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Qtc Interval Prolongation Is an Electrophysiological Hallmark among Hepatic Cirrhotic Patients with Cardiomyopathy

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Abstract: *Cirrhotic Cardiomyopathy is a relatively ill-characterized condition, ECG showing QTc Interval prolongation is the most option for diagnosis & it's prolonged in patients with cirrhosis, thus indicating delayed repolarization.*
Aim: *To determine the frequency of QTc interval prolongation in cirrhotic patients with cardiovascular diseases e.g: cardiomyopathy.*
Methods: *Cross sectional study, we assessed an ECG changes using calibrated machine, and the QT interval was measured. QTc was calculated using Bazett's formula and a QTc of more than 0.44 seconds was considered as being prolonged.*
Results: *A total 130 Patients with early cirrhotic with & without portal hypertension & cardiomyopathy. Representing aged 40 to ≤60 yrs 50%, 33.1% aged 60 yrs and 16.9% of them aged 31 to 39 yrs. A frequent occurrence of Q-T interval prolongation has been found in patients with cirrhotic liver with or without portal hypertension. Corrected QT Interval prolonged in 19.2%, while were normal with percentage of 80.8%.*
A significant correlations between Q-Tc and Child-Pugh score & several liver tests, 50% in class C, class B 37.5%, & class A 12.5%. Pearson correlation studies, represent no significant correlation between QT ms and portal vein parameters in studies groups (P>0.05). A positive correlation between QT dispersion (ms) in group III & portal vein parameters P<0.05.
Conclusion: *The delayed repolarization of the myocardium already occurs in cirrhotic patients with or without increase in portal pressure and advanced child pough classification. QTc interval was prolonged in 19.2% of cirrhotic patients, thereby indicating an association between QTc prolongation and the severity of cirrhosis.*
Keywords: *Liver cirrhosis, Portal hypertension, Cardiomyopathy (HCM), QT interval.*

I. Introduction

Cardiovascular disease associations with chronic liver disease are identified. Liver cirrhosis refers to a chronic diffuse progressive condition characterized by loss of the normal architecture of the liver, cirrhotic nodule, attenuated hepatic veins with irregular surfaces by abdominal Ultrasound, and can be caused by a number of conditions. Up to 90% of liver parenchymas undergo destruction before liver failure becomes clinically visible (Heidelbaugh, J.J. and Bruderly, M. (2006). In developing countries, Hepatitis B and C have been described as the leading causes of cirrhosis, whereas in developed countries, Alcoholic liver disease (ALD) and Non-Alcoholic Steatohepatitis (NASH), in addition to Hepatitis C, have been named as the leading causes (Stroffolini, T., et al. 2004).

Clinical Definition of HCM is a disease state characterized by unexplained LV hypertrophy associated with non-dilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient. Cirrhotic cardiomyopathy (CMP) is now a well-established condition, defined as the presence of blunted ventricular response to stress, in cirrhotic patients, with a raised basal cardiac output accompanied by systolic, diastolic, structural, histological, biochemical and electrophysiological changes such as prolongation of repolarization

time (QT interval prolongation) (A. Páll, et al; 2014).

Various biochemical and electrophysiological markers have been identified to aid in the diagnosis of cirrhotic cardiomyopathy, such as raised Atrial Natriuretic Peptide (ANP) and B-Type Natriuretic Peptide (BNP) levels, elevated Cardiac Troponin I, and specific changes on Echocardiography. However, due to its widespread availability and cost-effectiveness, for many, the most suitable screening option is electrocardiography (ECG), which shows a prolonged corrected QT interval (QTc) in the case of cirrhotic cardiomyopathy (**Abelmann, W.H 1995**).

Almost one third of cirrhotic patients can be shown to have evidence for a cardiomyopathy. Both systolic and diastolic blood pressure levels are abnormal in cirrhotic patients and parallel the degree of liver dysfunction **(Valeriano et al., 2000)**. The QT interval, measured from the onset of the QRS complex to the end of the T wave on a standard 12-lead electrocardiogram (ECG), measures ventricular electrical repolarization and is typically corrected for heart rate (QTc). Prolongation of the QTc interval is associated with ventricular arrhythmias, namely torsade de pointes, and increased mortality. The QTc is also known to be prolonged in the setting of various medical conditions, such as coronary ischemia, electrolyte abnormalities, and end-stage liver disease (ESLD), as well as it well known to occur with several classes of medication, including antiarrhythmic, certain antibiotics and some antidepressants, **Bernardi M et al; 1998**. Special attention needs to be directed at the detection of a prolonged QT interval and its worsening with the use of drugs known to increase the QT interval particularly those used commonly in cirrhotic patients **(Trevisani et al., 2003)**. One of the most common and clinically important electrophysiological changes reported in cirrhotic patients is a prolongation of the QT interval detected by ECG**.** This interval is a measure of the time from the earliest activation (depolarization) of myocardial cells to the end of ventricular repolarization **(Munger et al., 1991)**.

Women have longer QT intervals than do males. The QT interval is affected by heart rate and the corrected QT interval (QTc) is the QT interval corrected for the heart rate. A prolonged QTc can occur as a consequence of slowed progressive depolarization or prolongation of the repolarization process**.** QT dispersion or inter lead QT interval variability, has been proposed as a simple noninvasive measure for identifying patients at risk of many cardiac disorders **(Day C. et al.,1993**). QTc prolongation has been associated with an enhanced risk of a number of life-threatening cardiac arrhythmias, such as torsades de pointes (TdP) and ventricular fibrillation (VF), as well as with sudden cardiac death**.** Frequency of QTc prolongation increases with a worse Child Pugh score, and it has been shown to positively correlate with a reduced heart rate variability, both of which are independent prognostic factors, **Bernardi M et al; 1998**. A QTc interval >0.440msec is a well-recognized risk factor for serious ventricular arrhythmias and a potential for sudden death **(Moss and Robinson, 1992)**.

The specific mechanisms responsible for QT prolongation in cirrhotic patients are controversial. Several investigators have shown a relationship between diseases severity as defined by the **Child-Pugh score** that occurs independently of the specific disease etiology **(Singh-Bal and Thuluvath, 2003)**. Splanchnic arterial relaxation is the most important pathology in systemic circulation of portal hypertensive patients.

II. Patients And Methods

This study was conducted at Prince Sattam Bin Abdul Aziz university hospital & in collaboration with King Khalid Hospital in Alkharj City, Saudi Arabia were enrolled in this study period between 2014–2015) on 130 persons divided into four groups as well as healthy person as control group:

Group I: 30 healthy persons as a control group**.**
Group II: 40 early cirrhotic patients without portal hypertension
Group I1I: 40 patients with portal hypertension due to liver cirrhosis.
Group 1V: 20 patients with cardiomyopathy (HCM).

Patients responded to a questionnaire to investigate possible liver cell failure with one of any manifestations of hepatic cirrhosis such as liver stigmata (spider nevi, palmer erythema, gynecomastia, duptryen contracture) either compensated or decompensated liver cirrhosis (ascites, hypoalbumeniemia, hyperbilirubinemia) and patients with cardiovascular diseases e.g: cardiomyopathy, cardiac assessment & ECG was done using calibrated ECG machine and the QT Interval was measured and then underwent.

Informed consent was obtained from all patients prior to participation in this study and before any procedure. The Institutional Review Board (IRB) of the University Hospital at Prince Sattam Bin Abdel Aziz University approved this study. The study was conducted according to the principles of the 1974 Declaration of Helsinki.

The studied groups were subjected to the following:

A- Thorough clinical assessment

B- Through of Routine laboratory investigations including:

- CBC and ESR
- Stool and urine analysis
- Liver function test and Kidney function test
- Fasting and postprandial blood glucose level

C- Radiological imaging assessments by abdominal ultrasonography evaluation were performed with special stress on PV diameter and PV (A).

D- Doppler and colored duplex was used for measuring PV (V), PV (F) and CI. Doppler and duplex examination showed significant differences between normal persons, cirrhotic & patients of Porto-systemic anastomosis in all values of the portal vein. Portal hypertension was diagnosed on basis of Doppler and colored duplex findings (hepatofugal or bidirectional flow in the portal venous system, PV (A) > 1.1973 C^{2}, PV (V) <13 cm/sec, and CI> 0.1 cm X sec ^{m}

E- Twelve-lead ECG was carried out, with special stress on Q-T interval.

Exclusion Criteria:

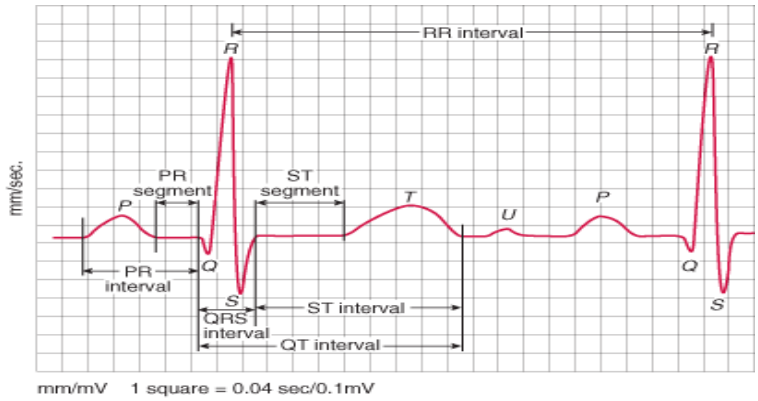
1) Patients who were suffering from any cardiac problem including ischemic heart disease, hypertension, conduction defects, and atrial fibrillation.

2) Patients taking drugs that may have prolonged the QT Interval, including (beta-adrenergic blocking agents, calcium channel blockers, anti-histamines, antipsychotics, macrolides, quinolones, and amiodarone or vasoactive substances), cancer or any other major disease were excluded.

3) Patients suffering from any other condition causing prolongation of QT interval.

QTc Interval Calculation:

The QT interval was measured from the beginning of the QRS complex to the termination of the T wave (defined as the return to the isoelectric line). QTc was calculated manually using Bazett's formula: QTc= QT interval (sec)/ (R -R interval1/2) (sec). Bazett's formula was chosen because the QTc interval calculated, this way has been shown to be a predictor of cardiovascular mortality. Lead II was the first choice for calculating the QTc; however, if lead II could not be used due to poor T-wave visualization, the lead with the clearest T wave was utilized. A dramatic QTc decrease was defined as a reduction ≥60 ms. A prolonged QTc interval was defined as a QTc >440 ms for men and >460 ms for women Different QTc cutoff values were used based on sex, because women are known to have longer QTc values than men and sex-specific QTc cutoff values frequently are used when looking at QTc prolongation
(**Goldenberg I**. et al; 2006).



QT dispersion was calculated as the difference between the maximum and minimum values of the QT interval measured among the 6 precordial unipolar (V_1 through V_6) leads. The standard deviation of the QT intervals (SDQT) was calculated from the 6 precordial unipolar (V_1 through V_6) Leads.

III. Statistical Analysis

The statistical package for social sciences (IBM SPSS STATISTICS, version 20) was used to enter and analyze the data. Mean (X) and standard deviation (SD) frequencies and percentages were produced. P-values were calculated. Pearson correlation coefficient(r) for the correlation between variables and t-student test (t) to compare means, Chi-square test utilized for cross tabulation between variables. (McDonald, J.H., 2008).

IV. Results

The characteristics of studied groups regarding age and gender are displayed in table (1) which shows that the majority of them were males with percentage of (56.9%), while females represent 43.1% of the total sample. Regarding age, most of the subjects aged 40 to less than 60 years with percentage of 50%, whereas 33.1% aged 60 years and more and 16.9% of them aged 31 to 39 years.

Table 1: Personal Characteristics of the studied groups

Characteristics	**No.**	**Percentage %**
Gender		
Male	74	56.9
Female	56	43.1
Age group (years)		
31-39	22	16.9
40- <60	65	50.0
60 and above	43	33.1

Concerning distribution of cirrhosis patients according to Child Pugh Class, the results revealed that 40 patients representing 50% in class Child C, and the cirrhosis patients in class B were 30 patients representing 37.5%, but cirrhosis patients in class A were 10 patients 12.5%.

Table (2): Relation between cirrhotic patients (Group II and Group III) and Child Pugh Classification by using Chi-square test (n=80)

			Groups		Total
			Group II	Group III	
Child-Pugh class	Child A	No	10	0	10
		%	25.0%	0.0%	12.5%
	Child B	No	19	11	30
		%	47.5%	27.5%	37.5%
	Child C	No	11	29	40
		%	27.5%	72.5%	50.0%
Total		No	40	40	80
		%	100.0%	100.0%	100.0%

X^2value = 20.233 p value = 0.000

Table (2) showed if there is a relationship between cirrhotic patients groups and Child Pugh Classification, this tells us that there is a statistically significant association between Child Pugh Classification and groups (cirrhotic patients) that most of Group II patients with Child B class (47.5%), whereas the majority of Group III patients with Child C class (72.5%), and Child A class was concentrated in group II (25.0%)

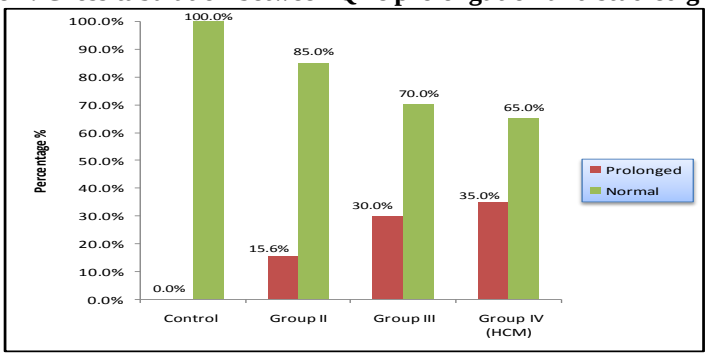
Table (3): Cross tabulation by using Chi-square test for QTc prolongation in cirrhosis patients (Group II, Group III and Group IV "HCM"):

			Groups				Total
			Control	Group II	Group III	Group IV (HCM)	
QTc prolongation	Prolonged	No	0	6	12	7	25
		%	0.0%	15.0%	30.0%	35.0%	19.2%
	Normal	No	30	34	28	13	105
		%	100.0%	85.0%	70.0%	65.0%	80.8%
Total		No	30	40	40	20	130
		%	100.0%	100.0%	100.0%	100.0%	100.0%

X^2value = 13.792, P value = 0.003

Pearson's chi-square test in (table 3) results showed that Pearson Chi-Square value was χ^2 = 13.792, P = 0.003, As regard to the corrected QT Interval we found that it was prolonged in 25 out of 130 patients, representing 19.2%, while 105 out of 130 were normal with percentage of 80.8%. This tells us that there is a statistically significant association between QTc prolongation and groups (cirrhotic patients). That QTc prolonged in Groups II, II and IV and not in control, while the entire control group was normal.

Figure 1: Cross tabulation between QTc prolongation and studied groups:



Doppler and duplex examination showed significant differences between healthy persons, early cirrhotic patients without portal hypertension and patients with portal hypertension due to liver cirrhosis in all values of the portal vein and HCM patients. We conclude that the control group were not significantly differ from early cirrhotic patients without portal hypertension in group II regarding portal vein parameters, but they were significantly differences regarding these parameters when compared to group III or patients with portal hypertension due to liver cirrhosis, the difference trends was in favor of group III due to the highest mean values as well as for the differences between Group II and III , the difference trends was in favor of group III patients with cardiac liver cirrhosis. There was significant difference between group I (control group) and patients with cardiomyopathy (HCM) regarding portal vein parameters, the difference trends was in favor of group IV (HCM) patients due to the highest mean values.

Table 4: Correlation between Q-T and PV values of the studied groups (Pearson Correlation Co-efficient):

		Caliber	PV(A)	PV(V)	PV(F)	CI
QT (ms)	GROUP I	0.55	0.64	-0.41	0.43	0.53
	GROUP II	0.55	0.60	-0.48	0.58	0.61
	GROUP III	0.54	0.61	-0.40	0.42	0.48
	GROUP IV	0.30	0.21	0.35	0.40	0.45
Q-T dispersion (ms)	GROUP I	0.54	0.48	-0.38	0.40	0.49
	GROUP II	0.48	0.61	-0.50	0.49	0.55
	GROUP III	0.56	**0.71	**0.73	**0.79	**0.70
	GROUP IV	0.41	0.39	0.22	0.25	0.37
QTc (ms)	GROUP I	0.50	0.48	-0.38	0.40	0.50
	GROUP II	0.56	0.60	-0.50	0.54	0.38
	GROUP III	0.52	0.51	-0.50	0.51	0.50
	GROUP IV	0.49	0.43	0.32	0.42	0.33

*Significant at level 0.05, ** significant at level 0.01

The Q-T dispersion was correlated with the PV (A), PV (V), PV (F) and CI, in patients of group III. The results of Pearson correlation in the above table shows that there was no significant correlation between QT ms and portal vein parameters in group I, II, III and IV (P>0.05). Similarly, there was no significant correlation between corrected QTc prolongation and portal vein parameters in group I, II, III and IV (P>0.05). However, for the Q-T dispersion (ms) in Group I, II and IV there was no significant correlation regarding portal vein parameters (P>0.05), while there was statistically significant positive correlation between Q-T dispersion (ms) in Group III & portal vein parameters P<0.05, which was an indication to the relationship between QT dispersion and patients with cardiac liver cirrhosis.

V. Discussion

Cirrhosis is a leading cause of morbidity and mortality not only in middle east, but worldwide, and each year, thousands of patients are affected by this chronic condition. The prevalence of cirrhosis has been demonstrated to be increasing in Mideast, largely owing to the rapid spread of hepatitis C and B. Cirrhotic cardiomyopathy is one relatively common cardiovascular complication arising secondary to liver cirrhosis, and despite an increased baseline cardiac output, cirrhotic patients have a suboptimal ventricular response to stress (Ripoll, C., et al; 2008).

We compared the Q-T & PV values between 40 early cirrhotic patients without portal hypertension (group II), 40 patients with radiologically confirmed portal hypertension on top of cirrhosis (group III), 20 with cardiomyopathy group 1V and 30 healthy persons (group I). A frequent occurrence of Q-T interval

prolongation has been found in patients with cirrhotic liver with or without portal hypertension. As regard to the corrected QT Interval we found that it was prolonged in 25 out of 130 patients, representing 19.2%, while 105 out of 130 were normal with percentage of 80.8%. These results are in agreement with those of Mohamed et al.,(1996) who found that Q-Tc is significantly longer in cirrhotic patients. Q-Tc was prolonged above 440 ms in 46.8% of cirrhotic patients and 5.4% of normal persons (P .001).

The frequency of QTc prolongation in our study population was found to be 19.2%. This is typically similar to the results presented by Zuberi et al; 2007 in their study, in which they showed the frequency of QTc prolongation to be 19.2%. Other international studies have shown a wide range of values. It was found to be 46.2% in a study by Bernardi et al.; 1998; 46.93% in a study by Li et al.2007 and Bal et al.; demonstrated a QTc prolongation frequency of 56% in their study and Kosar et al; determined the frequency of QTc prolongation to be 32% in their study population.

This discrepancy may be explained to my knowledge by the presence of other compounding risk factors such as electrolyte disturbances, concomitant cardiac problems, or use of QTc prolonging drugs, which were excluded in our study but might have been included in other studies. Moreover, the variable spread of severity of cirrhosis as shown by Child Pugh Score or any other model in all these studies would also have played a role in this wide range of results. Prolonged Q-T tended to be more frequently seen in those with hepatic encephalopathy and rough evidence of portal hypertension.

We found majority of studied groups were males with percentage of (56.9%), while females represent 43.1% of the total sample. Regarding age, we note that all QT values were higher in older ones. Most of the subjects aged 40 to less than 60 years with percentage of 50%, whereas 33.1% aged 60 years and more and 16.9% of them aged 31 to 39 years. Similarly to our study, Genovesi et al.; showed in their study that most of the patients were >45 years of age (86.1%), with the majority being in the 40-59 year age group (51.2%), indicating an increased prevalence of cirrhosis in higher age groups, which is understandable considering the long natural history of cirrhosis; it may take up to 30 years from the onset of infection to development of cirrhosis (Makkar, R.R. et al; 1993).

Statistically significant correlations were found between QTc and Child-Pugh score & several liver tests, the results revealed that 40 patients representing 50% in class Child C, and the cirrhosis patients in class B were 30 patients representing 37.5%, but cirrhosis patients in class A were 10 patients 12.5%. This results agreement with Zuberi, B.F. et al; 2007 also described a similarly skewed distribution of patients with more than half of them being in Child Pugh Grade C.

Mohamed et al., 1996, and Bernardi et al., (1991 found that QTc prolongation is independent of the etiology of cirrhosis. This finding recalls that the alterations in cardiac function, as assessed by systolic time intervals, occurred regardless of the etiology of cirrhosis. Lehmann M. (1997) explained the QTc prolongation seen in cirrhotic patients by their higher heart rates. However, this should not have substantially affected our results, because the prevalence of abnormal QTc did not significantly differ in patients with heart rate above or below70 beats/ minute, a rate beyond which QTc can be strongly influenced.

We noticed that a progressive increase in the frequency of QTc prolongation with the worsening of the Child Pugh Score, hence indicating a direct relationship between the stage of cirrhosis and the development of cirrhotic cardiomyopathy. On other hands, the more advanced the cirrhosis, the greater the chances of developing cirrhotic cardiomyopathy and the associated symptoms. QT values in the studied groups, we note that all values of QT were high in Groups II, III and IV) and low in the control group (Group I).

The Q-T dispersion was correlated with the PV (A), PV (V), PV (F) and CI, in patients of group III. The results of Pearson correlation in the above table shows that there was no significant correlation between QT ms and portal vein parameters in group I, II ,II and IV ($P>0.05$). Similarly, there was no significant correlation between corrected QTc prolongation and portal vein parameters in group I, II, III and IV ($P>0.05$). However, for the Q-T dispersion (ms) in Group I, II and IV there was no significant correlation regarding portal vein parameters ($P>0.05$), while there was statistically significant positive correlation between Q-T dispersion (ms) in Group III portal vein parameters $P<0.05$, which was an indication to the relationship between QT dispersion and patients with cardiac liver cirrhosis.

Patients with cirrhotic portal hypertension have Q-T dispersion correlated with their PV (A), PV (V), PV (F) and CI. This result is in agreement with that of (Hartleb M., 2005) who found that cirrhotic patients with mild portal hypertension have a high frequency of prolonged Q-Tc intervals, as have those with clinically significant portal hypertension. There was significant difference between group I (control group) and patients with cardiomyopathy (HCM) regarding portal vein parameters, the difference trends was in favor of Group IV (HCM) patients due to the highest mean. As regard congestion index (CI (cm/sec) values in the studied groups, where we note that all its values were higher in Groups II, III and IV and low in the control group (Group I) and the highest value was in Group III.

VI. Conclusions:

The delayed repolarization of the myocardium already occurs in cirrhotic patients with or without increase in portal pressure, but it's related mainly to the presence of portal hypertension and advanced child pough. Also there is a significant correlation in QT interval with PV parameters.

VII. Recommendations:

1) ECG should be made an integral part of the work-up and follow-up of every patient with cirrhosis.
2) QTc interval measurement and rate correction should be taught to all health professionals, and its uses and implications should be explained thoroughly.
3) Electrolyte disturbances such as hypokalemia and hypomagnesimia, which can lead to further prolongation of QT interval, should be closely monitored and corrected as soon as possible.
4) All QT interval-prolonging drugs should be used very carefully and after considering the risk to benefit ratio in patients of cirrhosis, especially those with QTc prolonged (Adnan Bashir Bhatti et al; 2014).

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