The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 3138-3142

Correlation of QT Interval in Stress Hyperglycemia among Patients at Intensive Care Unit

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ABSTRACT

Background: In the intensive care unit (ICU), stress hyperglycemia is a relatively prevalent occurrence. It has a number of underlying reasons, including neuroendocrine and inflammatory abnormalities in critically sick patients, which promote insulin resistance and excessive hepatic glucose production.

Objective: The aim of the present study was to detect the relation between corrected QT interval (QTc) and non-diabetic stress hyperglycemia in critically ill patients.

Patients and methods: This cohort study included non-diabetic stress hyperglycemia that was conducted at ICU, Internal Medicine Department, Zagazig University Hospitals. These patients with stress hyperglycemia were further subdivided into two groups according to QT maxc Interval prolongation.

Results: There was statistically non-significant relation between gender of patients and either QT prolongation (65.3% versus 64.6% in males and females respectively), QTII, QT max or QT maxc. There was statistically significant relation between QT prolongation and QT maxc (significantly higher in those with prolonged QT), QT max (significantly higher in those with prolonged QT). There was statistically non-significant relation between QT prolongation and QTII interval. There is statistically non-significant relation between QT prolongation and either LVEDD, LVESD, EF, DMR or EPSS

Conclusion: Prolongation of QT maxc interval is frequent in critically ill patients during stress hyperglycemia. There was statistically significant relation between QT prolongation and APACHEII (significantly higher in prolonged QT interval).

Keywords: Stress hyperglycemia, QT interval, ICU, Hospital outcomes.

INTRODUCTION

In the intensive care unit (ICU), stress hyperglycemia is a very frequent occurrence. It has a number of underlying causes, including inflammatory and neuro-endocrine disturbances in critically sick patients, which result in insulin resistance and excessive hepatic glucose production [(1)]. The presence of excessive amounts of the counter regulatory hormones glucagon, growth hormone, catecholamine, and glucocorticoid, either endogenous or exogenous, as well as high levels of the cytokines tumour necrosis factor (TNF) and interleukin-1 in the blood or tissues, are the main causes of stress hyperglycemia. Excessive glucose synthesis in comparison to glucose clearance is likely the main cause of stress hyperglycemia [(2)].

At a corrected QT (QTc) interval longer than 0.440 seconds, there is cause for worry regarding an increased risk of arrhythmias. In healthy individuals with acute hyperglycemia or high fasting blood glucose levels, QTc has been demonstrated to be extended. Patients who have long QT syndrome, myocardial infarction, left ventricular systolic dysfunction, diabetes, and otherwise appear healthy are more likely to die suddenly when their QTc interval is prolonged [(3)]. An increased risk of developing corrected QT (QTc) interval prolongation, a precursor to the potentially deadly dysrhythmia torsades de pointes, is linked to elevated blood sugar levels when receiving medical care. There is a link between QTc interval extension, hyperglycemia, and mortality, and studies have found that individuals who experience both during hospitalisation have a greater death rate (16%) than those who have normal QTc interval estimations and normal blood glucose levels (0.7%) [(4)].

The optimal method for controlling hyperglycemia in a non-intensive therapy unit is subcutaneous insulin. Nonetheless, for the reasons previously noted, critically sick patients in a non-intensive care unit setting should still be treated with IV insulin therapy. Thus, individuals with newly diagnosed hyperglycemia or type 2 diabetes mellitus who are not in severe condition are preferred to use subcutaneous insulin [(5, 6)].

Therefore, this study aimed to evaluate relation between corrected QT interval (QTc) and non-diabetic stress hyperglycemia in critically ill patients.

PATIENTS AND METHODS

This cohort study was conducted in the period extending form February 2021 to February 2022 at Medical Intensive Care Unit of Internal Medicine Department, Zagazig University Hospitals, Egypt.

Inclusion criteria: All subjects of non-diabetic stress hyperglycemia with different etiologies of both gender and age above 18 years old until 70 years old. These patients with stress hyperglycemia were further subdivided into two groups according to QT maxc interval prolongation: (i) Not prolonged (n=36) and (ii) prolonged (n=64).

Exclusion criteria: History of D.M and HbA1c > 5.7. Patients having any underlying condition that may predispose the prolongation of the QTc interval e.g., structural heart disease (left ventricular hypertrophy,

Received: 10/10/2022
Accepted: 13/12/2022

heart failure, myocardial ischemia), hyperthyroidism, electrolyte abnormalities hypokalemia, hypocalcaemia and hypomagnesaemia.

All the patients were subjected to the following:

1. Full history and clinical examination in addition to anthropometric study for measuring of the body mass index.
2. Routine laboratory investigations that including CBC, HbA1c, random blood glucose, serum Na^+, K^+, Ca^{2+}, Mg^{2+}, creatinine, CRP, lipid profile and TSH).

• **Sampling:** 5 ml venous blood were collected and divided into 2 ml blood collected on EDETA for CBC and HbA1c and 3 ml blood in plain tube, let stand for 30 minutes for clotting, serum was separated and stored at -20 ˚C for assessment of liver function tests, kidney function tests and lipid profile. 1ml blood in heparinized syringe, mixed well immediately after collection not more than 30 min at room temperature for assay of blood gases. 2.5 ml blood in gold- top (serum separator) tube, serum was allowed to clot and centrifuged at 1100-2000g for a minimum of 10 minutes for assay TSH, FT4 and CRP.

3. **Resting 12- lead electrocardiography:** ECG was recorded during stress hyperglycaemia in ICU at admission and after seven days. QT interval was measured manually from at least 8 leads, from the beginning of the QRS till the end of the T-wave. QT interval in lead II (QTII), mean of QT intervals in all measurable leads (QTm), maximum QT interval in all measurable leads (QTmax) and heart rate corrected QTmax (QTmaxc) using Bazett's formula. QTmaxc = QTmax/√R-R interval where QTmaxc equal to or above 450 milliseconds in men or equal to or above 460 milliseconds in women were considered prolongation.
4. **Severity assessment:** by using, the most commonly used scoring system in medical ICU APACHE II score.

Ethical Consideration: The Academic and Ethical Committee of Zagazig University approved the project. Written informed permission was acquired from each participant. The Declaration of Helsinki, the International Medical Association's code of ethics for studies involving humans, guided the conduction of this work.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS version 20.0) software was used to analyse the data after they were first imported into Microsoft Excel. Quantitative data were grouped and represented by mean ± SD whereas qualitative data is represented as numbers and percentages. Variations between quantitative independent multiples using Kruskall Wallis or ANOVA. $P \leq 0.05$ was regarded as significant.

RESULTS

The present study showed that the age ranged from 18 to 70 years with mean 33.06 years. Male represented 52% of patients. Mean BMI was 20.88 kg/m^2 (Table 1).

Table (1): Demographic and laboratory data of the studied patients

	Mean ± SD	Range
Age (year)	**33.06 ± 10.14**	**18 – 70**
Male gender (%)	**52**	**52%**
BMI	**20.88 ± 1.53**	**19 – 24**
Heart rate (beat/min)	**98.34 ± 23.62**	**50 – 153**
Serum sodium (mEq/L)	**139.07 ± 2.26**	
Serum potassium (mEq/l)	**4.09 ± 0.50**	
Serum calcium (mg/dl)	**9.47 ± 0.39**	
Serum magnesium (mg/dl)	**2.05 ± 0.21**	
Serum creatinine (mg/dl)	**0.93 ± 0.18**	
HbA1c (%)	**4.8 ± 0.45**	
CRP (mg/L)	**20.8 ± 3.86**	
WBC (103/mm3)	**12.12 ± 3.01**	
TSH (mIU/L)	**2.72 ± 0.57**	
Total cholesterol (mg/dl)	**200.81 ± 18.68**	
Triglycerides (mg/dl)	**117.54 ± 18.26**	
HDL cholesterol (mg/dl)	**51.94 ± 5.75**	
LDL cholesterol (mg/dl)	**112.61 ± 11.03**	
RBS (mg/dl)	**199.63 ± 48.53**	
APACHE II score	**12.1 ± 3.00**	
ICU stay	**6.98 ± 4.63**	

RBS random blood sugar; HDL high density lipoprotein; LDL low density lipoprotein; CRP C reactive protein; WBC white blood cells BMI body mass index.

Mean QTII, QT max, QT maxc were 389.92, 413.48 and 493.29 respectively. QT maxc was prolonged in 64% of studied patients. Mean LVEDD, LVESD, EF and EPSS were 4.16 mm, 2.94 mm, 54.59% and 5.64 (with only two patients had abnormal EPSS) and 55% had mild mitral regurge (Table 2).

Table (2): QT interval and ECHO parameters of the studied patients at time of admission

	Mean ± SD	Range
QTII msec	389.92 ± 41.62	350 – 532
QT max msec	413.48 ± 52.57	330 – 543
QT maxc msec	493.29 ± 43.34	421 – 564
Prolonged QT maxc msec	64	64%
LVEDD mm	4.16 ± 0.83	2 – 5.7
LVESD mm	2.94 ± 0.6	2 – 4
EF (%)	54.59 ± 4.24	50 – 67
EPSS (%)	5.46 ± 0.92	2 – 7.6
Normal	98	98%
Abnormal	2	2%
DMR:		
Mild	55	55%
Moderate	45	45%

QTII: QT in lead II QTmax: maximum QT interval in all leads QTmaxc: heart rate corrected maxc EF: ejection fraction EPSS: e point septal separation DMR: Degree of mitral Regurge.

There was statistically non-significant relation between gender of patients and either QT prolongation (65.3% versus 64.6% in males and females respectively), QTII, QT max or QT maxc **(Table 3)**.

Table (3): Comparison of QT interval measurement according to gender at time of admission

Parameter	Gender		Test	
	Males (n=52)	Females (n=48)	t	p
	Mean ± SD	Mean ± SD		
QTII	393.12 ± 48.28	386.46 ± 33.1	0.809	0.42
QT max	418.81 ± 52.71	407.71 ± 52.36	0.409	0.683
QT maxc	498.88 ± 46.83	491.56 ± 39.63	0.461	0.646
QT maxc:			χ^2	
Not prolonged	19 (36.5%)	17 (35.4%)	0.014	0.907
Prolonged	33 (63.5%)	31 (64.6%)		

t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant QTII QT in lead II QTmax maximum QT interval in all leads QTmaxc heart rate corrected maxc χ^2chi square test.

There was statistically significant relation between QT prolongation and all of serum creatinine (significantly higher in those with prolonged QT), random blood glucose (significantly higher in those with prolonged QT) and total cholesterol (significantly higher in those with prolonged QT). There was statistically non-significant relation between QT prolongation and either age, heart rate, or other laboratory parameters (Table 4).

Table (4): Comparison of demographic and laboratory data between prolonged and non-prolonged QTmaxc in nondiabetic stress hyperglycemic subjects

Parameter	QT interval		Test	
	Not prolonged (n=36)	Prolonged (n=64)	t	p
	Mean ± SD	Mean ± SD		
Age (year)	35.42 ± 8.53	31.73 ± 7.90	1.578	0.121
BMI (kg/m²)	21.03 ± 1.41	20.8 ± 1.6	0.729	0.468
Heart rate (beat/min)	97.42 ± 24.02	98.86 ± 24.32	-0.249	0.804
Serum sodium (mEq/L)	138.93 ± 2.55	139.14 ± 2.68	-0.391	0.697
Serum potassium (mEq/l)	4.16 ± 0.53	4.05 ± 0.50	0.988	0.326
Serum calcium (mg/dl)	9.85 ± 0.34	9.47 ± 0.42	0.303	0.763
Serum magnesium (mg/dl)	2.07 ± 0.22	2.03 ± 0.21	0.808	0.421
Serum creatinine (mg/dl)	0.88 ± 0.16	0.96 ± 0.18	-2.23	**0.028***
CRP (mg/L)¥	14.5 (4 – 33.25)	20 (6 – 32.5)	-0.631	0.528
WBC (10^3/mm³)	11.68 ± 2.61	12.36 ± 3.00	-0.745	0.458
TSH (mIU/L) ¥	2.8 (1.75 – 3.5)	2.8 (1.93 – 3.5)	-0.043	0.986
Total cholesterol (mg/dl)	171.54 ± 17.12	177.85 ± 19.4	1.635	0.016*
Triglycerides (mg/dl)	117.01 ± 17.46	118.28 ± 18.82	0.193	0.847
HDL cholesterol (mg/dl)	53.15 ± 6.75	51.26 ± 5.03	1.469	0.147
LDL cholesterol (mg/dl)	82.9 ± 11.54	84.01 ± 10.81	-0.483	0.63
RBS (mg/dl)	175.56 ± 42.76	213.17 ± 52.09	-3.617	**<0.001 ** **
HbA1c	4.79 ± 0.47	4.83 ± 0.42	-0.411	**0.682**

Median and interquartile range: non parametric test, t: independent sample t: test, *p<0.05 is statistically significant, **p≤0.001 is statistically highly significant, χ2: chi square test, ¥: data is represented as median and interquartile range and compared using Mann Whitney test, RBS: random blood sugar, HDL: high density lipoprotein, LDL: low density

lipoprotein, CRP: C-reactive protein, WBC: white blood cells, BMI: body mass index.

There was statistically significant relation between QT prolongation and QT maxc (significantly higher in those with prolonged QT), QT max (significantly higher in those with prolonged QT). There was statistically non-significant relation between QT prolongation and QTII interval (Table 5).

Table (5): Comparison of ECG data between prolonged and non-prolonged QT maxc in nondiabetic stress hyperglycemic subjects

Parameter	QT interval		Test	
	Not prolonged (n=36)	Prolonged (n=64)	t	p
	Mean ± SD	Mean ± SD		
QTII	384.17 ± 34.75	393.16 ± 41.71	-1.037	0.302
QT max	397.5 ± 41.71	422.47 ± 56.11	-2.529	0.013*
QT maxc	439.97 ± 8.45	523.28 ± 19.32	-29.795	<0.001**

t independent sample t test *p<0.05 is statistically significant **p0.001 is statistically highly significant QTII QT in lead II QTmax maximum QT interval in all leads QTmaxc heart rate corrected maxc

There was statistically non-significant relation between QT prolongation and either LVEDD, LVESD, EF, DMR or EPSS (Table 6).

Table (6): Comparison of ECHO data between prolonged and non-prolonged QT maxc in non-diabetic stress hyperglycemic subjects

Parameter	QT interval		Test	
	Not prolonged (n=36)	Prolonged (n=64)	t	p
	Mean ± SD	Mean ± SD		
LVEDD (mm)	4.1 ± 0.78	4.18 ± 0.87	-0.468	0.641
LVESD (mm)	2.98 ± 0.55	2.92 ± 0.63	0.409	0.683
EF (%)	54.78 ± 4.69	54.48 ± 4.0	0.331	0.742
DMR Mild Moderate	17 (47.2%) 19 (52.8%)	38 (59.4%) 26 (40.6%)	χ^2 1.375	0.241
EPSS	5.51 ± 0.86	5.44 ± 0.95	0.37	0.713

t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant χ^2chi square test

EF ejection fraction EPSS e point septal separation DMR Degree of mitral Regurge.

DISCUSSION

Patients with diabetes and those without the disease may experience stress hyperglycemia, which is widely established to be linked to unfavourable outcomes. Inflammatory and neuroendocrine abnormalities in critically sick individuals that result in insulin resistance and increased hepatic glucose production that are two of the many factors that contribute to stress hyperglycemia [(7)].

On an electrocardiogram, the QT interval is the distance between the beginning of the QRS complex and the end of the T wave. It shows the duration of ventricular repolarization. After accounting for heart rate, the QTc interval is the corrected QT interval. A potentially fatal ventricular dysrhythmia called Torsade de pointes can be preceded by QTc prolongation. Extended QTc is linked to unfavourable cardiovascular events including abrupt cardiac death [(8)]. Therefore, the aim of this work was to detect any relation between corrected QT interval (QTc) and stress hyperglycemia in non-diabetic patients admitted to medical ICU.

Our cohort study was carried out on 100 non-diabetic critically ill patients with stress hyperglycemia who had been admitted to ICU with different causes, their age ranged from 18-70 years old with the mean value 33.06 ± 10.14 years. QTmaxc was found to be prolonged (more than 493.29 ± 43.34 ms) in 64 patients with prevalence 64% (range 421-564ms). The mean QT maxc values of those 64 patients during stress hyperglycemia was 493.29 ± 43.34 ms, which was significantly decreased after correction of stress hyperglycemia (443.92 ± 38.12) (P<0.001). This is consistent with **Pickham *et al.*** [(4)] who found that there is an association between stress hyperglycemia and QT interval prolongation with no electrolytes disturbances that could account for QTC prolongation, which was significantly decreased after correction of stress hyperglycemia. While, these findings are in contrast with **Glaser *et al.*** [(9)] who claimed that the prolongation of QTc interval, cardiac arrhythmias and cardiac arrest presumed to be caused by electrolytes abnormalities, which was not present in our patients.

Our study showed no statistically significant differences between males and females in the mean QT II, QT max and QT maxc intervals (P > 0.05). Our results were concomitant with **Helmy *et al.*** [(10)] who found in their studies non-significant prolongation of QT interval in one sex compared to the other. These findings are in contrast with **Giunti *et al.*** [(11)] who stated that the incidence of prolonged QTc interval is significantly prevalent in women (24.5%) versus men (13.9%). While, **Whitsel *et al.*** [(12)] found that QTc prolongation is more sensitive in men than in women. The antiarrhythmic effect of HDL was explored in the context of atrial fibrillation, demonstrating a significant gender difference, with a significant increase per 10-

mg/dl of HDL cholesterol decrease HR 1.32 (1.66-1.05) of risk in women but not in men. As well as the association between HDL concentration and QTc interval has been investigated only in one study on 440 primary hypercholesterolemic patients, which failed to show any association between HDL cholesterol levels and the QTc interval. **DelGiorno *et al.* [(13)]** found that total cholesterol was also associated with a significant reduction of the risk of prolonged QTc (P value < 0.001).

In our study there was statistically non-significant relation between QT prolongation and either LVEDD, LVESD, EF, DMR or EPSS (P value > 0.05). In contact to our results **Nilsson *et al.* [(14)]** who reported that the length of QTc is closely associated with echocardiography determined left ventricular wall-motion index, LVEF and left ventricular mass, LVEF (p value= 0.002), left ventricular wall-motion index (p value< 0.001), left ventricular mass (m^2) (p value< 0.001).

CONCLUSION

Prolongation of QT maxc interval was frequent in critically ill patients during stress hyperglycemia. There was statistically significant relation between QT prolongation and APACHEII (significantly higher in prolonged QT interval).

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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