Journal of Advances in Medicine and Medical Research

24(8): 1-7, 2017; Article no.JAMMR.37987
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Study of Myocardial Dysfunction in Patients with Cirrhosis of Liver

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Authors' contributions

This work was carried out in collaboration between all authors. Author LD designed the study. Author PKM helped data collection, statistical analysis and wrote the manuscript. Authors JRM and LKM helped in literature search. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2017/37987
Editor(s):
(1) Georgios Tsoulfas, Assistant Professor of Surgery, Aristoteleion University of Thessaloniki, Thessaloniki, Greece.
Reviewers:
(1) Ramesh Gurunathan, Monash University, Australia.
(2) Nasser Mousa, Mansoura University, Egypt.
Complete Peer review History: http://www.sciencedomain.org/review-history/22105

Original Research Article

Received 5th November 2017
Accepted 25th November 2017
Published 30th November 2017

ABSTRACT

Aim: To evaluate the myocardial dysfunction in patients with liver cirrhosis and its relationship with the aetiology and severity.
Study Design: Cross sectional study.
Methodology: A study was carried out in the Department of General Medicine in MKCG Medical college, Odisha between 2014-2016. After explaining the nature of study and obtaining proper consent 60 patients in the age group of 21-65 years fulfilling the inclusion criteria were included in the study. Out of 60 cases of liver cirrhosis 46 were alcoholic and 14 non-alcoholic. A thorough cardiac evaluation was done with recording of ECG and echocardiography findings.
Results: 1) Diastolic dysfunction was found in 19 (32%) cases of cirrhosis of liver out of which 15 were alcoholic and 4 were non alcoholic. 2) Systolic dysfunction was present in 6 (10%) cases and all of them were alcoholic. 3) Prolonged QTc interval was found in 27 (45%) cases of liver cirrhosis. The difference of mean QTc interval between patients of Child Pugh stage A, B, C was statistically significant.(p-value <0.05). 4) The difference of E/A ratio and that of decelearion time between

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alcoholic and non-alcoholic group is not statistically significant. (p value >0.05) 5) the difference of E/A ratio and that of deceleration time between patients of Child pugh A, B and C is not statistically significant. (p value>0.05).

Conclusion: Diastolic dysfunction was present in 32% cases which is not related of severity and etiology of cirrhosis of liver. Systolic dysfunction was present in 10% cases which could be related to etiology of alcohol consumption. Prolongation of QTc interval is related to disease severity. However echocardiographic parameters of diastolic dysfunction have no relation to aetiology and severity of disease.

Keywords: Cirrhotic cardiomyopathy; diastolic dysfunction; QTc interval.

1. INTRODUCTION

Cirrhosis is associated with a hyperdynamic circulatory state, characterized by an increase in cardiac output and a decrease in peripheral vascular resistance which may give rise to cardiac dysfunction [1,2]. The precise mechanism leading to systemic vasodilatation in advanced cirrhosis is unclear, however, several humoral substances such as nitric oxide, adrenomedullin, natriuretic peptides, cytokines, hydrogen sulphide, endothelins and endocannabinoids have been identified as possible mediators [2,3].

Cirrhotic cardiomyopathy (CCM) is defined as cardiac dysfunction in patients with liver cirrhosis characterized by impaired contractile responsiveness to stress, diastolic dysfunction, electrophysiological abnormalities in the absence of known cardiac disease [4]. Overt heart failure is not a feature of CCM.

Although the presence of cardiomyopathy in cirrhotic patients has been described since 1960s, it had been largely attributed to alcoholic cardiotoxicity [5]. Only in the last 2 decades it has been shown that cardiac dysfunction is also present in nonalcoholic cirrhosis and is characterized by depressed cardiac contractility in response to stimuli. Blendis L and Wong F introduced the term “cirrhotic cardiomyopathy” to describe this cardiac dysfunction in patients with liver cirrhosis [6,7].

The pathophysiological background of the diastolic dysfunction in cirrhosis is the increased stiffness of the myocardial wall which is often caused by myocardial hypertrophy and fibrosis due to activation of the renin angiotensin aldosterone system (RAAS) [8]. Subendothelial edema and increased interstitial collagen deposition play a further role in the decreased ability for relaxation [9,10,11].

Prolonged QT interval has also been reported to be a common finding in patients with cirrhosis of liver [12].

2. MATERIALS AND METHODS

All patients admitted to General Medicine Department of M.K.C.G Medical College and Hospital presenting with cirrhosis of liver were included in the study and evaluated clinically with special emphasis on cardiovascular abnormalities in ECG and echocardiography. Echocardiography was performed by cardiologists who were blind about the clinical profile of the patients. The study was an observational, hospital based cross-sectional study, conducted from 2014-2016.The patients of both sex and age group 21-65 yrs having cirrhosis of liver were included in this study.

Patients of >65 yrs age, myocardial ischemia, hypertension, diabetes mellitus, septicaemia, valvular and congenital heart disease, pregnant/peripartum females, anaemia (Hb<7 gm/dl), raised serum creatinine (>1.5 mg/dl), HIV infection, metabolic disorders, Hepatocellular carcinoma, non alcoholic fatty liver disease were excluded from our study.

Cirrhosis of liver was diagnosed by using laboratory findings (thrombocytopenia ,raised serum bilirubin, decreased serum albumin, raised gamma globulin, raised serum alkaline phosphatise, raised serum transaminase, transudate type of ascitic fluid, increased PT INR) and radiological findings (nodularity, irregularity, increased parenchymal echogenicity of liver, atrophy, ascites on ultrasonography). Liver biopsy (regenerating nodules of hepatocytes, presence of fibrosis / deposition of connective tissue between the nodules) is the gold standard method for diagnosis of cirrhosis of liver. It was done in selected cases where there was some doubt about the diagnosis of cirrhosis by laboratory parameters and USG.

Table 1. Child-Turcotte-Pugh classification

Clinical and lab criteria	Points		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dl)	<2	2-3	>3
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalised ratio	<1.7	1.7-2.3	>2.3
Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points) Class A= 5 to 6 points (least severe liver disease) Class B=7 to 9 points (moderate to severe liver disease) Class C= 10 to 15 points (most severe liver disease)			

All the cases were classified under 3 classes according to Child-Turcotte-Pugh classification to know the severity of liver disease (above Table 1).

Cardiological evaluation of the patients was done by using Echocardiography and Electrocardiography (ECG).

Diastolic dysfunction was analysed by:

a. E/A ratio; Early (E) and Late (A) peak velocity across mitral valve
b. Deceleration time of the E wave (DT) in msec.

Grade I (mild) diastolic dysfunction (DD) is defined as: E/A < 0.8, DT > 200 msec, Grade II (medium) DD as: 0.8 < E/A < 1.5 and the DT is 160-200 msec and Grade III (severe) DD as: E/A > 2, DT < 160 msec. Systolic dysfunction was diagnosed by reduced ejection fraction (<55%). Grading of systolic dysfunction was done as mild (45-54%), moderate (30-44%) severe (<30%). QT interval was recorded by Electrocardiography and corrected QT interval (QTc) was calculated. QTc interval >0.44 sec in males, >0.45 sec in females was taken as prolonged.

Statistical analysis was done using unpaired t-test and P value was calculated. The difference was considered significant if the p-value was <0.05. All statistical analysis was done by using SPSS 14.0 for Windows.

3. OBSERVATION

Out of the 60 patients 52 (86.65%) were males and 8 (13.35%) were females. Maximum number of patients were of age group 41-50 yr (38.33%) followed by 51-60 yrs (35%). According to aetiology of cirrhosis of liver, out of 60 patients 46 cases (76.67%) were alcoholic, 12 cases (20%) of hepatitis B , 1 case (1.67%) of hepatitis C and 1 case (1.67%) was of idiopathic cirrhosis. (Table 2) Out of 60 cases taken all patients presented with ascites, 20 cases (33.3%) were having hepatic encephalopathy and variceal bleeding was present in 8 patients (13.3%). Laboratory parameters of the patients are depicted in Table 3.

27 cases (45%) were having prolonged QTc interval out of which 25 were male (mean 0.57±0.06) and 2 were females (mean 0.57±0.01) (Table 4).

Table 2. Aetiology of liver cirrhosis

Aetiology	No. of cases	Percentage
Alcoholic	46	76.67
Hepatitis B	12	20.00
Hepatitis C	1	1.67
Idiopathic	1	1.67
Total	**60**	**100.00**

2 cases (40%) of class A (mean QTc 0.63±0.14), 6 cases (30%) of class B (mean QTc 0.51±0.06), 19 cases (54%) of class C (mean QTc 0.58±0.05) patients according to Child-Turcotte-Pugh classification were having prolonged QTc interval. Prolonged QTc interval was related to severity of liver cirrhosis as the p-value (<0.05) was significant (Table 5).

The mean ejection fraction was 59.03±4.76 %, mean E/A ratio 1.35±0.43 and mean deceleration time in msec 199.5±29.36 (Table 6).

19 cases (31.66%) out of 60 cirrhotic patients were found to have diastolic dysfunction and 41 cases (68.34%) had normal diastolic function. 16 cases were having mild degree of diastolic dysfunction out of which 12 cases were alcoholic and 4 cases were non-alcoholic. Rest 3 cases having moderate degree of diastolic dysfunction were alcoholic. None of the patients were having severe degree of diastolic dysfunction. Systolic dysfunction was found in 6 alcoholic patients (mild in 4 cases and severe in 2 cases) (Table 7).

Table 3. Laboratory parameters

Investigation	Mean ± SD
Platelet (lakhs/cumm)	1.79±0.65
RBS (mg/dl)	147.21±21.49
Serum protein (gm/dl)	5.47±1.13
Serum albumin (gm/dl)	2.73±0.80
Serum urea (mg/dl)	39.28±13.86
Serum creatinine (mg/dl)	1.01±0.54
SGOT (mg/dl)	101.46±53.65
SGPT (mg/dl)	72.53±30.77
SGOT/SGPT Ratio	1.49±0.67
ALP (IU)	178.93±67.91
Bilirubin (T) (mg/dl)	4.25±2.23
Bilirubin (D) (mg/dl)	1.47±0.88
Ascitic fluid sugar (mg/dl)	98.2±28.61
Ascitic fluid protein (gm/dl)	3.40±0.97
Ascitic fluid albumin (gm/dl)	2.25±0.83
PT INR	1.67±0.22

Diastolic dysfunction was found in 15(32.6%) cases of alcoholic cirrhosis and 4 cases (28.6%) of non-alcoholic cirrhosis. According to Child-Pugh score 5 cases (8.33%) belonged to stage A, 20 cases (33.33%) belonged to stage B and 35 cases (58.33%) belonged to stage C. Diastolic dysfunction was found in 2 cases (40%) of stage A , 2 cases (10%) of stage B and 15 cases (42.85%) of stage C cirrhosis of liver.

E/A ratio of alcoholic and non-alcoholic cirrhosis patients was compared which was not significant as the p-value was 0.68 (>0.05) and the deceleration time was also not significantly changed as the p-value was 0.70(>0.05) (Table 8). E/A ratio of patients of class A with class B and C according to Child-Pugh classification was compared and the p-value was found to be 0.67 and that of deceleration time was 0.31 and thus insignificant.

4. DISCUSSION

In our study, out of total 60 cirrhosis cases, 46 patients (76.67%) were alcoholic, 12 patients (20%) of hepatitis B, 1 patient (1.67%) of hepatitis C and 1(1.67%) idiopathic. Most common etiology of cirrhosis was found to be alcoholic which could be due to higher prevalence of alcohol abuse in this part of the state.

According to our study prolonged QTc interval was found in 27 cases (45%) out of which 25 cases were males (mean 0.57±0.06 sec) and 2 cases were females (mean 0.57±0.01 sec). We found 2 cases (40%) in class A, 6 cases (30%) in class B and 19 cases (54%) in class C of Child-Turcotte-Pugh classification were having prolonged QTc interval. Thus prolonged QTc interval was more common in stage C of cirrhosis of liver. Difference of QTc interval between 3 classes of liver disease according to Child-Pugh classification was calculated and the p-value was found significant (<0.05). Prolongation of QTc interval was related to the severity of liver cirrhosis in our study.

Table 4. Showing QTc interval in ECG

Corrected QT interval (sec)	No. of cases	Percentage	Mean	
			Male	Female
Prolonged	27	45	25(0.57±0.06)	2(0.57±0.01)
Normal	33	55	27(0.39±0.03)	6(0.4±0.02)

Table 5. QTc interval and Child Pugh classification

Child Pugh score	Having prolonged QTc	Total no of cases	Percentage	Mean QTc interval in sec	p-value
A	2	5	40	0.63±0.14	0.0228
B	6	20	30	0.51±0.06	
C	19	35	54	0.58±0.05	

Table 6. Echocardiographic finding of patients

Echocardiographic parameter	Mean ± SD
Ejection fraction in %	59.03±4.76
E/A ratio	1.35±0.43
Deceleration time in msec	199.5±29.36

Al Khatib SM et al. demonstrated prolonged QTc interval as values >0.44 sec for males and >0.45 sec for females [13]. In the present study QTc interval >0.44 sec for males and >0.45 sec for females has been taken into account as prolonged. The mean QTc interval was 0.41 second in the series reported by Kamal Naik et al. [14]. Bernardi M et al. in their study found 45% cirrhosis patients were having prolonged QTc interval irrespective of the etiology of the disease and was broadly proportional to severity of cirrhosis, rising from 25% in class A to 51% in class B and upto 60% or more in class C of Child Pugh classification [12].

In the present study, diastolic dysfunction was diagnosed by echocardiography was present in 19 cirrhosis patients (31.66%). This study reveals out of 19 cases with diastolic dysfunction 16 cases were having mild degree of diastolic dysfunction and 3 cases were having moderate degree of dysfunction. Out of the 16 mild (grade I) diastolic dysfunction cases 12 had alcoholic cirrhosis and 4 cases had non-alcoholic cirrhosis. Moderate (grade II) degree of diastolic dysfunction was found in 3 cases and all of them were alcoholic. None of the patients were having severe degree of diastolic dysfunction.

Timoh T et al. in their study found 40-50% cases were having diastolic dysfunction irrespective of etiology of liver cirrhosis [15]. Piyush O. Somani in their study found 15 cases (83.33%) were having grade I and 3 cases (16.66%) were having grade II diastolic dysfunction. Grade III diastolic dysfunction was not found in their study according to American Society of echocardiographic guidelines. They did not find any systolic dysfunction in their study [16]. Nazar et al in a study found diastolic dysfunction is frequent in cirrhosis but in most cases it is of mild degree. They found diastolic dysfunction of grade I in 41% grade II in 16% but none of the patients were having grade III diastolic dysfunction [17].

Systolic dysfunction was found only in 6 patients of alcoholic cirrhosis patients but diastolic dysfunction was present in both alcoholic and non-alcoholic group of patients. Therefore, systolic dysfunction in alcoholic cirrhosis patients is likely to be due to direct toxic effect of alcohol. Diastolic dysfunction which is characteristic feature of cirrhotic cardiomyopathy was present in cirrhosis patients irrespective of the aetiology. However studies with larger sample size are required to establish the hypothesis that systolic dysfunction is likely due to direct toxic effect of alcohol.

According to our study out of 46 alcoholic cirrhosis cases 15 cases (32.6%) were having diastolic dysfunction in echocardiography. Similarly among the 14 non-alcoholic cirrhosis patients 4 cases (28.6%) were having diastolic dysfunction.

In this study E/A ratio of both alcoholic (1.34±0.42) and non-alcoholic patients (1.4±0.47) were compared and the p-value was found to be 0.68 (P value >0.05, statistically nonsignificant) and that of deceleration time (in msec) of alcoholic (198.70±29.107) and non-alcoholic (202.14±31.17) was 0.70 (Pvalue>0.05) which is also not significant. There was no significant difference in E/A ratio and deceleration time between the alcoholic and non-alcoholic groups. Therefore, cirrhosis of liver itself leads to myocardial dysfunction (cirrhotic cardiomyopathy) irrespective of the etiology of the disease.

Diastolic dysfunction was found in 40% (2 cases) of class A, 10% (2 cases) of class B and 42.85% (15 cases) of class C cirrhosis patients. E/A ratio of class A cirrhotic patients in comparison to class B & C patients according to child –pugh classification was having p-value 0.67 (>0.05) which is not significant. Similarly the difference in deceleration time was not significant as the p-value was 0.31 (>0.05). These echocardiography parameters do not show any significant difference in severity of diastolic dysfunction between 3 classes of cirrhosis patients according to Child Pugh classification. Piyush et al in their study series found 30% of cirrhotics were having diastolic dysfunction. Diastolic dysfunction was present in 2 patients (25%) with Child A and 8patients (30.76%) each in Child B and Child C stage. There was no difference in echocardiographic parameters when Child A status patients were compared to Child B/C status patients. Systolic and/or diastolic dysfunction was not influenced by severity of liver impairment [16].

Table 7. Echocardiographic parameters (myocardial dysfunction)

Aetiology	No. of cases with diastolic dysfunction				Systolic dysfunction			
	Mild (Grade I)	Moderate (Grade II)	Severe (Grade III)		Mild	Moderate	Severe	
Alcoholic	12	3	0	15	4	2	0	6
Non-alcoholic	4	0	0	4	0	0	0	0
Total	16	3	0	19	4	2	0	6

Table 8. Echocardiographic parameters according to etiology and severity of liver disease

Parameters	Alcoholic (n=46)	Non-alcoholic (n=14)	p-value	Child-pugh class A(n=5)	Child-pugh class B/C(n=55)	p-value
E/A Ratio	1.34±0.42	1.4±0.47	0.68	1.28±0.54	1.36±0. 42	0.67
Deceleration time	198.70±29.10	202.14±31.17	0.70	212±30.33	198.18±29. 38	0.31

5. CONCLUSION

In conclusion prolonged QTc interval was related to severity of liver cirrhosis based on Child Pugh classification. Systolic dysfunction was found in 6 (10%) cases of cirrhosis of liver and all of them were alcoholic. Hence it could be due to direct effect of alcohol but further studies of greater sample size required to establish this. Diastolic dysfunction was present in 19 (31.66%) cases of cirrhosis of liver. There was no correlation of echocardiography parameters of diastolic dysfunction with aetiology and severity (child pugh classification) of liver cirrhosis.

CONSENT

All authors declare that written informed consent was obtained from the patients for publication of this original article.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/22105