**Name of Journal: *World Journal of Gastrointestinal Pathophysiology***

**Manuscript NO: 35785**

**Manuscript Type: Original Article**

***Observational Study***

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

Tsiompanidis E *et al.* QT interval in cirrhosis

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**Institutional review board statement:** The experimental protocol was reviewed and approved by the Ethics Committee of Laiko General Hospital (Number of Permission: 2903/10-12-2014).

**Informed consent statement:** The study was approved by the ethics committee of Laiko General Hospital and written informed consent was obtained from all individuals before participation in the study.

**Conflict-of-interest statement:** There are no conflicts of interest related to this work.

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**Manuscript source:** Unsolicited manuscript

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**Received:** August 6, 2017

**Peer-review started:** August 7, 2017

**First decision:** September 7, 2017

**Revised:** October 4, 2017

**Accepted: October 30, 2017**

**Article in press:**

**Published online:**

**Abstract**

***AIM***

Toexamine 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:** Liver cirrhosis; QT interval; Cardiac autonomic neuropathy; Cirrhotic cardiomyopathy; Child-Pugh score; MELD score

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**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)， severity of CAN is associated strongly with the severity of cirrhosis.

Tsiompanidis E, Siakavellas S, 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* 2017; In press

**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 ≥ 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 with 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 oC-24 oC). 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 ≥ 20 mmHg and/or a fall in diastolic blood pressure ≥ 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/sec 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/√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.

**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 ± 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. Three patients (42.9%) who had both cirrhosis and diabetes had CAN as compared to 25 (56.8%) to those who had cirrhosis without diabetes (*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).

***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], use of diuretics (beta = 0.55, *P* = 0.03) and there was a trend for association with HOMA-IR (beta = 0.40, *P* = 0.058); 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 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, 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 were 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; (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.

**REFERENCES**

1 **Møller S**, Henriksen JH. Cardiovascular complications of cirrhosis. *Postgrad Med J* 2009; **85**: 44-54 [PMID: 19240290 DOI: 10.1136/gut.2006.112177]

2 **Fede G**, Privitera G, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in patients with liver cirrhosis. *Ann Gastroenterol* 2015; **28**: 31-40 [PMID: 25608575]

3 **Ruiz-del-Árbol L**, Serradilla R. Cirrhotic cardiomyopathy. *World J Gastroenterol* 2015; **21**: 11502-11521 [PMID: 26556983 DOI: 10.3748/wjg.v21.i41.11502]

4 **Ates F**, Topal E, Kosar F, Karincaoglu M, Yildirim B, Aksoy Y, Aladag M, Harputluoglu MM, Demirel U, Alan H, Hilmioglu F. The relationship of heart rate variability with severity and prognosis of cirrhosis. *Dig Dis Sci* 2006; **51**: 1614-1618 [PMID: 16927142 DOI: 10.1007/s10620-006-9073-9]

5 **Puthumana L**, Chaudhry V, Thuluvath PJ. Prolonged QTc interval and its relationship to autonomic cardiovascular reflexes in patients with cirrhosis. *J Hepatol* 2001; **35**: 733-738 [PMID: 11738100 DOI: 10.1016/S0168-8278(01)00217-3]

6 **Dümcke CW**, Møller S. Autonomic dysfunction in cirrhosis and portal hypertension. *Scand J Clin Lab Invest* 2008; **68**: 437-447 [PMID: 18609092 DOI: 10.1080/00365510701813096]

7 **Tentolouris N**, Katsilambros N, Papazachos G, Papadogiannis D, Linos A, Stamboulis E, Papageorgiou K. Corrected QT interval in relation to the severity of diabetic autonomic neuropathy. *Eur J Clin Invest* 1997; **27**: 1049-1054 [PMID: 9466135 DOI: 10.1046/j.1365-2362.1997.2300776.x]

8 **Voulgari C**, Psallas M, Kokkinos A, Argiana V, Katsilambros N, Tentolouris N. The association between cardiac autonomic neuropathy with metabolic and other factors in subjects with type 1 and type 2 diabetes. *J Diabetes Complications* 2011; **25**: 159-167 [PMID: 20708417 DOI: 10.1016/j.jdiacomp.2010.06.001]

9 **Maser RE**, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care* 2003; **26**: 1895-1901 [PMID: 12766130 DOI: 10.2337/diacare.26.6.1895]

10 **Bernardi M**, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, Schepis F, Mandini M, Simoni P, Contin M, Raimondo G. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology* 1998; **27**: 28-34 [PMID: 9425913 DOI: 10.1002/hep.510270106]

11 **Mohamed R**, Forsey PR, Davies MK, Neuberger JM. Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease. *Hepatology* 1996; **23**: 1128-1134 [PMID: 8621144 DOI: 10.1002/hep.510230529]

12 **Dillon JF**, Plevris JN, Nolan J, Ewing DJ, Neilson JM, Bouchier IA, Hayes PC. Autonomic function in cirrhosis assessed by cardiovascular reflex tests and 24-hour heart rate variability. *Am J Gastroenterol* 1994; **89**: 1544-1547 [PMID: 8079935]

13 **Kim SM**, George B, Alcivar-Franco D, Campbell CL, Charnigo R, Delisle B, Hundley J, Darrat Y, Morales G, Elayi SC, Bailey AL. QT prolongation is associated with increased mortality in end stage liver disease. *World J Cardiol* 2017; **9**: 347-354 [PMID: 28515853 DOI: 10.4330/wjc.v9.i4.347]

14 **Zhao J**, Qi X, Hou F, Ning Z, Zhang X, Deng H, Peng Y, Li J, Wang X, Li H, Guo X. Prevalence, Risk Factors and In-hospital Outcomes of QTc Interval Prolongation in Liver Cirrhosis. *Am J Med Sci* 2016; **352**: 285-295 [PMID: 27650234 DOI: 10.1016/j.amjms.2016.06.012]

15 **Bal JS**, Thuluvath PJ. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. *Liver Int* 2003; **23**: 243-248 [PMID: 12895263 DOI: 10.1034/j.1600-0676.2003.00833.x]

16 **Liu H**, Jayakumar S, Traboulsi M, Lee SS. Cirrhotic cardiomyopathy: Implications for liver transplantation. *Liver Transpl* 2017; **23**: 826-835 [PMID: 28407402 DOI: 10.1002/lt.24768]

17 **Bajaj BK**, Agarwal MP, Ram BK. Autonomic neuropathy in patients with hepatic cirrhosis. *Postgrad Med J* 2003; **79**: 408-411 [PMID: 12897221 DOI: [10.1136/pmj.79.933.408](https://doi.org/10.1136/pmj.79.933.408)]

18 **Desmet VJ**. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, Wollman J. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis [Hepatology 1981;1:431-435]. *J Hepatol* 2003; **38**: 382-386 [PMID: 12663226 DOI: [10.1016/S0168-8278(03)00005-9](https://doi.org/10.1016/S0168-8278%2803%2900005-9)]

19 **Kamath PS**, Kim WR; Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). *Hepatology* 2007; **45**: 797-805 [PMID: 17326206 DOI: 10.1002/hep.21563]

20 **American Diabetes Association**. (2) Classification and diagnosis of diabetes. *Diabetes Care* 2015; **38** Suppl: S8-S16 [PMID: 25537714 DOI: 10.2337/dc15-S005]

21 **World Medical Association**. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191-2194 [PMID: 24141714 DOI: 10.1001/jama.2013.281053]

22 **Matthews DR**, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412-419 [PMID: 3899825 DOI: [10.1007/BF00280883](https://doi.org/10.1007/BF00280883)]

23 **Ewing DJ**, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985; **8**: 491-498 [PMID: 4053936 DOI: [10.2337/diacare.8.5.491](https://doi.org/10.2337/diacare.8.5.491)]

24 **Pop-Busui R**, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017; **40**: 136-154 [PMID: 27999003 DOI: 10.2337/dc16-2042]

25 **Psallas M**, Tentolouris N, Papadogiannis D, Doulgerakis D, Kokkinos A, Cokkinos DV, Katsilambros N. QT dispersion: comparison between participants with Type 1 and 2 diabetes and association with microalbuminuria in diabetes. *J Diabetes Complications* 2006; **20**: 88-97 [PMID: 16504837 DOI: 10.1016/j.jdiacomp.2005.05.012]

26 **Luo S**, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. *J Electrocardiol* 2004; **37 Suppl**: 81-90 [PMID: 15534815 DOI: 10.1016/j.jelectrocard.2004.08.030]

27 **Trevisani F**, Merli M, Savelli F, Valeriano V, Zambruni A, Riggio O, Caraceni P, Domenicali M, Bernardi M. QT interval in patients with non-cirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic porto-systemic shunt. *J Hepatol* 2003; **38**: 461-467 [PMID: 12663238 DOI: 10.1016/S0168-8278(03)00057-6]

28 **Cichoż-Lach H**, Tomaszewski M, Kowalik A, Lis E, Tomaszewski A, Lach T, Boczkowska S, Celiński K. QT Interval Prolongation and QRS Voltage Reduction in Patients with Liver Cirrhosis. *Adv Clin Exp Med* 2015; **24**: 615-622 [PMID: 26469105 DOI: 10.17219/acem/28681]

29 **Tuttolomondo A**, Buttà C, Casuccio A, Di Raimondo D, Serio A, D'Aguanno G, Pecoraro R, Renda C, Giarrusso L, Miceli G, Cirrincione A, Pinto A. QT Indexes in Cirrhotic Patients: Relationship with Clinical Variables and Potential Diagnostic Predictive Value. *Arch Med Res* 2015; **46**: 207-213 [PMID: 25843561 DOI: 10.1016/j.arcmed.2015.03.008]

30 **Day CP**, James OF, Butler TJ, Campbell RW. QT prolongation and sudden cardiac death in patients with alcoholic liver disease. *Lancet* 1993; **341**: 1423-1428 [PMID: 8099138 DOI: [10.1016/0140-6736(93)90879-L](https://doi.org/10.1016/0140-6736%2893%2990879-L)]

31 **Hansen S**, Møller S, Bendtsen F, Jensen G, Henriksen JH. Diurnal variation and dispersion in QT interval in cirrhosis: relation to haemodynamic changes. *J Hepatol* 2007; **47**: 373-380 [PMID: 17459513 DOI: 10.1016/j.jhep.2007.03.013]

32 **Pagliaro L**. Lebrec D, Poynard T, Hillon P, Benhamou J-P. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis. A controlled study [N Engl J Med 1981;305:1371-1374]. *J Hepatol* 2002; **36**: 148-150 [PMID: 11830324 DOI: 10.1056/NEJM198112033052302]

33 **Chirapongsathorn S**, Valentin N, Alahdab F, Krittanawong C, Erwin PJ, Murad MH, Kamath PS. Nonselective β-Blockers and Survival in Patients With Cirrhosis and Ascites: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016; **14**: 1096-1104.e9 [PMID: 26829026 DOI: 10.1016/j.cgh.2016.01.012]

34 **Aytemir K**, Aksöyek S, Ozer N, Gürlek A, Oto A. QT dispersion and autonomic nervous system function in patients with type 1 diabetes. *Int J Cardiol* 1998; **65**: 45-50 [PMID: 9699930 DOI: [10.1016/S0167-5273(98)00091-6](https://doi.org/10.1016/S0167-5273%2898%2900091-6)]

35 **Kim YK**, Hwang GS, Shin WJ, Bang JY, Cho SK, Han SM. Effect of propranolol on the relationship between QT interval and vagal modulation of heart rate variability in cirrhotic patients awaiting liver transplantation. *Transplant Proc* 2011; **43**: 1654-1659 [PMID: 21693252 DOI: 10.1016/j.transproceed.2011.02.017]

**P-Reviewer:** Abadi ATB, Liu DY, McMillin MA, Morini S **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Greece

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): D

Grade E (Poor): 0

**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/m2) | 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) × 103 | 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) × 103 | 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* (%) |  |  |  |
| Current smokers | 16 (31.4) | 1. 43.1)
 |  |
| Non-smokers  | 26 (51.0) | 1. (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.

**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 Β | *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.

**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.

**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.