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ORIGINAL ARTICLE

QT Adaptation during Exercise in Cirrhosis

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ABSTRACT

AIM: QT-interval prolongation is frequently seen in cirrhosis; whether it is simply a marker of disease severity is debated. Analysis of QT-interval behavior during physical exercise may disclose more specific abnormalities of cardiac repolarization of cirrhotic cardiomyopathy.

MATERIALS AND METHODS: Thirty-eight out-patients with non-alcoholic liver cirrhosis and portal hypertension (32 males, aged 62 ± 9 years) and 36 sex- and age-matched healthy volunteers (32 males; aged 59 ± 7 years) underwent bicycle exercise test with QT-interval measurement, echocardiographic and Doppler analysis of systolic and diastolic left ventricular function, determinations of systemic hemodynamic and pro-brain natriuretic peptide concentration.

RESULTS: Patients had longer Fridericia-corrected QT-interval than healthy subjects at baseline and peak-exercise, and reduced chronotropic index, despite similar predicted workload. Corrected-QT shortening extent at peak-exercise was the same; however, in early-exercise, corrected-QT increased in 6 healthy subjects versus 25 patients, and in patients the increase was greater and significantly delayed. QT hysteresis was greater in patients. Abnormal repolarization during exercise and recovery in patients with normal baseline corrected-QT did not correlate to Child-Pugh class and hemodynamic alterations, whereas patients with > 440 ms corrected-QT (n = 16) showed diastolic dysfunction and increased pro-brain natriuretic peptide.

CONCLUSIONS: QT behavior during physical exercise supports the hypothesis of anomalous modulation of potassium currents in cirrhosis; only long rest corrected-QT correlates to clinical signs of cirrhotic cardiomyopathy.

Key words: Non-alcoholic liver cirrhosis; Exercise test; Diastolic function; Long QT syndrome; QT-interval

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INTRODUCTION

Cirrhotic cardiomyopathy is a "chronic cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of other known cardiac disease"[1]. Along with chronotropic incompetence and electromechanical uncoupling, QT interval prolongation is one of the three principal key features of the disease and it represents the most frequent electrophysiological finding, irrespective of gender[2]. Corrected-QT interval (QTc) longer than 440 ms can be found in almost half of the patients with cirrhosis[3,4,5] and has been correlated

with progression of liver disease[3,6-,7]. Its presence represents a negative prognostic indicator, due to the increased risk of potentially fatal cardiac arrhythmias.

The reasons for QT prolongation in cirrhotic patients are still under investigation. Electrolyte unbalance, metabolic abnormalities and impaired β-adrenoceptor signaling, due to sympathetic hyperactivity and prolonged exposure to increased levels of plasma noradrenaline, were proved to take part in the phenomenon[8-9]. By analogy to drug-acquired QT interval prolongation[10], dysregulation of potassium channels, which reduces conductance of the potassium delayed rectifier channel (I_{Kr} current), may represent another interdependent factors contributing to long QT in cirrhotic cardiomyopathy.

Sudden stressful events such as acute gastrointestinal bleeding are able to prolong QT interval in cirrhotic patients, via an abrupt burst of sympathetic activity[11]. Physical exercise is a "controlled stressful situation" characterized by complex physiologic adaptations which involve vagal withdrawal, sympathetic activation and a surge of serum catecholamines. Physical exercise was used to study the cardiovascular response in cirrhosis, and contributed to the definition of cirrhotic cardiomyopathy because of the blunted ability of cirrhotic patients to increase their heart rate (HR) or left ventricular (LV) ejection fraction during appropriate stimulation[12].

To our knowledge, no study investigated the behavior of QT duration during physical exercise testing. We hypothesized that the analysis of QT-interval duration during physical exercise and early recovery would shed some light on the abnormalities of myocardial repolarization of cirrhosis.

The aim of this study was to analyze QT-interval duration changes induced by graded upright bicycle exercise test in a population of non-alcoholic cirrhotic patients.

METHODS

Thirty-eight outpatients (32 males; mean age 62 ± 9 years) with non-alcoholic liver cirrhosis and portal hypertension were recruited to undergo upright bicycle exercise test. Cirrhosis diagnosis was based on clinical history, physical examination, liver ultrasonography and biochemical parameters, and was confirmed by liver biopsy, when not contraindicated. Portal hypertension was demonstrated by the presence of oesophageal varices at endoscopy in all patients, ascites was detected by physical examination and confirmed by ultrasound scan in 15. The Child-Pugh classification[13] was used to assess the severity of cirrhosis. Exclusion criteria were recent gastrointestinal haemorrhage (North Italian Endoscopic Club score > 35[14]), organic kidney disease, renal dysfunction (serum creatinine ⩾ 133 μmol/L)[15], pulmonary or cardiovascular diseases, bladder dysfunction, malignancies or infections, use of long-QT inducing drugs and beta-blockers.

Cirrhosis was HCV-correlated in 28 patients, HBV-correlated in 10; 22 patients were in Child-Pugh class A, 12 in class B, 4 in class C.

Thirty-six sex- and age-matched healthy volunteers (32 males; mean age 59 ± 7 years) without cardiovascular risk factors, clinical history and instrumental (ECG and echocardiogram) evidence of heart disease were also recruited.

Informed consent was obtained by all subjects included in the study which conformed to the principles outlined in the Helsinki Declaration and was approved by the Local Ethical Committee.

On examination day, after overnight fasting serum sodium, potassium, calcium, creatinine, and N-terminal pro-brain natriuretic peptide (NT-proBNP; proBNP II Cobas ® diagnostic system) were measured.

Exercise test

Subjects underwent bicycle exercise tolerance test (GE Medical System Case®). Aerobic exercise capacity was estimated by a questionnaire-based nomogram[16]. The most appropriate ramp protocol to achieve maximum exercise capacity in 10 to 12 minutes[17,18] was selected. No test was terminated because of an untoward response (hypotension, hypertension, clinically relevant arrhythmias). All tests resulted negative for coronary artery disease.

Standard 12-lead ECG was acquired at baseline and continuously recorded during exercise. Baseline ECG was normal except for QT prolongation in some patients. Maximal HR was corrected for age according to the equation: 208 - (0.7 × age in years) beats/min[19]. Chronotropic index was obtained as $(HR_{peak}–HR_{rest})/(\text{predicted } HR_{peak}–HR_{rest})$[20].

QT-interval was measured manually on 12-lead ECG as the time interval between QRS onset and the end of T wave, that was identified by the intersection between the tangent to the downward limb of T wave and the isoelectric line[21]. The longest QT interval measured at baseline, at any minute of the exercise ramp protocol, at peak exercise and at minute 2 of recovery was recorded, the mean of three consecutive QT-interval measurements at a stable RR interval was used in the analysis. Two investigators blinded to the subjects' status carried out measurements. Interobserver variability was tested in 10 randomly selected patients with no significant difference of the measured data between observers ($r^2 = 0.98$, $p < 0.0001$, K = 0.92).

The HR correction of QT interval was computed by applying the Fridericia correction formula[22], that is the QT correction method more specifically proposed for cirrhosis[4].

QT adaptation during exercise was examined by plotting QTc against the percentage of maximal predicted HR[23]. QT hysteresis was analyzed by comparing 2-minute recovery QT with QT measured during exercise test at the same HR[24].

Hemodynamic measurements

Echocardiography was performed before exercise test (iE33 platform, Philips Medical Systems Andover, Massachusetts, equipped with S5-1 (1-5 MHz) probe). LV end-diastolic and end-systolic volumes, ejection fraction and end-systolic left atrial volume were measured on biplane apical views (Simpson rule).

LV mass was calculated in a standard fashion using M-mode measurements of the left ventricle[25]. Blood pressure was simultaneously measured by using a semiautomatic oscillometric method (Siemens-Sirecust 888, Solna, Sweden).

Doppler mitral E-to-A-wave velocity ratio, E-wave deceleration time and isovolumic relaxation time were measured. The ratio of mitral E velocity to mean mitral annular e' velocity (E/e') was calculated as an estimate of LV filling pressure[26]. Data were used to calculate stroke volume (SV), cardiac output (CO=SVxHR), mean arterial pressure (MAP = diastolic arterial pressure + 1/3 pulse pressure), and systemic vascular resistances (MAPx80/CO).

Echocardiographic and Doppler measurements were made in triplicate and averaged; they were indexed for body surface area when appropriate.

Statistical analysis

Data were analysed by means of SPSS for Windows statistical package version 22.0 (SPSS Inc. Chicago, Ill.) and reported as mean value ± standard deviation. Differences between cirrhotic patients and healthy subjects and between QT subsets were assessed by *t*-test after Lévene test for variance or chi-square test. Comparisons among groups were performed by ANOVA and *t*-test with Bonferroni correction.

Cohen's kappa was used to measure repeatability of QT measures (0 = agreement no better than chance, 1 = perfect agreement).

RESULTS

Cirrhotic patients had longer QTc at baseline; resting QTc was ≥ 440 ms in 16 patients, of whom 6 in Child class A (27.3%), 7 in Child class B (58.3%) and 3 in Child class C (75%). Electrolytes were in the normal range in all patients.

Exercise data

Exercise test data are reported in Table 1. Cirrhotic patients showed similar predicted work capacity as healthy subjects, but they performed less workload. Their peak HR was lower and hence their chronotropic index was reduced.

Baseline and peak-exercise QTc values were significantly higher in cirrhotic patients; QT-interval shortened in a similar fashion during exercise in healthy subjects and in patients (Figure 1).

Six healthy subjects and 25 cirrhotic patients (chi-square = 18.325 $p < 0.0001$) showed a non-linear shortening of QTc in the early phase of exercise (Figure 2). QTc increased only slightly (8.8 ± 3.6 ms) and in a very early phase of exercise, i.e.: within the first 8.1 ± 4.9% of the predicted maximal HR in the six healthy subjects, whereas the QTc increase was greater (28.5 ± 22.9ms, $p < 0.001$) and significantly delayed, i.e.: within 16.4 ± 9.1% of the predicted maximal HR ($p = 0.004$) in the 25 cirrhotic patients. The extent of QTc increase was the same between patients with and without long rest QTc (27.9 ± 30.4 ms vs. 28.8 ± 18.7 ms, respectively: p ns) but it occurred earlier in the former (11.9 ± 4.2 ms vs. 18.7 ± 10.2 ms, $p < 0.05$).

QT hysteresis was greater in cirrhotic patients than in healthy subjects ($p < 0.0001$); it did not differ between patients with normal and long QTc at baseline (Figure 1). QT hysteresis was significantly greater in cirrhotic patients with non-linear QT shortening during exercise (27.8 ± 18.5 ms vs. 16.9 ± 7.4 ms, $p < 0.05$).

Echocardiographic and hormonal data

Cirrhotic patients had higher ejection fraction, lower end-systolic volume index, lower mean arterial pressure and a pattern of eccentric hypertrophy as detailed in Table 2. Mean arterial pressure and systemic vascular index were lower in Child C patients and in patients with long QTc. Statistically significant left atrial volume enlargement and higher than healthy subjects' E/e' ratio were present in cirrhotic patients. Significant left atrial dilation was observed in patients with long QTc (Figure 3).

NT-proBNP values were significantly higher only in cirrhotic patients with long QTc (Figure 3).

DISCUSSION

The hemodynamic data presented in this study confirm the well-known pattern of cirrhotic cardiomyopathy[20]. The incidence of long rest QTc increased with Child-Pugh class; patients with long QTc had more evident signs of diastolic dysfunction and higher NT-proBNP values.

As a general rule, QT interval shortens during exercise[27]. Accordingly, QTc shortened during exercise in cirrhotic patients and in healthy subjects.

The time-course of QT behaviour during exertion deserves more detailed analysis. Several authors have reported a linear relationship between QT and both HR and RR interval during exercise[28,29]. On the contrary, Kligfield *et al*[25] reported a pattern characterized by either an initial QT increase or no QT shortening during the early phases of exercise in 28% of normal men and in 33% of normal woman. In our healthy subjects, 12.5% of males and 33% of females showed a maximal QT increase of 13 ms in the early phases of exercise. In the cirrhotic group such an increase was observed in 25 subjects (72% males), its magnitude was greater and it occurred later

Table 1 Exercise data

	Healthy subjects (n = 36)	Cirrhotic patients					
		All (n = 38)	Child-Pugh class A (n = 22)	Child-Pugh class B (n = 12)	Child-Pugh class C (n = 4)	QTc < 440 ms (n = 22)	QTc ≥ 440 ms (n = 16)
Estimated work capacity (W)	132.4 ± 38.4	113.4 ± 44.4	117.4 ± 40.0	108.3 ± 56.1	106.7 ± 35.9	116.9 ± 37.8	108.7 ± 53.1
Measured peak work (W)	141.1 ± 41.2	88.3 ± 39.9‡	90.9 ± 38.8‡	85.8 ± 46.3†	81.2 ± 33.3*	94.3 ± 36.2	80.0 ± 44.3
Work capacity (%)	108.2 ± 23.7	77.3 ± 15.4‡	76.6 ± 17.2‡	79.4 ± 3.8‡	75.3 ± 11.1*	79.9 ± 14.9	73.7 ± 15.8
Maximal estimated HR (bpm)	172.7 ± 4.4	164.6 ± 6.0‡	166.0 ± 5.6‡	162.2 ± 6.6‡	163.9 ± 5.4*	165.5 ± 4.9	163.3 ± 7.4
Peak reached HR (bpm)	152.8 ± 6.7	116.1 ± 20.2‡	116.0 ± 22.9‡	117.7 ± 16.7‡	112.0 ± 16.8‡	120.4 ± 19.6	110.2 ± 20.1
Chronotropic index	0.79 ± 0.05	0.47 ± 0.18‡	0.47 ± 0.20‡	0.49 ± 0.14‡	0.43 ± 0.17‡	0.51 ± 0.16	0.42 ± 0.19

Abbreviations: HR, heart rate. Statistical analysis: t-test between healthy subjects and cirrhotic patients, between Child class patients, between cirrhotic patients with QTc <440 ms and ≥ 440 ms; statistical significance: * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

Table 2 Hemodynamic data.

	Healthy subjects (n = 36)	Cirrhotic patients					
		All (n = 38)	Child-Pugh class A (n = 22)	Child-Pugh class B (n = 12)	Child-Pugh class C (n = 4)	QTc < 440 ms (n = 22)	QTc ≥ 440 ms (n = 16)
LV EDD (mm/m²)	28.1 ± 1.9	28.8 ± 2.6	28.9 ± 2.4	28.1 ± 2.7	30.5 ± 3.5	28.7 ± 2.6	29.0 ± 2.7
LV EDVI (mL/m²)	73.8 ± 12.6	73.5 ± 10.0	73.2 ± 10.5	71.1 ± 9	81.9 ± 8.2	72.5 ± 8.5	74.7 ± 12.0
LV ESVI (mL/m²)	27.9 ± 5.7	19.9 ± 4.0‡	19.5 ± 4.0‡	19.7 ± 4.1‡	22.2 ± 4.4	20.5 ± 3.7	19.0 ± 4.5
LV EF (%)	62.1 ± 4.0	69.5 ± 5.2‡	70.6 ± 4.2‡	67.7 ± 7.0†	68.6 ± 1.5	68.9 ± 4.8	70.3 ± 5.7
LV mass (g/m²)	87.0 ± 16.8	117.4 ± 22.5‡	116.4 ± 23.9‡	115.9 ± 23.9‡	127.4 ± 3.9†	116.8 ± 20.0	118.1 ± 26.3
MAP (mmHg)	95.0 ± 5.6	88.9 ± 11.5†	91.5 ± 11.5	89.8 ± 8.0	72.2 ± 7.4‡	94.2 ± 8.8	81.7 ± 11.1‡
HR (bpm)	69.1 ± 5.0	70.8 ± 11.1	70.8 ± 11.6	69.3 ± 11.8	75.3 ± 4.3	70.9 ± 12.1	68.4 ± 10.4
CI (L/min/m²)	3.6 ± 0.7	3.8 ± 0.8	3.8 ± 0.9	3.5 ± 0.4	4.5 ± 0.4	3.7 ± 0.7	3.9 ± 0.8
SVRI(dyne·sec·cm-5/m^2)	2176.4 ± 426.1	1970.8 ± 547.3	2036.9 ± 615.4	2077.4 ± 303.6	1287.4 ± 69.2†	2138.5 ± 559.1	1749.4 ± 443.0*

Abbreviations: LV, left ventricular; EDD, end-diastolic diameter; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; MAP, mean arterial pressure; CI, cardiac index; HR, heart rate; SVRI, systemic vascular resistance index. Statistical analysis: t test between healthy subjects and cirrhotic patients, Bonferroni t test between healthy subjects and Child class patients and t test between cirrhotic patients with QTc ≤ 440 ms and > 440 ms; statistical significance: * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$.

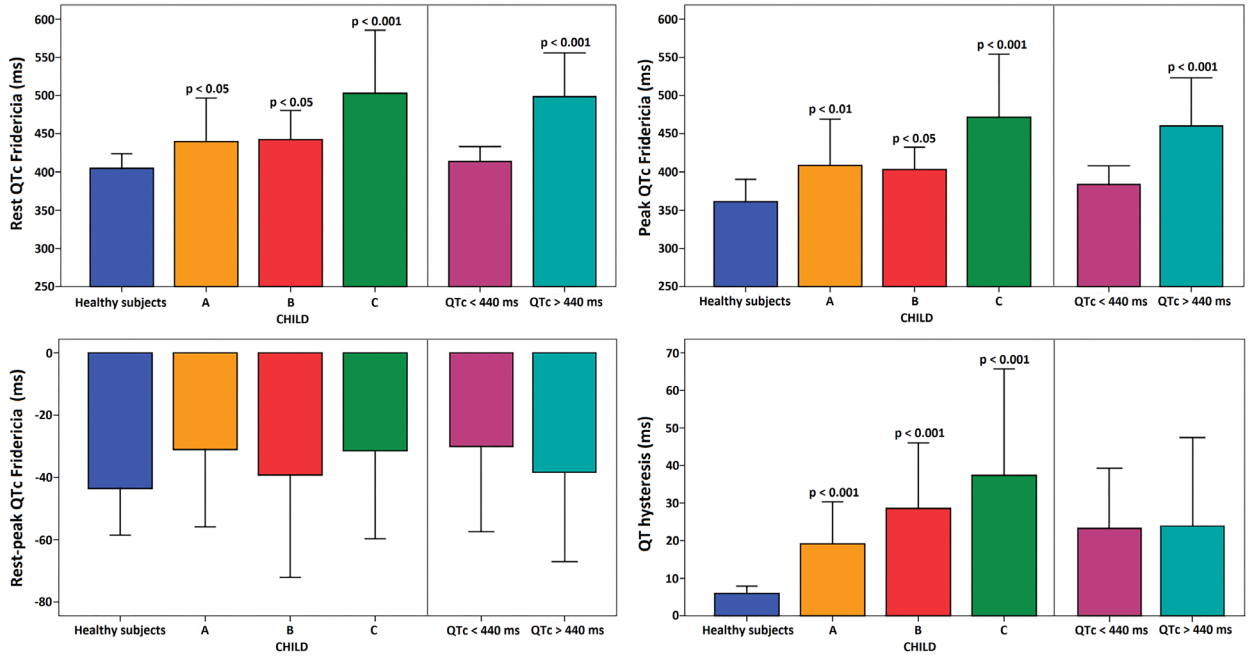

Figure 1 Fridericia-corrected QT-interval behavior and QT hysteresis during exercise. Rest, peak stress and the relative difference Fridericia-corrected QT values and QT hysteresis values are reported as mean ± standard deviation for healthy subjects and cirrhotic patients. Data of cirrhotic patients are displayed by Child-Plough class and baseline Fridericia-corrected QT interval (whether < or > 440 ms).

with respect to predicted maximal HR than in the healthy subjects.

Physiology teaches us the electrical events which underlay the QT interval. The interval between the onset of the Q wave and the beginning of the S wave of the QRS complex on surface ECG corresponds to the initial rapid upstroke of the action potential (AP - phase 0) and the early phase of repolarization (phase 1). The intervals S wave-to- peak of T wave, and peak-to-end of T wave correspond, respectively, to the plateau phase of the AP (phase 2) and to the final repolarization phase (phase 3). The duration of the AP (and, therefore, the duration of QT interval) is mostly affected by alterations of phases 2 and 3. During phase 2, the L-type calcium channel current ($I_{Ca,L}$) plays a dominant role[30]: upregulation of $I_{Ca,L}$ lengthens QT, its downregulation shortens it. During phase 3, the delayed rectifier potassium channel currents [consisting of the rapidly activating (I_{Kr}) and slowly activating (I_{Ks}) channel types] and the inward rectifier current (I_{K1}) take over[31]: upregulation of these currents shortens the QT, their downregulation lengthens the QT.

Also adrenergic drive plays an important role in the modulation of Ca^{2+} and K^+ channels function, via the β_1 adrenoceptors. Kass and Wiegers demonstrated that $I_{Ca,L}$ and K^+ currents are both upregulated by noradrenaline in an experimental model of calf cardiac Purkinje fibers. They found that the net effect on myocytes' repolarization depended on the intensity of the sympathetic stimulation[32]: at high noradrenaline plasma concentrations, the effect on K^+ currents (especially I_{Kr}) was approximately twice as the one elicited on $I_{Ca,L}$.

During periods of increased sympathetic activity such as exercise, I_{Kr} current shortens QT duration at intermediate heart rates in early exercise, the so-called "I_{Kr} zone". Subsequently, starting at 100 beats per minute, recruitment of I_{Ks} current takes over, and QT-interval shortening progresses into peak exercise, persisting into the recovery phase[33]. If cirrhotic patients had decreased expression of potassium currents, as it was suggested in experimental cirrhosis[10], substantial increase in AP duration (and hence increase in QTc duration) during sympathetic activation should be expected[34]. In the present study we describe a non-linear shortening of QTc in the early phase of exercise

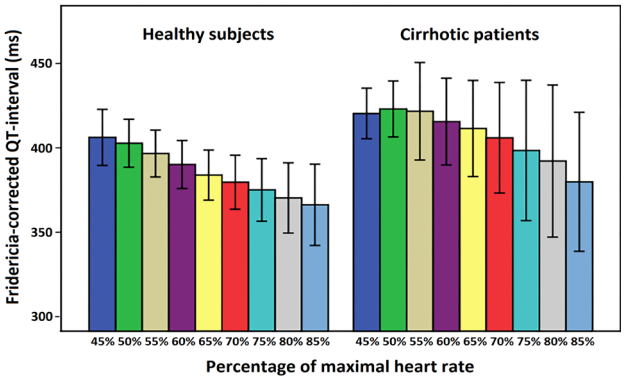

Figure 2 Fridericia-corrected QT-interval behavior in healthy subjects and cirrhotic patients during exercise. QT-interval behavior during exercise is displayed as a function of the percentage of maximal heart rate in healthy subjects (left group of bars) and cirrhotic patients (right group of bars). Bars represent mean ± standard deviation of Fridericia-corrected QT values measured every 5% increase in heart rate over the range 45% to 85% of maximal heart rate.

in cirrhosis. A similar non-linear pattern of QTc behaviour with HR increase during exercise was described in congenital long QT syndrome type 2 that is characterized by impaired I_{Kr}[29].

Increased QT hysteresis seem to be another shared feature of cirrhotic cardiomyopathy and long QT syndrome type 2: QT hysteresis of cirrhotic patients was greater in our study, increased QT hysteresis was demonstrated in patients with long QT syndrome[31] and a greater increase was reported in patients with long QT syndrome type 2.

The hysteresis phenomenon consists of longer QT intervals at a given RR interval while HR is increasing during exercise and shorter QT intervals at the same RR interval when HR is decreasing during recovery. The lag of QT interval adaptation to RR interval changes from peak exercise into recovery has been attributed to alterations in autonomic tone. Specifically, enhanced sympathetic tone and minimal parasympathetic effects characterize late exercise. In contrast, early recovery is characterized by rapid parasympathetic reactivation with

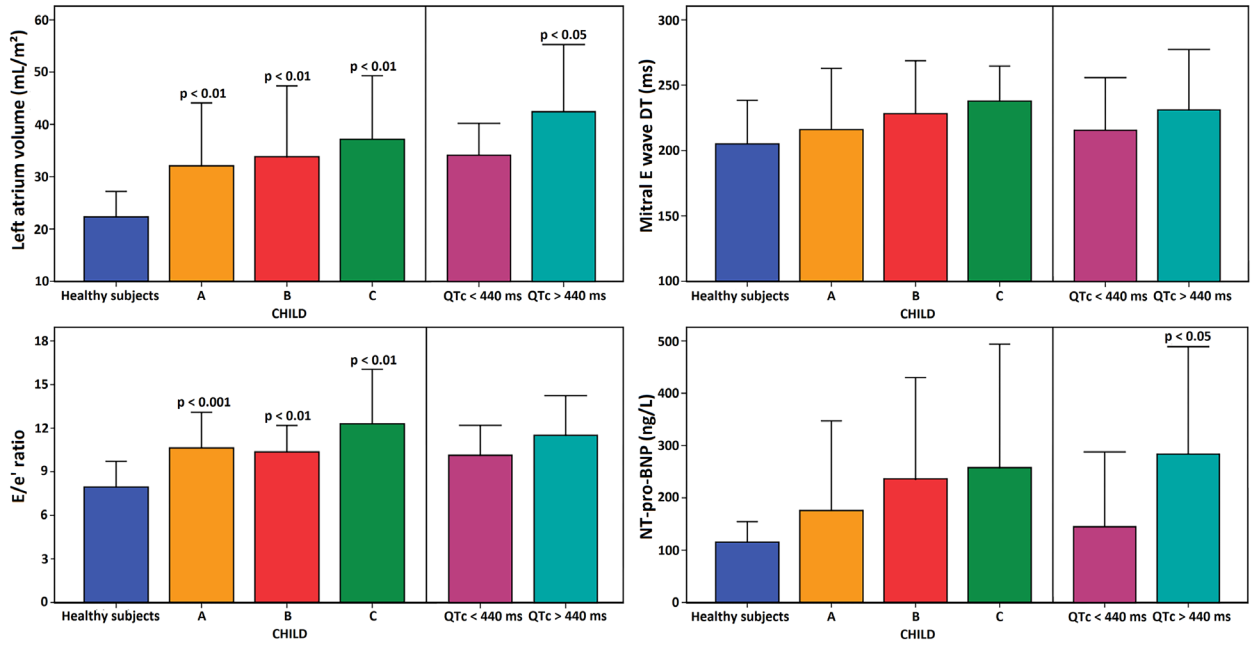

Figure 3 Echocardiographic and hormonal data. Left atrial volume index, mitral E wave deceleration time, mitral E/e' ratio and NT-pro-BNP mean values ± standard deviation are reported for healthy subjects and cirrhotic patients. Data of cirrhotic patients are displayed by Child-Plough class and baseline Fridericia-corrected QT interval (whether < or > 440 ms).

persistent, although declining sympathetic excitation. Evaluation of this QT-RR relationship during exercise and recovery has shown some clinical value in certain situations, such as differentiation between patients with long QT syndrome and patients with borderline QT duration[35].

The results of our study seem consistent with the hypothesis that I_{Kr} impairment characterizes the phenotype of cirrhosis; its clinical evidence is amplified by exercise when the net effect of increased adrenergic drive reflects non-efficiently counterbalanced $I_{Ca,L}$ upregulation.

CONCLUSIONS

During physical exercise, non-linear QTc behavior with increasing HR and greater QT hysteresis observed in cirrhotic patients add new evidence to the working hypothesis that anomalous myocardial repolarization ion currents, together with their abnormal modulation by sympathetic drive changes, may represent an adjunctive character of cirrhotic cardiomyopathy. Only long rest QTc appears correlated to the clinical signs of cirrhotic cardiomyopathy

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