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Alterations in Q-T Interval in Portal Hypertensive Cirrhotic Patients

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Abstract: **The effect of these cardiovascular diseases on the natural history of the underlying liver disease is considered. Their recognition and management is important in the long term care of patients with chronic liver disease, (Maisaia et al., 2001). Almost one third of cirrhotic patients can be shown to have evidence for a cardiomyopathy. The Q-T interval is prolonged in a substantial fraction of patients with cirrhosis, thus indicating delayed repolarization. However, no information is available in portal hypertensive patients. More specifically, QTc-interval prolongation has been found in association with both alcoholic and nonalcoholic liver disease.**

Objective is to evaluate any alternative changes in Q-T interval in portal hypertensive cirrhotic patients.

Patients presented to our clinics at Salman Bin Abdul Aziz University hospital with any of any manifestations of hepatic cirrhosis such as liver stigmata (spider nevi, palmer erythema, gynecomastia, duptryen contracture) with compensated or decompensated liver (ascites, hypoalbumeniemia, hyperbilirubinemia etc..) were enrolled from the Salman Bin Abdel Aziz University Hospital, Al Kharj, Saudi Arabia at that period between 2012-2013. Patients responded to a questionnaire to investigate possible liver cell failure, and then underwent.

This study was rolled on 80 patients and healthy as a control, 30 patients with early cirrhotic patients without portal hypertension (group II), compared with 30 patients with radiologically confirmed portal hypertension on top of cirrhosis (group III) and 20 healthy persons (group I).

The studied groups were subjected to thorough clinical assessment, routine laboratory investigations, ECG and radiological imaging assessments by: abdominal ultrasonography, Doppler and colored duplex. Doppler and duplex examination showed significant differences between normal persons, cirrhotic & patients of portosystemic anastomosis in all values of the portal vein.

There was a significant difference between normal persons, cirrhotic & patients of portosystemic anastomosis in all values of Q-T interval. The Q-T dispersion was correlated with the PV (A), PV (V), PV (F) and CI, in patients of group III.

The delayed repolarization of the myocardium already occurs in cirrhotic patients with or without increase in portal pressure but, it is related mainly to the presence of portal hypertension.

Keywords: **Portal hypertension, Liver cirrhosis, ECG changes: Q-T interval.**

1. INTRODUCTION

Cardiovascular disease associations with chronic liver disease are identified. The effect of these cardiovascular diseases on the natural history of the underlying liver disease is considered. Their recognition and management is important in the long term care of patients with chronic liver disease, **(Maisaia et al., 2001).** 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. Is well known to occur with several classes of medication, including antiarrhythmics, certain antibiotics, and

some antidepressants. The QTc is also known to be prolonged in the setting of various medical conditions, such as coronary ischemia, electrolyte abnormalities, inherited genetic mutations causing various ion-channel disorders, and end-stage liver disease (ESLD). More specifically, QTc-interval prolongation has been found in association with both alcoholic and nonalcoholic liver disease **Day CP** et al; 1993, **Mohamed R et al; 1996, & 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 (**Trevisani et al., 2003)**.

Coronary vascular diseases occur less often in cirrhotic than in the general population (**Kaya et al., 2003)**. Pericardial effusions can occur in cirrhotic as a consequence of an overall defect in fluid and electrolyte to regulation **(De et al., 2003)**.

One of the most common and clinically important electrophysiological changes reported in cirrhotic is a prolongation of the QT interval detected by ECG **(Munger et al., 1991).** This interval is a measure of the time from the earliest activation (depolarization) of myocardial cells to the end of ventricular repolarization. A prolongation of the QT can occur either as a congenital abnormality or be acquired **(Karjalainen et al., 1997)**.

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 interlead QT interval variability, has been proposed as a simple, noninvasive measure for identifying patients at risk of many cardiac disorders **(Day 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**, Chugh, S.S**. 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)**. QT prolongation has been reported to occur in 37-84% of cirrhotic individuals with either alcoholic or nonalcoholic liver disease **(Sawicki et al.; 1996)**.

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)**. Moreover, some have reported an independent effect of the QTc on mortality **(Zekiet al., 2004).** Splanchnic arterial relaxation is the most important pathology in systemic circulation of portal hypertensive patients. Progressive decline of splanchnic vascular resistance is responsible for development of circulatory dysfunction syndrome (CDS), associated with reduction of effective blood volume within central vascular compartment and compensatory stimulation of vasopressin and natrium retaining hormonal mechanisms **(Hartleb, 2005)**.

2. PATIENTS AND METHODS

This study was conducted at Salman Bin Abdul Aziz university hospital & collaboration with King Khalid Hospital in Alkharj City, Saudi Arabia were enrolled in this study period between 2013 - 2014) on 80 persons divided into three groups;

Group I: 20 healthy persons as a control group**.**
Group II: 30 early cirrhotic patients without portal hypertension
Group I1I: 30 patients with portal hypertension due to liver cirrhosis.
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 cm^2, PV (V) <13 cm/sec. and CI > 0.1 cm X sec**.**

EXCLUSION CRITERIA:

Patients had a positive history of recent gastrointestinal bleeding, encephalopathy, heart failure, organic renal disease, diabetes, alcohol abuse, drugs intake (beta-adrenergic blocking agents, calcium channel blockers, digoxin, antiarrhythmic agents or vasoactive substances), cancer or any other major disease were excluded. 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 of Salman 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- Full clinical assessment

B- Routine laboratory investigations including

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

C- Abdominal ultrasonographic evaluation was 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.

E- Twelve-lead ECG was carried out, with special stress on Q-T 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 **Goldenberg I**. 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, **Lunzer MR** & **Locati ET.** We wanted to be able to account for baseline QT differences due to gender irrespective of liver disease and other risk factors for QT prolongation.

When U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves. Leads in which the end of the T wave could not be reliably determined were excluded from analysis. Three consecutive QT intervals were measured, and the results were averaged for each lead.

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.

3. STATISTICAL ANALYSIS

Calculation of the mean (X) and the standard deviation (SD), correlation coefficient (r) of two variables, t-student test (t), Chi-square test (X^2) and probability (P).

RESULTS:

Doppler and duplex examination showed significant differences between normal persons, cirrhotic & patients of portosystemic anastomosis in all values of the portal vein (table 1).

There was a significant difference between normal persons, cirrhotic & patients of portosystemic anastomosis in all values of Q-T interval (table 2)

The Q-T dispersion was correlated with the PV (A), PV (V), PV (F) and CI, in patients of group III (table 3).

Table 1: Portal vein parameters in the studied groups

Parameter	Group I	Group II	Group III	
PV caliber (mm)	8.35 + 0.851	9.5 + 1.5	13.7 + 3.40	**A=NS, B=S & C=S**
A (cm^2)	0.887 + 0.078	0.97 + 0.09	2.43 + 0.322	**A=NS, B=S & C=S**
PV (V) (cm\sec.)	14.8+1.03	12.8+1.3	9.57 + 1.62	**A=NS, B=S & C=S**
PV (F) (cm^3\sec.)	786+101	811+112	1401 + 294.	**A=NS, B=S & C=S**
CI (cmXsec.)	0.061 + 0.0057	0.07 + 0.009	0.26 + 0.0559	**A=NS, B=S & C=S**

A= group I *v* group II, B= group I *v* group III, C= group II *v* group III,
S= significant & NS=Non-Significant.

Table 2: Q-T values in the studied groups:

	Group I	Group II	Group III	
Q-T (ms)	350 + 95	450 + 95	456 + 101	**A=S, B=S & C=NS**
Q-T dispersion (ms)	61.9+40	81.9+61	87.3+69	**A=S, B=S & C=NS**
Q-Tc (ms)	371+100	463+113	471+119	**A=S, B=S &**
				C=NS

A= group I *v* group II, B= group I *v* group III, C= group II *v* group III, S= significant & NS = Non-Significant.

Table 3: Correlation between Q-T and PV values of the studied groups

		Caliber	PV (A)	PV (V)	PV (F)	CI
Q-T (ms)	**Gp. I**	0.57	0.66	- 0.43	0.45	0.55
	Gp. II	0.58	0.63	-0.51	0.61	0.64
	Gp. III	0.58	0.65	- 0.43	0.45	0.51
Q-T dispersion (ms)	**Gp. I**	0.59	0.53	- 0.43	0.45	0.54
	Gp. II	0.54	0.67	-0.56	0.55	0.61
	Gp. III	0.61	*0.74	*0.79	*0.8	*0.75
Q-Tc (ms)	**Gp. I**	0.55	0.53	- 0.43	0.45	0.55
	Gp. II	0.61	0.66	-0.55	0.55	0.41
	Gp. III	0.58	0.54	-0.56	0.54	0.55

* = significant

4. DISCUSSION

We compared the Q-T & PV values between 30 patients with radiologically confirmed portal hypertension on top of cirrhosis (group III), 30 early cirrhotic patients without portal hypertension (group II) and 20 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.

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). Prolonged Q-T tended to be more frequently seen in those with hepatic encephalopathy and rough evidence of portal hypertension. Statistically significant correlations were found between Q-Tc and Child-Pugh score, several liver tests (**Mohamed et al., 1996)**.

Bernardi et al., (1991) found that Q-Tc prolongation is independent of the aetiology of cirrhosis. This finding recalls that the alterations in cardiac function, as assessed by systolic time intervals, occurred regardless of the aetiology of cirrhosis. **Lehmann, (1997)** explained the Q-Tc prolongation seen in cirrhotic patients by their higher heart rates. However, this should not have substantially affected our results, because the prevalence of abnormal Q-Tc did not significantly differ in patients with heart rate above or below 70 bests per minut, a rate beyond which Q-Tc can be strongly influenced.

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 **(Henriette et al., 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. The mechanisms by which cirrhosis affects ventricular repolarization and thereby the Q-Tc is still known. Several interferences related to liver dysfunction, alcoholic intake, portal hypertension, systemic circulatory disturbances, autonomic dysfunction, and, recently, portosystemic shunting have been suggested **(Singh-Bal and Thuluvath, 2003)**.

The suggestion of a role of portosystemic shunting was based on findings of a prolonged Q-Tc in non-cirrhotic portal hypertensive patients and a further prolongation of the Q-Tc interval in some cirrhotic patients after insertion of TIPS **(Zekiet al., 2004)**.

5. CONCLUSIONS

The delayed repolarization of the myocardium already occurs in cirrhotic patients with or without increase in portal pressure but, it is related mainly to the presence of portal hypertension.

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KEY POINT:

- It is very important to examine heart to most of cirrhotic hepatic patients for early detection or any ECG changes.
- ECG is mandatory for chronic liver cirrhosis eg: Alcoholic & Non Alcoholic liver diseases to monitor any alternative ECG changes.
- Portal hypertensive cirrhotic patients need special care for cardiac exam.

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LIST OF ABBREVIATIONS:

PV: portal vein.
PV (A): portal vein cross-sectional area
PV (V): Portal veins mean velocity
PV (F): portal vein flow volume
CI: congestion index
ESLD: End-Stage Liver Disease
CBC: complete blood count
ESR: erythrocyte sedimentation rate
ECG: electrocardiogram
QTc: corrected QT interval