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ORIGINAL ARTICLE

Observational Study

Liver cirrhosis-effect on QT interval and cardiac autonomic nervous system activity

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Abstract

AIM

To examine the impact of liver cirrhosis on QT interval and cardiac autonomic neuropathy (CAN).

METHODS

A total of 51 patients with cirrhosis and 51 controls were examined. Standard 12-lead electrocardiogram recordings were obtained and QT as well as corrected QT interval (QTc) and their dispersions (dQT, dQTc) were measured and calculated using a computer-based program. The diagnosis of CAN was based upon the battery of the tests proposed by Ewing and Clarke and the consensus statements of the American Diabetes Association. CAN was diagnosed when two out of the four classical Ewing tests were abnormal.

RESULTS

QT, QTc and their dispersions were significantly longer ($P < 0.01$) in patients with cirrhosis than in controls. No

significant differences in QT interval were found among the subgroups according to the etiology of cirrhosis. Multivariate regression analysis after controlling for age, gender and duration of cirrhosis demonstrated significant association between QT and presence of diabetes mellitus [standardized regression coefficient (beta) = 0.45, P = 0.02] and treatment with diuretics (beta = 0.55, P = 0.03), but not with the Child-Pugh score (P = 0.54). Prevalence of CAN was common (54.9%) among patients with cirrhosis and its severity was associated with the Child-Pugh score (r = 0.33, P = 0.02). Moreover, patients with decompensated cirrhosis had more severe CAN that those with compensated cirrhosis (P = 0.03). No significant association was found between severity of CAN and QT interval duration.

CONCLUSION

Patients with cirrhosis have QT prolongation. Treatment with diuretics is associated with longer QT. CAN is common in patients with cirrhosis and its severity is associated with severity of the disease.

Key words: QT interval; Cardiac autonomic neuropathy; Cirrhotic cardiomyopathy; Child-Pugh score; Model for end-stage liver disease score; Liver cirrhosis

Core tip: QT interval is significantly prolonged in patients with liver cirrhosis and its duration is associated with the use of diuretics but not with the severity of the disease. More than half of the patients with cirrhosis have cardiac autonomic neuropathy (CAN), while CAN severity is associated strongly with the severity of cirrhosis.

Tsiompanidis E, Siakavellas SI, Tentolouris A, Eleftheriadou I, Chorepsima S, Manolakis A, Oikonomou K, Tentolouris N. Liver cirrhosis-effect on QT interval and cardiac autonomic nervous system activity. *World J Gastrointest Pathophysiol* 2018; 9(1): 28-36 Available from: URL: http://www.wjgnet.com/2150-5330/full/v9/i1/28.htm DOI: http://dx.doi.org/10.4291/wjgp.v9.i1.28

INTRODUCTION

Cirrhosis can affect many organs and systems of the body including cardiovascular and autonomic nervous system (ANS)[1-3]. Among the cardiovascular manifestations often encountered in cirrhotic patients, most common are increased baseline cardiac output, attenuated systolic and diastolic function, blunted ventricular response to stimuli and electrophysiological abnormalities, comprising a group of phenomena, commonly referred to as "cirrhotic cardiomyopathy"[1-3].

As for the involvement of the ANS in the cirrhotic-related manifestations, it has been considered as being the result of toxic, metabolic and immunologic disturbances affecting both the sympathetic and parasympathetic constituents of ANS[3,4]. Due to the close interrelation of the two systems-cardiovascular and ANS-an abnormal ANS function in cirrhotic patients has been shown to be reflected in several cardiac- and vascular-related parameters such as QT interval prolongation, heart rate variability (HRV) and arterial pressure changes, all components of the so-called cardiac autonomic neuropathy (CAN)[5,6].

Previous data in patients with diabetes mellitus have shown that CAN is associated with prolongation of QT interval[7]. Both CAN, even subclinical, and QT prolongation have been associated with increased all-cause mortality in patients with diabetes[7-9]. Interestingly, some studies have shown that the prolongation of QT interval in patients with cirrhosis has been associated with the severity and progression of the disease and with poorer survival in cirrhotic patients[10-13]. On the other hand, in other studies, even though prolonged QT was associated with more severe liver dysfunction, this has not been translated to higher mortality[14,15]. Moreover, it is interesting that the prolonged QTc was improved in most patients after liver transplantation, although the extent and degree of improvement is variable, indicating a functional and reversible "nature" of such dysfunction[16]. Similarly, in some studies CAN has been associated with the severity of liver disease[6,17].

In the present cross-sectional study, we examined the association between QT interval-related parameters with presence and severity of cirrhosis. In addition, we examined the prevalence of CAN and its association with QT interval in patients with cirrhosis.

MATERIALS AND METHODS

Participants

A total of 102 participants were recruited, 51 cirrhotic patients followed consecutively at the outpatient clinic of our hospital and 51 age- and gender-matched healthy controls who were hospital staff and relatives of the patients with cirrhosis. The diagnosis of cirrhosis was established by liver biopsy in 25 subjects. In cases where biopsy was contraindicated (n = 26), the patients had clinical, biochemical and ultrasonographical findings of cirrhosis. The patients were further classified according to the Child-Pugh grading system as having decompensated (Child-Pugh score $\geqslant$ 7, n = 29) or compensated (Child-Pugh score < 7, n = 22) cirrhosis. In addition, the model for end-stage liver disease (MELD) score was measured and the histologic activity index was used to stage liver disease in patients who underwent a liver biopsy[18,19]. Diabetes mellitus was diagnosed using the American Diabetes Association criteria[20].

Criteria for exclusion from the study were as follows: (1) any electrolyte disturbance; (2) diseases which may affect ANS activity and QT interval duration such as coronary artery disease, heart failure, atrial fibrillation,

amyloidosis, hepatocellular carcinoma, episode of infection or gastrointestinal bleeding in the last two months prior to the study; (3) medications which affect ANS activity and QT interval duration like calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, digitalis, tricyclic antidepressants, sympathomimetics and anticholinergics; and (4) patients with any degree of hepatic encephalopathy. Patients receiving propranolol or other beta blockers were included in the study after they had stopped the medication for at least ten days prior to examination. In order to minimize the risk of variceal bleeding due to discontinuation of propranolol, only patients at low risk, documented through esophago-gastro-duodenoscopy (varices with a diameter less than 5 mm and without signs of bleeding), were recruited.

The study was approved by the ethics committee of our hospital and informed consent was obtained from all participants according to the principles of the Declaration of Helsinki[21].

Procedures

Blood, urine sampling and all tests were carried out early in the morning after overnight fast of 8-10 h in a room of stable temperature (22 ℃-24 ℃). All individuals refrained from smoking or drinking coffee prior to the examination. Body weight and height was measured in light clothing and body mass index (BMI) was calculated. Blood pressure was measured in the sitting position three consecutive times with 1 min interval in between and the mean value of the second and third measurements was calculated and used in the analysis.

Blood was drawn for determination of hemoglobin (Hb), white blood cell count, platelet count and biochemical measurements. Biochemical determinations were made on an automatic analyzer. Glycosylated hemoglobin (HbA1c) was measured using HPLC. Plasma insulin (Biosure, Brussels, Belgium; coefficient of variation < 5%) was determined by radioimmunoassay. Insulin resistance was calculated by the homeostasis model assessment equation (HOMA-IR)[22].

Assessment of CAN

The diagnosis of CAN was based upon the battery of the tests proposed by Ewing and Clarke and the consensus statements of the American Diabetes Association[23,24]. The heart rate response to slow deep breathing (deep breathing test), the Valsalva maneuver and the assumption of upright position (lying-to-standing test) were assessed from electrocardiographic (ECG) recordings of RR intervals automatically using the computer-aided examination system VariaCardio TF4 (Medical Research, Leeds, United Kingdom). The change in systolic blood pressure upon standing, expressed as the difference between the mean of the last two values obtained in the supine position and the value obtained 60 s after standing up, were recorded. The first three tests were evaluated according to the published age-related heart rate tests, while orthostatic hypotension was diagnosed when a fall in systolic blood pressure $\geqslant$ 20 mmHg and/or a fall in diastolic blood pressure $\geqslant$ 10 mmHg were observed. Diagnosis of CAN was established when at least two out of four tests were abnormal[23,24]. In order to evaluate the severity of the CAN, each normal test was graded with 0.0, each borderline with 1.0 and each abnormal with 2.0. On the basis of the sum of these scores, we calculated the total score of CAN, which is the sum of the partial scores corresponding to each one of the four individual tests (minimum 0, maximum 8)[23].

Assessment of QT interval

Standard 12-lead ECG recordings at a paper speed of 25 mm/s were obtained. The paper recordings were then scanned to an image at high resolution (300 dpi), edited, and converted to a digital ECG recording, which was analyzed interactively using an ECG analysis program[25]. QT interval was measured from the beginning of the QRS complex to the end of the downslope of the T wave (crossing the isoelectric line). Corrected QT interval for heart rate (QTc) was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$)[26]. QT dispersion (dQT) and QTc dispersion (dQTc) were calculated as the difference between the longest and the shortest QT and QTc intervals, respectively in any of the 12 leads. All measurements were performed by a single experienced investigator who was blind to the participants' characteristics. The QTc interval was considered prolonged if it was > 440 msec (the upper normal limit commonly used).

Statistical analysis

Statistical analysis was performed using programs available in the SPSS statistical package (IBM SPSS software version 22.0 for Windows, Armonk, NY, United States) by four co-authors who have experience in statistical analysis and a biomedical statistician. All variables were tested for normal distribution of the values using the Kolmogorov-Smirnov test. Differences between groups and variables were tested by the Student's *t*-test for continuous variables, while the χ^2 test was used for categorical variables. Differences in nonparametric variables were compared using the Mann-Whitney test, while bivariate correlations were assessed by Spearman correlation for ordered variables. Multivariate linear regression analysis was performed in the patients with cirrhosis to examine for associations between QT interval parameters and the variables of interest. *P* values < 0.05 were considered statistically significant.

Table 1 Demographic and clinical characteristics as well as laboratory results of the study subjects

	Controls (n = 51)	Patients (n = 51)	P value
Male, n (%)	28 (54.9)	32 (62.7)	0.42
Age (yr)	53.8 ± 13.9	55.2 ± 14.2	0.60
BMI (kg/m^2)	26.0 ± 3.5	26.1 ± 4.4	0.95
Systolic blood pressure (mmHg)	128.3 ± 18.5	127.4 ± 27.1	0.84
Diastolic blood pressure (mmHg)	79.0 ± 10.0	76.0 ± 15.1	0.26
Heart rate (beats/min)	77.05 ± 49.82	76.74 ± 15.82	0.96
Fasting insulin (μU/mL)	10.6 (7.7-12.4)	13.3 (10.6-24.4)	< 0.001
HbA1c (%)	4.97 ± 0.50	4.03 ± 0.74	< 0.001
HOMA-IR	2.40 (1.59-3.08)	3.39 (2.74-5.50)	< 0.001
White blood cells (n/μL) × 10^3	7.4 ± 2.6	5.5 ± 4.6	0.13
Hemoglobin (g/dL)	14.8 ± 1.2	11.8 ± 2.1	< 0.001
Platelets (n/μL) × 10^3	225.766 ± 36.24	122.17 ± 94.23	< 0.001
Diabetes, n (%)	1 (2.0)	7 (13.7)	0.02
Use of diuretics, n (%)	0	14 (27.5)	< 0.001
Smoking status, n (%)			34.34
Current smokers	16 (31.4)	22 (43.1)	
Non-smokers	26 (51.0)	23 (45.1)	
Ex-smokers	9 (17.6)	5 (9.8)	

Data presented as mean ± SD or as n (%) or as median value (interquartile range). BMI: Body mass index; HbA1c: Glycated hemoglobin 1c; HOMA-IR: Homeostasis model assessment equation.

RESULTS

Demographic and clinical characteristics of the study participants

The demographic and clinical characteristics of the participants are shown in Table 1 and Table 2. Control subjects and patients with cirrhosis did not differ in terms of age, gender, BMI, arterial blood pressure, white blood cell count or smoking habits. Patients with cirrhosis had significantly higher blood glucose (P = 0.006), fasting insulin (P < 0.001) and HbA1c (P = 0.007), as well as lower Hb and platelet count levels (P < 0.001), compared to control group. A total of 27.5% of the patients received diuretics (combination of furosemide and spironolactone) (Table 1). The main causes of cirrhosis were viral hepatitis (47.1%) and alcohol abuse (33.3%), while 39% of the patients had decompensated cirrhosis (Table 2).

The association between QT-related parameters and presence as well as severity of cirrhosis

The values of all QT interval-related parameters were higher (P < 0.001) in patients with cirrhosis than those in controls (Table 3). None of the controls had a QTc interval longer than 440 msec, while 43.1% of the patients had QTc intervals longer than 440 msec. Considering 60 msec as the highest normal value for dQT, the number of individuals with dQT > 60 msec was higher in patients than in controls [n = 18 (35.3%) *vs* n = 7 (13.7%), respectively, χ^2 = 6.41, P = 0.011].

In cirrhosis group, QT parameters did not differ significantly between patients with alcoholic and non-alcoholic cirrhosis (QT: 383.8 ± 44.1 msec and 389.9 ± 36.0 msec, respectively, P = 0.98; QTc: 437.1 ± 30.5 msec and 423.7 ± 30.8 msec, P = 0.16; dQT: 65.6 ± 28.6 msec and 54.5 ± 21.2 msec, P = 0.13; dQTc: 74.4 ± 29.5 msec and 60.5 ± 23.1 msec, P = 0.12). Furthermore, patients with decompensated cirrhosis, in comparison with those with compensated cirrhosis, had longer dQTc (72.2 ± 26.6 msec *vs* 56.3 ± 22.5 msec, P = 0.03) and tended to have longer QTc (435.3 ± 30.4 msec *vs* 419.0 ± 30.1 msec, P = 0.070) as well as dQT (64.1 ± 25.4 msec *vs* 50.8 ± 20.7 msec, P = 0.053). No significant differences were found in QT (P = 0.55) between the two groups. Moreover, no significant correlations were found between the Child-Pugh score and QT (r = 0.11, P = 0.45), dQT (r = 0.20, P = 0.17), QTc (r = 0.22, P = 0.13) or dQTc (r = 0.26, P = 0.08). The same was valid for the MELD score (QT: r = -0.06, P = 0.71; dQT: r = -0.23, P = 0.12; QTc: r= 0.16, P = 0.30; dQTc: r = -0.18, P = 0.21).

Assessment of CAN

A total of 28 patients (54.9%) had CAN. All indices of cardiac ANS activity were worse and the total score, an index of the severity, of CAN was higher in patients than in controls (Table 4). Prevalence of CAN was not different between patients with compensated and decompensated cirrhosis [n = 9 (40.9%) and n = 19 (65.5%), respectively, χ^2 = 3.06, P = 0.08]. However, the severity of CAN assessed by the total score of CAN was higher in patients with decompensated than in those with compensated cirrhosis [3.0 (0.8-6.0) *vs* 4.0 (3.0-6.5), P = 0.03]. No significant correlations were found between total score of CAN and QT (r = -0.12, P = 0.40), dQT (r = 0.04, P = 0.78), QTc (r = -0.01, P = 0.98) or dQTc (r = 0.11, P = 0.43). The total score of CAN was significantly correlated with the Child-Pugh score (r = 0.33, P = 0.02) and the MELD score (r = 0.36, P = 0.01).

In addition, mean QT interval duration was not different between patients having both cirrhosis and diabetes (n = 7) and those having cirrhosis without diabetes (n = 44): 395.7 ± 41.2 msec *vs* 381.9 ±

Table 2 Clinical characteristics and associated laboratory test results of patients with cirrhosis

	n	%
Child-Pugh score	7 (5-9)	
Child-Pugh Grade A (score: 5-6)	22	43.1
B (score: 7-9)	18	35.3
C (score: 10-15)	11	21.6
MELD score	29.8 (14.4-39.6)	
Decompensated cirrhosis	29	56.9
Alcohol	17	33.3
Viral Hepatitis	24	47.1
Hepatitis B	10	*19.6*
Hepatitis C	12	*23.5*
Hepatitis B + C	2	*3.9*
Other	10	19.6
Systematic use of beta-blockers (yes)	16	31.4
Ascites (yes)	23	45.1
Esophageal varices (yes)	28	54.9
Liver biopsy	25	49.0
Histologic activity index	8.6 ± 2.9	
Disease duration (yr)	3 (0.8-7)	
INR	1.41 ± 0.41	
AST (U/L)	43.0 (34.0-66.0)	
ALT (U/L)	36.0 (24.0-50.0)	
ALP (U/L)	262.7 ± 121.8	
LDH (U/L)	392.4 ± 123.0	
γ-GT (U/L)	39.0 (28.0-76.0)	
Cholesterol (mg/dL)	175.9 ± 56.2	
Triglycerides(mg/dL)	76.0 (50.0-108.0)	
Total bilirubin (mg/dL)	1.25 (0.68-2.29)	
Direct bilirubin (mg/dL)	0.75 (0.30-1.13)	
Total proteins (g/dL)	7.5 ± 0.8	
Albumin (g/dL)	4.0 ± 0.8	
Blood potassium (meq/L)	4.2 ± 0.4	
Blood sodium (meq/L)	138.1 ± 4.6	

Data are presented as mean ± SD or as *n* (%) or as median value (interquartile range). MELD: Model for end-stage liver disease.

38.0 msec, respectively (P = 0.38). Furthermore, the values of the autonomic function tests did not differ significantly between participants having both cirrhosis and diabetes and those having cirrhosis without diabetes; deep breathing test: 1.09 ± 0.05 *vs* 1.14 ± 0.14, respectively, P = 0.29; Valsalva test: 1.40 ± 0.25 *vs* 1.32 ± 0.35, respectively, P = 0.48; lying-to-standing test: 1.09 ± 0.08 *vs* 1.08 ± 0.09, respectively, P = 0.86; orthostatic hypotension: 12.85 ± 9.50 mmHg *vs* 11.52 ± 9.73 mmHg, respectively, P = 0.73. CAN was present in 3 patients with both cirrhosis and diabetes and in 25 patients with cirrhosis but without diabetes (42.9% *vs* 56.8%, P = 0.49).

Associations between insulin resistance index (HOMA-IR) with QT-related parameters

In patients with cirrhosis, HOMA-IR values did not correlate significantly with QT (r = -0.09, P = 0.56), QTc (r = 0.18, P = 0.24), dQT (r = -0.03, P = 0.82) or dQTc (r = 0.03, P = 0.84). HOMA-IR was associated significantly with the Child-Pugh score (r = 0.43, P = 0.002) and the MELD score (r = 0.65, P < 0.001).

Table 3 Comparison of QT-related parameters between patients and controls

	Controls	Patients	*P* value
Mean QT (msec)	341.6 ± 29.4	383.9 ± 38.4	< 0.001
QT max (msec)	358.1 ± 56.6	413.5 ± 46.1	< 0.001
QT min (msec)	320.5 ± 28.1	355.4 ± 38.2	< 0.001
dQT (msec)	44.8 ± 14.2	65.6 ± 28.6	0.001
QTc (msec)	364.0 ± 20.6	428.1 ± 31.0	< 0.001
dQTc (msec)	47.6 ± 14.7	65.0 ± 25.9	< 0.001
Mean RR (msec)	863.6 ± 177.0	812.9 ± 159.8	0.13

Data are shown as mean values ± SD. QTc: Corrected QT; dQT: QT dispersion; dQTc: QTc dispersion.

Multivariate regression analysis on the association between QT interval with the study parameters

Multivariate linear regression analysis in patients with cirrhosis with QT interval as dependent variable, after controlling for age, gender and duration of cirrhosis demonstrated significant and independent associations with diagnosed diabetes [standardized regression coefficient (beta) = 0.45, P = 0.02] and use of diuretics (beta = 0.55, P = 0.03). A trend for association with HOMA-IR was observed (beta = 0.40, P = 0.058), while no significant associations were found with the Child-Pugh or the MELD score, the histology activity index, Hb, serum potassium, the total score of CAN, and previous use of beta blockers. The same analysis with either QTc, dQT or dQTc as dependent variables did not show significant associations with the aforementioned parameters.

DISCUSSION

In the present study, we found that QT and QTc intervals as well as their dispersions were substantially prolonged in patients with cirrhosis in comparison with healthy controls. In addition, we demonstrated that patients with cirrhosis were diagnosed more often with CAN.

The importance of normal liver function on preservation of the electrophysiological properties of the heart is supported by several studies that have examined the prolongation of QTc before and after liver transplantation[16]. Although the results are not unanimous, most of the data suggest that liver transplantation improved the prolonged QTc; however, the extend and the degree of the improvement was variable[16]. Thus, our data of prolonged QT interval in patients with liver cirrhosis agree and corroborate these findings.

Previous data showed abnormal QT prolongation in 37% to 84% of patients with cirrhosis of either alcoholic or nonalcoholic etiology[5,10,11,15,27,28]. However, literature data on QT dispersion in cirrhosis are scarce. Dispersion of QT interval is probably a better index of left ventricular dispersion of repolarization than QT or QTc interval and high values of dQT predict cardiovascular mortality in patients with diabetes or

Table 4 The results of the cardiac autonomic function tests in controls and patients

	Controls	Patients	*P* value
Deep breathing test (value, N/A)	1.25 ± 0.16 (48/3)	1.13 ± 0.13 (23/28)	< 0.001
Valsalva test (value, N/A)	1.45 ± 0.24 (45/6)	1.33 ± 0.25 (30/21)	0.01
Lying-to-standing test (value, N/A)	1.17 ± 0.24 (45/6)	1.08 ± 0.10 (29/22)	0.01
Systolic blood pressure fall to standing (value, N/A)	0 (0-5) (50/1)	10 (0-20) (35/16)	< 0.001
CAN, *n* (%)	3 (5.9)	28 (54.9)	< 0.001
Total score of CAN	1 (0-2)	4 (2-6)	< 0.001

Data are shown as mean ± SD or as *n* (%) or as median value (interquartile range). CAN: Cardiac autonomic neuropathy; N: Number of subjects with normal test; A: Number of subjects with abnormal test.

coronary artery disease[25]. In the literature, there are no data on the potential association between dQT and mortality in patients with liver cirrhosis. Herein we found that both dQT and dQTc were more prolonged in patients with cirrhosis. One previous study has shown that QT and dQt is prolonged in patients with cirrhosis[29], while another study shown that QT, but not dQT, is prolonged in patients with alcoholic cirrhosis in comparison with controls[30]. In contrast, in another study, no differences were found in dQT between patients with cirrhosis and controls[31]. Our findings showed that the etiology of cirrhosis was not associated with either QT or dQT prolongation.

One of the mechanisms suggested to play an important role in the pathogenesis of QT prolongation in patients with cirrhosis, is the enhanced sympathetic nervous system activity[5]. This process, which in normal subjects would reduce the QT interval, seems to participate in QT prolongation in cirrhosis. This is further elaborated with the increased circulating levels of noradrenalin, and it is an index of enhanced sympathoadrenal activity, observed in patients with advanced liver disease[10]. One would expect that the heart rate would be affected by this situation, but this is not usually the case, probably due to a downregulation of beta-adrenergic receptors[31]. Likewise, our results did not establish any substantial differences of the RR interval, which represents mean heart rate, between patients and controls. It is possible that the complex physiological changes that occur in chronic liver disease, modulate the cardiac function and may prolong the QT interval-related parameters. Moreover, although it is known that the use of propranolol reduces the risk of gastrointestinal bleeding in patients with cirrhosis[32], there are no data on the potential effect of beta-blockers on cardiovascular mortality in such patients. One systematic review and meta-analysis concluded that the use of non-selective beta-blockers was not associated with a significant increase in all-cause mortality in patients with cirrhosis and ascites or refractory ascites[33].

In our study, no differences between the cirrhotic subgroups (alcoholic *vs* non-alcoholic cirrhosis) were noticed. Thus, based upon the data originating from current study, no relationship between an increased QT interval and the cause of cirrhosis can be established. These findings are in agreement with those of previous studies and may imply that QT prolongation is a phenomenon that derives from the pathophysiology of cirrhosis itself and does not reflect abnormalities related to certain causes of cirrhosis[10]. However, in a previous study, patients with alcohol–related liver cirrhosis had a significantly (P = 0.001) higher prevalence of QTc interval prolongation than those with HBV–related liver cirrhosis[14].

Besides, no significant association was found between the values of QT parameters and the severity of cirrhosis, as assessed by the Child-Pugh or the MELD score in either univariate or multivariate analysis. In a previous study with 94 patients with cirrhosis, the Child-Pugh score and plasma norepinephrine were significant and independent determinants of QTc duration[10]. Similarly, in two other studies the prevalence of prolonged QTc increased with the severity of chronic liver disease[5,14]. The discrepancies in the results of these studies may be explained in part by differences in the studied populations. In the present study only patients with low or moderate risk of variceal bleeding were included in order to be able to discontinue safely beta-blockers, medications affecting ANS activity. However, we showed that patients with decompensated cirrhosis had longer dQTc and tended to have longer QTc as well as dQT in comparison to patients with compensated cirrhosis. This finding implies that when liver disease progresses to a point where the human body cannot overcome the cirrhosis effects, one of the clinical features of this process is the exacerbation of the cardiac electrical conductance abnormalities.

According to our findings a substantial percentage of patients have CAN, but interestingly, the severity of CAN was not associated with QT prolongation. These findings are in contrast with those seen in patients with diabetes mellitus[7]. However, our results agree with previous data in patients with cirrhosis[5,11]; thus, a previous study has shown that prolonged QTc is independent of CAN in patients with cirrhosis[5]. Moreover, diabetes was independently associated with QT in multivariate analysis confirming previous reports for association between QT prolongation in subjects with diabetes[7]. The autonomic dysfunction has been shown to correlate with the severity of liver

disease[5], a finding also observed in our study, as total score of CAN was correlated significantly with the Child-Pugh and the MELD score. Besides, patients with decompensated cirrhosis had more severe CAN than patients with compensated cirrhosis, although the prevalence of CAN was not different between the two groups. Even though experimental and clinical data suggest that ANS influence QT interval[7,34], in the present study no relationships were found between the total score of CAN and the values of QT-related parameters.

Interestingly, insulin resistance was not associated with QT-related parameters in this study, but there was a strong association between HOMA-IR and severity of cirrhosis assessed by the Child-Pugh and the MELD score. This finding implies that insulin resistance *per se* does not affect QT interval duration and that other mechanisms associated with cirrhosis affect QT interval.

Multivariate analysis demonstrated that use of diuretics was associated with QT prolongation; noteworthy, this effect was seen independently from serum potassium concentrations. This finding emphasizes the need for QT monitoring in patients with cirrhosis who are on treatment with diuretics.

It is known that diabetes is associated with higher prevalence of CAN[24] and with QT prolongation[7]. In our study, we did not find significant differences in these between patients having both diabetes and cirrhosis than those having cirrhosis without diabetes. However, the number of the participants with diabetes was small in our study and we cannot conclude robustly if presence of diabetes burdens further CAN or QT interval in patients with cirrhosis.

The strength of our study is that we examined subjects under controlled conditions and the potential confounding effects of medications, food intake and coffee consumption have been avoided. With regards, to medications, recent data suggested that propranolol administration reduces QT interval in patients with advanced liver cirrhosis waiting for liver transplantation[35]. Thus, discontinuation of beta blockers from our patients eliminated the effect of this medication on QT interval duration and allowed us to examine the net effect of the disease on QT interval duration. However, the number of the participants was not large and the study did not have enough power to support the findings. Furthermore, we did not examine for the presence of cirrhotic cardiomyopathy to look for associations between QT-related parameters and indices of systolic or diastolic function of the heart. Finally, this was a cross-sectional study and a cause and effect relationship cannot be established.

In conclusion, this study has shown that QT interval is prolonged in patients with cirrhosis compared with controls. QT prolongation is independent of the etiology and severity of cirrhosis, as well as of CAN, suggesting that this prolongation probably reflects the liver damage itself or the sympathetic nervous system predominance because of cirrhosis. Therefore, cirrhosis, even in the early stages, affects QT interval. Moreover, patients with diabetes and those on treatment with diuretics have longer QT interval independently from serum potassium levels, suggesting that they need monitoring for QT prolongation.

ARTICLE HIGHLIGHTS

Research background

Cirrhosis can affect many organs and systems of the body including cardiovascular and autonomic nervous system (ANS). Cirrhotic patients have abnormal ANS function and it is reflected in several cardiac- and vascular-related parameters such as QT interval prolongation, heart rate variability (HRV) and arterial pressure changes, all components of the so-called cardiac autonomic neuropathy (CAN). Both QT prolongation and CAN have been associated with increased cardiovascular and all-cause mortality. The findings of this study show that cirrhotic patients and, in particular those who have at the same time diabetes or who are on treatment with diuretics, have longer QT interval independently from serum electrolyte levels, suggesting that they need monitoring for QT prolongation.

Research motivation

This study has shown that patients with cirrhosis have more often CAN and QT prolongation; however, this is a cross-sectional study and a cause and effect relationship cannot be established. A prospective study is needed to examine whether patients with cirrhosis develop autonomic dysfunction and QT prolongation. Moreover, it would of interest to know the potential impact of treatment with b-blockers on QT interval or cardiac ANS activity. An important finding of this study is that the etiology of cirrhosis does not impact QT prolongation or cardiac autonomic activity.

Research objectives

The main aim of this study was to examine the impact of liver cirrhosis on QT-related parameters and on CAN. The authors' hypothesis was confirmed and implies that cardiac autonomic dysfunction and/or QT prolongation may contribute to the increased mortality in patients with cirrhosis.

Research methods

In this study, the authors managed to collect complete data related to full blood count and biochemical analyses, while the diagnosis of cirrhosis was confirmed with liver biopsies when it was indicated. The diagnosis of cardiac autonomic dysfunction was based upon robust criteria such as the battery of the tests proposed by Ewing and Clarke by determination of the HRV. QT intervals were measured using a standard 12-lead ECG recordings. Statistical analysis was performed using programs available in the SPSS statistical package by four co-authors who have experience in statistical analysis and a biomedical statistician.

Research results

In the present study, the authors found that QT and QTc intervals as well as their dispersions were substantially prolonged in patients with cirrhosis in comparison with healthy controls. In addition, the authors demonstrated that patients with cirrhosis were diagnosed more often with cardiac autonomic dysfunction. Additionally, the authors found that severity of cirrhosis does not impact QT interval but it affects severity of cardiac autonomic dysfunction.

Research conclusions

The novel finding of this study is that not only QT, but also QT dispersion is prolonged in patient with cirrhosis. Furthermore, CAN or QT prolongation is not associated with the etiology of cirrhosis. Patients with cirrhosis, especially those who have diabetes or an on treatment with diuretics should be screened for cardiac autonomic dysfunction an QT prolongation. Patients with cirrhosis have often CAN and QT prolongation. The original insights of this study are: (1) the authors measured QT dispersion, which is considered as an excellent marker of left ventricular repolarization abnormalities and better than QT prolongation, which has not been studied so far; and (2) the authors found that severity of cirrhosis affects strongly cardiac ANS activity and probably contributes to

the development of the cirrhotic myocardiopathy. The new methods used in this study is the robust methodology for the diagnosis of cardiac autonomic dysfunction and presence as well as severity of cirrhosis.

Research perspectives

The results of this study suggest that patients with cirrhosis often have QT prolongation and cardiac autonomic dysfunction and therefore, they should be screened for these comorbidities; especially those who have diabetes or an on treatment with diuretics. Future research should be directed to the potential impact of treatment with b-blockers on QT interval or cardiac ANS activity. In addition, a prospective study is needed to examine whether patients with cirrhosis develop autonomic dysfunction and QT prolongation.

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