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QT INTERVAL PROLONGATION AND DECREASED HEART RATE VARIABILITY IN CIRRHOTIC PATIENTS: RELEVANCE OF HEPATIC VENOUS PRESSURE GRADIENT AND SERUM CALCIUM

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Short title: Determinants of QT prolongation in cirrhosis.

Abbreviations: ECG, electrocardiogram; HRV, heart rate variability; HVPG, hepatic venous pressure gradient; QTc, QT interval corrected for heart rate; HCV, hepatitis C virus; HBV, hepatitis B virus; CV_{QTc}, coefficient of variation of mean QTc; SD_{RR}, standard deviation of RR intervals; CV_{RR}, coefficient of variation of RR intervals; SDANN, standard deviation of the averages of RR intervals in all 5 minute periods; pNN50, % of RR intervals differing by more than 50 ms from the adjacent RR interval; SWT, septal wall thickness at end diastole; PWT, left ventricular posterior wall thickness at end diastole; LVDd, left ventricular internal dimension at end diastole; LVM, left ventricular mass; LVMI, left ventricular mass indexed for body surface area; LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; LVEF, left ventricular ejection fraction; Ca, plasma total calcium; Ca^{++}, plasma ionized calcium.

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ABSTRACT

A prolongation of QT interval has been shown in patients with cirrhosis and it is considered as part of the definition of the so-called "cirrhotic cardiomyopathy". The aim of the present study was to assess the determinants of QT interval prolongation in cirrhotic patients. Forty-eight male patients with different stages of liver disease were divided in three subgroups according to Child-Pugh classification. All patients underwent a 24-hours electrocardiogram (ECG) Holter recording. The 24-hours mean of QT intervals corrected for heart rate (QTc) and the slope of the regression line QT/RR were calculated. Heart rate variability (HRV), plasma calcium and potassium concentration and hepatic venous pressure gradient (HVPG) were measured. QTc was progressively prolonged from Child A to Child C ($p=0.001$). A significant correlation between QTc and HVPG was found ($p=0.003$). Patients with alcohol-related cirrhosis presented QTc prolongation more frequently than patients with post-viral cirrhosis ($p<0.001$). A QT/RR slope was steeper in subjects with alcoholic aetiology as compared to viral aetiology ($p=0.02$), suggesting that these patients have a further QTc prolongation when heart rate decreases. Plasma calcium concentration was inversely correlated with QTc ($p<0.001$). The presence of severe portal hypertension was associated with decreased HRV ($p<0.001$). Cirrhotic patients with a more severe disease, especially of alcoholic aetiology, who show greater venous pressure gradient and lower calcium plasma levels, have an altered ventricular repolarization and a reduced vagal activity to the heart that may predispose to life-threatening arrhythmias**.**

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INTRODUCTION

A wide spectrum of cardiovascular changes characterizes liver cirrhosis, ranging from the subtle subclinical alterations of preascitic stages to the hyperkinetic syndrome observed when decompensation develops [1,2]. A prolongation of QT interval has been shown in patients with cirrhosis [3], and represents the most common electrocardiographic finding in this setting. Accordingly, altered ventricular repolarization is considered as part of the definition of the so-called "cirrhotic cardiomyopathy"[4-7].

A prolonged QT interval is associated with a higher risk of sudden death and cardiac mortality in patients with inherited and acquired forms of long-QT syndrome, after myocardial infarction and even in healthy individuals [8-10]. A relationship between prolonged QT interval and overall mortality in subjects with liver failure has been suggested [3], although clear evidence showing a significant increase in the incidence of sudden cardiac death in this population is still lacking. Episodes of "Torsade de pointes" in patients with liver disease have been reported, but in most cases they occurred concomitantly with the administration of drugs known to induce QT interval prolongation [11-14].

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 aetiology, concomitant therapies and gender [3,15,16], factors that may have affected the results. Moreover, several mechanisms may be responsible of the alterations in ventricular repolarization duration in cirrhosis, such as electrolytes' imbalance or changes in sympathetic activity: these factors should be taken into account when QT interval is analyzed in patients with advanced liver disease. The aim of the present study is to assess the potential determinants of QT interval prolongation in patients with chronic liver disease. For this purpose the duration of ventricular repolarization has been evaluated in a population of patients with significant liver disease, carefully characterized in terms of severity, aetiology and plasma electrolytes' concentration. In order to overcome the limitations of standard electrocardiogram (ECG) tracing, 24-hour Holter recordings have been analyzed, and the long term variation of QT interval has been evaluated. Furthermore, the relationship between QT interval and cardiac cycle length was analyzed as well as the heart rate variability (HRV) in the time domain. To carefully assess the influence of the severity of liver disease on QT interval, patients were classified according to the Child-Pugh score [17] and the hepatic venous pressure gradient (HVPG) was also measured.

METHODS

Study population.

Forty-eight male cirrhotic patients (median age 57, range 38-77yrs) were studied. In all patients without ascites a liver biopsy was performed for histological staging (Ishak score). Patients were classified according to Child-Pugh classification:

- Child A: 26 patients, 22 with a viral aetiology (18 HCV-RNA+ and 4 HBV-DNA+) and 4 with alcohol-related cirrhosis.
- Child B: 15 patients, 7 with a viral aetiology (6 HCV-RNA+ and 1 HBV-DNA+) and 8 with alcohol-related cirrhosis.
- Child C: 7 patients, 1 with a viral aetiology (HCV-RNA+) and 6 with alcohol-related cirrhosis.

None of the patients had a mixed aetiology.

Exclusion criteria were any systemic, endocrine, lung and neoplastic disease; diabetes; arterial hypertension; recent haemorrhage (<3months); anaemia (Hb<11g/dL), serum creatinine>1,5mg/dL;

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alcohol consumption in the previous 6 months; treatment with beta-blockers, antivirals and any drug that may prolong-QT interval. Patients with evident cardiac disease such as valvular disease, depressed systolic function and myocardial dilatation were also excluded.
The study has been performed in accordance with the Declaration of Helsinki (2000) of the World Medical Association and it has been approved by the Ethics Committee of our Institution. All patients signed an informed consent.

Portal pressure measurements

HVPG measurements have been performed in all patients. A 7F venous introducer (Cordis Corporation, Miami, U.S.A.) was inserted in the right jugular vein under local anaesthesia and a 6F catheter (Meditech, Boston Scientific Corporation, Waterton, U.S.A.) was positioned under fluoroscopic guidance in a hepatic vein. The catheter was then substituted with a 6F balloon catheter which was used for measurements. HVPG was obtained by means of a pressure recorder (Sirecust 1260, Siemens Medical Electronics, Danvers, U.S.A.) in the occluded position and then after deflation of the balloon, after having checked that the tip of the catheter was freely floating in the middle of the hepatic vein. HVPG was calculated as the difference between the occluded and free hepatic venous pressure (mmHg). Three measurements were averaged.

Electrocardiographic Holter recordings and analysis.

A 24-hour ECG Holter monitoring was recorded in each subject. Holter recording was performed within 24–48 hours of HVPG measurement. All recordings were obtained using a portable battery-operated 3-channel Holter recorder. The digitized three-channel ECG signals were processed by the Synescope Holter analysis software (ELA Medical, Mountrouge, France), which sampled the 24-hour recording into 2880 templates obtained by 30-second time intervals. To improve the signal-to-noise ratio, one median complex was computed every 6 seconds from the consecutive sinus beats: then the five median beats within each 30-second template were averaged in order to obtain single representative PQRST complexes for each of the 2880 templates. For each template, an algorithm automatically measured the QT and the RR interval (ms). Measurements from the channel of lead V5 were used for the analysis. Each QT value was plotted against the cycle length, and the program automatically computed the linear regression (QT/RR) for the entire 24-hours or for pre-specified periods, and automatically provided the slope, the intersect and the correlation coefficient of the linear regression line. The program also provided for each hour the mean of QT intervals corrected for HR according to the Bazett's formula (QTc). Mean QTc, the coefficient of variation of mean QTc (CV_{QTc}= SD_{QTc}/$mean_{QTc}$*100) and QT/RR slopes were calculated: the analysis was performed for the whole 24-hours and the periods of wakefulness/sleep.
HRV has been analyzed by time domain parameters. Mean and standard deviation of RR intervals (SD_{RR}) were analyzed for the whole 24-hours and the periods of wakefulness/sleep. Also the coefficients of variation of RR intervals (CV_{RR}=SD_{RR}/$mean_{RR}$*100) have been calculated for the same periods. The SD of the averages of RR intervals in all 5 minute periods (SDANN) and the % of RR intervals differing by more than 50 ms from the adjacent RR interval (pNN50) have been calculated. All measurements have been performed by an investigator who was blinded to the patient condition.

Cardiac ultrasound examination.

The echocardiograms were obtained in the standard precordial positions using digital echocardiography equipment (Aloka ProSound SSD Alpha 10, Tokyo, Japan) with 1-5MHz transducers. We followed the recommendations for standard measurements from M-mode echocardiograms [18]. Instantaneous measurements were made from three cardiac cycles and the average values of the following parameters were obtained for each subject: septal wall thickness at end-diastole (SWT), left ventricular posterior wall thickness at end-diastole (PWT) and left ventricular internal diameter at the end of diastole (LVDd). Left ventricular mass (LVM) was

calculated according to the formula modified by Deveraux [19] using the American Society of Echocardiography convention and indexed for body surface area (LVMI). The presence of left ventricular hypertrophy was defined as LVMI grater than 125g/m^2 [18]. Left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were calculated by two-dimensional measurements for volume calculations using biplane method of disks (modified Simpson's rule) in apical 4-chamber and apical 2-chamber views and indexed for body surface area. Left ventricular ejection fraction (LVEF) was calculated as LVEF= (LVEDV-LVESV)/LVEDV. Echocardiographic measurements were performed by an investigator who was blinded to the patient condition.

Blood samples.

Plasma concentration of potassium, total calcium (Ca) and ionized calcium (Ca^{++}) were measured in all patients. Plasma aldosterone was measured after 3 hours of recumbent position. Potassium was measured by indirect potenziometry ISE (OMNI-S gas analyser Roche Diagnostics GmbH, Mannheim, Germany), Ca by photometry (O-cresolphtalein Complex, Modular P Roche-Hitachi Diagnostics, Tokyo, Japan) and Ca^{++} by direct potenziometry ISE (OMNI-S gas analyser Roche Diagnostics GmbH, Mannheim, Germany). Plasma aldosterone concentration was measured by radioimmunoassay (RIA Kit DiaSorin, Vercelli, Italy).

Statistical analysis.

Results are expressed as mean±standard deviation. Comparisons between groups were performed by analysis of variance (ANOVA) followed by Fisher's post-hoc test. Differences in frequency of QT interval prolongation (QTc>440msec) between groups were analyzed by chi square test. Correlations between QTc, HRV measures, electrolytes' concentration, HVPG, and Child-Pugh score and age were evaluated by univariate and multivariate regression analysis. The following parameters were included in the multivariate analysis model: SD_{RR}, Ca^{++} and HVPG. The Statview Statistical package (Abacus Concepts, version 4.5) was used for statistical analysis. P values<0.05 were considered significant.

RESULTS

Characteristics of the patients.

Clinical, portal hemodynamic and biochemical data of the patients are shown in *Table1*. Child scores were significantly different among the three groups (p<0.001).
HVPG values were significantly lower in Child A as compared to both Child B and Child C patients (p=0.001). None of the patients had clinical history of heart failure.

QT interval during Holter monitoring.

None of the patients showed complex ventricular arrhythmias during Holter recording and the incidence of ectopic beats did not differ between the three groups.
Mean 24-hour QTc was progressively prolonged from Child A to Child C group. QTc was 425±24 msec in Child A, 452±30 msec in Child B, and 465±24 msec Child C (p=0.001, ANOVA. Child A vs Child B: p=0.002, Child A vs Child C: p=0.001). These differences in QTc were present both during the day and at night. Specifically, QTc was greater than 440 in 5/26 of Child A patients (19%), in 10/15 (67%) of Child B and in 6/7 (86%) of Child C (p<0.001). However, when we analyzed our data according to the aetiology, irrespective of disease severity, we found that 15/18 (83%) patients with alcohol-related disease had a QTc>440 msec, whereas QTc was prolonged in only 6/30 (20%) patients with post-viral cirrhosis (p=0.001). Interestingly, the patient with the

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longest QT interval (502 msec), although affected by alcohol-related disease, belongs to Child B group (*Figure1*).
No differences in QTc were found between patients with HCV or HBV-related aetiology.
Twenty-four-hour CV_{QTc} did not differ between Child groups, suggesting that QT interval variability was not affected by the liver disease stage.
The slope of the linear regression line, which expresses the relation between QT interval and cardiac cycle length in the 24-hours, was slightly but not significantly flatter in Child A group as compared with the other two groups (Child A: 0.16±0.04, Child B: 0.19±0.10, Child C: 0.18±0.07). Patients with alcohol-related cirrhosis had a steeper slope than patients with post-viral cirrhosis, irrespective of disease severity (0.21±0.06 vs 0.16±0.04, p=0.02),suggesting that these subjects have a further QT interval prolongation when heart rate decreases (*Figure2)*.

Heart rate and heart rate variability.

Mean 24-hour RR intervals were shorter in Child C patients as compared with the other two groups. HRV measured in the time domain showed significant differences between groups. 24-hour SD_{RR}, SDANN and pNN50 progressively decreased with the increase of liver diseases severity. Of note, the difference in HRV in the three groups of patients was not affected by different heart rates, as also the CV_{RR} progressively decreased (*Table2*).

Echocardiographic findings.

The echocardiographic variables in the population studied did not significantly differ between groups (*Table3*). Specifically, all patients showed normal left ventricular systolic function. Although patients belonging to Child B and C group had a slightly greater values of LEDVI, none of the patients had left ventricular dilatation. LVMI was not different in the three groups although left ventricular hypertrophy was present in 6/25 (24%) Child A patients, in 3/14 (21%) Child B patients and in 1/6 (16%) Child C.

Electrolytes' concentration.

Calcium and Ca^{++}serum concentrations differed in the three groups *(Table1).* In details, Ca serum levels were significantly higher in Child A group as compared to the other two groups (p=0.001), whereas the difference in Ca^{++} serum levels was significant between Child C and Child A patients (p=0.05). However, Ca serum levels were below the lower normal limits (2.15mmol/L) in only 7 patients (4 Child B and 3 Child C), while Ca^{++} serum levels were in the normal range in all patients.

Regression analysis.

At univariate analysis mean 24-hour QTc duration was significantly and directly correlated with HVPG values (r=0.43, p=0.003, *Figure3A*) and Child score (r=0.51, p<0.001). SD_{RR} was significantly and inversely correlated with HVPG values (r=0.59, p<0.001, *Figure3B*). A correlation between SD_{RR} and QTc was also found (r=0.44, p=0.002, *Figure3B*). Twenty-four-hour mean QTc was inversely correlated with Ca (r=0.58, p<0.001) and with Ca^{++} (r=0.51, p<0.001, *Figure3A*) serum levels. No correlation was found between QTc, SD_{RR} values, HVPG and the echocardiographic parameters. Also age did not correlate with electrocardiographic or portal hemodynamic parameters.
At multiple regression analysis only HVPG and Ca^{++} were independently correlated to QTc (p=0.002 and p=0.05, respectively).

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DISCUSSION

In our study, strict inclusion criteria have been adopted. In fact, patients who had characteristics which may potentially affect ventricular repolarization duration, i.e. co-morbidities, drug able to prolong QT interval, major complications of disease, have been excluded.

The present study has shown that QT interval measured from ECG Holter monitoring is prolonged in a significant portion of patients with cirrhosis. The duration of ventricular repolarization was normal in the majority of patients with less severe liver disease, while it was markedly altered in patients with more severe cirrhosis. As most of the patients with a QT interval prolongation were affected by alcohol-related cirrhosis, independently of the severity of the disease, it is possible that aetiology might have played a role. Also the relation between QT interval and cardiac cycle length in the 24 hours, expressed as the slope of the QT/RR regression line, was altered in patients with alcoholic cirrhosis, suggesting that these patients have a further QT interval prolongation when heart rate decreases. A significant correlation between QTc duration and HVPG, a reliable marker of the degree of portal hypertension, has been found. This suggests that portal hypertension may represent a major pathophysiological mechanism involved in the alterations of ventricular repolarization. The presence of severe portal hypertension was also associated with decreased heart rate variabilty, likely reflecting a higher sympathetic tone. Interestingly, QTc was inversely correlated with plasma ionized calcium concentration, although all patients showed values within the normal limits.

Mechanisms of QT interval prolongation.

QT interval was more prolonged in patients with greater Child-Pugh score, corresponding to clinically significant liver disease, in agreement with previous studies [5,7,20]. The majority of patients with higher Child-Pugh score were affected by alcohol- related cirrhosis and most of them showed a prolongation of the QT interval duration independently of the severity of liver disease. Data on the role of cirrhosis aetiology in the genesis of ventricular repolarization alterations seem controversial. In the study by Bernardi [3] the prevalence of QT interval prolongation did not differ between patients affected by 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 aetiology. In a study by Bal [20] a prolonged QTc was seen more commonly in patients with alcoholic cirrhosis (60%) as compared to non-alcoholic cirrhosis (35%) and alcoholic cirrhosis was one of the independent predictors of QT interval prolongation. The present study suggests that the alcoholic aetiology may indeed play a role in the prolongation of QT interval in cirrhotic patients, although the relative small size of the population does not allow the exact definition of its contribution. Of note, although patients belonging to Child B and C group had a slightly greater values of left end-diastolic volumes, none of our patients had left ventricular dilation and the prevalence of left ventricular hypertrophy was not affected by aetiology. The absence of marked alterations in left ventricular function or size in our population may be partly explained by our strict exclusion criteria. In fact, patients with overt structural heart disease and those with atrial fibrillation had been excluded. Thus, it seems unlikely that the abnormalities in ventricular repolarization might have been caused by structural cardiac alterations related to long-term alcohol exposure.

In the present study, we have also measured the HVPG to better characterize the population [21]. The observation in our study that HVPG is significantly correlated with QT interval duration indicates that ventricular repolarization is prolonged particularly when clinically significant portal hypertension develops. Portal hypertension may represent a major pathophysiological mechanism involved in the alterations of ventricular repolarization. It has been shown that QT interval may be prolonged also in patients with non-cirrhotic portal hypertension and preserved liver function [16] and it has been hypothized that in portal hypertension with portosystemic shunting a dumping into the systemic circulation of splanchnic-derived substances, such endotoxins and cytokines, or

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autocoids, substances that are produced locally in the heart, may contribute to the alterations in ventricular repolarization [7].

We have found a significant negative correlation between QT interval duration in the 24-hours and both total and ionized plasma calcium values, although ionized plasma levels were within the normal limits in all patients. This finding is in agreement with our previous results obtained in a population of patients with end stage renal disease undergoing haemodialysis [22]. In that study changes in plasma calcium concentration induced by the haemodialysis session were inversely correlated with changes in QT interval. It has been demonstrated that a decrease in plasma calcium concentration is associated with an increase in ventricular action potential duration and QT interval prolongation [23]. In the present study we have shown that in patients with cirrhosis even small differences in calcium plasma levels are associated with significant differences in QT interval duration. As patients with advanced cirrhosis show an alteration of calcium homeostasis [24,25] a close monitoring of both total and ionized plasma calcium concentration should be performed in this clinical setting.

QT interval and its relationship with cardiac cycle length in liver cirrhosis.

The duration of ventricular repolarization is traditionally assessed by measuring the QT interval from a short surface electrocardiogram. Moreover, as the QT interval is affected by the cardiac cycle length, a correction for heart rate is necessary. Although several formulas for heart rate correction have been proposed, the most commonly used is the Bazett's formula, the standard for clinical use. In the context of studies performed in cirrhotic patients a novel formula has been proposed [26] and utilized. However, even if a particular formula may be more accurate in a defined population of patients and can be utilized in clinical research, its widespread use is not warranted, as a comparison with other populations of patients with different clinical conditions becomes unfeasible.

To overcome the limitations inherent to the measurement from a short ECG tracing, at variance with previous studies, except one [27], QT interval was analyzed from a 24-hour Holter recording, by using a robust dedicated algorithm which automatically measures QT interval and RR interval [28]. As Bazett's formula may not be accurate at high and low heart rate, the relationship between the absolute value of QT interval and the cycle length expressed as the slope of linear regression line was also considered. Interestingly, patients with alcohol-related cirrhosis had a steeper slope than patients with post-viral cirrhosis, irrespective of disease severity, suggesting that also these alterations in ventricular repolarization may be partly explained by the aetiology of cirrhosis. We do not have a clear explanation of this finding that may have clinical relevance as the further prolongation of QT interval at long cycle lengths may favour the occurrence of bradycardia-related "Torsades des pointes" [29].

Clinical relevance of electrocardiographic abnormalities.

Prolongation of QT interval is associated with an increased risk of sudden death and cardiovascular mortality in several clinical conditions [8-10]. Sudden death is considered uncommon in cirrhosis. However, a study performed in subjects with alcoholic cirrhosis showed a higher incidence of sudden death in those with QT interval prolongation [30]. In fact QT interval prolongation was independently associated with the risk of mortality. "Torsades de pointe" have been sporadically described in cirrhotic patients, although in concomitance with the use of drugs which may induce QT interval prolongation [11-14]. An increased sympathetic activity to the heart has been shown to favour life-threatening arrhythmias. In our study we have found that heart rate variability, which reflects the balance between the parasympathetic and the sympathetic tone to the heart, progressively decreased with the increase of portal pressure, independently of the basal heart rate. Patients with advanced cirrhosis have increased levels of plasma catecholamines [31,32] and of muscle sympathetic nervous traffic, a direct index of autonomic nervous system activity [33,34]. Cirrhotic patients with oesophageal varices are currently treated with beta-blockers to decrease

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portal pressure and the bleeding risk. These agents also reduce the sympathetic activity to the heart and are the treatment of choice of the long-QT syndrome, significantly improving survival in these patients as well as in those with myocardial infarction or heart failure [35-38]. We cannot exclude that these beneficial effect of beta-blockers may have played a role in the reduction of risk of cardiovascular mortality in patients with cirrhosis. Interestingly, in cirrhotic patients with a more prolonged QT interval the administration of beta-blockers reduces sympathetic activity to the heart and decreases the duration and the spatial dispersion of QT interval [39,40], as already demonstrated in other clinical conditions [41].

In conclusion, cirrhotic patients with a more severe disease, especially of alcoholic aetiology, who show greater venous pressure gradient and lower calcium plasma levels, have an altered ventricular repolarization and a reduced vagal activity to the heart that may predispose to life-threatening arrhythmias**.** Further studies are necessary to prospectively assess the time-course of changes of heart rate variability and QT interval duration in cirrhotic patients.

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Figures and Tables

	Child A (n=26)	Child B (n=15)	Child C (n=7)	p (ANOVA)
Age (years)	53.9 ± 10.9	58.7 ± 11.8	59.0 ± 11.1	NS
Child score	5.1 ± 0.2	7.7 ± 0.7	10.6 ± 0.8	<0.001
HVPG (mmHg)	11.8 ± 5.0	21.8 ± 5.6	22.0 ± 3.9	0.001
K^+ (mmol/L)	4.2 ± 0.3	4.1 ± 0.5	4.1 ± 0.3	NS
Aldosterone (pg/mL)	134.0 ± 87.8 (n=22)	131.8 ± 91.5 (n=13)	210.8 ± 85.8 (n=6)	NS
Calcium (mmol/L)	2.37 ± 0.09	2.22 ± 0.12	2.15 ± 0.10	0.001
Ionized Ca^{++} (mmol/L)	1.26 ± 0.04	1.24 ± 0.05	1.22 ± 0.04	0.05

Table 1. Demographic, clinical, portal hemodynamic and biochemical characteristics of 48 patients according to Child-Pugh classification.
HVPG: hepatic venous pressure gradient.

	Child A (n=26)	Child B (n=15)	Child C (n=7)	p (ANOVA)
RR (msec)	850 ± 105 †	856 ± 160 †	740 ± 79	0.05
CV_{RR}	13.5 ± 3.4 * †	11.1 ± 3.3	9.1 ± 2.2	0.002
pNN50 (%)	5.9 ± 7.1 †	4.5 ± 6.2	1.2 ± 0.6	0.05
SDANN (msec)	109 ± 30 * †	88 ± 40	67 ± 17	0.008
SD_{RR} (msec)	115 ± 30 †	98 ± 40 †	67 ± 17	0.004

Table 2. Heart rate variability parameters (time domain).
RR: RR interval; SD_{RR}: standard deviation of RR intervals; SDANN: SD of the averages of RR intervals in all 5 minute periods; pNN50: percentage of RR intervals differing by more than 50 ms from the adjacent RR; CV_{RR}: coefficient of variation of RR intervals.
*: $p<0.05$ vs Child B; †: $p<0.05$ vs Child C.

	Child A (n=25)	Child B (n=14)	Child C (n=6)	p (ANOVA)
SWT (cm)	1.05 ± 0.11	1.04 ± 0.9	1.04 ± 0.09	NS
PWT (cm)	0.94 ± 0.14	0.96 ± 0.07	1.04 ± 0.05	NS
LVDd (cm)	4.89 ± 0.40	5.01 ± 0.54	4.70 ± 0.50	NS
LVMI (g/m^2)	108.1 ± 20.6	116.4 ± 28.4	112.0 ± 28.5	NS
LVEDV I (mL/m^2)	51.5 ± 10.2	58.6 ± 15.7	56.1 ± 10.2	NS
LVEF (%)	64.3 ± 5.0	63.3 ± 4.7	64.1 ± 3.2	NS

Table 3. Echocardiographic parameters.

SWT, septal wall thickness at end diastole; PWT, left ventricular posterior wall thickness at end diastole; LVDd, left ventricular internal dimension at end diastole; LVMI, left ventricular mass indexed for body surface area; LVEDVI, left ventricular end-diastolic volume indexed for body surface area; LVEF, left ventricular ejection fraction.

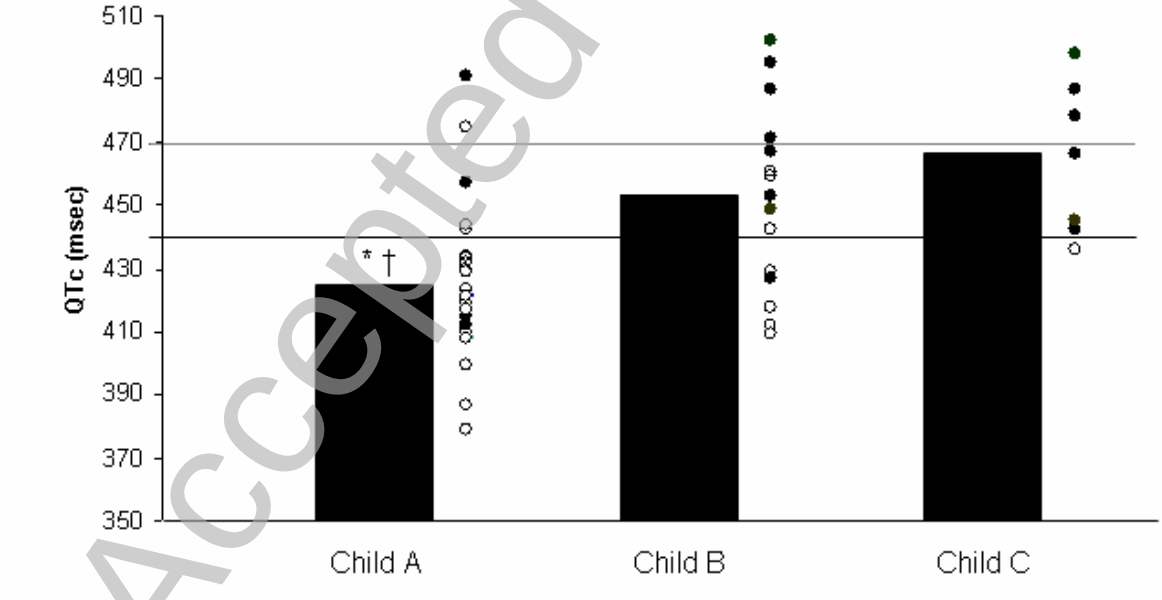

Figure 1. QTc mean and single QTc values according to Child-Pugh classification.

White points: patients with viral aetiology; black points: patients with alcohol-related disease.

*: $p<0.05$ vs Child B; †: $p<0.001$ vs Child C.

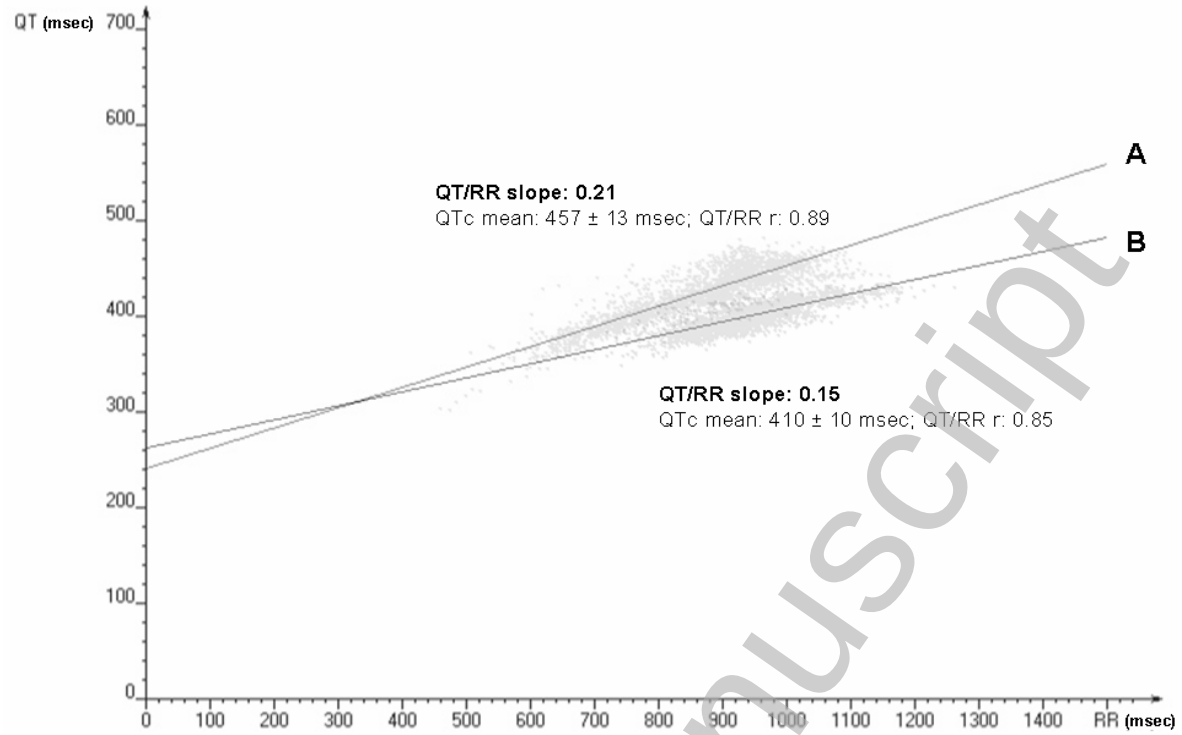

Figure 2. Example of QT/RR linear regression slopes recorded from a patient with alcohol-related cirrhosis (A) and from a patient with viral aetiology (B).
QTc: QT intervals corrected for heart rate; r: correlation coefficient.

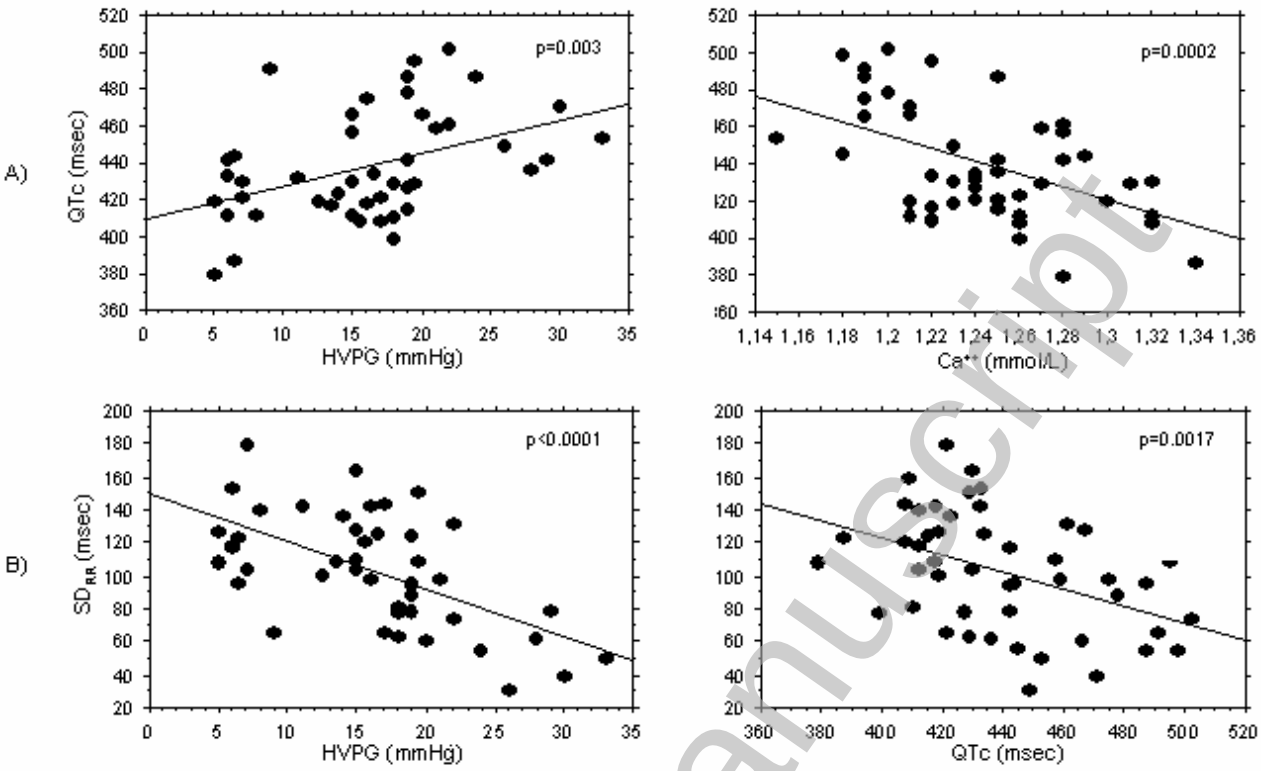

Figure 3. A) Scatter plot of QTc versus HVPG and Ca^{++} values; B) Scatter plot of SD_{RR} versus HVPG and QTc values.

QTc: QT intervals corrected for heart rate; HVPG: hepatic venous pressure gradient; SD_{RR}: standard deviation of RR intervals.