Cirrhotic Cardiomyopathy

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ABSTRACT

Introduction: Liver cirrhosis is a major health problem both in the developed and developing countries. The natural history of cirrhosis depends on both the cause and treatment of underlying cause(s). Some of these patients show the symptoms and sign of cardiac dysfunction. Objective: To evaluate left ventricular (dys) function in patients with cirrhosis of the liver.

Material and Methods: The study group comprised of 70 cases of liver cirrhosis. They were either newly diagnosed or follow up cases. Cirrhosis of liver was diagnosed on the basis of characteristic clinical history and examination, liver biomarkers and USG (abdomen). Echocardiography was performed with GE VIVID S5 Machine, using a transducer of 3.0 MHz.

Result: LV dysfunction was present in 41(58.57%) patients either in form of diastolic or diastolic plus systolic dysfunction. Diastolic dysfunction was more common compared to systolic dysfunction

Conclusion: LV dysfunction is common findings in patients of cirrhosis and their prevalence is irrespective of the etiology of cirrhosis and seems to correlate with severity of the disease. However, it's clinical significance remains unknown probably because of it's subclinical course. Keyword: Cirrhosis, Cardiomyopathy, Cirrhotic cardiomyopathy

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INTRODUCTION

Liver cirrhosis, which continues to be a major health problem both in the developed and developing countries, is a disease with characteristic clinical findings and histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, leading to portal hypertension and end stage liver disease.[1] Cirrhosis is the twelfth commonest cause of death in the United States, with more than 27,000 deaths and more than 421,000 hospitalisations annually[2] while no such data is available for our country. Alcoholic liver disease and chronic hepatitis C Virus (HCV) infection are the most common causes of cirrhosis in developed world, where as chronic hepatitis B virus (HBV) infection is the prevailing cause in most parts of Asia and sub Saharan Africa.[3,4]

The natural history of cirrhosis depends on both the cause, and treatment of underlying cause(s). The course in most cirrhotic patients is dominated by complications of portal hypertension such as bleeding from esophageal varices and ascites with the development of spontaneous bacterial peritonitis, renal impairment and encephalopathy. Some patients however, seem to die of causes unrelated to these complications, ACloser clinical look shows that a number of these patients displays sign of Cardiovascular disturbances secondary to hyperdynamic circulation and depressed ventricular contractile response to stimuli leading to increased cardiac output and augmented cardiac work, which could cause cardiac failure.[5]

Heart failure indeed is responsible for 7-15% of mortality following liver transplantation, and in the some series is the third leading cause of death, in patients of liver transplant, after graft rejection and infection.[6]

The hyperdynamic syndrome was first described 50 years ago as in these patients cardiac output increases whereas systemic vascular resistance and arterial blood pressure decrease[7,8] Despite the increased basal cardiac output, cardiac response to physiologic or pharmacologic stimuli is known to be subnormal,[9,10] a phenomenon called "cirrhotic cardiomyopathy.[11,12] When first described more than 3 decades ago in cirrhotic patients cardiac dysfunction was presumed to be a result of alcoholic cardiotoxicity, specifically latent alcoholic cardiomyopathy.[13,14,15] However, during the past 2 decades, it has become clear that blunted ventricular contractility with stress is also present in patients with nonalcoholic cirrhosis and animal models of cirrhosis.[16,17,18]

Despite the recognition of cirrhotic cardiomyopathy, its clinical significance has always been questioned, as frank cardiac failure is not a prominent feature of cirrhosis. Thus, the entity of cirrhotic cardiomyopathy may not be simply a medical curiosity, but rather an entity that deserves further investigations and therapeutic interventions.

The present study is a step towards this problem, identification of diastolic and systolic (dys)function.

Study aimed to evaluate left ventricular (dys) function in patients with cirrhosis of liver.

MATERIAL AND METHODS

This study was conducted on 70 patients between December 2017 - March 2018 in GRMC Gwalior.

The study group comprised of 70 cases of liver cirrhosis. They were either newly diagnosed or follow up cases. Cirrhosis of liver was diagnosed on the basis of characteristic clinical history and examination, liver biomarkers and USG (abdomen).

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Written consent prior to enrollment of study had been taken.

Exclusion criteria

Patients suffering from other diseases, which are likely to affect the LV function, were excluded from this study. These were:

1. Clinical evidence of myocardial ischemia and effort angina
2. Hypertension
3. Diabetes mellitus
4. Valvular heart disease

A detailed history was taken regarding presentation Of disease, duration of illness and co morbid illness eg. hypertension, chest pain, diabetes. Personal history of diet, smoking and alcoholism was taken. Family history of diabetes, hypertension, and ischemic heart disease was enquired.

Treatment history was also obtained regarding the use of drugs causing QTc interval prolongation.

Thorough general and systemic examination eg. blood pressure, pulse, icterus, pedal edema, asterixis, fetor hepaticus was done. Systemic examination of cardiovascular system was done with special emphasis to detect clinical cardiovascular abnormalities.

Routine investigations like complete blood counts, serum creatinine, S.urea, random blood sugar, urine examination were done. Various liver markers eg. Serum bilirubin, Serum amino transferases, Serum alkaline phosphatase,S.albumin, Prothombin time, INR, HBS Ag, anti HCV were estimated.

Twelve lead electrocardiograph

Routine Twelve lead electrocardiograph was recorded.QTc interval was measured using Bazzet's formula.

Qlc interval >440ms was considered as prolonged QTc.

Echocardiography

Echocardiography was performed with GE VIVID T8 Machine, using a transducer of 3.0 MHz. Two-dimensional mode, M -mode and transmitral blood flow pattern was evaluated by Doppler echocardiograph; color Doppler study was done in each case to excludevalvular abnormalities. Subjects were examined in the supine and left lateral decubitus position using standard parasternal short axis and long axis, and apical views. All recording and measurements were obtained by the same observer according to the recommendations of the American Society ofEchocardiography and were always performed at midday to avoid the influence of circadian rhythm on left ventricular diastolic function. AllDoppler measurements were assessed at end expiration.Mitral inflowvelocity pattern was recorded by placing the pulsed wave Doppler sample Volume between the mitral valvular endings. Left ventricle outflow pattern was recorded from the apical window by placing the pulsed wave Doppler sample volume just under aortic valve.

In Doppler echocardiography peak early velocity (E wave), peak atrial systolic velocity (A wave),early and late mitral diastolic flow ratio (E/A), ratio of E and A VELOCITY time integrals. With M-mode measurements, interventricular septum (IVS) and left ventricular posterior wall(LVPW) thickness separately at diastole and systole and left ventricle end –diastolic (LVED) and end systolic (LVES) diameter

Indices of left ventricular function: Following indices were studied

A). Direct parameters

1. Mitral valve E point septal separation (EPSS)
2. Left ventricular internal diameter in diastolic (LVIDd)
3. Left ventricular internal diameter in systolic (LVIDs)
4. Wall thickness
   a) Interventricular septal thickness in diastole (IVST)
   b) Left ventricular posterior wall thickness in diastole
5. Left ventricular ejection time (ET)
6. Peak velocity of early left ventricular diastolic filling [A(cm/s)]
7. Peak velocity of late left ventricular diastolic filling [E(cm/s)]
8. Ratio of early and late ventricular diastolic filling [El/A]

B) Derived parameters:

Left ventricular ejection (EF%)

Measurement and calculation

1. Mitral Valve: E point septal separation (EPSS)

EPSS was measured as distance between the E point of anterior mitral leaflet and trailing edge of interventricular septum

2. Left ventricular internal diameter in diastole (LVIDd)

It was measured as the ventricular distance from the anterior edge of the left

side of the interventricular septum, echo to the anterior edge of the lelt

posterior wall endocardial, echo at the onset of QRS complex. The normal

value of LVIDd =36 to 52 mm.(Feigenbaum, 1986)

3. Left ventricular internal diameter in systole (LVIDs)

lt was measured in mm as the shortest distance between the endccardial surface of the left side of interventricular septum and lelt ventricular posterior wall during the systole. The normal Value of LVIDs =23 to 39mm (Feigmbaum, 1986)

4). Wall thickness

a) Intraventricular septal thickness

It was measured in mm as the distance betweenthe right and left endocardial surface of the interventricular septum. The normal value is 6 to 11 mm (mean 9mm) [Feigenbaum 1986)]

b) Left ventricularposterior wall thickness

It was measured in mm as the distance from left ventricular endocardial to epicardial surface. The normal value is 6 to 11 mm (mean 9mm) [Feigenbaum 1986)]

5). Peak velocity of early left diastolic filling [E(cm/s)]

It was measured as the peak transmitral filling velocity during early diastole by color Doppler method. Normal

Age Group	Male(%)	Female (%)	Total(%)
<30	1(1.43%)	-	1(1.43%)
30-39	7(10%)	3(4.28%)	10(14.3%)
40-49	18(25.7%)	12(17.17%)	30(42.85%)
50-59	18(25.7%)	4(5.7%)	22(31.43%)
>60	4(5.7%)	3(4.28%)	7(10%)
Total	48(68.57%)	22(31.43%)	70(100%)

Table-I: Demographic profile

ETIOLOGY	Male (%)	Female (%)	Total (%)
Alcoholic	28(40%)	-	28(40%)
Hepatitis B	14(20%)	8(10.14%)	22(31.43%)
Hepatitis C	-	1(1.43%)	1(1.42%)
Unknown	6(8.57%)	13(18.57%)	19(27.14%)

Table-2: Etiology of cirrhosis of liver

Sex	Pure diastolic dysfunction(x)	Diastolic +systolic dysfunction (y)	Lv dysfunction (X+y)	Normal lv function	Total
Male	18(25.71%)	11(15.71%)	29(41.14%)	19(27.14%)	48(68.57%)
Female	8(1.14%)	4(5.71%)	12(17.14%)	10(14.28%)	22(31.42%)
Total	26(37.14%)	15(21.43%)	41(58.57%)	29(41.43%)	70%(100%)

Table-3: Prevalence of LV Dysfunction in patients with cirrhosis

Etiology	Pure diastolic dysfunction (X)	Systolic + Diastolic dysfunction (Y)	Left ventricular dysfunction(X+Y)	Normal LV function
Alcoholic (n=28)	12(42.86%)	8(28.56%)	20(71.42%)	8(28.56%)
Nonalcoholic (n=42)	14(33.33%)	7(16.66%)	21(50%)	21(50%)

Table-4: LV function in alcoholic v/s nonalcoholic

value is 0.66_+ 0.15m/s.

6) Peak velocity of late left diastolic filling [A (cm/s)]

It was measured as the peak transmitral filling velocity during early diastole by color Doppler method. Normal value is 0.67_+ 0.16m/s.

STATISTICAL ANALYSIS

Statistical analysis was done with the help of chi-square test. A p value of <0.05 is cosidered as significant.

RESULT

Out of the total of 70 patients included in the study, 48 (68.57%) were males and 22 (31.43%) females and the male to female ratio being 2.18:1 (Table No.1). The mean age of the patient was 49 _+9 years. Most of the patients belonged to 40-49 years (n =30,42.85%) and 50-59 years (n=22,31.43%) age groups.

We divided our patients in different subgroups on the basis of etiology of cirrhosis as shown in Table 2**.**

Alcohol was the most common cause of cirrhosis of liver. Although alcohol was the leading cause of cirrhosis in both, males 28/48 (58.33%) and overall 33/70(40%) cases, none of the female was alcoholic (Table No.2). Chronic HBV infection was the second common cause of cirrhosis in this population. Only a single female was diagnosed as HCV positive. In 19 (27.14%) cases, cause of cirrhosis was unknown. While the mean age of presentation in alcoholic patients was 52.75+_8.35 years, it was 46.0+_8.44 years in nonalcoholic patients.

A total of 26 (37.14%) patients, 18 (25.71%) males and 8 (1.14%) females, had pure diastolic dysfunction. Combined, diastolic and systolic dysfunction was present in 15 (21.43%) patients including 11 (15.71%) males and 4 (5.71%) females. Over all LV dysfunction was present in 41 (58.57%), out of them 29 (41.4%) were males and 12 (17.14%) females (Table No. 3).

Out of 28 alcolhilic patients LV dysfunction was present in 20(71.42%) patients, while in nonalcoholic it was present in 21(50%) patients (table 9). In alcoholics, pure diastolic dysfunction was found in 12(42.86%) and diastolic plus systolic dysfunction in 8(28.56%) cases. Among the non alcoholic, 14(33.33%) had pure diastolic and 7(16.66%) had combined, systolic and diastolic dysfunction (Table No.4).

DISCUSSION

Heart diseases can affect the liver with development of, for instance, a wide spectrum of liver diseases including cardiac cirrhosis and liver diseases may affect the heart with development of wide spectrum of cardiovascular abnormalities leading to cirrhotic cardiomyopathy. Cardiac and liver diseases may also have a common etiology, as is seen in metabolic and infectious diseases. Alterations in cardiovascular function in patients with liver cirrhosis have been extensively described during the last decades. The observation of a “hyperdynamic” state in the circulation of these patients, characterized by decreased peripheral vascular

resistance and increased cardiac output, was followed by the description of a novel type of "cardiomyopathy" with specific functional and electrocardiographic characteristics. There have been efforts to correlate the cardiovascular disturbances with the etiology or the severity of the hepatic failure, but with controversial results. Most of the data on cardiac dysfunction in patients of cirrhosis are from western studies where alcohol is the most common etiology. The issues are complicated by the fact that in western countries, alcohol use represents one of the commonest causes of both cirrhosis and cardiomyopathy, thus separating the effect of alcohol and the possible effects of liver disease on ventricular function is sometime difficult.[19,20] In our country seroprevalence of HBV is high and chronic HBV infection is considered to be the commonest cause of cirrhosis, hence a difference may be expected in the pattern of cardiovascular dysfunction compared to western world.The purpose of the present study was to evaluate left ventricular function in patients with cirrhosis of liver in the absence of clinical signs or symptoms of cardiac dysfunction.

Out of the 70 patients, 48(68.57%) were males with male to female ratio 18:1. Patient's age ranged from 24 to 72 years with mean age being 48.7 plus minus 8.98 years and the maximum number (n=30,42.85%) of cases was in the range of 40-49 years of age followed by 22(31.43%) cases in the range of 50-59 years of age and 10(14.3%) cases in 30-39 years of age. In a similar study of 30 patients, all having viral etiology[21] and the mean age of presentation was 43 years with a male to female ratio of 2:1. Similar type of presentation was recorded in another study by Joshi N et al[22] including 133 patients of chronic liver diseases in the age group of 1 1-75 years; the mean age of patients being 45.7 +14.0 years. In our study mean age of presentation was nearly similar to other studies.

Alcohol was the most common cause of cirrhosis in our study group. Alcohol was found to be the etiological factor in 28 (40%) patients, followed by chronic HBV infection in 22 (31.43%) and cryptogenic cirrhosis in 19 (27%) cases. Only one patient was HCV positive. Most of the studies from our country and South East Asia had reported chronic HBV infection as the commonest cause of cirrhosis. In the study by Joshi N et al[22] the most common cause of cirrhosis was HBV (29.3%), followed by alcohol (21.1%), HCV (14.2%), HBV and HCV dual infection (1.5%) and cryptogenic cirrhosis (23.3%). The remaining cases were Budd Chiari syndrome (2%), autoimmiune (1%), Wilson's disease (2%) and acute on chronic liver disease (2%). In a study from Bangladesh by Afroz S[23] et al the common causes of cirrhosis reported were chronic viral hepatitis (B and C) and nonalcoholic steatohepatitis. HBV was responsible for 76.3% of cases of chronic hepatitis and 61.15% of cases of cirrhosis in Bangladesh. In Nepal[24] 40% of cases of cirrhosis of the liver are due to HBV.

Despite HBV being reported as the most common cause of cirrhosis of liver in our country and most parts of Asia, the pattern of liver disease in our study group is different. The explanation for the difference in thepattern of cirrhosis is not known. Possible explanations include social andcultural differences in attitudes to alcohol, the quantities and qualities of alcohol consumed and genetic differences in the metabolism and effectsof alcohol.

Alcohol is a most frequent cause of liver disease in western countries.[25] LV dysfunction was present in more than half [41(58.57%)] of the patients with cirrhosis of liver either in form of diastolic, systolic or both. Present Study shows that pure diastolic dysfunction was present in 26 (37.14%) cases. Systolic LV dysfunction was present in 15(21.43%) patients. All the case ofsystolic LV dysfunction had diastolic dysfunction as well. Bernardi et al. found the ratio of pre-ejection period to left ventricular ejection time, which is a reliable method of assessing ventricular function, to be prolonged in 22 alcoholic and nonalcoholic cirrhotic patients both at rest and after exercise, an indication of contractile dysfunction. Most of the other studies reported systolic dysfunction after stress either in form of physical[26], physiological[27] and pharmacological stimuli and postulated an abnormalcardiac response to physiological and pharmacological stress in cirrhotics.

Diastolic dysfunction has been found to be more prevalent in our study. Some authorities contend that some degree of diastolic dysfunction is present in virtually every patient with cirrhosis[26,27,28,29] and in contrast to systolic dysfunction; a significant stimulus may not be required to detect diastolic dysfunction. Echocardiography may reveal abnormal diastolic function even at rest.

On analyzing association of LV dysfunction with etiology of cirrhosis, we found no significant correlation between LV dysfunction and etiology of cirrhosis ($p>0.05$), which is similar to the result of various

studies done on either rat models of nonalcoholic cirrhosis or numerous studies done in patients with nonalcoholic cirrhosis where depressed ventricular contractile response was reported in all form of cirrhosis.[16-20]

CONCLUSION

Alterations in cardiovascular function in patients with liver cirrhosis have been extensively described during the last decades. The observation of a hyperdynamic state in cirrhotics, was followed by the description of a novel type of "cardiomyopathy", with specific functional and electrocardiographic characteristics. There have been efforts to correlate the cardiovascular disturbances with the etiology or the severity of the hepatic failure. but with controversial results.

LV dysfunction was present in 41(58.57%) patients either in form of diastolic or diastolic plus systolic dysfunction. Diastolic dysfunction was more common compared to systolic dysfunction.

Therefore, to conclude, LV dysfunction is common findings, and their prevalence is irrespective of the etiology of cirrhosis and seems to correlate with severity of the disease. However, it's clinical significance remains unknown probably because of it's subclinical course. Further studies are required to know the exact prevalence of this entity and its impact on

the outcome of the patients with cirrhosis of liver.

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