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Original article

Prolongation of the QTc interval in patients with cirrhosis

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SUMMARY

QT interval prolongation predicts severe ventricular arrhythmias and sudden death. The aim of this work was to confirm the prevalence of QT interval prolongation in patients with liver cirrhosis due to alcoholism and chronic hepatitis B or C and define its association with the severity of the disease. Fifty-two patients with cirrhosis (29 due to alcohol abuse and 23 due to chronic hepatitis B or C) were enrolled. In all patients QT interval corrected (QTc) for ventricular heart rate was assessed along with Child-Pugh score. QTc was found prolonged in both groups of patients with alcoholic and postviral cirrhosis (0,471 sec, P=0,0007 and 0,461 sec, P=0,0017 respectively) with no difference between the two groups (P=0,3142). Prolongation of the QTc interval was statistically confirmed in Child-Pugh C and B groups (0,489 sec, P=0,0019 and 0,480 sec, P=0,0002 respectively) but not in Child-Pugh A group (0,445 sec, P=0,4366). These data show that QTc interval prolongation in cirrhotic patients refers to Child-Pugh B and C but is independent from the etiology of cirrhosis.

Key words: QT interval, cirrhosis, alcoholism, chronic hepatitis, hepatitis B, hepatitis C.

INTRODUCTION

The QT-interval represents the length of ventricular electric systole, and its prolongation may provide the substrate for ventricular arrhythmias or sudden death[1-3]. The presence of this alteration has been reported in health and in many congenital and acquired conditions as cardiac disease, electrolyte abnormalities, and many commonly used drugs. Additionally, acquired prolongation of QT interval has been documented in alcoholic liver disease[3], cirrhosis[4] and liver failure[5]. Liver transplantation in the latter group has been shown to reverse this anomaly[6]. The QT prolongation was found to be independent of the etiology of the hepatic disease[7], and positively associated with the severity of the disease as expressed by Child-Pugh score[7,8] in a way that may have prognostic value[7]. However, the cause of prolonged QT interval in liver disease remains obscure.

The aim of this study was to confirm the QTc interval prolongation in a well-defined group of patients with alcoholic and postviral liver cirrhosis and investigate the relevance of this abnormality with the severity of the disease.

MATERIALS AND METHODS

Fifty-two patients with cirrhosis due to alcohol abuse and chronic hepatitis B or C, consecutively seen at two centers participating in the study from April 2000 to September 2002, were enrolled. The diagnosis of cirrhosis was either confirmed histologically or based on clinical and ultrasonographical criteria. Indirect evidence of portal hypertension was ascertained by finding esophageal varices at endoscopy or enlarged portal vein and its collaterals at ultrasonography. The presence ofascites was documented by ultrasonography. Severity of cirrhosis was assessed according to Child-Pugh score. Patients with coronary artery disease, conduction abnormalities or arrhythmias, chronic lung disease, arterial hypertension, thyroid disease and intrinsic renal disease were a priori excluded from the study.

Liver function tests, blood cell count, plasma electrolytes and thyroid hormones were determined by standard laboratory techniques.

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QT interval and corrected QT (QTc) were read from a 12-lead electrocardiogram recorded at 50 mm/s. QT was measured from the beginning of the QRS complex until the termination of the T-wave. Since heart rate was a major determinant of the duration of ventricular repolarization, QT interval had to be corrected for the heart rate. hi this study, QTc (QT interval corrected for heart rate) was calculated as the ratio of the calculated QT interval in seconds to the square root of RR interval in seconds (Bazett's formula). This method was selected despite its decreased accuracy regarding correction in order to obtain comparable data with previously reported studies[9,10].

Patients were divided in two groups according to the underlying cause of cirrhosis (alcohol and postviral) as well as to three groups according to the severity of the disease (Child-Pugh C, B and A) (Table 1). Every group was checked for biases referring to sex ratio and mean age (Table 2). The Kolmogorov-Smimov test was applied on all groups to ensure a statistically accepted correlation of curves to standard curve.

Statistical analysis for confirmation of the QTc prolongation was separately performed on all five groups using the Students' t-test for single means accepting as reference value 0,440 sec. The bi-directional Student's t-test for two independent variables was performed between alcohol and postviral group as well as between Child-Pugh C, B and A groups for estimation of possible differences between them. The level of statistical significance was set to P=0,01.

RESULTS

QTc was found prolonged in both groups of patients with alcoholic and postviral cirrhosis (0,471 sec, P=0,0007 and 0,461 sec, P=0,0017 respectively) with no difference between the two groups (P=0,3142).

Prolongation of the QTc interval was statistically confirmed in Child-Pugh C and B groups (0,489 sec, P==0,0019 and 0,480 sec, P=0,0002 respectively) but not in Child-Pugh A group (0,445 sec, P=0,4366) (Figure 1). There was a statistically significant difference between Child-Pugh group C and A (P=0,0004) as well as between B and A (P=0,0010) but not between B and C (P= 0,5453).

When the patients of Child-Pugh A group were divided according to the etiology of cirrhosis, the QTc interval did not show statistically significant prolongation in neither alcoholic (0,443 sec, P=0,773) nor postviral (0,449 sec, P=0,151). Similarly, there was no difference between the two subgroups (P=0,601).

A bias referring to sex ratio within Child-Pugh groups (P=O,036) could be argued to intervene in the results. Indeed, there is a clear-cut influence of sex on the QT interval[11]. Nevertheless, the Child-Pugh C group, which delineates, consists of only 10 patients and its potent confusing contribution to the final result is debatable though obscure.

DISCUSSION

Several investigators have previously confirmed the prolongation of the QT interval in cirrhosis[7,8]. This anomaly was unrelated to the etiology of cirrhosis but was positively related with the severity of the disease as expressed by Child-Pugh score. Other variables (prothrombin time, serum albumin, serum bilirubin, hemoglobin, serum sodium, mean arterial pressure and plasma renin, plasma aldosterone and plasma atrial natriuretic factor) were not independently related with QT prolongation[7].

The QTc prolongation may reflect electrolyte abnormalities and especially those of calcium, hyperbilirubinemia, myocardial ischaemia, drugs and alcohol toxicity and hypersensitivity of the autonomous nervous system. Additionally, gender influences QT probably due to hormone differences. Some of these factors may be present in a cirrhotic patient, but the fact that QT prolongation has been also detected in early-stage cirrhosis (Child-Pugh A) is only partially explained by the above changes.

Our study confirms the QTe prolongation in two subgroups of cirrhotic patients representing the two major causes of cirrhosis: alcoholic and postviral. The results were similar in a way that suggests the independence of QTg prolongation from the etiology of cirrhosis. This may imply that the QTc prolongation m cirrhosis is a phenomenon, which derives from the pathophysiology of cirrhosis itself and does not reflect a primary abnormality related to certain causes of cirrhosis.

Additionally, our study focuses on the relationship of QTc prolongation with the severity of the disease. Although it fails to statistically confirm QTc prolongation for Child-Pugh A cirrhotic patients, the statement becomes true for Child-Pugh B and C cirrhotic patients. It is interesting that B and C group do not have any difference between them. A possible explanation for these results is that the QT prolongation may depend on factors absent in the Child-Pugh score, arising at later stages of cirrhosis and significantly contributing in the evolution of the disturbance.

Table 1. Raw data of the patients enrolled in the study.

Name	sex	age	child-pugh	type	QT	RR	QTc
K.S.	M	76	B	HBV	0,39	0,73	0,456
T.P.	F	81	C	HCV	0,41	0,71	0,487
N.N.	M	65	A	ALC	0,41	0,88	0,437
S.I.	M	83	B	HBV	0,55	1,03	0,542
T.N.	M	60	A	HBV	0,46	1,03	0,453
G.K.	M	39	A	HCV	0,46	1,17	0,425
T.T.	M	72	A	HCV	0,43	0,88	0,458
M.T.	F	71	A	HBV	0,41	0,80	0,458
M.A.	M	66	B	HBV	0,45	0,94	0,464
Z.A.	F	65	A	HCV	0,43	0,91	0,451 ·
B.A.	F	51	A	HBV	0,44	0,88	0,469
K.A.	M	72	B	HBV	0,37	0,53	0,508
C.S.	M	57	A	HBV	0,43	1,06	0,418
G.E.	F	45	C	HBV	0,38	0,68	0,461
A.N.	M	66	B	ALC	0,38	0,68	0,461
M.A.	M	37	B	ALC	0,37	0,48	0,534
M.C.	M	40	A	ALC	0,45	1,02	0,456
K.T.	M	66	A	ALC	0,50	1,11	0,475
O.G.	M	39	B	ALC	0,45	0,98	0,455
K.A.	F	60	C	ALC	0,42	0,71	0,498
T.C.	M	71	A	ALC	0,37	0,71	0,439
M.P.	M	62	C	ALC	0,50	0,96	0,510
K.G.	F	57	B	ALC	0,48	1,03	0,473
A.P.	M	73	C	ALC	0,45	0,70	0,538
K.M.	F	48	C	ALC	0,36	0,56	0,481
C.C.	M	50	B	ALC	0,52	1,11	0,494
Z.C.	M	67	A	ALC	0,39	0,65	0,484
V.N.	M	56	C	ALC	0,40	0,90	0,422
A.I.	M	46	A	ALC	0,41	0,75	0,473
G.P.	M	66	B	ALC	0,47	0,73	0,550
C.D.	M	70	C	ALC	0,39	0,56	0,521
T.A.	M	68	C	ALC	0,35	0,60	0,452
A.P.	M	55	B	ALC	0,46	0,69	0,554
L.A.	M	49	A	ALC	0,45	0,95	0,462
R.K.	M	65	A	ALC	0,38	0,96	0,388
L.G.	M	53	C	ALC	0,43	0,69	0,518
G.T.	M	56	A	HBV	0,44	0,89	0,466
A.K.	M	55	A	ALC	0,48	1,27	0,426
T.I.	F	70	B	ALC	0,42	0,83	0,461
I.M.	M	50	A	HBV	0,42	1,02	0,426
P.A.	F	52	B	HBV	0,41	0,83	0,450
C.E.	M	65	A	ALC	0,46	1,04	0,451
M.A.	F	68	A	HBV	0,40	0,78	0,452
M.G.	M	56	B	HBV	0,44	1,00	0,440
A.X.	M	68	B	ALC	0,41	0,89	0,435
M.E.	M	68	A	HBV	0,42	0,96	0,429
S.G.	F	71	B	HBV	0,42	0,78	0,476
Z.A.	M	81	B	HBV	0,46	1,05	0,449
Z.E.	F	68	B	HCV	0,48	1,03	0,473
S.K.	M	66	B	ALC	0,41	0,87	0,440
K.G.	M	63	A	HBV	0,43	0,79	0,484
S.A.	M	61	A	ALC	0,37	0,94	0,382

Table 2. Demographic profile of the groups of patients enrolled in the study

Group	Number of patients	Sex ratio (females/males)	Mean age±SD
Alcoholic cirrhosis	29	4/25	63,96±11,78
Postviral cirrhosis	23	9/14	59,10±10,22
Child-Pugh A cirrhosis	23	4/19	59,57±9,76
Child-Pugh B cirrhosis	19	5/14	63,11±12,61
Child-Pugh C cirrhosis	10	4/6	61,60±11,48

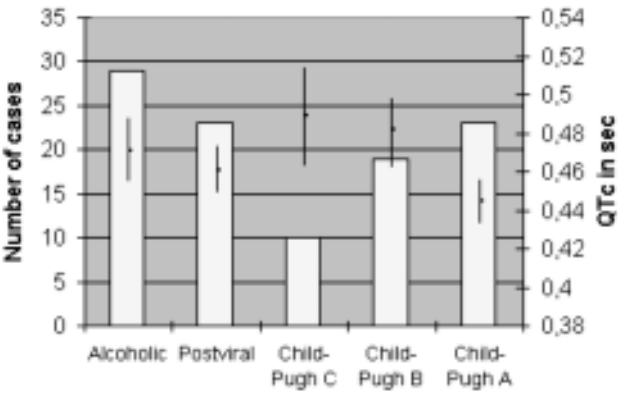

Figure 1. Chart depicting sample size (left y axis) and QTc ± 95% confidence limits (right y axis) for each group.

The above statement may be true in case of autonomous neuropathy, which is present in cirrhosis albeit its underlying pathophysiology is still poorly understood. Nevertheless, a recent study failed to show a direct dependency of QT prolongation from autonomie heart function[8].

In conclusion, the QTc interval is elongated in Child-Pugh B and C cirrhotic patients independently of the etiology of cirrhosis. The reason for this abnormality remains unclear. Nevertheless, the additional risk for severe arrhythmias and sudden death should be evaluated before any pharmaceutical or iatrogenic intervention in these patients.

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