Original Research Paper

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Internal Medicine

ELECTROCARDIOGRAPHIC FINDINGS IN CIRRHOSIS AND CHRONIC LIVER DISEASE AND THEIR ASSOCIATION WITH THE SEVERITY OF DISEASE.

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INTRODUCTION:

Liver cirrhosis is associated with a wide range of cardiovascular abnormalities including hyperdynamic circulation, cirrhotic cardiomyopathy, and pulmonary vascular abnormalities [1]. In patients with advanced cirrhosis, physical and/or pharmacological stress may reveal a reduced cardiac performance with systolic and diastolic dysfunction and electrophysical abnormalities termed cirrhotic cardiomyopathy [2]. The risk of prevalence of cardiac disease has been rekindled as orthotopic liver transplantation is being more frequently done[3]. The recognition of clinical and subclinical cardiac disease is of paramount importance to ensure that the perioperative mortality is avoided. An ECG can be a useful tool to recognize cardiac involvement in cirrhosis. It is a simple inexpensive routine investigation. It is widely available and can be used as a tool for the purpose of establishing cardiac involvement in cases of cirrhosis. The objective of this research was to study the clinical profile of the patients with chronic liver disease, to find out the incidence of electrocardiographic changes in these patient, and also to look for relation of the electrocardiographic changes in reference to the severity of the chronic liver disease.

Purpose/Aim:

To study ECG changes in cirrhosis. A study conducted over a period of two years in patients of Index Medical College admitted to the department of General Medicine with a diagnosis of **cirrhosis/chronic liver disease** and to see ECGs and see their correlation with the disease severity.

Methods:

A hundred patients with **cirrhosis/chronic liver disease** were examined. The ECGs were examined for rhythm disturbances, PR prolongation, voltage, ST-T changes. A correlation was made between the severity of liver cirrhosis and ECG changes. The severity of **cirrhosis/chronic liver disease** was determined by Child Pugh Classification [4].

Inclusion Criteria

Patients Of Cirrhosis/Chronic Liver Disease

Patients of chronic liver disease diagnosed by

1. History jaundice for more than six month and signs of cirrhosis of liver e.g. hematemesis or melena or ascites, or splenomegaly.
2. Altered LFT for more than six months
3. Ultrasound showing shrunken or nodular liver with features of portal hypertension
4. Biopsy if available showing chronic liver disease or cirrhosis.

Exclusion Criteria

a. Patients with primary cardiac or pulmonary disease
b. Diagnosed hypertensive patients
c. Anemia (Hb less than 8 gm %)
d. Diabetes mellitus
e. Post-partum and pregnancy
f. Uremic cardiomyopathy

Following Investigation Were Included In The Study

a. Complete blood count with ESR.
b. Blood urea, serum creatinine, serum sodium., serum potassium and serum calcium.
c. Liver function test
d. Lipid profile: Serum cholesterol, triglyceride, HDL, LDL, VLDL
e. Blood sugar fasting and postprandial
f. HBsAg
g. HCV
h. HIV
I. Urine routine/ microscopy
j. Slit-lamp examination for KF ring
k. Alphafeto protein (AFP)
l. US Abdomen
m. X-ray chest PA view
n. ECG

A twelve lead electrocardiogram was obtained. Electrocardiographic analysis was made for all patients on admission. A calibrated electrocardiographic device was used with a paper speed of 25 mm/second and standard amplitude of 10 mm /mV. The ECG tracings were separately assessed by the investigators by manual measurements and calculations.

The following parameters were evaluated:

1. Rate
2. Rhythm
3. P wave morphology
4. PRinterval
5. QRS amplitude in all limb (Lead I, Lead II, Lead III, aVL, aVF and aVR) and precordial (V1-V6) leads was determined. Criteria for low-voltage QRS was amplitude of less than 0.5 mV in one of the limb leads and less than 1 mV in one of the precordial leads [27]. Mean values for QRS voltage in the limb leads and QRS voltage in the precordial leads were also calculated;

6. QT interval, measured in leads lead II and V6, from the beginning of the QRS interval to the end of the T wave. The lead with the longest QT interval was then considered, and the average QT interval from three consecutive heartbeats was recorded. Corrected QT (QTc) was calculated using Bazzet's formula: QTc= QT/√ RR.(all in seconds) [26]. QT prolongation was defined as a corrected length interval of over 440 ms in male patients and over 460 ms in female patients.

7. Tpe was calculated in all the leads using the tangent method, and a mean value was recorded. The peak was measured at the highest amplitude of the T wave relative to the isoelectric line. The T-end was defined as the intersection of the downslope of the T wave with the isoelectric line [28]. If there was a U wave present, the end of the T wave was considered at the lowest point between the T and the U waves. The normal Tpe was 50 to 90 ms.[30]

Statistical Analysis

Data were evaluated using statistical software SPSS 18.0 (SPSS Inc., Chicago, IL, USA). The primary endpoints for the study were the evaluation of electrocardiographic changes, estimation of QT prolongation and Tpe shortening. Numerical variables were expressed as mean +/− standard deviation, and ANOVA test was used to compare between groups, with statistically significant p-values of less than 0.05.

RESULTS

A total number of 100 patients chronic liver disease and with cirrhosis were studied. Seventyone of the hundred patients were male (71%) and the remaining 29 were female (29%). The most commonly affected age group was 50 to 59 years in both male and female patients. This age group accounted for 57 % of total patients. Table 1. Overall the most common cause of cirrhosis was alcoholic cirrhosis (47%) followed by hepatitis B, (40%) and hepatitis C (4%). In the remaining patients, the etiology was unknown (9%).Table -2. However no case of alcoholic cirrhosis was found in female patients. Table -3

Table 1 Age and sex distribution of the study population

Age in years	Male	Female	Total
30 to 39	2	0	2
40 to 49	26	6	32
50 to 59	39	18	57
60 to 69	3	4	7
Above 70	1	1	2
Total	71	29	100

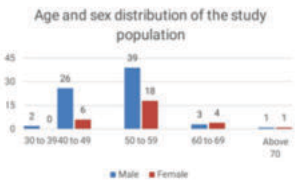


Table 2 Etiology of Cirrhosis

Alcohol	47
Hepatitis B	39
Hepatitis C	5
Other etiologies	9

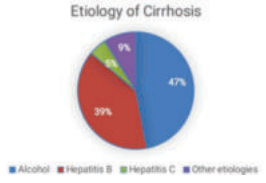
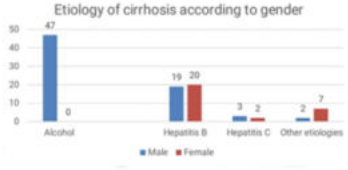


Table 3 – Etiology of cirrhosis according to gender.

Etiology	Gender		
	Male	Female	Total
Alcohol	47	0	47
Hepatitis B	19	20	39
Hepatitis C	3	2	5
Other etiologies	2	7	9
Total	71	29	100



The 100 patients were divided into 3 groups according to their Child–Pugh classification: 14 patients (14%) in Class A, 38 patients (38%) in Class B and 48 patients (48%) in Class C (Table -4).

Various physical findings as compared between patients in the three Child Pugh classes were also compared (Table 6). The heart rate, which increased with progression of Child class severity. As seen in Table 6 the mean heart rate rose in more severe stages of disease. Class A: 82 ; Class B: 85.5; Class C: 90.04 beats/min, *p* insignificant). The mean arterial pressure was found to be decreased in a significant manner according to the severity of chronic liver disease .

Table 4 – Child–Pugh classification and etiology of cirrhosis

Etiology	Child–Pugh Class		
	A	B	C
Alcohol	4	19	24
Hepatitis B	8	12	20
Hepatitis C	1	2	1
Other etiologies	1	5	3

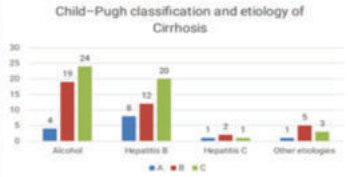
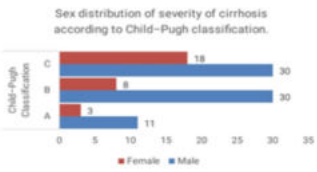


Table 5 – Sex distribution of severity of cirrhosis according to Child–Pugh classification.

Etiology	Child–Pugh Class			
	A	B	C	Total
Male	11	30	30	71
Female	3	8	18	29
Total	14	38	48	100



In this study it was observed there was statistically significant hypovoltage in all electrocardiographic leads except aVF, V3 and V5. Table-7-

Table 6 – Comparison of physical findings in cirrhotic patients based on Child–Pugh classification.

	Class A N=14	Class B N=38	Class C N=48	P value	Sig.
	Mean ± SD	Mean ± SD	Mean ± SD		
Heart Rate	82.07 ± 10.9	85.55 ± 13.88	90.04 ± 11.18	0.61	NS
Blood Pressure (MAP)	77.29 ± 6.64	70.95 ± 6.97	70.08 ± 6.34	0.002	Sig.

	Class A N=14	Class B N=38	Class C N=48
Ascites (mild)	10 (71.4 %)	18 (47.3 %)	0 %
Ascites (moderate)	0 %	20 (52.6 %)	16 (33.3 %)
Ascites (severe)	0 %	0 %	32 (66.7 %)
No ascites	4 (28.6 %)	0 %	0 %
Encephalopathy	0 %	6 (15.8 %)	44 (91.7 %)

Table 7 – Comparison of electrocardiographic findings in cirrhotic patients based on Child–Pugh classification. (Voltage criteria)

Variable	Class A N=14	Class B N=38	Class C N=48	P value	Sig.
	Mean ± SD	Mean ± SD	Mean ± SD		
I	7.43 ± 0.65	5.11 ± 0.80	4.98 ± 0.79	0	Sig.
II	7.79 ± 0.97	5.05 ± 0.93	4.92 ± 0.54	0	Sig.
III	7.57 ± 0.65	5.08 ± 0.67	4.58 ± 0.58	0	Sig.
aVR	8.86 ± 2.18	5.34 ± 1.60	4.52 ± 0.58	0	Sig.
aVL	7.00 ± 0.78	4.53 ± 0.60	4.25 ± 0.48	0	Sig.
aVF	4.57 ± 0.85	4.26 ± 0.50	4.23 ± 0.47	0.119	NS.
V1	9.14 ± 1.17	8.61 ± 0.55	8.60 ± 0.54	0.022	Sig.
V2	8.79 ± 0.97	8.37 ± 0.55	8.27 ± 0.82	0.08	NS
V3	9.21 ± 1.12	8.18 ± 0.77	8.65 ± 0.89	0.001	Sig.
V4	9.07 ± 1.14	8.63 ± 0.94	8.44 ± 1.31	0.187	NS
V5	9.5 ± 1.29	8.42 ± 0.68	8.27 ± 0.84	0	Sig.
V6	10.21 ± 1.31	8.61 ± 0.75	7.63 ± 1.00	0	Sig.

QTc-interval increased in proportion to severity of C Child class. Child class demonstrated a prolonged QTc-interval (35.7 % in Child class A, 50% in Child class B and 52% in Child class C, (P 0.003). In this study QTc increases with severity odds ease and in Class 3 The QTc is most prevalent in the class 3 patients .

Tpe was found to be below 50 in 14 % patients in class A 45% patients in class B and in Class C in 58 % patients the Tpe was found to be below 50. It was clear that percentage of patients with low Tpe increased with severity of disease. Table-8.

Table-8 Comparison of other electrocardiographic criteria

	Child Pugh Class A	Child Pugh Class B	Child Pugh Class C	P -value	Significance
QRS duration in milliseconds	85 ± 14	83 ± 12	84 ± 17	0.901	Non Significant.
QTc in milliseconds	435.10 ± 26.63	459.70 ± 38.60	460.01Significant.5	0.044	Significant.
Criteria for prolonged QT	5 (35.7 %)	19 (50%)	24 (52 %)	NA	NA
Mean Tpe	72.22 ± 30.78	71.88 ± 23.74	60.01 ± 20.87	0.044	Significant.
Criteria for shortened Tpe	2 (14 %)	17 (45 %)	28 (58 %)	NA	NA

DISCUSSION:

Cirrhosis is a condition marked by the diffuse transformation of the entire liver into regenerative parenchymal nodules surrounded by fibrous bands and variable degrees of vascular (often portosystemic) shunting [5]. Cardiac dysfunction in cirrhotic patients, which was once believed to be the result of alcoholic toxicity, is now considered because of the disease process related to the liver. [6,7,8]. Interactions between the functioning of the heart and the liver have been described, with heart diseases affecting the liver, liver diseases affecting the heart, and conditions that simultaneously affect both[19].

Prolongation of QT-interval is a common electrocardiographic (ECG) finding in cirrhotic patients that is an indication of extended repolarization phase prolongation in cardiac muscle [9]. The QT interval varies from daytime to night time due to the diurnal variations in autonomic tone, circulatory status and oxygen demands[10]. The minimum value of the corrected QT (QTc), rather than the maximum value, shows a significant diurnal variation[11]. Patients with liver cirrhosis exhibit intense system activity and hyperdynamic circulation which brings a high cardiovascular output and decreased vascular resistance. These progressions may actuate myocardial redesigning which may lead to changes in systolic function, diastolic dysfunction and cardiomyopathy. [12, 13,14]. Several electrophysiological mechanisms have been suggested for cardiac contractility conduction abnormalities, including low beta-adrenoceptor density, post-receptor

signal defects, abnormal excitation-contraction coupling, and molecular abnormalities [15,16]. Density and sensitivity of beta-adrenoreceptors are reduced in patients with cirrhosis, and calcium channel transport function is also affected [17,18]. Abnormalities of ventricular repolarization seen more in more advanced stages of chronic liver disease. The Tpe corresponds to the transmural dispersion of repolarization, and is a predictor of ventricular arrhythmias and sudden cardiac death. Liver cirrhosis affects ventricular repolarization via electrolyte imbalances, impaired autonomic function, subclinical cardiomyopathy, reduced β-adrenergic receptor function, post-receptor pathway defects, altered physical properties of myocyte plasma membranes, elevated levels of cardiotoxins, ion channel remodeling, portosystemic shunting, and systemic circulatory disturbances[19]. Tpe is a useful parameter in evaluating the transmural dispersion of repolarization [29] and a marker for ventricular arrhythmogenesis. The Tpe/QT ratio is also used as an index of ventricular arrhythmogenesis[9]. Several published investigations demonstrated that a longer T-peak to T-end interval (Tpe) implies increased risk for ventricular tachyarrhythmia (VT/VF) and mortality. [28 .]A prolonged Tpe interval and Tpe/QT interval ratio have been reported in patients with chronic hepatitis B infection, indicating an increased ventricular repolarization heterogeneity[20]. Liver cirrhosis affects ventricular repolarization via electrolyte imbalances, impaired autonomic function, subclinical cardiomyopathy, reduced β-adrenergic receptor function, post-receptor pathway defects, altered physical properties of myocyte plasma membranes, elevated levels of cardiotoxins, ion channel remodeling, portosystemic shunting, and systemic circulatory disturbances[10,21,22,23,24,25].

In patients with cirrhosis there is a statistically significant incidence in the ECG of prolonged QTc, hypovoltage and shortened Tpe. [32]. Studies suggest that QT prolongation can be found in more than 50% of patients with cirrhosis [31]. In our study the QT prolongation was found in 52% patients having class C Child Pugh disease and it was 50% in and 37.5 % in class B and A Child Pugh disease respectively. A direct association between minimum Tpe and negative outcome of the patients suggests that this is an important prognostic marker in CCM [32]. In this study we found the that Tpe decreased more in advanced deompensation of liver disease.

CONCLUSIONS :

Subclinical cirrhotic cardiomyopathy may exist silently for many years[32]. cirrhotic cardiomyopathy may have a huge impact on the prognosis of patients with cirrhosis.

As the ECG changes appear early in the evolution of cirrhotic cardiomyopathy a regular follow-up monitoring of ECGs along with standard monitoring of laboratory parameters of liver cirrhosis may identify patients with higher risks. In the ECG the parameters such as QTc, QRS voltage and Tpe appear to be well correlated to the severity of the liver disease. Therefore the ECG may be used as diagnostic markers in the initial cardiologic evaluation of cirrhotic patients to detect the cases of cirrhotic cardiomyopathy early.

REFERENCES:

1. Waleed K. Al-Hamoudi. Cardiovascular Changes in Cirrhosis: Pathogenesis and Clinical Implications; Saudi J Gastroenterol. 2010 Jul; 16(3): 145–153.
2. Maneerat Chayanupatkul . Cirrhotic cardiomyopathy: review of pathophysiology and treatment. ; Hepatol Int. 2014;8(3):308-315.
3. Giuseppina Pisano. Cardiovascular risk after orthotopic liver transplantation, a review of the literature and preliminary results of a prospective study.; World J Gastroenterol. 2016 Oct 28; 22(40): 8869–8882.
4. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973 Aug;60(8):646-9.
5. Pathologic Basis of Disease Robbin 9th edition.
6. Y.Y. Yang, H.C. Lin, The heart: pathophysiology and clinical implications of cirrhotic cardiomyopathy, Journal of the Chinese Medical Association 75 (2012) 619–623.
7. J.S. Bal, P.J. Thuluvath, Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation, Liver International 23 (2003) 243–248
8. M. Bernardi, S. Calandra, A. Colantoni, et al., Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors, Hepatology 27 (1998) 28–34
9. Mozos I. Arrhythmia risk in liver cirrhosis. World J Hepatol 2015; 7(4): 662-672
10. Zardi EM, Abbate A, Zardi DM, Dobrina A, Margiotta D, Van Tassell BW, Afeltra A, Sanyal AJ. Cirrhotic cardiomyopathy. J Am Coll Cardiol. 2010;56:539-549.
11. M Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. J Clin Invest. 1953;32:1025-1033.
12. Lantelme P, Khettab F, Custaud MA, Rial MO, Joanny C, Gharib C, Milon H. Spontaneous baroreflex sensitivity: toward an ideal index of cardiovascular risk in hypertension? J Hypertens, 2002, 20(5):935-944.
13. Okada N, Takahashi N, Yufu K, Murozono Y, Wakisaka O, Shinohara T, Anan F, Nakagawa M, Hara M, Saikawa T, Yoshimatsu H. Baroreflex sensitivity predicts cardiovascular events in patients with type 2 diabetes mellitus without structural heart disease. Circ J, 2010, 74(7):1379-1383.
14. Yufu K, Takahashi N, Okada N, Wakisaka O, Shinohara T, Nakagawa M, Hara M, Yoshimatsu H, Saikawa T. Gender difference in baroreflex sensitivity to predict cardiac and cerebrovascular events in type 2 diabetic patients. Circ J, 2011, 75(6):1418-1423.
15. Liu H, Song D, Lee SS. Cirrhotic cardiomyopathy. Gastroenterol Clin Biol, 2002, 26(10): 842-847.
16. Zavecz JH, Bueno O, Maloney RE, O'Donnell JM, Roerig SC, Battarbee HD. Cardiac excitation-contraction coupling in the portal hypertensive rat. Am J Physiol Gastrointest Liver Physiol, 2000, 279(1):G28-39.
17. Henriksen JH, Bendtsen F, Hansen EF, Moller S. Acute non-selective beta-adrenergic blockade reduces prolonged frequency-adjusted Q-T interval (QTc) in patients with cirrhosis. J Hepatol, 2004, 40(2):239-46.
18. Grose RD, Nolan J ,Dillon JF, Errington M, Hannan WJ, BouchierI A, et al. Exercise-induced left ventricular dysfunction in alcoholic and non-alcoholic cirrhosis. J Hepatol, 1995, 22(3):326- 332.
19. Mozos I, Costea C, Serban C, Susan L. Factors associated with a prolonged QT interval in liver cirrhosis patients. J Electrocardiology 2011; 44: 105-108
20. Demir C, Demir M. Evaluation of Tp-e interval and Tp-e/QT ratio in patients with chronic hepatitis B. Prague Med Rep 2013; 114: 239-245
21. Wong F. Cirrhotic cardiomyopathy. Hepatol Int 2009; 3: 294-304
22. Genovesi S, Prata Pizzala DM, Pozzi M, Ratti L, Milanese M, Pieruzzi F, Vincenti A, Stella A, Mancia G, Stramba-Badiale M. QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium. Clin Sci (Lond) 2009; 116: 851-859.
23. Ytting H, Henriksen JH, Fuglsang S, Bendtsen F, Møller S. Prolonged Q-T(c) interval in mild portal hypertensive cirrhosis. J Hepatol 2005; 43: 637-644.
24. Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. J Hepatol 2006; 44: 994-1002
25. Møller S, Hove JD, Dixen U, Bendtsen F. New insights into cirrhotic cardiomyopathy. Int J Cardiol 2013; 167: 1101-1108
26. Kowalski, H.J.; Abelmann, W.H. The cardiac output at rest in Laennec's cirrhosis. J. Clin. Investig. 1953, 32, 1025–1033.
27. Madias, J.E. Low QRS voltage and its causes. J. Electrocardiol. 2008, 41, 498–500.
28. Rosenthal, T.M.; Masvidal, D.; Abi Samra, F.M.; Bernard, M.L.; Khatib, S.; Polin, G.M.; Rogers, P.A.; Xue, J.Q.; Morin, D.P. Optimal method of measuring the T-peak to T-end interval for risk stratification in primary prevention. EP Eur. 2018, 20, 698–705.
29. Arteyeva, N.V.; Goshka, S.L.; Sedova, K.A.; Bernikova, O.G.; Azarov, J.E. What does the T(peak)-T(end) interval reflect? An experimental and model study. J. Electrocardiol. 2013, 46, 296.e1–296.
30. Hasan Koca et al; What is the Normal Value of Tpe Interval and Corrected Tpe Interval ? Acta Medica 2020; 51(4): 10-15
31. Pourafkari, L.; Ghaffari, S.; Nazeri, L.; Lee, J.B.; Masnadi-Shirazi, K.; Tajlil, A.; Nader, N.D. Electrocardiographic findings in hepatic cirrhosis and their association with the severity of disease. Cor et Vasa 2017, 59, e105–e113.
32. Letitia Toma, Adriana Mercan Stanciu, Anca Zgura, Nicolae Bacalbasa, Camelia Diaconu and Laura Iliescu; Electrocardiographic Changes in Liver Cirrhosis—Clues for Cirrhotic Cardiomyopathy. Medicina 2020, 56, 68; doi:10.3390/medicina56020068 www.mdpi.com/journal/medicina.