The Effect of Liver Cirrhosis Severity on Left Ventricular Systolic and Diastolic Functions

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Abstract

Background: Alteration of cardiovascular functions in patients with liver cirrhosis has been described and it correlates with severity of hepatic failure. But cardiac function by conventional echocardiography has limitations and cardiac decompensation occurs when the heart is challenged.

Aim: To evaluate cardiac systolic and diastolic functions in patients with liver cirrhosis by conventional Doppler echocardiography and tissue Doppler image (TDI) and correlate the results with severity of cirrhosis based on Child-Pugh score.

Methods: 624 patients with liver cirrhosis divided into 3 groups according to Child pugh score then systolic and diastolic functions were evaluated with conventional echo (2D, PW Doppler and MM and by TDI (Sm, Em and Am) then E/Em was calculated.

Results: By conventional echo LV dimensions and systolic function were normal and hyperdynamic in Child C, diastolic dysfunction was diagnosed in 67% and difference between 3 groups was insignificant, by TDI diastolic dysfunction was diagnosed in 89% in cirrhotic patients and there were statistically significant systolic dysfunction in the form of lower Sm (p=0.001) and there was significant +ve correlation between severity of cirrhosis and Sm and diastolic dysfunction in the form of lower Em (p=0.005) and there was significant +ve correlation between severity of cirrhosis and Em also higher E/Em (p=0.0001) with significant –ve correlation.

Conclusion: TDI is simple, non invasive, bedside, being cheap and more accurate test that can be used to detect early subclinical left ventricular systolic and diastolic dysfunction in cirrhotic patients especially in Child B cirrhosis.

Key Words: Liver cirrhosis – Severity – Left ventricular – Systolic – Diastolic – Function.

Introduction

CIRRHOSIS refers to a progressive, diffuse, fibrosing condition that disrupts the normal architecture of the liver, caused by a myriad of conditions with the most common being: Alcohol, viral and non alcohol fatty hepatitides [1]. Liver Cirrhosis is the 12th leading cause of death in the US with mortality rate of 9.7 per 100,000 persons [2].

Liver cirrhosis is associated with a wide range of cardiovascular abnormalities including hyperdynamic circulation, pulmonary vascular abnormalities, attenuated systolic contraction or diastolic relaxation in response to physiologic, pharmacologic and surgical stress, and electrical conductance abnormalities (prolonged QT interval) in the absence of any known cardiac disease [3].

Left ventricular ejection fraction (LVEF), which reflects systolic function, has been found normal at rest in patients with cirrhosis but, an attenuated LVEF has been shown after several stimuli such as exercise, sodium load or erect posture. This can be attributed to a blunted heart rate response to stress, reduced myocardial reserve and impaired muscular oxygen extraction [4].

LV diastolic dysfunction may be a consequence of cardiac hypertrophy, patchy fibrosis and subendothelial edema [4]. Determinant of diastolic dysfunction by Doppler echocardiogram is abnormal

Abbreviations:

LVDd : Left ventricle dimension in diastole.
LVDs : Left ventricle dimension in systole.
MM : M-mode.
PASP : Pulmonary artery systolic pressure.
PW : Pulsed wave.
RVD : Right ventricular dimension.
TDI : Tissue Doppler image.
Am : Late diastolic velocity.
DT : Deceleration time.
Ep% : Ejection fraction.
Em : Early diastolic velocity.
LAV : Left atrial volume.
LV : Left ventricle.
E/A ratio which is the ratio of early to late atrial phases of ventricular filling. The E/A ratio is decreased in cirrhotic patients, especially in those with ascites. However, a low E/A is highly preload-determined, and also E/A <1 may be a normal age-related finding. TDI measures the slow velocity high amplitude tissue motion which is less affected by preload [4].

However these abnormalities were initially thought to be a manifestation of latent alcoholic cardiomyopathy. But later in the mid-1980s, studies in non-alcoholic patients and in experimental animal models showed a similar pattern of blunted cardiac contractile responsiveness. Thus these cardiovascular changes are now termed “cirrhotic cardiomyopathy” [5].

This syndrome is seen in approximately 40-50% of adult patients with cirrhosis and in children with biliary atresia. In the majority of cases, diastolic dysfunction precedes systolic dysfunction which tends to manifest only under conditions of stress. Cardiac response to physical exercise in cirrhotic patients is blunted, with subnormal responses in echocardiographic ejection fraction and contraction time [6].

Cardiac dysfunction can be reversible and can improve due to effective medical treatment and also after liver transplantation. Echocardiography is essential tool for recognizing the characteristic changes in the myocardial function [7]. Tissue Doppler Imaging (TDI) is more sensitive for assessing left ventricular function [8].

Aim:
The current study was conducted to evaluate cardiac systolic and diastolic functions in patients with liver cirrhosis by conventional Doppler echocardiography and TDI and correlate the results with severity of cirrhosis based on Child-Pugh score.

Patients and Methods
This is a single center observational prospective study, approved by the Medical Ethical Committee of the Benha University and informed consent was obtained from all patients included in the study.

All cirrhotic patients who were admitted in the Hepatology Department in Benha University Hospital from January 2013 to June 2014 were enrolled. Patients with history or clinical evidence of cardiovascular disease, major lung disease, diabetes mellitus, major arrhythmias, severe anemia (Hb <7gm/dL), and patients on renal dialysis were excluded from the study.

Diagnosis of cirrhosis was based on clinical grounds (chronic liver disease stigmata, jaundice, ascites and esophageal varices), impaired liver function tests and ultrasonographic features consistent with cirrhosis (diffuse alteration and nodular transformation of liver parenchyma, and signs of portal hypertension) by using LOGIQ P6 PRO Device with 2-5MHZ, Multi angel, Reusable Probe (GE Health Care). Liver profile tests (alanine amino transferase “ALT”, aspartate amino transferase “AST”, serum bilirubin, serum albumin, and INR) was performed to all patients using standard methods. Severity of cirrhosis was evaluated by Child-Pugh score [9].

Echocardiography: Echocardiographic studies were performed using GE, vivid 7 Norway) equipped with 2 to 4MHZ probes allowing M-mode, two dimensional, and pulsed Doppler measurements.

Left atrial volume was measured by tracing the endocardial border in the apical four chamber view by modified Simpson rule and then indexed to BSA and LV ejection fraction was obtained by MM (LVDd, LVDs and EF%), RVD and PASP on the tricuspid inflow is calculated. Measurements were made from three consecutive beats and the average of three beats was used for analysis. Doppler recording of diastolic mitral flow was obtained by using apical four-chamber view and measurements were made by taking an average of two consecutive beats. Early (E) and late (A) diastolic velocities (transmitral), deceleration time and E/A ratio was calculated.

Activation of the PW TDI and measurement of mitral peak systolic annular velocity (Sm), early diastolic (Em) and late diastolic annular velocity (Am) were measured at four different sites at mitral annulus (anterior, inferior, lateral and septal). An average of all four velocities was taken as mean velocity at mitral annulus. E/Em ratio was calculated.

Diastolic dysfunction was diagnosed by PW Doppler based on:
- Normal: E/A 0.75-1.5 and DT >140msec.
- Grade 1: E/A < 0.75 and DT >140msec.
- Grade 2: E/A 0.75-1.5 and with valsalva E/A <0.75 and DT <140msec.
- Grade 3: E/A > 1.5 and reversible and DT <140msec.
- Grade 4: E/A >1.5 and irreversible and DT <140msec.
Diastolic dysfunction was diagnosed by TDI based on:
- \( \text{Em} < 8 \text{cm/s} \).
- \( \text{E/Em} > 8 \).

Systolic dysfunction was diagnosed by PW Doppler based on:
- \( \text{Sm} < 10 \text{cm/s} \).

Statistical analysis:
Parametric data are expressed as mean values and standard deviation (SD) and categorical variables as percentages. The Chi-square test or Fisher’s exact was used for the comparison of dichotomous variables and the Student’s \( t \)-test for continuous variables. ANOVA one-way was used to calculate \( p \)-value in comparisons of more than two continuous variables. \( p < 0.05 \) was considered statistically significant.

Results
The present study was conducted on 624 subjects classified into three groups according to Child score group (I): Child A consisted of 197 patients, group (II): Child B included 228 patients and group (III): Child C included 199 patients, all patient were hepatitis C virus antibodies positive and were of comparable age \( (p\text{-value}=0.27) \), male gender was more prevalent about 75% of the study population but there was no significant difference between the 3 groups \( (p\text{-value}=0.37) \). Also there was no statistically significant difference between the 3 groups as regard to risk factors \( (p\text{-value was 0.57 for smokers, 0.28 for hypertension and 0.45 for diabetes}) \) Table (1).

<table>
<thead>
<tr>
<th>Group I Child A (n=197)</th>
<th>Group II Child B (n=228)</th>
<th>Group III Child C (n=199)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) mean±SD</td>
<td>49.5±5.2</td>
<td>52.8±5.9</td>
<td>59.9±8.04</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>149 (76%)</td>
<td>166 (73%)</td>
<td>155 (77%)</td>
</tr>
<tr>
<td>Female</td>
<td>48 (24%)</td>
<td>62 (27%)</td>
<td>44 (23%)</td>
</tr>
<tr>
<td>Risk factors: Smoker</td>
<td>102 (52%)</td>
<td>122 (54%)</td>
<td>91 (46%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75 (38%)</td>
<td>52 (23%)</td>
<td>41 (21%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>62 (31%)</td>
<td>48 (21%)</td>
<td>38 (19%)</td>
</tr>
</tbody>
</table>

There was statistically insignificant difference between the three groups as regard laboratory investigations: serum level of AST \( (p\text{-value}=0.08) \), serum ALT \( (p\text{-value}=0.13) \), serum Bilirubin \( (p\text{-value}=0.39) \) and INR \( (p\text{-value}=0.05) \) but was significant for Albumin \( (p\text{-value}=0.009) \) Table (2).

<table>
<thead>
<tr>
<th>Group I Child A (n=197)</th>
<th>Group II Child B (n=228)</th>
<th>Group III Child C (n=199)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab.</td>
<td>AST (IU/L) Mean±SD</td>
<td>27±5</td>
<td>38.4±29.5</td>
</tr>
<tr>
<td></td>
<td>ALT (IU/L) Mean±SD</td>
<td>27±6</td>
<td>65.2±31</td>
</tr>
<tr>
<td></td>
<td>Albumin (g/dL) Mean±SD</td>
<td>4.2±0.4</td>
<td>3.15±0.2</td>
</tr>
<tr>
<td></td>
<td>Bilirubin (mg/dL) Mean±SD</td>
<td>0.9±0.2</td>
<td>2.61±0.82</td>
</tr>
<tr>
<td></td>
<td>INR Mean±SD</td>
<td>1±0.05</td>
<td>1.55±0.3</td>
</tr>
</tbody>
</table>

By conventional echo assessment there was significant increase in the RVD \( (p\text{-value}=0.001) \) and PASP \( (p\text{-value}=0.001) \) but there weren’t statistically significant difference between the 3 groups as regard left atrial volume, E velocity, A velocity, deceleration time and E/A ratio \( p\text{-value=0.35, 0.20,0.24 and 0.57 respectively. Also there were normal LV dimensions in the 3 groups (LVDd and LVDs) and hyperdynamic function especially in group (III) (p=0.005) Table (3).
By TDI there were statistically significant systolic dysfunction in the form of lower Sm ($p=0.001$) and there was significant +ve correlation between severity of cirrhosis and Sm (Fig. A) and diastolic dysfunction in the form of lower Em ($p=0.005$) and there was significant +ve correlation between severity of cirrhosis and Em (Fig. B) and there was higher E/Em ($p=0.0001$) with significant –ve correlation (Fig. C) Table (3).

Table (3): Echocardiographic parameters.

<table>
<thead>
<tr>
<th></th>
<th>Group I Child A (n=197)</th>
<th>Group II Child B (n=228)</th>
<th>Group III Child C (n=199)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAV index (mL/m$^2$)</td>
<td>25.8±5.8</td>
<td>27.3±10.3</td>
<td>28.5±5.4</td>
<td>0.35</td>
</tr>
<tr>
<td>$LVD$:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LVDd</td>
<td>4.59±0.19</td>
<td>4.73±0.2</td>
<td>4.89±0.35</td>
<td>0.01</td>
</tr>
<tr>
<td>LVDs</td>
<td>2.45±0.14</td>
<td>2.55±0.13</td>
<td>2.61±0.11</td>
<td>0.04</td>
</tr>
<tr>
<td>EF%</td>
<td>67.95±2.56</td>
<td>70±3.62</td>
<td>71.1±1.66</td>
<td>0.005</td>
</tr>
<tr>
<td>RVD (cm)</td>
<td>1.59±0.2</td>
<td>1.86±0.09</td>
<td>2.91±0.11</td>
<td>0.001</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>37.2±5</td>
<td>40.5±7</td>
<td>52.8±11</td>
<td>0.001</td>
</tr>
<tr>
<td>$PW$:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (m/s)</td>
<td>0.57±0.16</td>
<td>0.64±0.12</td>
<td>0.66±0.13</td>
<td>0.20</td>
</tr>
<tr>
<td>A (m/s)</td>
<td>0.84±0.16</td>
<td>0.89±0.13</td>
<td>0.89±0.16</td>
<td>0.15</td>
</tr>
<tr>
<td>Decel.e.t (m/s)</td>
<td>253.4±56</td>
<td>283.2±78</td>
<td>291.2±51</td>
<td>0.24</td>
</tr>
<tr>
<td>E/A</td>
<td>1.13±0.11</td>
<td>0.99±0.14</td>
<td>0.90±0.12</td>
<td>0.57</td>
</tr>
<tr>
<td>$TDI$:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sm (cm/s)</td>
<td>11.55±0.82</td>
<td>8.15±0.48</td>
<td>6.12±0.36</td>
<td>0.001</td>
</tr>
<tr>
<td>Em (cm/s)</td>
<td>9.9±1.9</td>
<td>7.41±1.5</td>
<td>6.5±1.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Am (cm/s)</td>
<td>12.6±2.1</td>
<td>11.9±2.1</td>
<td>11.4±1.5</td>
<td>0.28</td>
</tr>
<tr>
<td>E/Em ratio</td>
<td>5.5±1.1</td>
<td>9.1±1.3</td>
<td>11.4±1.19</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

By PW Doppler LV diastolic dysfunction was diagnosed in 67% (13% in Child A, 25% in Child B and 29% in Child C) but with TDI LV diastolic dysfunction was diagnosed in 89% (20% in Child A, 36% in Child B and 33% in Child C) Fig. (D).

Fig.: (A) Correlation between severity of cirrhosis and Sm, (B) Correlation between severity of cirrhosis and Em and (C) Correlation between severity of cirrhosis and E/Em.

Fig. (D): % of patients diagnosed to have LV diastolic dysfunction by PW and TDI.
Fig. (E): Case of Child B shows normal LV systolic function by MM (EF=68%) and diastolic function by PW Doppler but with TDI there is systolic and diastolic dysfunctions (Sm=5cm/s), (Em=5.4cm/s) and (E/Em=17).

**Discussion**

Patients with liver cirrhosis are reported to have a hyperdynamic circulation, which is manifested as high cardiac output, decreased systemic vascular resistance, and widespread arterial vasodilatation. In previous studies, cirrhosis is associated with cardiovascular abnormalities [3,4]. And the term Cirrhotic cardiomyopathy is the term used to describe a collection of characters expressive of abnormal heart structure and function in patients with cirrhosis.

Reduced left ventricular ejection fraction was found to be an important determinant for the development of the hepatorenal syndrome and diastolic dysfunction is an important underlying factor in the development of certain arrhythmias, especially in the genesis of atrial fibrillation [7].

Since cardiac function is nearly normal at rest, the diagnosis of this disorder is not easy. In most cases this condition is well tolerated and may be asymptomatic for a long period of time, and it is often impossible to distinguish the clinical signs and complaints from those of the underlying disease [7].

Most of the patients are diagnosed during the worsening of the liver disease when the main clinical characteristics of diastolic heart failure and high-output heart failure usually appear. The decrease of systolic ventricular competence may enhance the development of complications, such as sodium and water-retention, ascites formation and worsening of the kidney function [7].

Regardless of clinical manifestation, systolic and diastolic heart failure are an independent risk factor for cardiovascular mortality in both symptomatic and asymptomatic patients [7].

Latent systolic and diastolic cardiac dysfunction is present in patients with cirrhotic cardiomyopathy and become manifested if the heart is challenged [10] and the risk of decompensation increase following invasive procedures [11].

This highlights the need for a rigorous cardiovascular risk assessment in patients with liver cirrhosis who will undergo surgery. However, there are currently no specific guidelines in this patient population, and clinicians use general guidelines for the preoperative assessment before surgery [12].

The current study was conducted to evaluate cardiac systolic and diastolic functions in patients with liver cirrhosis by conventional Doppler echocardiography and TDI and correlate the results with severity of cirrhosis based on Child-Pugh score.

By conventional echo assessment there was significant increase in the RVD and PASP which is explained as an adaptation of cardiac hemodynamics to changes in peripheral circulation. The mechanism of increased PAP is not fully understood, but previous studies suggested that increased levels of vasoactive substances in pulmonary circulation and the probable toxic effect of these substances on endothelial cells. Some authors have suggested that microthrombi can migrate to pulmonary vascular bed along porto-systemic shunts and can cause increase in vascular resistance [13].

However, similar changes could not be found in left ventricular diameters. A probable reason for this could be the facilitation of left ventricle performance because of decreased peripheral vascular resistance.

Yasemin et al., concluded that cirrhosis disrupts right ventricle function together with dilatation of both atria, increases pulmonary artery pressure but does not affect left ventricle functions [14].
In the present study, conventional echo parameters were within normal range in the 3 groups and were hyperdynamic in Child C. Also for diastolic parameters there wasn’t significant difference between 3 groups for PW parameters and diastolic dysfunction was diagnosed only in 67%.

These results are in agreement with a recent study by Piyush et al who compared cardiac status in patients with liver cirrhosis and healthy controls by conventional echo parameters, it was found that echocardiographic parameters of systolic and diastolic functions were not different in compensated versus decompensated patients in different Child-Pugh classes or cirrhosis etiologies. Diastolic dysfunction is a frequent event in cirrhosis; it is usually of mild degree and does not correlate with severity of liver dysfunction. There are no significant differences in echocardiographic parameters with increased severity of the disease [14].

And in another study by Sunil et al., there was no evidence of systolic dysfunction noted in the study population and there was no correlation between severity of cirrhosis and echocardiographic changes [15].

In our study systolic and diastolic dysfunction that was evident in Child B and C and diastolic dysfunction was diagnosed in 89% by TDI.

In a recent study conducted on 60 patients with liver cirrhosis by TDI it was found that left ventricular diastolic dysfunction is commonly associated with advancement of hepatic dysfunction while systolic function is maintained till advanced hepatic failure [16].

**Conclusion:**

Our study was able to discover latent systolic and diastolic cardiac dysfunction that wasn’t diagnosed by conventional echo and to discover it early in Child B.

**Recommendation:**

We recommend examining patients with liver cirrhosis with TDI whatever the stage of the disease routinely and especially before invasive procedure.

**References**


