

Cirrhotic Cardiomyopathy in Egyptian Patients

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Abstract

Background: Cirrhotic cardiomyopathy is the term used to describe a constellation of features indicative of abnormal heart structure and function in patients with liver cirrhosis. **Aim of this study** is to assess the pattern and the extent of cardiac affection in cirrhotic patients and its relation to the presence or absence of ascites. **Patients and methods:** This study included 70 patients with liver cirrhosis and 30 healthy controls. All persons were subjected to careful history taking, physical examination, laboratory investigations, abdominal ultrasonography, and echocardiography. **Results:** Left ventricle end diastolic diameter was significantly increased in cirrhotic patients with ascites (5.40 ± 0.58) and without ascites (5.31 ± 0.51), compared to the control group (4.52 ± 0.58) ($p < 0.05$), left ventricle end systolic diameter was increased in cirrhotic patients with ascites (3.57 ± 2.2) and without ascites (3.46 ± 3.1), compared to the control group (3.18 ± 2.5) ($p > 0.05$). Left atrium diameter, right ventricular end diastolic diameter and pulmonary artery systolic pressure were significantly increased in cirrhotic patients compared to the control group ($p < 0.05$). **Conclusion:** Liver cirrhosis was associated with significant enlarged cardiac chambers and diastolic dysfunction compared to the control group especially in the presence of ascites.

Keywords: Cirrhosis, Ascites, Echocardiography, Cardiomyopathy, Diastolic Dysfunction

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1 Introduction

Liver cirrhosis is a health care problem in Egypt caused by the high prevalence of hepatitis C virus infection (HCV) infection that affects 15-20 % of the general population [1]. Liver cirrhosis is associated with a wide range of cardiovascular abnormalities including hyperdynamic circulation, enlargement or hypertrophy of different cardiac chambers and electrophysiological changes such as QT prolongation [2]. In cirrhosis, despite the increased basal cardiac output, cardiac response to physiologic or pharmacologic stimuli is known to be subnormal a phenomenon called cirrhotic cardiomyopathy. The pathogenesis of cirrhotic cardiomyopathy is multifactorial and still incompletely defined; it includes abnormalities in the b-adrenergic signaling pathway, altered cardiomyocyte membrane fluidity, increased myocardial fibrosis, cardiomyocyte hypertrophy and ion channel defects [3]. Accumulating evidence suggests that cirrhotic cardiomyopathy plays a major role in the pathogenesis of cardiac dysfunction following liver transplantation or trans-jugular intra-hepatic porto-systemic shunt placement and contributes to the pathogenesis of hepatorenal syndrome [2]. Recognition of cirrhotic cardiomyopathy will depend on a high level of awareness and potentially will help better management of patients with cirrhosis [4].

2 Aim of the Work

The aim of this work is to study the pattern and the extent of cardiac affection in cirrhotic patients and its relation to the presence or absence of ascites.

3 Patients and Methods

This study was done in the department of internal medicine, Fayoum teaching hospital; it was carried on 30 patients with liver cirrhosis and without ascites (10 females and 20 males) (Group -1), 40 patients with liver cirrhosis and ascites (12 females and 28 males) (Group - 2), and 30 healthy controls (14 females and 16 males) (Group - 3).

3.1 Inclusion Criteria

Patients diagnosed with liver cirrhosis depending on clinical evidence of stigmata of chronic liver disease (e.g. jaundice, ascites, palmer erythema, etc) and ultrasonographic coarse echo texture and shrunken liver.

3.2 Exclusion Criteria

Patients with cardiovascular diseases e.g. hypertension, ischemic heart disease, valvular heart disease and atrial fibrillation, patients with severe anemia, renal failure and diabetes mellitus.

3.3 Each Person included in the Study was subjected to

- Careful history taking and thorough physical examination.
- **Laboratory investigations:** Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), serum alkaline phosphatase, serum albumin, Prothrombin concentration, total and direct bilirubin and hepatitis markers for HBV and HCV
- **Abdominal ultrasonography:** Using GE LOGIQ9 apparatus (GE Healthcare., Milwaukee, WI) with a 2–5 MHz convex array transducer (low frequency probe) and a 5–12 MHz convex array transducer (high frequency probe). recording both static and B-mode imaging in the fasting state. Series of images of both lobes of the liver were obtained for evaluation of the parenchymal echo texture, focal lesions, volumetric changes, and edge evaluation. High-resolution images of the surface of the right and left lobes of the liver were obtained with high-frequency probes for evaluation of the surface of the liver. Additional images were obtained if required to assess portal tracts as well as and splenic veins and assessment of size of the spleen and the presence of ascites or retroperitoneal masses.
- **Standard twelve-lead electrocardiogram (12-lead ECG):** For assessment of cardiac rhythm and features suggesting of chamber enlargement or coronary artery disease (CAD).
- **Echo Doppler study:** Echocardiography was performed using and ACUSON CV70 machine equipped with a 2.5/3.25 MHz annular array transducer. Patients underwent a complete echocardiographic examination including 2-D transthoracic imaging, pulsed wave Doppler, continuous wave Doppler, and color flow mapping. The patients were monitored through a single-lead electrocardiogram. Left ventricular (LV) internal dimension, left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) interventricular septal thickness (IVS), posterior wall thickness (PWT), right ventricular end-diastolic (RVEDD) and end-systolic (RVESD) and left atrium (LA) end-systolic diameter were obtained; left ventricular ejection fraction (EF) was calculated by Simpson's biplane method of disks. Pulsed wave Doppler echocardiography was used to evaluate trans-mitral LV filling velocities at the tips of the mitral valve leaflets and trans-tricuspid RV filling velocities at the tips of the tricuspid valve leaflets on the apical four chamber view and the peak early diastolic flow velocities (E), the peak of atrial flow velocities (A) and the ratio of E/A were determined. Color Doppler interrogation of mitral regurgitant jet in 2 orthogonal views to assess the severity of mitral regurgitation (MR) (mild MR: mean color flow jet area in the left atrium $<4\text{cm}^2$; moderate MR: mean color flow jet area 4 to 8cm^2 , mean color flow jet area $> 8\text{cm}^2$, and tricuspid regurgitation (TR) jet to assess the severity of TR (mild TR: mean color flow jet area in the right atrium $<5\text{cm}^2$, m2; moderate TR: mean color flow jet area 5 to 10cm^2 ; severe TR: mean color flow jet area $> 10\text{cm}^2$). Pulmonary artery systolic pressure (PASP) was calculated pulmonary artery systolic pressure using the simplified Bernoulli equation from the velocity of the TR jet and right atrial (RA) pressure [5].

4 Statistical Analysis

Collected data were computerized and analyzed using Statistical Package for Social Science (SPSS) version 16. Descriptive statistics were used to describe variables; percent,

proportion for qualitative variables. Mean \pm SD and range for Quantitative variables. Student's t-test was used to compare the normally distributed continuous variable between the patients with aortic valve stenosis and the healthy control group. Fisher-exact test and Chi-square test were used to compare categorical variables. P values with significance of less than 5% were considered statistically significant. For all statistical tests, a P value less than 0.05 was used to indicate significance.

5 Results

5.1 Demographic, Clinical and Laboratory Findings

This study was done in Fayoum university hospital; it was carried on 30 liver cirrhosis patients without ascites (Group 1), 40 liver cirrhosis patients with ascites (Group 2), and 30 healthy controls (Group 3). Group 1: Included 10 female and 20 male patients with mean age 46.9 ± 7.2 years, 22 patients had HCV infection, 8 patients had HBV, 9 patients had jaundice, 4 patients had hematemesis, 3 patients had melena and none of the patients were alcoholic. Group 2: Included 12 female and 28 male patients with 10 female and 20 male patients with mean age 48.3 ± 4.4 years, 30 patients had HCV infection, 10 patients had HBV, 24 patients had jaundice, 26 patients had hematemesis, 10 patients had melena, 35 patients had pitting edema of lower limbs and none of the patients were alcoholic. Group 3: Included 14 female and 16 male normal subjects with mean age 49.5 ± 4.5 years and normal parameters of all liver function tests. There was significantly lower serum albumin and prothrombin concentration level in patients of group 2 compared to group 1 ($p < 0.001$). On the other hand, there was higher total and direct bilirubin level and prolonged prothrombin time in patients of group 2 compared to group 1 ($p < 0.001$).

5.2 Echocardiographic Findings

There was significantly higher LVEDD in group 1 and 2 compared to group 3 (5.28 ± 0.51 mm, 5.41 ± 0.58 mm vs. 4.72 ± 0.58 mm; $p < 0.05$). There was no significant difference in LVESD in group 1 and 2 compared to group 3 (3.46 ± 3.1 and 3.57 ± 2.2 vs. 3.28 ± 2.5 mm; $p > 0.05$). There was no significant difference in LV ejection fraction in group 1 and 2 compared to group 3 (60 ± 4.56 % and 61 ± 6.61 % vs. 60.6 ± 1.9 %; $p > 0.05$). There was significantly higher LA in group 1 and 2 compared to group 3 (4.46 ± 0.4 mm, 4.72 ± 0.44 mm vs. 2.98 ± 0.31 ; $p < 0.001$). There was significantly higher RVEDD in group 1 and 2 compared to group 3 (3.03 ± 0.57 mm, 3.66 ± 0.37 mm vs. 1.95 ± 0.13 mm; $p < 0.001$). There was significantly higher PASP size in group 1 and 2 compared to group 3 (25.38 ± 6.94 mmHg, 39.29 ± 7.1 mmHg vs. 13.2 ± 1.93 mmHg; $p < 0.001$). LV diastolic dysfunction manifested as mitral valve E/A ratio < 1 was found in 12 patients of group 1, 30 patients of group 2 and 1 person from group 3 ($p < 0.001$). RV diastolic dysfunction manifested as tricuspid valve E/A ratio < 1 was found in 7 patients of group 1, 35 patients of group 2 compared to two persons of group 3 ($p < 0.001$) as shown in table 1 and 2.

Table 1: Echocardiographic findings in the study groups

Parameter	Group 1	Group 2	Group 3
IVS	0.85 ± 0.11	0.81±0.12	0.82±0.14
	P > 0.05	P > 0.05	
PWT	0.78 ± 0.09	0.79±0.10	0.77±0.12
	P > 0.05	P > 0.05	
LVEDD (n: 3.7-5.6cm)	5.31±0.51	5.40±0.58	4.52±0.58
	P < 0.05	P < 0.05	
LVESD (n: 24-37mm)	3.46±3.1	3.57±2.2	3.18±2.5
	P > 0.05	P > 0.05	
EF% (n: 55- 75%)	60±4.56	61±6.61	60.6±1.9
	P > 0.05	P > 0.05	
LA size (n: 1.9- 4 cm)	4.46±0.4	4.72±0.44	2.98±0.31
	P < 0.001	P < 0.001	
RVEDD (n: 0.7- 5.6cm)	3.03±0.57	3.66±0.37	1.95±0.13
	P < 0.05	P < 0.001	
PASP (n: 12-28mmHg)	25.38±6.94	39.29±7.1	13.2±1.93
	P < 0.05	P < 0.001	

Abbreviation: IVS, inter ventricular septum thickness in diastole; PW, posterior wall thickness in diastole; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; EF%, ejection fraction; LA, left atrium diameter in end systole; RVEDD, right ventricular end diastolic diameter ;PASP, peak pulmonary artery pressure.

Table 2: Prevalence of diastolic dysfunction among the study groups

E/A ratio		Group 1		Group 2		Group3	
		No	%	No	%	No	%
Mitral valve	Normal E/A ratio	18	60%	10	25%	29	96.7
	Reversed E/A ratio	12	40%	30	75%	1	3.3
Tricuspid valve	Normal E/A ratio	23	69 %	5	12.5 %	28	93.3%
	Reversed E/A ratio	7	21%	35	87.5%	2	6.7%

Abbreviations: E, early diastolic velocity; A, late diastolic velocity.

5.3 Correlations of Echocardiographic Parameters

Univariate regression analysis revealed significant correlations between presence of LV diastolic dysfunction and age ($r=0.239$, $p < 0.001$), ascites ($r=0.155$, $p = 0.002$), RVEDD ($r=0.123$, $p = 0.037$) and PASP ($r=0.190$, $p = 0.005$). Univariate regression analysis revealed significant correlations between presence of RV diastolic dysfunction and ascites ($r=0.154$, $p = 0.004$), RVEDD ($r=0.161$, $p = 0.015$) and PASP ($r=0.211$, $p = 0.001$) as shown in table [3].

Table 3: Correlations of LV & RV diastolic dysfunction with different parameters in liver cirrhotic patients

Variables	LV Diastolic dysfunction		RV Diastolic dysfunction	
	r	P. value	r	P. value
Age	0.239	0.001	0.062	0.17
Age				
Jaundice	0.115	0.10	0.078	0.11
Haematemesis	0.035	0.58	0.011	0.86
Melena	0.064	0.32	0.033	0.57
Ascites	0.155	0.002	0.154	0.004
AST	0.081	0.16	0.022	0.73
ALT	0.043	0.51	0.038	0.42
Serum albumin	0.007	0.90	0.009	0.89
PT	0.064	0.32	0.050	0.48
LVEDD	0.142	0.042	0.062	0.17
LVESD	0.105	0.081	0.078	0.11
EF	0.068	0.24	0.058	0.26
LA Diameter	0.104	0.13	0.089	0.15
RVEDD	0.123	0.037	0.161	0.015
PASP	0.190	0.005	0.211	0.001

Abbreviations: AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; PT, prothrombin time; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; EF%, ejection fraction; LA, left atrium diameter in end systole; RVEDD, right ventricular end diastolic diameter; PASP, pulmonary artery systolic pressure.

6 Discussions

Liver cirrhosis is associated with a wide range of cardiovascular abnormalities including hyperdynamic circulation, cirrhotic cardiomyopathy, and pulmonary vascular abnormalities [6]. Cirrhotic cardiomyopathy is a clinical syndrome in patients with liver cirrhosis characterized by an abnormal and blunted response to physiologic, pathologic, or pharmacologic stress but normal to increased cardiac output and contractility at rest. As many as 50% of cirrhotic patients undergoing liver transplantation show signs of cardiac dysfunction, and 7% to 21% of deaths after orthotopic liver transplantation result from overt heart failure [7]. Strict diagnostic criteria for cirrhotic cardiomyopathy are lacking and the presence of this syndrome should be suspected in patients with worsening hemodynamic [8].

Our study included 30 liver cirrhosis patients without ascites and 40 liver cirrhosis patients with ascites and fulfilling the criteria of liver cirrhosis diagnosed clinically by the stigmata of chronic liver disease and ultrasonographically by shrunken liver and coarse echo texture. We found that, patients with liver cirrhosis had higher LVEDD when compared to control group ($P < 0.05$) and there was no significant difference in the LV EF % in patients with liver cirrhosis when compared to control group ($P > 0.05$). Left ventricular EF has been reported to be normal in some studies [9,10], increased in others [11, 12, 13] and decreased

only in one study of patients with cirrhosis and ascites [14]. A relative increase in the EF of patients with cirrhosis could be explained by the hyperdynamic circulation as a result of splanchnic vasodilatation. LV systolic function is usually normal at rest and systolic incompetence is most evident under stress, whether physical or pharmacological, or when the extent of peripheral arterial vasodilatation demands an increased cardiac output as in the case of bacterial infections. Acute volume overload after insertion of a trans-jugular intra-hepatic porto-systemic shunt or after liver transplantation can also precipitate LV systolic dysfunction [6]. In our study, we found that patients with liver cirrhosis had higher LA diameter and RVEDD when compared to control group ($P < 0.001$). Our results came in agreement with Papastergiou et al. [15] who found echocardiographic evidence of mild to moderate left atrium enlargement was found in 36% of the studied population. Significant correlation between left atrial size and intrapulmonary right to left shunt, characterizing hepatopulmonary syndrome was observed in a previous report [16]. Furthermore Valeriano et al [17]. found that right and left atrium and right ventricular diameters were significantly enlarged in cirrhotic patients versus controls. These abnormal structural findings in cirrhotic patients seem to be an adaptation of cardiac hemodynamic to the changes in the peripheral circulation and thus the role of the rennin-angiotensin-aldosterone system (RAAS) and adrenergic hyperactivity has been considered. In addition, Wong, [2] found an increased diameter of the left atrium and some degree of diastolic dysfunction in 39 pre-ascitic and ascitic patients and concluded that ascitic patients had a thicker left ventricular wall and a lower E/A ratio, indicating greater impedance to venous return than pre-ascitic cirrhotic patients.

In our study, we found significant abnormalities in both left and right ventricular diastolic function in patients with liver cirrhosis in the form of reversed E/A ratio with significant decrease in E wave average velocity of both mitral and tricuspid annulus with reversed E/A ratio. LV diastolic dysfunction was detected in 12 patients with liver cirrhosis without ascites and 30 patients with ascites and correlated with age ($r=0.239$, $p < 0.001$), presence of ascites ($r=0.155$, $p=0.002$), RVEDD ($r=0.123$, $p=0.037$) and PASP ($r=0.190$, $p=0.005$). RV diastolic dysfunction was detected in 7 patients with liver cirrhosis without ascites and 35 patients with ascites and correlated with presence of ascites ($r=0.154$, $p=0.004$), RVEDD ($r=0.161$, $p=0.015$) and PASP ($r=0.211$, $p=0.001$).

In our study, diastolic dysfunction appears to be more common in cirrhotic patients with ascites than those without ascites and that some degree of diastolic dysfunction is present in the majority of patients with cirrhosis. Right ventricle diastolic dysfunction may be due to the decrease in cardiac preload, increase in the afterload or right ventricular relaxation or other abnormalities in compliance [18]. Left ventricle Diastolic dysfunction is often linked to cardiac structure abnormalities including a combination of myocardial hypertrophy, fibrosis, and sub-endothelial edema. [19]. The stiff and noncompliant ventricles cannot accommodate the venous return to the heart in early and middle-late diastole. Significant stimulus may not be required to precipitate diastolic dysfunction so that echocardiography may reveal abnormal diastolic function even at rest. Functional component cannot be also excluded, as improvements in diastolic dysfunction have been reported after paracentesis in patients with tense ascites and port systemic shunt insertion [20]. Decrease in cardiomyocyte metabolism has been recently proposed in order to explain diastolic dysfunction and its reversibility after liver transplantation [15].

Our results came in agreement with Salari et al. [21] who reported that diastolic dysfunction was significantly present in all cirrhotic patients but the severity was increased with the increased severity of the chronic liver disease. Møller et al [11] showed that A wave

velocities and deceleration times are much increased and the E/A-ratio is decreased in cirrhotic patients, especially in those with ascites. Pozzi et al. [14] found that in cirrhotic patients with tense ascites, the A wave velocity is markedly increased, the E/A ratio is markedly reduced, and the deceleration time is significantly prolonged. Furthermore, removal of the ascitic fluid by rapid total paracentesis was associated with reduction in A wave velocity and increases the E/A ratio to values similar to those of cirrhotic patients without ascites but still abnormal as compared with healthy controls.

Another important finding in our study was the significantly higher pulmonary artery systolic pressure in liver cirrhosis patients (25.38 ± 6.94 mmHg in patients without ascites and 39.29 ± 7.1 mmHg in patients with ascites) compared to control group (13.2 ± 1.93 mmHg, $p < 0.001$). In fact, pulmonary vascular resistance was tended to decrease in cirrhotic patients. The mechanism of increased PASP is not fully understood, but previous studies suggested the increased levels of vasoactive substances in pulmonary circulation and the probable toxic effect of these substances on endothelial cells [18]. Some authors have suggested that micro thrombi can migrate to pulmonary vascular bed along porto-systemic shunts and can cause increase in vascular resistance [22].

7 Conclusions

Liver cirrhosis is associated with echocardiographic changes in the form of enlarged right cardiac chambers, diastolic dysfunction and pulmonary hypertension and these changes are more evident in cirrhotic patients with ascites than those without ascites. Echocardiography should be part of the screening of patients with chronic liver disease, because patients with systolic and / or diastolic dysfunction and porto-pulmonary hypertension could be at higher morbidity and mortality risk.

8 Limitations of the Study

The number of the patients was not large enough to have more valuable correlation between the severity of the disease and the prevalence of cardiovascular abnormalities. More sophisticated echocardiographic tools (e.g., tissue Doppler imaging), which could have increased the reliability of our results, were not used. We cannot rule out the decreased cardiac reserve in stress conditions because we evaluated all of our patients in the resting position.

9 Conflict of Interest

Mohamed Mashahit, Hany Younan, Maher El-Amir, Amal Mohamed, Hala Farawela and Alaa Abd El-Hamed declare that they have no conflict of interest.

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