Evaluation of Cardiac Function in Patients with Liver Cirrhosis

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Abstract

Aim of the study  To study the cardiac function in patients with liver cirrhosis.

Methods  Thirty patients with liver cirrhosis, referred to as group I (G I), were selected. They were subdivided according to Child-Pugh classification into 3 groups: A, B, and C. Thirty healthy subjects, referred to as group II (G II), were selected as a control group. All persons were examined by resting ECG, abdominal ultrasound, laboratory tests, and echo-Doppler evaluation of systolic and diastolic functions of both ventricles using 2-D, M-mode, conventional Doppler, and tissue Doppler parameters.

Results  Systolic and diastolic blood pressures were significantly reduced with increased resting HR and CO in G I (p<0.05). The QTc interval was prolonged in G I (0.45±0.03 ms; p<0.001) but EDV, ESV, EF%, and S’ velocity were not significantly different in both study groups for both ventricles. LAD, MPI, LVPWT, and IVST were significantly increased in G I (p<0.05). E/A and E’/A’ ratios were reversed in G I with increased DT/E for both ventricles (p<0.001). No significant difference was found among Child A, B, C subgroups except for the LAD which was significantly increased in Child C (p<0.05). There was a significant inverse correlation between serum albumin and left ventricular MPI (r = −0.4, p<0.05).

Conclusion  Many cardiovascular abnormalities occur in patients with liver cirrhosis that mandate echocardiographic evaluation especially in cases who undergo any procedure which may affect the hemodynamics.

Key words: liver cirrhosis, echo-doppler, cardiac function

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Introduction

The comorbidity of liver cirrhosis and heart failure has always been a matter of interest. While the occurrence of liver cirrhosis in cases of advanced heart failure was well recognized long ago, the development of heart failure as a complication of liver cirrhosis was only brought to light few decades ago. In 1953, Kowalski and Abelmann described the possibility of cardiac dysfunction in patients with liver cirrhosis and attributed its occurrence to the eventual metabolic complications of alcohol intake or hemochromatosis (1). Since then, collective evidence has led to the development of the term “cirrhotic cardiomyopathy” which refers to a state of hyperdynamic circulation with a baseline increase in cardiac output, decrease in peripheral vascular resistance, blunted systo-diastolic response to physical and pharmacological stress, electrophysiological abnormalities, and slight histo-morphological changes in the context of liver cirrhosis (2). The pathophysiology of cirrhotic cardiomyopathy is not yet fully understood, but abnormal membrane biophysical characteristics, impaired β-adrenergic receptor signal transduction and increased activity of negative inotropic pathways mediated by cGMP may be implicated (3).

Although some authorities contend that cirrhotic cardiomyopathy is a latent pathology which manifests only under stress, we hypothesize that patients with liver cirrhosis may exhibit clinical and/or echocardiographic signs of cardiac dysfunction even at rest. This research is meant to evaluate the cardiac function in cirrhotic patients at rest which may be of value when screening for the prevalence of cardiac dysfunction in cirrhotic patients and which may help in de-

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terminating candidacy for liver transplantation without the need for more stressful testing techniques.

**Patients and Methods**

**Patients**

Thirty patients fulfilling the criteria of liver cirrhosis (all were of viral etiology) were selected and referred to as group I (G I). They were further subdivided according to Child-Turcotte-Pugh scoring system (4) into 3 groups; A, B and C. The following exclusion criteria were considered during the patient selection:

1. Patients with any cardiovascular diseases e.g. hypertension, ischemic heart disease, valvular heart disease and congenital heart disease.
2. Severe anemia and other causes of hyperdynamic circulation.
3. Disturbance of rhythm e.g. A.F.
4. Renal failure.
5. Diabetes Mellitus.

**Control**

Thirty healthy age- and sex-matched subjects with no evidence of any cardiovascular or hepatic affection were taken as a control group and referred to as group II (G II).

**Methods**

All persons were subjected to all of the following:

1. Complete history taking and thorough clinical examination.
2. Resting ECG: The QT intervals were determined. Heart rate correction of the QT interval (QTc) was calculated using the Bazett formula (5).
3. Liver function tests and complete blood count.
4. Echo-Doppler evaluation: The machine used was Hewlett Packard Sonos 5500 ultrasound system with 2.5 MHz transducer. Images were taken with the patient supine or in the left lateral position, utilizing the two-dimensional (2-D), M-mode and Doppler echocardiographic techniques. All of the echocardiographic measurements were performed blindly.

The following measures were selected for analysis:

1) Left atrial diameter (LAD): by M-mode and 2-D measurements.
2) Interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), LV systolic function parameters: End systolic (LVIDs) and end diastolic (LVIDd) dimensions and volumes (EDV and ESV) were calculated and hence EF % and FS% were measured by M-mode and modified Simpson technique.
3) Right ventricular end diastolic dimension (RVIDd), end diastolic (EDV), and end systolic (ESV) volumes were calculated and hence EF % and FS% were measured by modified Simpson technique.

Left ventricular systolic dysfunction was defined as EF of less than 50% (6), while right ventricular systolic dysfunction was defined as EF of less than 45% (7).

4) Evaluation of diastolic function of both ventricles was carried out by placing a sample volume at the tip of the mitral and the tricuspid valves in the apical four-chamber view and aligning the ultrasound beam direction with ventricular inflow tract. The following measures were selected for analysis: E wave velocity, A wave velocity, E/A ratio, deceleration time (DT) of E wave. Then, pulsed wave Doppler sample volume was directed to measure Doppler timed intervals from the mitral inflow and left ventricular outflow and from the tricuspid inflow and right ventricular outflow. The following velocity time intervals were measured: Isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), ejection time (ET). The myocardial performance index (MPI) was calculated as the sum of IVCT and IVRT divided by ET.

5) Tissue Doppler indices (TDI) of mitral and tricuspid annular velocities:

TDI was applied in the pulsed Doppler mode to allow for a spectral display and recording of mitral and tricuspid annular velocities at septal and lateral corners (8).

Systolic (Sa), early diastolic (Ea), and late diastolic (Aa) velocities were measured, and the Ea/Aa ratio was computed and the average results in septal and lateral views were used.

**Data analysis**

Data were checked, entered and analyzed using Epi-INFO software computer package, and were expressed as Mean ± standard deviation for quantitative variables; number and percentage for qualitative variables. ANOVA, Chi-square, and correlation were also used. P-value was found from special tables for \( \chi^2 \) and t according to the degree of freedom. A P-value of less than 0.05 was considered significant (9).

**Abbreviations:** QTc: corrected QT interval, LAD: left atrial diameter, IVST: interventricular septum thickness, LVPWT: left ventricular posterior wall thickness, EF: ejection fraction, MPI: myocardial performance index

**Results**

- Blood pressure (systolic and diastolic) was significantly reduced with significantly increased HR as well as QTc interval in resting ECG in GI versus G II (Table 1).
- Left atrium was significantly enlarged with significantly increased IVST, LVPWT, and cardiac output in G I versus G II but no difference was found between the two groups regarding LVEF% (Table 2).
- Regarding RV diameter, RV stroke volume and RV EF %, there was no significant difference between GI and GII (Table 3).
- E/A and E′/A′ ratios of both transmitral and transticruspid flow were significantly reduced with a significantly increased DT/E wave in G I. Myocardial performance index of the LV and RV was significantly increased in G I as well
Liver cirrhosis is a major health problem that is associated with a host of cardiovascular abnormalities in systemic and pulmonary circulation. From a functional point of view, the heart in cirrhosis is both hyperdynamic and dysfunctional (10). This dysfunction may be great and manifest in some situations like liver transplantation which constitutes a great physical stress for the cardiovascular system, during both the trans-operative and the postoperative period. Characteristically, 56% of patients in certain series exhibited acute pulmonary edema during the early postoperative period, while 7-21% of post-operative deaths were attributed to heart failure (11).

So, it is important to evaluate cardiovascular function in every patient with liver cirrhosis especially if that patient is a candidate for any intervention that may affect hemodynamics. This study showed a significant decrease in both systolic and diastolic blood pressure in cirrhotic patients. This is in agreement with Baik et al (12) and is probably attributed to arterial vasodilatation characteristic to cirrhosis (13). Also, patients with liver cirrhosis showed higher heart rates in agreement with Baik et al (12) and this may be attributed to the presence of autonomic dysfunction (14) or hypervolemia (15) in those patients.

Concordant with Ho and Youshida (10) who reported that the hyperdynamic circulation in cirrhotic patients is characterized by peripheral vasodilatation and increased resting cardiac output, this study showed that resting cardiac output was significantly higher in cirrhotic patients inspite of the insignificantly increased stroke volume, and this may be due to the increased resting heart rate. Many subsequent theories have been expounded to explain the underlying mechanism of this peripheral arterial vasodilatation. Most suggest the production of, or failure to metabolize, circulating vasodilator substances that cause decreased vascular tone, recruitment of arterio-venous anastomoses and systemic hypotension. Various candidate vasodilators have been proposed, including nitric oxide, eicosanoids, bile salts, adenosine and tachykinins, such as substance P, and calcitonin-gene-related peptide (16).

Baik et al (12) found that 30-60% of cirrhotic patients had a prolonged QT interval. In this study, the QT interval was found to be prolonged in 12 cirrhotic patients (40%). This prolongation may be due to alterations of ion channel activity in cardiomyocyte plasma membranes (17). Many previous studies have found dilatation of the left atrium, and hypertrophy or dilatation of the left ventricle in patients with liver cirrhosis. The right atrium and right ventricle generally have normal dimensions and wall thickness in the absence of the uncommon syndrome of porto-pulmonary hypertension (18). In this study, left atrial diameter was found to be significantly increased in cirrhotic patients. Also, LVPW thickness and IVS thickness were found to be significantly increased indicating the pres-

Table 1. Demographic, Clinical, and ECG Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>G I (Patients) n=30</th>
<th>G II (Control) n=30</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: M</td>
<td>22 (73.3%)</td>
<td>21 (70%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>F 8 (26.7%)</td>
<td>9 (30%)</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>49.3 ± 3.67</td>
<td>51.2 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>109 ± 8.7</td>
<td>120 ± 6.1</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.8 ± 5.9</td>
<td>76 ± 5.5</td>
<td>0.03</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>94.9 ± 9.3</td>
<td>78.9 ± 8.4</td>
<td>0.001</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>0.45 ± 0.03</td>
<td>0.4 ± 0.02</td>
<td>0.001</td>
</tr>
</tbody>
</table>

M Male, F Female, SBP Systolic Blood Pressure, DBP Diastolic Blood Pressure, HR Heart Rate, NS Not Significant

Table 2. Left Atrial Diameter & Left Ventricular Systolic Function and Dimensions

<table>
<thead>
<tr>
<th>Variable</th>
<th>G I</th>
<th>G II</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD (cm)</td>
<td>3.96 ± 0.55</td>
<td>3.35 ± 0.52</td>
<td>0.001</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.64 ± 2.23</td>
<td>5.4 ± 0.7</td>
<td>0.004</td>
</tr>
<tr>
<td>EF %</td>
<td>61 ± 9.6</td>
<td>62.7 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>4.7 ± 0.6</td>
<td>4.8 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>LVPWT (cm)</td>
<td>0.96 ± 0.14</td>
<td>0.88 ± 0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>IVST (cm)</td>
<td>0.97 ± 0.16</td>
<td>0.88 ± 0.15</td>
<td>0.02</td>
</tr>
</tbody>
</table>

LAD Left Atrial Diameter, EDV End Diastolic Volume, ESV End Systolic Volume, SV Stroke Volume, CO Cardiac Output, EF Ejection Fraction, LVIDd Left Ventricular Internal Diameter in diastole, LVPWT Left Ventricular Posterior Wall Thickness, IVST Intraventricular Septum Thickness

Table 3. Right Ventricular Volumes, Systolic Function and Dimension

<table>
<thead>
<tr>
<th>Variable</th>
<th>G I</th>
<th>G II</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV (mL)</td>
<td>52.5 ± 10.5</td>
<td>55.8 ± 12.6</td>
<td>NS</td>
</tr>
<tr>
<td>ESV (mL)</td>
<td>23.4 ± 6.1</td>
<td>25.6 ± 7.8</td>
<td>NS</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>31.1 ± 7.6</td>
<td>34 ± 7.3</td>
<td>NS</td>
</tr>
<tr>
<td>EF %</td>
<td>56.6 ± 11.0</td>
<td>57.5 ± 3.3</td>
<td>NS</td>
</tr>
<tr>
<td>RVdId (cm)</td>
<td>2.8 ± 0.45</td>
<td>2.9 ± 0.46</td>
<td>NS</td>
</tr>
</tbody>
</table>

EDV End Diastolic Volume, ESV End Systolic Volume, SV Stroke Volume, CO Cardiac Output, EF Ejection Fraction, RVdId Right Ventricular Internal Diameter in diastole

(Table 4).

- Regarding G I subgroups, there was no significant difference among the three groups regarding BP, QTc interval, cardiac output, EF% or myocardial performance index either for LV or RV but there was significant LA enlargement in subgroup C > B > A (Table 5).
- There was a significant negative correlation between serum albumin level and myocardial performance index (MPI) of the left ventricle in GI (Fig. 1).

Abbreviation: HR: heart rate, DT/E: deceleration time of E wave

Discussion

Liver cirrhosis is a major health problem that is associated with a host of cardiovascular abnormalities in systemic and pulmonary circulation. From a functional point of view, the heart in cirrhosis is both hyperdynamic and dysfunctional (10). This dysfunction may be great and manifest in some situations like liver transplantation which constitutes a great physical stress for the cardiovascular system, during both the trans-operative and the postoperative period. Characteristically, 56% of patients in certain series exhibited acute pulmonary edema during the early postoperative period, while 7-21% of post-operative deaths were attributed to heart failure (11).

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ence of left ventricular hypertrophy in those patients (19). These abnormal structural findings in cirrhotic patients seem to be an adaptation of cardiac hemodynamics to the changes in the peripheral circulation and thus the role of the rennin-
angiotensin-aldosterone system (RAAS) and adrenergic hyperactivity has been considered (20). These results disagree with the results of Soyoral et al (21), who found no changes in ventricular dimensions and explained this by the facilitation of left ventricle performance because of decreased peripheral vascular resistance.

Inspite of the generally insignificant changes in EF% and S’ wave velocity (parameters of systolic function) (19) of both left and right ventricles in cirrhotic patients compared with control group, 3 patients (10%) were found to have left ventricular systolic dysfunction when we used “50%” as the cut off value for normal LV EF % and “7.5 cm/s” as the cut off value for normal S’ wave average velocity of the mitral valve annulus (22).

Also, we found that 6 patients (20%) had right ventricular systolic dysfunction when we used “45%” as the cut off value for normal RV EF% and “11.5 cm/s” as the cut off value for normal S’ wave average velocity of the tricuspid valve annulus (7). Gruber et al (23) invasively assessed RV hemodynamics in two groups of patients with acute liver failure and with acutely decompensated chronic liver disease. They found that all patients showed evidence of RV dysfunction when “52%” was used as the cut off value for normal RV EF% and “92 mL/m²” as the cut off value for normal RV end diastolic volume index (RVEDVI).

In contrast to systolic dysfunction, diastolic dysfunction appears to be more prevalent and some degree of diastolic dysfunction is present in virtually every patient with cirrhosis (24).

In this 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 a significant increase in DT of E wave, IVRT, significant decrease in E’ wave average velocity of both mitral and tricus-
Diastolic dysfunction often leads to lengthening of the ET. Thus, both systolic and diastolic dysfunction will result in an increase in the MPI. Values greater than 0.50 were considered abnormal (27).

In cirrhotic patients, MPI was significantly increased in both left and right ventricles. This result was considered a marker for impaired global left and right ventricular function.

The increase in right ventricular MPI may be either due to the same factors that affected the left ventricle or due to pulmonary hypertension as an increased right ventricular MPI is a sensitive and specific marker of pulmonary hypertension (27). Comparison between patients in G I based upon the severity of the disease (i.e. Child A, B, and C) revealed no significant difference among the three groups regarding the prevalence of cardiovascular abnormalities except for the left atrial diameter which was found to be significantly increased in Child C > Child B > Child A patients.

This result disagrees with the results of Trevisani et al (28), and Baik et al (12) who reported that the degree of circulatory hyperkinesis, electrophysiological abnormalities in the form of QT prolongation, and structural changes correlate with the degree of severity of liver cirrhosis.

This disagreement could be due to the small number of the studied population and also because the study was done at rest. Subjecting the study population to stress either physically or pharmacologically may unmask hidden cardiovascular abnormalities and show the differences among the three groups (13).

Finally, the correlation between laboratory and echocardiographic data of the cirrhotic patients has revealed the presence of a significant negative correlation between serum albumin levels and left ventricular MPI. This finding may draw attention to the role of albumin deficiency in the pathophysiology of heart failure, especially considering that previous studies had presumed that normal levels of serum albumin may have direct protective effects such as anti-apoptotic and antioxidant activity (29).

**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. We cannot rule out the decreased cardiac reserve in stress conditions because we evaluated all of our patients in the resting position. Pulmonary changes were not studied to confirm whether RT sided affection had occurred due to pulmonary abnormalities or due to the same factors affecting the left side. Re-evaluating the cardiac function after procedures which are commonly done for cirrhotic patients such as ascetic fluid tapping or TIPSS operation to evaluate the impact of such procedures on the cardiovascular system was not included in the study.

In conclusion many cardiovascular abnormalities occur in patients with liver cirrhosis and the role of the cardiologist to unmask these abnormalities may help management of this group of patients. Thus, we recommend that every patient with liver cirrhosis should be thoroughly evaluated by echocardiography to be able to predict any possible deterioration of cardiac function specially in the case of undergoing any procedure which may affect the hemodynamics, e.g. paracentesis and TIPSS operation, suffering diseases other than cirrhosis or occurrence of hematemesis. Particular concern should be directed to those who are candidates for liver transplantation as cardiovascular decompensation can be a leading cause of operative failure.

**Abbreviation:** CO: cardiac output

**Acknowledgement**

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**References**


