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ORIGINAL RESEARCH

Cardiac Dysfunction in Alcoholic and Non alcoholic Cirrhosis

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Abstract

Background and Aim: Cirrhosis of liver is a chronic illness, it affects all over body hence it may be considered as a systemic disease. Cardiac involvement diastolic dysfunction, prolong QT interval is common and underdiagnosed in cirrhosis. The aim is to assess the cardiac systolic and diastolic dysfunctions in alcoholic and non-alcoholic cirrhosis patients and controls and compare the cardiac functional status between alcoholic and non - alcoholic cirrhosis patients.

Material and methods: The study was conducted in department of gastroenterology at JLN medical college and hospital Ajmer. A total 100 newly diagnosed patients of cirrhosis of liver were selected based on inclusion and exclusion criteria. Alcoholic cirrhosis was present in 40 patients. Age and sex matched 40 healthy subjects without any history of cardiac and liver disease selected as a control.

Results: Our study showed statically significantly increased in the ejection fraction in cirrhosis patients compare to controls, A significant increase in PASP was seen in cirrhotics compared to controls in study. Prevalence of diastolic dysfunction in this study in cirrhotic patients was significantly high compared to controls.

Conclusions: Cirrhotic patient's higher occurrence of diastolic dysfunction irrespective of etiology. PASP and EF was significantly higher in cirrhotic patients compare to controls. QTc interval prolongation significantly high in cirrhotic patients and also significantly high in alcoholic cirrhosis compare to non alcoholic cirrhosis patients.

Keywords: Cardiac Dysfunction, Cirrhosis, Alcoholic, Non alcoholic

Introduction

Hyperdynamic syndrome is a well-known clinical condition found in patients with cirrhosis and portal hypertension from more than half a century. It is characterized by high cardiac output, decreased systemic vascular resistance, and widespread arterial vasodilatation, decreased arterial blood pressure and prolonged QT interval.[1-4]

Cardiomyopathy is derived from the Greek roots: cardia (heart), mys (muscle) pátheia/páthesis (disease), that is, it is a condition affecting the heart muscles. The term "cirrhotic cardiomyopathy" is generally defined by the following clinical criteria: (1) baseline increased cardiac output but blunted ventricular response to stimuli, (2) systolic and/or diastolic dysfunction, (3) absence of overt left ventricular failure at rest, and (4) electrophysiological abnormalities including prolonged QT interval on electrocardiography and chronotropic incompetence.[5-7] Only in the last 2 decades has it been shown that cardiac dysfunction is also present in nonalcoholic cirrhosis. Symptoms and signs of CCM are difficult to identify because this syndrome is clinically silent. In the majority of cases, diastolic dysfunction precedes systolic dysfunction. Stress and other conditions such as liver transplantation and transjugular intrahepatic portosystemic shunt (TIPS), surgical portocaval shunts may unmask CCM and the adverse consequences of cardiac dysfunction become evident[8]. Cardiac failure with pulmonary edema following liver transplantation may be explained by underlying systolic and diastolic dysfunctions.

Repolarization abnormalities is manifested by a increased QT interval on the electrocardiogram and is present in 30 – 60 % of patients with cirrhosis[9]. QT interval prolongation correlate with severity of liver dysfunction (25%

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in cirrhosis Child Pugh class A vs 51% in Child Pugh class B, vs 60% in Child Pugh class C)[10]. Prolongation of QT interval is considered to be the earliest sign of cirrhotic cardiomyopathy[10,11] .It is estimated that up to 50% liver transplant candidates have features of cardiac dysfunction and 7% - 21% of post-operative deaths were attributed to heart failure [12-13]

Echocardiographic features of CCM include prolonged isovolumic relaxation time (>80 msec), E/A ratio(early to late (atrial) phases of ventricular filling) ≤ 1, and decreased pattern of contractility with preserved systolic function (LVEF > 50%) during the hyperdynamic state, as well as decreased wall motion, increased thickness of wall and enlarged atrium during acute decompensation and hypotension [14-17]

Pathophysiology of CCM include impairment of β-adrenergic receptor , increased endogenous cannabinoids and presence of cardio-suppressants such as nitric oxide and inflammatory cytokines.[18-19] Activation of renin-angiotensin system and salt retention may also play role in the development of cardiac hypertrophy and diastolic dysfunction[20].

In CCM patients with diastolic dysfunction and normal systolic function at rest but systolic dysfunction occurs under conditions of stress.[21] while in alcoholic cardiomyopathy there is a dilated cardiomyopathy characterized by increased ventricular volumes and a decreased ejection fraction.[22]

There is scarcity of data on the status of cardiac abnormalities in Indian patients with cirrhosis[21] hence, it is worth comparing the cardiac parameters between alcoholic and non-alcoholic cirrhotics.

The current study was designed to precisely evaluate the cardiac function in alcoholic and non alcoholic cirrhotics patients based on clinical examination, elctrocardiography, and M- Mode 2-dimensional echocardiography .

Aims and objectives

- To assess the cardiac systolic and diastolic dysfunctions in alcoholic and nonalcoholic cirrhosis patients and controls.
- To compare the cardiac functional status between alcoholic and non - alcoholic cirrhosis patients.

Materials and methods

The study was conducted in department of gastroenterology at JLN medical college and Hospital Ajmer. A total one hundred newly diagnosed consecutive patients of child C cirrhosis of liver, not on medication were selected based on inclusion and exclusion criteria. Alcoholic cirrhosis was present in 40 patients. The diagnosis of cirrhosis was made on the basis of symptoms, physical examination, liver function tests, complete blood count and ultrasonographic examination of the liver . Age and sex matched forty healthy subjects without any history of cardiac and liver disease selected as a control . Written informed consent was obtained from all patients and the study was approved by the ethics committee of the Medical college. All the patients were categorised in group 1 and controls in group 2.

Group 1 is further sub divided in two sub groups on the basis of etiology :- group 1A-alcoholic cirrhosis patients(N=40) and group 1B-non alcoholic cirrhosis patients (N=60).

Exclusion criteria comprised:1) Age < 20 years and > 70years; 2)ystemic arterial hypertension; 3)Primary cardiac / pulmonary disease: 4)Anemia Hb<7gm/dl: 5)Gross ascitis requiring repeated tapping; 6)Diabetes mellitus ; 7)Thyroid dysfunction; 8)Active infection; 9)ollagen vascular diseases ; 10)alignancies; 11)Hepatotoxic and Cardiac drug intake; 12)Patients with mixed etiology (alcoholic+ positive viral serology); 13)Un co-operative patients.

Each one of them was subjected to all routine investigation included ultrasonography of abdomen, Upper GI endoscopy, Electro cardiogram. Colour Doppler Echocardiogram (VIVD-7:GE) was done to assess the cardiac function. The parameters studied were.

Pulmonary artery Systolic Pressure (PASP)

QT_c interval (sec)-Bazetts formula $QTc=QT/\sqrt{RR}$

Systolic function indices

- Left ventricular internal dimension in systole (LVIDs)
- Left ventricular internal dimension in diastole (LVIDd)
- Interventricular septal diameter in diastole (IVSd)
- Left ventricular posterior wall thickness in diastole(LVPWd)
- Ejection Fraction % (EF)
- Aortic flow
- Pulmonary flow
- LV Mass
- TR Jet velocity and gradient

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Diastolic function indices

- Tricuspid E and A velocities
- Mitral E and A velocities

Statistical Analysis

SPSS for Windows, version 16, was used for data analysis. The qualitative data were analyzed by chi-square and Fisher's exact test. Continuous variables are presented as mean ± standard deviation (SD); categorical variables are presented as percentages. We also use the multivariate analysis to reject confounders. *P* value <0.05 was considered significant.

Results

Table 1 show age distribution of study subjects between alcoholic cirrhotics, non alcoholic cirrhotics and controls.

Table 1: Age distribution of study subjects

Age (years)	Alcoholic Cirrhotics	Non alcoholic cirrhotics	Total	Controls
20-40	4 (10%)	37 (56%)	41 (41%)	16 (40%)
41-60	36 (90%)	23 (44%)	59 (59%)	24 (60%)
Total	40 (40%)	60 (60%)	100	40

I. CIRRHOSIS (N = 100 CASES) AND CONTROLS (n = 40)

Table 2: Comparison of various Parameters in cases and controls

Parameter	Cirrhosis (Mean ±SD)	Control (mean ±SD)	P value
LVIDs (cm)	3.19 ±0.48	3.14±0.15	NS
LVIDd (cm)	4.79±0.5	4.71±0.35	NS
EF (%)	68.56±6.79	63.13±3.70	<0.001 S
IVSd (cm)	0.86±0.19	0.89±0.09	NS
LVPWd(cm)	0.88±0.25	0.85±0.15	NS
LV Mass(gm)	162.26±50.65	159.33±41.77	NS
PASP(mm Hg)	28.64±9.06	20.4±4.21	<0.001(S)
QT_c interval(sec)	0.44±0.05(sec)	0.40±0.02(sec)	<0.001(s)

When the left ventricular systolic function parameters were compared, only the E.F. was significantly (P<0.001) higher in the cirrhosis cases then controls. There was no significant difference of LV mass between cirrhotic patients (162.26±50.65 grams) and controls (159.33±41.77grams) (P=NS). The mean PASP was significantly high in patients with cirrhosis(28.64±9.06 mmHg) than in controls (20.4±4.21 mmHg) (P=0.001). The QT_c interval of cirrhosis patients was significantly (P=0.001) higher (0.44 ± 0.05 sec.) then controls (0.40 ± 0.02 sec.).

II. ALCOHOLIC CIRRHOSIS (A=40) AND NON-ALCOHOLIC CIRRHOSIS (n=60) cases

Table 3: Comparison of various parameters in alcoholic and non alcoholic cirrhosis patients

Parameter	Alcoholic cirrhosis (mean ±sd)	Non alcoholic cirrhosis (mean ±sd)	P Value
LVIDs (cm)	3.25±0.58	3.17±0.41	NS
LVIDd (cm)	4.77±0.55	4.81±0.48	NS
EF (%)	67.88±7.14	69.23±5.99	NS
IVSd (cm)	0.91±0.21	0.84±0.17	NS
LVPWd (cm)	0.89±0.19	0.88±0.3	NS
LV Mass(gm)	175.5±57.4	154.1±44.6	NS
PASP(mm Hg)	28.24±8.54	28.88±9.42	NS
QT_c interval(sec)	0.46±0.05	0.43±0.04	<0.001(s)

When the LV systolic functions parameters (LVIDs, LVIDd, EF, IVSD, LVPDd) were compared between non-alcoholic and alcoholic cirrhotics, no statistically significant difference was found between the two groups.(table-3) LV mass is non significantly higher in alcoholic cirrhosis patients (175.5 ± 57.4 gm) then non alcoholic cirrhosis patients (154.1 ± 44.6 gm) (P=NS). In this study QT_c interval is significantly (p=0.001) higher in alcoholic cirrhosis patients (0.46 ± 0.05 sec) then in non alcoholic cirrhosis patients (0.43 ± 0.04 sec).

Table 4: Pattern of Left Ventricular Diastolic Dysfunctions in cirrhosis patients and controls

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Pattern of diastolic dysfunction	Controls (n=40)	Total Cirrhosis (n=100)	Alcoholic cirrhosis (n=40)	Non-alcoholic cirrhosis (n=60)
Impaired relaxation pattern	6(15%)	28(28%)	13(32.5%)	15(25%)
Pseudo normal pattern	2(5%)	11(11%)	4(10%)	7(11.6%)
Restrictive pattern	2(5%)	9(9%)	2(5%)	7(11.6%)
Total	10(25%)	48(48%)	19(47.5%)	29(48.2%)
P Value		<0.05 (S)*	<0.05 (S)*	<0.05 (S)* NS**

*Control V/s Cirrhosis

**Alcoholic V/s Non alcoholic cirrhosis

In this study diastolic dysfunction (DD) significantly high in cirrhotic patients compared to the control group ($p<0.05$). Patients of the alcohol cirrhotic had significantly high DD compared with controls ($p<0.05$). 29 (48.2%) non-alcoholic cirrhosis patients had DD compared with 10 (25%) individuals in the control group which was statistically significant ($p<0.05$). There was no statistically difference was found in DD in patients with alcoholic and non-alcoholic cirrhosis ($P>1$)

Discussion

Cirrhosis of liver affects multiple system in body hence it may be considered as a systemic disease[24]. Diastolic dysfunction is a complex process that arises from numerous interrelated contributing factors such as pressure variations in the ventricle, cardiac preload and afterload, and ventricular relaxation and compliance. Knowledge of cardiovascular system involvement in a cirrhotic patient is important to plan treatment and assessing the prognosis.

In this study, simple, non-invasive commonly available test, Colour Doppler Echocardiography and EEG was used as the main investigative modality to assess cardiac function. Procedures like cardiac catheterization are invasive, costly and available only in few selected centers. Hence it was not considered.

Our study showed statically significantly increased in the ejection fraction in cirrhosis patients(68.56%) compare to controls(63.13%) (table no. 2).

This had been explained by the hyperdynamic circulation with an increased cardiac preload and the decreased cardiac afterload in cirrhotic patients[14]. Left ventricular chamber dimensions were comparable with control. All systolic parameters ($LVID_S$, $LVID_d$, EF(%), IVS_d, $LVPW_d$) are comparable in alcoholic and non alcoholic cirrhosis .

There was no significant difference in LV mass between cirrhosis and controls and between alcoholics and non alcoholics similar to an Indian study published by Alexander et al[23] in 2006.

A significant increase in PASP wasseen in cirrhotics (28.64 mmHg) compared to controls(20.4mmHg) in the study (table no.2). Hypoxemia, intrapulmonary shunting, portal – pulmonary shunting and increased levels of several vasoactive mediators and cytokines may be involved in the development of pulmonary hypertension. Fallan M et al[25] was also reported a similar observation in 2000.

In CCM diastolic dysfunction occur due to increased myocardial wall stiffness, myocardial hypertrophy, fibrosis and subendothelial edema[26]. Sodium retention in patients with cirrhosis may lead to myocardial hypertrophy and diastolic dysfunction [27]. The rennin angiotensin- aldosterone system (RAAS) and ANP are associated with diastolic dysfunction in cirrhosis[28].Thus, there is evidence that the diastolic function is impaired in patients with cirrhosis and the diastolic dysfunction indicators can provide prognostic information that may affect the ventricular filling during the procedure.

In the present study, left ventricular (LV) diastolic functions are studied in depth using parameters like isovolumic relaxation time, mitral inflow velocity pattern and mitral E deceleration time and E/A ratio.

Prevalence of diastolic dysfunction in our study in cirrhotic patients was (48%) compared to controls (25%) Similar to previous study by Merli M et al[29]. Another study showed that left ventricular diastolic dysfunction can be seen in 50% (25% grade I and 25% grade II) of cirrhotic patients[30]. This finding was seen in both alcoholic and non - alcoholic patients. Majority of patients showed an impaired LV relaxation pattern (>50%) indicating that the initial energy consuming step is being affected in cirrhosis.

A few patients showed advanced diastolic dysfunction in the form of restrictive pattern. This usually occur when the passive stiffness of heart is affected by diffuse fibrosis or when the myocytes are hypertrophied. So, heart may also be influenced by growth factors which mediate fibrosis in liver.

However, there was no significant difference between the occurrence and pattern of diastolic dysfunction among alcoholic and non - alcoholic cirrhosis patients. This indicate cardiac dysfunction seemed to be consequence of cirrhosis itself rather than alcohol. This observation also similarly documented earlier by Alaxender et al.[23]

In present study there is highly significant prolongation of QT_c interval in cirrhotic patients compare to controls .In cirrhotic patient QT_c interval more in alcoholic patients then non alcoholic cirrhosis patient. In alcoholic

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patients, prolonged QT interval is associated with an increased risk of sudden cardiac death[29] this shows alcohol is a independent predictor of QT_c interval prolongation. These data consistent with previous study of Thuluvath[9] and Genovesi [32]. And different -from some studies[10,33-35] which found no statistical correlation between QTc prolongation and etiology of liver disease .

Conclusions

1. cirrhotic patients irrespective to etiology have higher occurrence of diastolic dysfunction (47.5% and 48.2%). However there was no significant difference between alcoholic and non alcoholic cirrhosis patients.
2. PASP a n d EF was significantly increased in cirrhotic patients compare to controls.
3. There is no difference in LV systolic function between alcoholic and non alcoholic cirrhotic patients.
4. QTc interval is significantly high in cirrhotic patients compare to controls ($p<0.001$). QTc interval also significantly high in alcoholic cirrhosis patients compare to non alcoholic cirrhosis patients ($p<0.01$).

In view of the above conclusions, it is suggested to take up a prospective study with long term follow up with and without modern cardio protective agents in order to find out the effective interventions which minimize the progression of cirrhosis and subsequent cardiac dysfunction.

References

1. Llach J, Ginés P, Arroyo V, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology 1988;94:482–7.
2. Møller S, Wiinberg N, Henriksen JH. Noninvasive 24-hour ambulatory arterial blood pressure monitoring in cirrhosis. Hepatology 1995;22:88–95.
3. Estruch R, Fernandez Sola J, Sacanella E et al; Relationship betweencardiomyopathy and liver disease in chronic alcoholism. Hepatology 1995; 22: 532.)
4. Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennecs cirrhosis. J Clin Invest 1953;32:1025–33.).
5. Liu H, Song D, Lee SS. Cirrhotic cardiomyopathy. Gastroente´rologie Clinique et Biologique. 2002;26(10):842-7.
6. Gaskari SA, Honar H, Lee SS. Therapy insight: cirrhotic cardiomyopathy. Nature Clin Pract Gastroenterol Hepatol. 2006;3(6):329-37.
7. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. Hepatology. 2006;43(2 Suppl 1):S121-31.
8. Van der Linden P, Le Moine O, Ghysels M, Ortinez M, Devière J. Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: effects on right ventricular function. Hepatology 1996;23: 982–7.
9. Bal JS, Thuluvath PJ. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. Liver Int 2003; 23: 243-248.
10. Bernardi M, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. Hepatology. 1998; 27:28–34. [PubMed: 9425913]
11. Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiologicalabnormalities in patients with cirrhosis. J Hepatol 2006;44:994–1002.)
12. Donovan, C.L., *et al*. (1996) Two dimensional and dobu- tamine stress echocardiography in the prospective as- sessment of patients with end stage liver disease prior to orthotopic liver transplantation. *Transplantation*, 61, 1180-1188.
13. Myers, R.P. and Lee, S.S. (2000) Cirrhotic cardiomyopa- thy and liver transplantation. *Liver Transplantation*, 6, S44-S52
14. Zardi, E.M., *et al*. (2010) Cirrhotic cardiomyopathy. *Journal of the American College of Cardiology*, 56, 539- 549.
15. Wong, F., Liu, P., Lilly, L., Bomzon, A. and Blendis, L. (1999) Role of cardiac structural and functional abnor- malities in the pathogenesis of hyperdynamic circulation and renal sodium retention in cirrhosis. *Clinical Science* (*London*), 97, 259-267.
16. Wong, F., *et al*. (2001) The cardiac response to exercise in cirrhosis. *Gut*, 49, 268-275.
17. Liu, H.Q., Gaskari, S.A. and Lee, S.S. (2006) Cardiac and vascular changes in cirrhosis: Pathogenic mechanisms. *World Journal of Gastroenterology*, 12, 837-842.
18. *Ward CA, Liu H and Lee SS. Altered cellular calcium regulatory systems in a rat model of cirrhotic cardiomyopathy. Gastroenterology 2001; 121: 1209– 1218.*
19. Wong F. Cirrhotic cardiomyopathy. Hepatol Int 2009;3:294–304..

ISSN:0975-3583,0976-2833 VOL14,ISSUE03,2023

20. Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. J Hepatol 2006;44:994–1002
21. Liu H, Lee SS. Cardiopulmonary dysfunction in cirrhosis.*J. Gastro.Hepatol.*1999;14: 600–8.
22. Guillo P, Mansourati J, Maheu B*et al.* Long-term prognosis in patients with alcoholic cardiomyopathy and severe heart failure after total abstinence. *Am. J. Cardiol.* 1997; 79 : 1276–8.
23. Alexander J, Mishra P, Desai N et al. Cirrhotic cardiomyopathy- Indian Scenario J Gastroenterol Hepatol. March 2007; 22 (3) 395-9.)
24. Gatta A, Merkel C et al. Cardiac involvement in liver cirrhosis. Ann. Ital Med int. 1993; 8(4):244 –7.)
25. Fallon M, Abrams G: Pulmonary dysfunction in chronic liver disease. Hepatology 2000, 32: 859-65.
26. Zandi EM, Abbate A. Cirrhotic Cardiomyopathy. J Am Cell Cardiology. 2010; 56 (7): 539-49
27. De BK, Majumdar D, Das D, Biswas PK, Mandal SK, Ray S et al. Cardiac dysfunction in portal hypertension among patients with cirrhosis and non-cirrhotic portal fibrosis. J Hepatol. 2003; 39: 315–9
28. Finucci G, Desideri A, Sacerdoti D, Bolognesi M, Merkel C, Angeli P et al. Left ventricular diastolic function in liver cirrhosis. Scand J Gastroenterol. 1996; 31: 279–284.
29. Merli M, Calicchia A, Ruffa A, et al. Cardiac dysfunction in cirrhosis is not associated with the severity of liver disease. Eur J Intern Med. 2013;24:172e176
30. L. Achecar and A. Gonzalec-Tallon, "Relationship between circulatory dysfunction and severity of cardiomyopathy in patients with cirrhosis," in *Proceedings of the 46th Annual Meeting of the European Association for the Study of the Liver (EASL '11)*, 2011.
31. Day PC, James FWO, Butler JT, Campbell RWF. Q–T prolongation and sudden cardiac death in patients with alcoholic liver disease. Lancet 1993;341:1423–1428.
32. 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 2009; 116: 851-859],
33. Mohamed R, Forsey PR, Davies MK, Neuberger JM. Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease. Hepatology 1996; 23: 1128-1134
34. Zambruni A, Trevisani F, Di Micoli A, Savelli F, Berzigotti A. Effect of chronic beta-blockade on QT interval in patients with liver cirrhosis. J Hepatol 2008; 48: 415-421.
35. Puthumana L, Chaudhry V, Thuluvath PJ. Prolonged QTc interval and its relationship to autonomic cardiovascular reflexes in patients with cirrhosis. J Hepatol 2001; 35: 733-738.