Biomedical Research 2017; 28 (3): 1130-1134

ISSN 0970-938X
www.biomedres.info

QT interval parameters and ventricular arrhythmic events in liver cirrhosis-correlation with severity and etiology.

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Abstract

Electrophysiological abnormalities in cirrhosis, such as the prolongation of the QT interval, are associated with higher risk of ventricular arrhythmias. Holter monitoring offers a full picture of these during 24 hour. Our study aimed to evaluate the extent of the QT interval prolongation, identify etiological and biochemical elements linked with it, and investigate the correlation with ventricular arrhythmic events related to etiology and severity of liver cirrhosis. We included 43 patients with cirrhosis and evaluated the maximal QT interval (maxQT), corrected QT interval (QTc) and its maximum (maxQTc), and ventricular arrhythmic events during 24 hour Holter monitoring. All parameters were prolonged and significantly increased in alcoholic cirrhosis when compared to viral C or B etiology (P<0.05). MaxQT and QTc moderately correlated with serum proteins (r=0.402; P<0.01 and r=0.308; P<0.05) and triglycerides (r=-0.357; P<0.05 and r=-0.344; P<0.05). Viral C etiology associated significantly more premature ventricular contractions than viral B (P<0.01), toxic (P<0.01), and mixed etiology (P<0.05). The ventricular arrhythmic events did not differentiate groups based on Child class or gender (P=NS). In liver cirrhosis, Holter monitoring confirms. QT interval prolongation particularly correlated with moderate severity, alcoholic etiology, and plasmatic level of total proteins and triglycerides but not with a higher incidence of ventricular arrhythmic events, except for hepatitis C virus etiology, supporting the novel hypothesis of a direct cardiac arrhythmic effect of this virus.

Keywords: Liver cirrhosis, Holter monitoring, Prolonged QT interval, Cardiac arrhythmias.

Accepted on July 27, 2016

Introduction

There is a common acceptance regarding the existence of the cirrhotic cardiomyopathy, which becomes evident during increased circulatory demands in cirrhotic patients and represents an association between systolic incompetence, diastolic dysfunction, and electrophysiological abnormalities, in the absence of any other known cardiac disease [1]. The most frequent electrophysiological abnormality associated with cirrhotic cardiomyopathy is the prolongation of the QT interval. The prevalence of QT prolongation in patients with liver cirrhosis is higher than 45% (as compared to approximately 5% of the general population) [2,3] and correlates with the severity of the disease and circulating plasma levels of norepinephrine [4]. The responsible mechanisms for QT prolongation are impaired function of the potassium channels [3] and increased levels of cytokines [5], followed by disturbances in the electrical and mechanical coupling, at the cardiomyocyte level. The correlation between QT interval prolongation and etiology of liver cirrhosis seems to be a subject under debate because researchers have not concurring opinions, mainly regarding the strong correlation between QT prolongation and alcoholic etiology [3,6], and the newer assumption of the direct cardiomyopathic and arrhythmic effect of the hepatitis C virus [7,8]. The significance of longer than normal corrected QT interval (QTc) is associated with an adverse cardiovascular risk profile and is a strong predictor of incident coronary heart disease and cardiovascular mortality [9]. Other studies indicate that prolonged QTc interval should be viewed as an independent risk factor for sudden cardiac death, due to the association with malignant ventricular dysrhythmias, including a predisposition to torsade des pointes [10,11]. In cirrhotic patients, QTc interval prolongation is associated with higher risk of ventricular arrhythmias during the stressful procedures. When it comes to investigating these electrophysiological abnormalities, Holter monitoring seems to be more advantageous when compared to short ECG recording, offering a full picture of the QT interval duration during a 24-hour period of time.

In this context, our study aims to evaluate the extent of the QT interval prolongation for all normal beats recorded during 24-hour Holter monitoring, identify any etiological and biochemical elements that link with this electrophysiological alteration, and investigate the potential correlation between QT interval abnormality and ventricular ectopic events in various etiology and severity of liver cirrhosis.

Materials and Methods

Patients

In this study, we included 43 patients admitted to the Institute of Gastroenterology and Hepatology-Iasi, Romania, between September 2012 and August 2013. The main inclusion criterion was the definite diagnosis of liver cirrhosis made on clinical examination, laboratory findings (including liver biopsy), ultrasonography, and endoscopy. We considered only patients with viral, alcoholic, and mixed etiology (viral and alcoholic), due to the higher prevalence of these in Romanian population. Patients with previous cardiovascular diseases (arterial hypertension, ischemic heart disease, heart failure, left ventricular hypertrophy, congenital long QT syndromes), diabetes mellitus, electrolyte imbalance (hypokalemia, hypomagnesemia) or clinical hypoxia as well as those who were on treatment with drugs known to influence QT interval (anti-arrhythmic, anti-infective, psychotropic, others) were excluded from the study. Also, the presence of atrial fibrillation and bundle branch block on resting electrocardiogram (ECG) was an exclusion criterion, due to a controversial and difficult assessment of the QT interval.

All patients provided a written consent and the protocol of the study was approved by the Institute of Gastroenterology and Hepatology Ethics Committee. Clinical details and biochemical data of the patients were extracted from the medical records, ensuring security and confidentiality of data.

Holter monitoring

All patients had a short discussion with the examining physician in order to give them the basic information about Holter monitoring. They were submitted to ECG examination for 24 hours, using the 300-3A recorders with 7 leads, a sampling rate of 4096 Hz and writing rate of 128 Hz for each channel, and CARDIOSCAN 11 software produced by DM Software-USA. All Holter reports were reviewed by one of the authors (RDN). The software automatically calculated the corrected QT interval for each normal beat, the mean QT corrected interval (mean QTc) of all sinus impulse beats recorded during 24-hour Holter monitoring, the maximal QT interval (max QT), and the maximal QT corrected interval (max QTc). The reference QTc value for diagnosing QT interval prolongation was 450 ms. No nicotine or coffee consumption was allowed during the 24-hour recording.

Statistical analysis

Statistical analysis of data was performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL). We have tested all variables for normal distribution. Parametric tests were applied to variables respecting the normal distribution; the means (± SD) were calculated and statistical significance of differences between groups (according to gender, etiology, and Child-Pugh classification of the severity of cirrhosis) was tested using t-Student test and One-way ANOVA F-test. Statistical significance was set at a P value of 0.05 or less. The distribution tables were obtained through cross-tabulation method. We established bivariate correlations using Pearson or Spearman correlation coefficients and two-tailed test of significance. In order to perform the analysis of variance between various groups, using ranks, we used Kruskal-Wallis H and Mann-Whitney U test.

Results

We analyzed 43 cirrhotic patients, female/male=22/21, mean age 62.81 ± 10.11 years for females, and 60.14 ± 7.82 years for men (P=0.34). The frequency of etiologies of liver cirrhosis was 49% (n=21 patients) alcoholic etiology, 12% (n=5 patients) hepatitis B, 33% (n=14 patients) hepatitis C, and 6% (n=3 patients) mixed etiology (alcoholic and virus B or C). The distribution of patients according to their gender and the Child-Pugh classification of the severity of cirrhosis are presented in Table 1.

Table 1. *The distribution of patients according to gender and severity of cirrhosis.*

	Child-Pugh class		
Gender	n=(%)		
	Child A	Child B	Child C
Females (n=21)	16 (76.2%)	3 (14.3%)	2 (9.5%)
Males (n=22)	11 (50%)	2 (9.1%)	9 (40.9%)

The biochemical profile of cirrhotic patients included in our study showed no statistical differences between male and female patients (P=NS).

The analysis of the QT interval for all patients revealed that the percentage of patients with mean QTc prolongation was between 50% and 82%, depending on the Child class, and the following mean values (± SD) were registered: mean QTc=457.26 ± 22.01 ms, max QTc=509.00 ± 32.09 ms, and max QT=474.40 ± 32.60 ms. Then, we took into account the Child-Pugh classification and the Child B group patients registered the highest value of the 24-hour mean QTc interval (QTc=475.80 ± 26.62 msec) and longest 24-hour mean QTc interval (Table 2). Thirteen patients (48%) in Child A group, 4 out of 5 patients (80%) in Child B group, and 9 out of 11 patients (81.8%) in Child C group, had the 24-hour QTc interval greater than 450 ms; subsequently, we have analyzed the QT interval prolongation according to the etiologic type of the cirrhosis (Table 2). A pathologic mean 24-hour QTc interval was recorded in 7 (36.8%) out of 19 patients with viral etiology (HVB and HVC) and in 15 (71.4%) of the 21 patients with alcoholic etiology of the cirrhosis.

In order to assess the arrhythmogenic risk of cirrhotic patients, we have also quantified the percentage of the sinus impulse beats having prolonged QTc interval (>450 msec), recorded in the 24-hour Holter monitoring, and have performed the comparative analysis between the same previous groups. We found no difference according to gender and Child class, and a

liminal non-significant difference in terms of etiology (χ^2=7.59; P=0.05), which favors the toxic and mixed etiologies.

Table 2. *Analysis of the QT interval, according to severity and etiology of cirrhosis.*

Child-Pugh class	Pts (n)	Mean QTc	Max QTc (msec) (mean ± SD)	Max QT
Child A*[1]	27	453.22 ± 23.45	504.15 ± 33.77	468.68 ± 29.3
Child B*	5	475.80 ± 26.62	519.40 ± 32.64	499.2 ± 42.67
Child C*	11	458.73 ± 10.25	516.18 ± 27.57	477.64 ± 33
Etiology				
Alcoholic** [2]	21	465.24 ± 21.59	520.76 ± 31.97	488.33 ± 34.32
Hepatitis C	14	448.50 ± 18.79	505.93 ± 30.42	467.5 ± 23.72
Hepatitis B	5	440.60 ± 19.85	479 ± 18.06	440 ± 12.1
Mixed etiology**	3	470 ± 17.08	491 ± 22	466.33 ± 34.12

[1] *P = NS (One-way ANOVA F-test ; A *vs.* B *vs.* C)

[2] **P<0.05 (One-way ANOVA F-test and t-Student)

Furthermore, we focused on the presence of the ventricular arrhythmic events: isolated premature ventricular contractions (PVC), ventricular bigeminy (VB), and ventricular tachycardia (VT) episodes, taking into account the gender, cirrhosis severity, and etiology, and performing the comparative analysis between groups (Table 3).

Table 3. *Ventricular arrhythmic events during 24-hour Holter monitoring.*

Grouping variable	PVC[3]	VB[4]	VT[5]
Child-Pugh class (A *vs.* B *vs.* C)	0.48	3.96	0.23
(df=2)	(P=NS)	(P=NS)	(P=NS)
Etiology of cirrhosis (alcohol *vs.* hepatitis B virus *vs*	13.89	4.23	0.71
hepatitis C virus *vs.* mixed) (df=3)	(P< 0.01)	(P=NS)	P=NS)

[3]PVC: premature ventricular contraction

[4]VB: ventricular bigeminy

[5]VT: ventricular tachycardia

It was a statistically significant difference between the different etiologies of liver cirrhosis only in terms of PVC (χ^2=13.897; P<0.01). Viral C etiology cirrhosis seemed to associate significantly more PVC than viral B (P<0.01), toxic (P<0.01) or mixed etiology (P<0.05). The ventricular arrhythmic events did not differentiate groups based on Child class of severity or patients' gender (P=NS).

No significant correlation between biochemical parameters tested and max QTc was found. Max QT showed moderate correlation with total proteins (r=0.402, P<0.01), triglycerides (r=- 0.357, P<0.05), total and direct bilirubin plasmatic levels (r=0.366, P<0.05; r=0.332, P<0.05). Mean QTc interval was significantly correlated only with total proteins and triglycerides (r=0.308, P<0.05; r=- 0.344, P<0.05) (Table 4).

Table 4. *Correlations between the QT interval and the biological parameters.*

Biological parameter (SI units)	QTc		MaxQT		MaxQTc	
	r*[6]	P	r*	P	r*	P
Gamma-Glutamyltransferase (GGT) (U/L)	0.19	0.21	0.10	0.51	-0.07	0.64
Alkaline phosphatase (U/L)	-0.29	0.76	-0.07	0.94	0.10	0.50
Total bilirubin (µmol/L)	0.33	0.03**[7]	0.31	0.03**	0.27	0.07
Direct bilirubin (µmol/L)	0.25	0.09	0.24	0.11	0.22	0.15
Proteins, total (g/L)	0.31	0.04**	0.40	0.01**	0.30	0.05
Aspartate aminotransferase (AST) (U/L)	0.22	0.14	0.19	0.20	0.07	0.44
Alanine aminotransferase (ALT) (U/L)	0,08	0.61	0.08	0.60	0.12	0.44
Glucose (mmol/L)	-0.14	0.36	-0.13	0.41	0.00	0.98
Cholesterol (mmol/L)	-0.21	0.19	-0.19	0.22	-0.05	0.73

Triglycerides (mmol/L)	-0.32	0.03**	-0.29	0.04**	-0.12	0.41
Serum creatinine (μmol/L)	0.16	0.31	0.06	0.71	-0.05	0.77
Blood urea nitrogen (mmol/L)	0.12	0.46	0.15	0.33	-0.01	0.93
Uric acid (μmol/L)	0.07	0.63	0.13	0.42	0.10	0.54
Iron, total (μmol/L)	0.10	0.51	0.14	0.38	0.05	0.75
Sodium (mmol/L)	-0.08	0.63	-0.12	0.46	0.00	0.98
Potassium (mmol/L)	0.00	0.98	0.02	0.91	-0.03	0.86

[6]*Pearson or Spearman correlation coefficient (as appropriate)

[7]** P<0.05

Discussion

In our study, the corrected QT interval values were analyzed as a mean of QTc intervals of all sinus impulse beats recorded during a 24-hour Holter monitoring for all patients and mean QTc value was significantly higher than the reference for diagnosing QT interval prolongation, namely 450 ms (457.26 ± 22.01 ms *vs.* 450 ms; P=0.04).

The percentage of patients with mean QTc prolongation (50%-82%, depending on the Child class) was higher than values recorded in other studies using 24-hour ECG Holter monitoring [6,12] or standard ECG [3,13] although we have chosen a higher value (450 ms *vs.* 440 ms) as a reference for QT prolongation, in order to encompass both gender abnormality of the QTc interval.

While some studies showed that QTc interval increases with the severity of liver disease, we have registered the highest values of mean QTc, significantly longer than the reference (P=0.02), in Child B class (Table 2), consistent with the findings of Genovesi et al. [6]. However, the comparative analysis of patients included in all Child classes-A, B, and C, showed no statistical significant difference between them in terms of mean QTc, max QTc or max QT interval, suggesting that patients with cirrhosis have high pathological values of QT interval, irrespective of severity, patients in Child B class being at the greatest risk, at least in our study.

According to the etiology of cirrhosis, we found the biggest value of mean QTc, max QTc, and max QT intervals, with definite pathological value and statistical significance versus reference value (P<0.001), in patients with alcohol-related liver disease (Table 2). Alcoholic etiology has been also associated with longer mean QTc interval compared to viral etiology (alcohol vs hepatitis B, P=0.03; alcohol vs. hepatitis C, P=0.02). Our findings are different from some researchers' results [4,14-16], which found no statistical correlation between QTc prolongation and etiology of liver disease but are consistent with those of Thuluvath [2] and Genovesi [6], who were suggesting a higher prevalence of QT interval prolongation in patients with alcoholic cirrhosis. It is important to mention that Genovesi et al. [6] also have used data recorded with 24-hour ECG Holter monitoring, while most negative studies have been done on resting ECG test, underlying the importance of assessing a larger number of QT intervals during the nictemeral cycle.

Similar to Bernardi et al. [5], we confirmed that max QT is positively correlated with the plasmatic level of total proteins and total bilirubin but we additionally have found a positive correlation with direct bilirubin levels and negative correlation with serum triglycerides. The mean QTc was correlated only with plasmatic levels of total proteins and triglycerides levels but not with uric acid level, as noticed by other researchers [17] while no biochemical parameter tested was correlated with max QTc.

Regarding the ventricular arrhythmic events, our study revealed statistically significant difference between alcoholic, viral, and mixed etiology of liver cirrhosis only in terms of isolated premature ventricular contractions (PVC) (χ^2=13.897, P<0.01). Unlike QT interval pathological changes, PVC is associated especially with hepatitis virus C. Although patients with toxic cirrhosis have the longest mean QTc interval, they do not have significantly more episodes of ventricular arrhythmias; instead, patients with viral C etiology seem to be at higher risk of PVC compared to other etiologies of cirrhosis, which supports the studies of Matsumori that suggests a direct cardiac effect of hepatic C virus, causing cardiomyopathies and having an arrhythmogenic effect [8].

Due to the fact that we have used 24-hours Holter monitoring as a source of our data, we were able to evaluate the extent of QT interval prolongation during the entire daytime and better correlate this extent with the etiology and the severity of liver cirrhosis. Moreover, as far as we know, it is the first study to evaluate the percentage of the normal beats having QT interval prolongation during a 24-hour period, correlated with an increased likelihood of ventricular arrhythmias, although we failed to demonstrate any significant differences between etiology and severity of liver cirrhosis from this point of view.

Our study confirmed that the QT parameters didn't register any statistically significant differences between male and female patients, supporting the hypothesis that the differences normally recorded between healthy male and female subjects regarding the shorter QTc interval in men [10] tend to disappear in chronic liver disease. The explanation could be a low testosterone level in men with cirrhosis [18], but there are also studies not supporting this opinion [3].

The limitations of the study are represented by the cross-sectional design and the absence of the follow-up associated with the evaluation of incidence of the cardiovascular events, the relatively small number of patients included in the study, the single cut-off value for prolongation of QT interval, irrespective of gender, because of the small number of patients.

In liver cirrhosis, the Holter ECG monitoring confirms the occurrence of a QTc interval prolongation, particularly associated with moderate cirrhosis severity (Child B class), with alcoholic etiology, and plasmatic level of total proteins and triglycerides. The pathological values for QT interval

parameters are not correlated with a higher incidence of ventricular arrhythmic events. Hepatitis C virus is the only etiology correlated with a higher incidence of ventricular arrhythmic events, this finding supporting the novel hypothesis of a direct cardiac arrhythmic effect of the hepatitis C virus.

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