ORIGINAL ARTICLE

QT Indexes in Cirrhotic Patients: Relationship with Clinical Variables and Potential Diagnostic Predictive Value

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Background and Aims. A wide spectrum of cardiovascular changes characterizes cirrhosis, ranging from subclinical alterations to hyperkinetic syndrome. We looked for ECG markers of ventricular repolarization in a population of patients with cirrhosis in comparison to patients without cirrhosis and we investigated the relationship between these and other clinical and laboratory variables.

Methods. In 149 patients with cirrhosis and 152 controls, we measured QT maximum interval (QTmax), QT corrected interval (QTc), QT minimum interval (QTmin), QT dispersion (QTdisp), QT peak and T peak-to-end (TpTe).

Results. In subjects with cirrhosis, in comparison with controls, we observed a higher mean QTmax, mean QTc, mean QTmin, mean QTdisp and mean TpTe. At Cox regression analysis, diastolic blood pressure and beta-blocker treatment were significantly associated with mean QTmax, hypertension with mean QTmin and mean QTc, diastolic blood pressure, beta-blockers and ACE-inhibitors/ARBs with QT disp, and beta-blockers with TpTe. Analysis of ROC curves showed a significant area under curve towards cirrhosis diagnosis, respectively, for a cut-off value of >400 msec of QTmax, >360 msec of QTmin, >450 msec of QTc, >105 msec of TpTe and >55 msec of QTdisp.

Conclusions. Our study shows that QT indexes are altered in cirrhotic patients and have a potential diagnostic predictive value. © 2015 IMSS. Published by Elsevier Inc.

Key Words: QT, Cirrhosis, ECG, Ventricular repolarization.

Introduction

QT indexes are electrocardiographic markers of autonomic nervous system function and sympathovagal balance (1,2). Recently, the presence of QT dispersion (QTdisp) on the 12-lead electrocardiogram (ECG) has been shown to reflect dispersion of ventricular refractoriness (3) and has been demonstrated to be a marker of arrhythmogenic potential in the absence (4) of an acquired long QT interval. Therefore, there is an ongoing search for other ECG indices of repolarization, for example, by analysis of the T-wave. One of these is Tpeak-to-Tend interval (TpTe). TpTe and QTdisp on the ECG have been recently reported to predict life-threatening arrhythmias in the long QT syndrome (5).

A wide spectrum of cardiovascular changes characterizes liver cirrhosis ranging from the subtle subclinical alterations of pre-ascitic stages to hyperkinetic syndrome observed when decompensation develops (6,7). A prolongation of QT interval has been shown in patients with
cirrhosis (8) but no study, to our knowledge, has evaluated the entire range of electrocardiographic markers of ventricular repolarization in cirrhotic patients.

On this basis, as primary endpoint, we looked for ECG markers of ventricular repolarization in a population of patients with cirrhosis in comparison with subjects without cirrhosis.

We also investigated, as primary endpoint, the relationship between laboratory and clinical variables and QT measurements in cirrhotic subjects.

Furthermore, in order to possibly extend the spectrum criteria of the definition of cirrhotic cardiomyopathy, we investigated, as secondary endpoints, the possible predictive role of these ECG measurements of ventricular repolarization towards cirrhosis diagnosis by means ROC curves construction and their analysis.

Materials and Methods

The study was carried out in accordance with the provisions of the Declaration of Helsinki and local regulations. Keeping in mind the expected frequency of QT abnormality in a normal population at 5.9% and that in cirrhosis at 37%, a sample size was estimated. We retrospectively analyzed data of patients with cirrhosis consecutively admitted to our Department of Internal Medicine from October 2004—October 2009 along with 152 control subjects. Control subjects were hospitalized patients without cirrhosis admitted to our ward for other causes, during the same period.

Cardiovascular risk factors were evaluated for both cases and controls on the basis of the criteria shown below. Hypercholesterolemia was defined as the presence of total cholesterol blood levels $\geq 200$ mg/dL. Hypertension was defined as present if subjects were previously diagnosed according to the World Health Organization/International Society of Hypertension guidelines and were routinely receiving antihypertensive therapy (9).

Patients were defined as having type 2 diabetes (T2D) if they had known diabetes treated by diet, oral hypoglycemic drugs or insulin before stroke.

Previous coronary artery disease was determined on the basis of a history of physician-diagnosed angina, myocardial infarction, or any previous revascularization procedure assessed by a questionnaire.

CKD was defined as follows:

- Kidney damage for $\geq 3$ months as defined by structural or functional abnormalities of the kidney with or without decreased glomerular filtration rate (GFR) that can lead to decreased GFR, manifest by either pathological abnormalities or markers of kidney damage including abnormalities in the composition of the blood or urine or abnormalities in imaging tests

- GFR < 60 mL/min/1.73 m$^2$ for $\geq 3$ months, with or without kidney damage (10).

Electrocardiogram

During retrospective analysis, we analyzed ECG data of patients with cirrhosis consecutively admitted to the Department of Internal Medicine of our institution from October 2004—October 2009 and control subjects. ECG tracings were registered during the patients’ hospital stay.

All 12-lead ECGs were recorded during supine rest and all tracings were performed at a paper speed of 25 mm/sec and an amplification of 10 mm/mV. On 12-lead ECG, we measured QT maximum (QTmax), QT maximum corrected (QTmaxc), QT minimum (QTmin), QT minimum corrected (QTminc), QTpeak, QTdisp and TpTe. A trained observer blinded to the subjects’ clinical data carried out the measurements manually (intra-observer reproducibility as “relative errors” was 17%).

QT intervals were measured according to standard criteria from the start of QRS complex to the end of the T wave. The end of the wave was defined as the point of return to the isoelectric line. If a U wave was present, the QT interval was measured to the nadir of the curve between the T and the U waves. In each patient, at least nine leads had to be clearly valuable.

QT-corrected interval (QTc) was calculated according to Bazett’s formula:

\[
QTc = \frac{QTmax}{\sqrt{R-R'}}
\]

QTdisp (the difference between the longest and the shortest QT interval from any lead of a 12-lead ECG) was calculated using previously described methods (4). It was rate corrected using the modified Bazett’s formula (QTdispc = QTdisp divided by $\sqrt{R-R'}$ interval between two R waves).

The TpTe was measured in each precordial lead and obtained from the difference between QT and QTpeak, measured from the beginning of the QRS to the peak of the T-wave. In the case of negative or biphasic T waves, QT peak was measured to the nadir of the T-wave. T waves $< 1.5$ mm in amplitude were not measured. The TpTe value reported was the maximum obtained by two observers in all precordial leads. The measurement of each parameter was obtained by averaging three consecutive beats (11).

Statistical Analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all items.

Continuous data are expressed as mean $\pm$ SD, unless otherwise specified. Baseline differences between groups were assessed by $\chi^2$ or Fisher exact test as needed for categorical variables, and with independent Student $t$ test for continuous parameters. Univariate analysis of variance (ANOVA) was performed to compare the electrocardiographic, clinical and laboratory variables between patient groups. Items of significance were determined and then were put through multivariate analysis to determine further
significance. The results were adjusted for age, T2D, hypertension, smoking, obesity, peripheral artery disease (PAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), beta-blocker use, ACE-inhibitors/angiotensin II receptor blockers (ARBs) use, nitrate use.

To assess variables that were independently predictive of prolonged QT measurements, we used a multivariate Cox proportional hazard regression model and nonstandardized and standardized coefficients with their 95% confidence intervals (CIs) were reported.

To assess the predictive rate of different cutoff values of QT measurements, a receiver operating characteristic (ROC) curve with calculations of area under the curve and 95% CIs was constructed and sensitivity and specificity values were calculated.

Data were analyzed by the Epi Info software v.6.0 (Centers for Disease Control and Prevention, Atlanta, GA) and with SPSS Software v.20.0 (SPSS, Inc., Chicago, IL). All p values were two sided; p values <0.05 were considered statistically significant.

Results

We enrolled 149 subjects with cirrhosis and 152 control subjects. Demographic, general and clinical variables in subjects with cirrhosis and in controls without cirrhosis are listed in Table 1. Among the two groups of enrolled patients, mean age was 66.2 ± 11.5 vs. 67.2 ± 12.1 (p = 0.463). With regard to cardiovascular risk factors, 68 (45.6%) vs. 21 (13.8%) (p = 0.0001) had T2D, 33 (22.1%) vs. 80 (52.6%) (p = 0.0001) had arterial hypertension, 33 (22.1%) vs. 41 (26.9%) (p = 0.0001) were active smokers, five (3.4%) vs. 28 (18.4%) (p = 0.0001) had obesity, 14 (9.4%) vs. 14 (9.2%) (p = 0.886) had previous CAD.

In cirrhotic patients, cirrhosis etiology was: 6.7% alcoholic, 5.4% hepatitis B-related, 70.5% hepatitis C-related, 4.7% cryptogenic, 5.4% hepatitis B/hepatitis C-related, 3.4% hepatitis B-related/alcoholic, and 4.0% hepatitis C-related/alcoholic. At admission, 57 (38.2%) were in Child-Pugh A class, 53 (35.6%) Child-Pugh B class, and 39 (26.2%) Child-Pugh C class.

With regard to current therapy, 56.4% were in treatment with furosemide, 55.7% with spironolactone, 12.8% with ACE-inhibitors/ARBs, 28.2% with beta-blockers, 9.4% with nitrates and 2.7% with neuroleptics.

Patients did not practice any of other drugs potentially affecting the QT interval such as antiarrhythmic drugs, antihistamines, macrolides, anxiolytics drugs, tricyclic antidepressants, drugs acting on the gastrointestinal motility (cisapride, domperidone) or analgesics (methadone).

With regard to ECG variables values in cirrhotic patients and in patients without cirrhosis, mean heart rate was 76.8 ± 11.1 vs. 78.4 ± 12.2 beats per minute (bpm)
Table 2. Multivariate analysis of electrocardiographic variables of patients with cirrhosis and controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cases</th>
<th>Controls</th>
<th>$p$ *</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTmax (msec)</td>
<td>415.9 ± 39.1</td>
<td>375.3 ± 30.4</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>470.6 ± 36.6</td>
<td>425.7 ± 30.5</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>QTmin (msec)</td>
<td>355.4 ± 38.9</td>
<td>337.2 ± 30.6</td>
<td>0.005</td>
</tr>
<tr>
<td>QTpeak (msec)</td>
<td>297.5 ± 38.6</td>
<td>291.1 ± 31.5</td>
<td>0.181</td>
</tr>
<tr>
<td>QTdisp (msec)</td>
<td>60.5 ± 17.5</td>
<td>38.1 ± 16.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tpeak to end (msec)</td>
<td>108.4 ± 25.7</td>
<td>84.2 ± 20.4</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

Table 3. Cox regression analysis of relationship between QT measurements, clinical variables and drugs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>QTmax</th>
<th>QTmin</th>
<th>QTc</th>
<th>QTdisp</th>
<th>Tpeak to end</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>12.68 (2.23–23.12)</td>
<td>0.018</td>
<td>12.56 (2.49–22.13)</td>
<td>0.015</td>
<td>6.62 (1.11–12.11)</td>
</tr>
<tr>
<td>DBP</td>
<td>16.86 (6.75–26.96)</td>
<td>0.001</td>
<td>7.70 (1.25–28.7)</td>
<td>0.002</td>
<td>8.47 (1.12–26.54)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>22.63 (7.32–67.14)</td>
<td>0.015</td>
<td>82.42 (7.2–87.8)</td>
<td>0.002</td>
<td>7.70 (1.25–28.7)</td>
</tr>
<tr>
<td>ACE-inhibitors/ARBs</td>
<td>-13.89 (–13.89–0)</td>
<td>0.001</td>
<td>-12.53 (–12.53–0)</td>
<td>0.001</td>
<td>-12.53 (–12.53–0)</td>
</tr>
<tr>
<td>PAD, peripheral artery disease;</td>
<td>CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ARBs, angiotensin receptor blockers.</td>
<td></td>
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</table>

Cox Regression Analysis

With regard to Cox regression analysis of relationship between QT indexes and clinical variables in cirrhotic subjects, diastolic blood pressure (DBP) ($p = 0.0001$) and beta-blocker treatment ($p = 0.014$) were significantly associated with mean QTmax, hypertension with mean QTmin ($p = 0.018$) and mean QTc ($p = 0.015$), DBP ($p = 0.001$), beta-blockers ($p = 0.002$) and ACE-inhibitors/ARBs ($p = 0.018$) with mean QTdisp, and beta-blockers ($p = 0.004$) with TpTe (Table 3).

ROC Curves

The sensitivity and specificity of QT measurements to predict cirrhosis diagnosis is shown in Table 4. At ROC curves analysis, with regard to predictive value of QT indexes towards diagnosis of cirrhosis, the best cut-off for the analyzed markers of ventricular dispersion were: QTmax (sensitivity: 71.99 [95% CI: 67.2–76.6], specificity: 75.13 [95% CI: 70.2–80.4], $p = 0.0001$) > 400 msec; QTmin (sensitivity: 81.14 [95% CI: 75.2–87.3], specificity: 55.03 [95% CI: 38.2–62.9], $p = 0.005$) > 360 msec; QTc (sensitivity: 74.13 [95% CI: 67.0–81.4], specificity: 73.04 [95% CI: 66.8–79.8], $p = 0.0001$) > 450 msec; TpTe (sensitivity: 71.38 [95% CI: 63.0–79.5], specificity: 82.42 [95% CI: 77.2–87.8], $p = 0.0001$) > 105 msec; QTdisp (sensitivity: 65.6 [95% CI: 59.7–71.8], specificity: 80.37 [95% CI: 72.2–88.6], $p = 0.0001$) > 55 msec.

Discussion

We reported a longer mean QTmax, QTc, QTmin, QTdisp and TpTe in subjects with cirrhosis in comparison with...
age- and sex-matched controls without cirrhosis. Whereas these findings with regard to QTc are confirmatory of previous data (12,13), our findings of a longer QTmax, QTmin, QTdisp and TpTe could appear original, owing to the fact that, to our knowledge, no study has addressed the whole spectrum of electrocardiographic markers of ventricular repolarization in cirrhotic patients.

It has been suggested that the prolongation of the QT interval in cirrhotic patients is associated with a greater severity of liver disease. However, the populations of patients studied are heterogeneous in terms of etiology, concomitant therapies and gender (8,14–16) and other factors that may have affected the results. Moreover, several mechanisms may be responsible for the alterations in ventricular repolarization duration in cirrhosis, such as electrolyte imbalance or changes in sympathetic activity and these factors should be taken into account when QT interval is analyzed in patients with advanced liver disease. Furthermore, results on the role of cirrhosis etiology in the genesis of ventricular repolarization alterations seem controversial.

In a study by Bernardi et al., (8), the prevalence of QT interval prolongation did not differ between patients with alcohol-related cirrhosis and those with the post-viral disease. However, only 7% of patients were affected by alcoholic cirrhosis and 12% had cirrhosis of mixed etiology. In a study by Bal and Thuluvath (15), a prolonged QTc was seen more commonly in patients with alcoholic cirrhosis (60%) compared to non-alcoholic cirrhosis (35%), and alcoholic cirrhosis was one of the independent predictors of QT interval prolongation. A study by Genovesi et al. (16) suggests that the alcoholic etiology may indeed play a role in the prolongation of QT interval in cirrhotic patients, although the relatively small size of the population does not allow a precise definition of its contribution.

In our study we had a clear majority of patients with viral etiology and only few patients with alcoholic pathogenesis. Despite this different distribution of etiologies we also observed a higher mean duration of several QT measurements that we evaluated.

In many diseases, QT interval may represent a possible predictor of cardiovascular mortality. Among these are coronary artery disease, heart failure from different etiologies, and T2D (17–21). A longer duration of QT interval has been associated with a higher risk of sudden cardiac death and cardiovascular death in several clinical conditions (12,22–25).

Nevertheless, sudden cardiac death is not frequent in subjects with cirrhosis. A study conducted in subjects with alcoholic cirrhosis showed a higher incidence of sudden death in subjects with longer QT interval (12). Other studies showed a higher risk of sudden cardiac death in subjects with cirrhosis in treatment with drugs potentially linked to lengthening of QT interval (25–27).

Although some studies have reported a longer QT interval in patients with cirrhosis, no study evaluated other components of QT interval in order to separately analyze variables characterizing this interval. Furthermore, regardless of clinical severity of the disease, not all patients with cirrhosis have a longer QTc because this finding, as reported by several authors, has been observed in ~50% of cirrhotic patients (28).

For this reason, other mechanisms have been suggested as being involved in lengthening of the QTc and the alteration of myocardial repolarization indexes, such as the presence of electrolyte abnormalities, the use of some drugs and the presence of comorbidities could be involved.

We evaluated, using Cox analysis, the role of other factors such as comorbidities, other clinical variables and drugs in terms of their association to QT measurements. Our findings show that variables related to blood pressure values such as a history of hypertension and a high DBP are significantly associated, respectively, with QTmin and QTmax duration, DBP, beta-blockers and ACE-inhibitors/ARBs use with QTdisp, and beta-blockers use with TpTe interval.

Studies on QTdisp in patients with cirrhosis have shown that the lengthening of QT interval is not associated with an increased QTdisp and on this basis some authors have suggested that there could be a delay of repolarization of the myocyte without a spatial and temporal heterogeneity of repolarization in the same level of the ventricular wall (29). On the other hand, studies on cardiac repolarization in hypertensive patients have shown abnormalities mainly due to the resulting lengthening of QT peak (30).

Another study (12) evaluated in 33 consecutive patients with cirrhosis and 35 sex- and age-matched healthy subjects QT intervals and QT dispersion indexes after correction for heart rate according to Bazett’s formula. Authors analyzed

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cut-off</th>
<th>Area under ROC curve (±SE)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTmax</td>
<td>&gt;400</td>
<td>0.704 (0.009)</td>
<td>71.99 (67.2–76.6)</td>
<td>75.13 (70.2–80.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>QTmin</td>
<td>&gt;360</td>
<td>0.593 (0.030)</td>
<td>81.14 (75.2–87.3)</td>
<td>55.03 (38.2–62.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>QTc</td>
<td>&gt;450</td>
<td>0.713 (0.031)</td>
<td>74.13 (67.0–81.4)</td>
<td>73.04 (66.8–79.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>TpTe</td>
<td>&gt;105</td>
<td>0.722 (0.028)</td>
<td>71.38 (63.0–79.5)</td>
<td>82.42 (77.2–87.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>QTdisp</td>
<td>&gt;55</td>
<td>0.686 (0.032)</td>
<td>65.60 (59.7–71.8)</td>
<td>80.37 (72.2–88.6)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

QTmax, QT interval; QT min, QT minimum; QTc, QT corrected; TpTe, T peak-to-end; QTdisp, QT interval dispersion.
the potential relationship between QT parameters and the disease severity according to Child-Pugh classification and compared these values between survivors and nonsurvivors after a 3-year follow-up. Child-Pugh classification is used to assess liver function in cirrhosis. The prevalence of increased (>70 msec) corrected QT dispersion (QTcd) was 45% in patients with cirrhosis. According to Child-Pugh criteria: QTd, maximum QT interval (QTMax), corrected QTmax (QTcmax), and QTcd in class C were significantly higher than those of class A and B (p < 0.05, for all comparison). Furthermore, this study revealed that QT dispersion parameters were better mortality indicators than other QT interval parameters and also may give additional prognostic information in patients with chronic liver disease.

The mechanisms of these alterations are different depending on the condition that we take into account and are not yet fully understood. Furthermore, in the case of multiple co-morbidities, several more or less important mechanisms probably come into play and then determine the phase of repolarization ECG changes, varying according to the predominant mechanism.

Our findings concerning a significant association between some electrocardiographic markers of ventricular dispersion and hypertension history and DBP values could confirm the findings of a recent study (29) showing in patients with QT interval ≥450 msec higher systolic and diastolic pressure values. Moreover, a lengthening of QT interval has been reported in patients with hypertensive left ventricular hypertrophy (LVH) (30).

In addition, previous studies have reported a prolongation of action potential only (or mainly) in epicardium (31–33) in subjects with hypertensive LVH.

Moreover, ROC curve analysis showed a significant predictive value of QTmax, QTmin, QTc, QTdisp and TpTe towards diagnosis of cirrhosis. This finding could offer the chance to use electrocardiographic markers of ventricular repolarization as possible candidate markers of cirrhosis, opening a possible discussion about the role of cardiac changes as an integral part of the clinical syndrome of hepatic cirrhosis.

Our findings also raise the question, at least on the basis of ECG, of a cirrhotic myocardioopathy independent of other cardiovascular co-morbidities. Cirrhotic cardiomyopathy is defined as chronic cardiac dysfunction in patients with cirrhosis characterized by blunted contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of known cardiac disease and irrespective of the causes of cirrhosis, although some etiologies (e.g., iron overload and alcohol consumption) further impact on myocardial structure and function (34).

According to some authors, QT interval prolongation may be an important sign helpful to identify patients with cirrhosis at risk of cirrhotic cardiomyopathy (35). A recalculation of QT intervals based on heart rate and other liver-related parameters are now indicated to better dissect the contribution of changes in QT-interval to heart-related morbidity and mortality in subjects with cirrhosis (36). Nevertheless, a better comprehension of both the complex hemodynamic changes during cirrhosis and role of co-morbidities involved in the contractile dysfunction of the cardiomyocyte may lead to improved care of patients with cirrhotic cardiomyopathy.

Some possible limitations of our study are 1) the retrospective design and lack of follow-up with evaluation of possible vascular and cardiac endpoints such as cardiovascular events incidence, sudden cardiac death incidence, cardiovascular death incidence; 2) the lack of a echocardiographic evaluation to evaluate a relationship between echocardiographic and electrocardiographic findings; 3) Bazett’s correction still provides a rate-dependent QTc value and may be misleading, particularly when assessing the overall preoperative cardiac risk and the effect of drugs affecting the QT interval. Nevertheless, most studies concerning QT intervals in cirrhosis used Bazett’s formula; thus in order to make our findings comparable with those just published, we used this formula to calculate QTc. Some possible strengths of our study are diagnostic accuracy, expertise in the reporting and existence of a control group.

Conflicts of Interest
None.

Uncited References
(37,38).

References


