
Sex (Male)	400 (57)	103 (44)	<0.05
Heart Failure	72 (10)	28 (12)	0.4
Diabetes	98 (14)	58 (25)	<0.05
Renal Disease	64 (9)	36 (15)	<0.05
Hepatic Disease	34 (5)	23 (10)	<0.05
Hypothyroid Disease	68 (10)	29 (12)	0.2
Proarrhythmic Drugs	369 (52)	176 (76)	<0.05
Class III Antiarrhythmic Action¥	26 (4)	41 (18)	<0.05
Potassium (mEq/L)	3.7 ± 0.4	3.4 ± 0.5	<0.05
Glucose (mg/dL)	151 ± 61	181 ± 69	<0.05
Calcium (mmol/dL)	8.2 ± 0.7	7.8 ± 0.7	<0.05
Magnesium (mg/dL)	1.8 ± 0.3	1.7 0.5	0.4
Mean Heart Rate (bpm)	80 ± 15	82 ± 13	0.2
Mean QTc Interval (msec)	425 ± 22	453 ± 34	<0.05

All laboratory values were defined as the peak level during hospitalization.

¥dofetilide, sotalol, ibutilide, amiodarone, quinidine

Table 3

Association of QTc Prolongation with Elevated Glucose

	Unadjusted Odds Ratio (95% CI)	Adjusted[1] Odds Ratio (95% CI)	Adjusted[2] Odds Ratio (95% CI)	Adjusted[3] Odds Ratio (95% CI)
Glucose (<140mg/dl reference)				
140 – 180mg/dL	2.1 (1.5, 3.1)	2.1 (1.5, 3.1)	1.8 (1.2, 2.7)	1.2 (0.8, 1.9)
>180mg/dL	3.8 (2.6, 5.5)	3.7 (2.5, 5.4)	2.9 (1.9, 4.3)	2.1 (1.4, 3.3)

[1] Adjusted for age and sex.

[2] Adjusted for age, sex, type-2 diabetes, renal disease, and liver disease, and class III antiarrhythmic drug use.

[3] Adjusted for age, sex, type-2 diabetes, renal disease, and liver disease, class III antiarrhythmic drug use, and electrolytes (Ca^{++}, Mg^{+}, K^{+}, Na^{+}, Cl

Table 4

Proportions of Death by QTc Interval and Peak Glucose (*n* = 39)

	<140mg/dL n (%)	140–180 mg/dL n (%)	>180 mg/dL n (%)	p-value
Normal QTc Interval (<500 msec)	5 (1.4)	9 (5)	6 (5)	<0.05
Prolonged QTc Interval (>500 msec)	3 (5)	3 (4)	13 (15)	<0.05