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Left Ventricular Dysfunction In Patients With Liver Disease

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Abstract

A. Background*: Both liver and heart diseases are considered a serious problem in the health system and a major reason for the deterioration of the quality of life and its short expected duration. Therefore, it is important to study the hepato-cardiac interactions.*

B. Aim & Objective: *studying the effects of liver diseases on left ventricle (LV) systolic, diastolic & electrophysiological functions.*

C. Material & Methods: *A total of 63 cases of diagnosed liver disease patients (22 without cirrhosis and 41 with cirrhosis) with 63 age sex-matched healthy control subjects were included in this study. Both those with liver disease and healthy subjects underwent an electrocardiogram and 2D Echocardiography.*

D. Results: *QTc interval in liver disease patients was longer than controls and abnormally prolonged in cirrhotic patients. The systolic function of LV in liver disease patients was mostly normal but increased in cirrhotic patients with a statistical significance when compared to non-cirrhotic patients and the control group. Diastolic dysfunction was noticed in cirrhotic and non-cirrhotic patients. In cirrhosis, there were a statistically significant increase in IVRT [92.36±12.2 ms] VS.[73.7±10.2 ms] in the control group (P<0.05). In noncirrhotic patients, there was a statistically significant increase in IVRT [88.77±13.1] VS. [73.7±10.2] in the control group (P<0.05). We noticed a statistically significant increase in Myocardial Performance Index(MPI) in cirrhotic and non-cirrhotic patients [0.43±0.1 and 0.39±0.05 respectively] VS. [0.33±0.04] in the control group (P<0.05).*

E. Conclusion: *In patients with liver disease, QTc interval was longer, and in addition to compromised LV diastolic function, MPI was also increased, which reflects both systolic and diastolic LV dysfunction.*

Keywords - *liver disease; cirrhosis; Left Ventricular function; Doppler Echocardiography.*

I. INTRODUCTION

Keeping a stable internal environment requires precise regulation of whole-body homeostasis in which organ-organ communication plays critical roles. Hence the importance of the interaction between the liver and the heart, as the liver is responsible for a variety of physiological processes. (1)

Anatomically and physiologically, the liver and the heart are connected with each other primarily via 'blood circulation. Pathologically, liver diseases can affect the heart, and conversely, heart diseases can affect the liver. (2)

Liver diseases are common and account for approximately 2 million deaths per year worldwide. Alcohol and non-alcoholic fatty liver disease are the most common causes of liver disease in developed countries, whereas viral hepatitis remains a major cause of liver disease in developing countries. (3)

Liver diseases may affect heart functions and electrophysiology in the absence of another cardiac disease. (4) Liver disease is associated with significant cardiovascular changes such as left ventricular systolic and diastolic dysfunction, in addition to electrophysiological abnormalities including Chronotropic incompetence, QT prolongation, decreased heart rate variability, and electromechanical dyssynchrony. (5)

This article highlights liver disease as a cause of heart disease.

II. AIM OF THE STUDY

This study aims to highlight the effect of liver disease on the cardiovascular system.

III. MATERIALS AND METHODS

This case-control study was conducted at the Cardiology and Gastroenterology departments in Tishreen University Hospital between April 2020 and September 2021 and included 63 patients(38 males and 25 females) with diagnosed liver disease categorized into patients with and without evidence of liver cirrhosis (41 and 22 patients respectively), who were compared with 63 healthy participants (41 males and 22 females) as a control group. The two groups were matched in terms of age, gender, and cardiovascular risk factors. We excluded patients with ischemic heart disease, rheumatic heart disease, valvular heart diseases, endocarditis, diabetes mellitus,

hypertension, chronic kidney disease, and alcoholic patients. The two groups were scrutinized for electrocardiogram and Transthoracic echocardiography, where QT interval, systolic and diastolic functions of the left ventricle, and MPI measurements were performed. Bi-dimensional, pulsed Doppler, M-mode, and color flow Doppler echocardiographic examinations were performed. Using Fukuda CardiMax FX-7102 Electrocardiograph machine, QTc interval was measured. Using Siemens Acuson x300 premium ultrasound machine, the LV diastolic function was evaluated according to the recommendations of the American Society of Echocardiography 2016, the LV systolic function was evaluated using the modified Simpson method, and Myocardial Performance Index (MPI), which is a Compound index of LV systolic and diastolic functions was also evaluated.

All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical assessment of our study was performed by using IBM Statistical Package for Social Sciences (SPSS) for Windows, version 20, manufactured by IBM Corp., located in Armonk, N.Y., USA, and summarized as frequencies and proportions. $P<0.05$ value was accepted to be statistically significant. The results were indicated in average ±SD and in percentage (%). One-way ANOVA was used for comparing groups. The independent-samples t-test was used for comparing the 2 groups, and the t-test was used for variables.

IV. DEFINITIONS

A. QT interval: The QT interval extends from the onset of the QRS complex to the end of the T wave. Thus, it includes the total duration of ventricular activation and recovery and, in a general sense, reflects the duration of the ventricular action potential. When the interval is measured from a single lead, the lead in which the interval is the longest (most frequently lead V2 or V3) and in which a prominent U wave is absent (usually aVR or aVL) is preferred.

Numerous formulas have been proposed to correct the measured QT interval for this rate effect, including one proposed by Bazett in 1920. The result is the *corrected QT interval*, or *QTc*, defined by the following equation: $QTc = QT / \sqrt{RR}$.(6)

B. Mitral E/A ratio: Mitral valve E velocity divided by A-wave velocity is used to identify the filling patterns: normal, impaired relaxation (grade I), pseudonormal (grade II), and restrictive filling (grade III).

***C. IVRT*:** Isovolumic relaxation time is the Time between aortic valve closure and MV opening. IVRT is=<70 ms in normal subjects and is prolonged in patients with impaired LV relaxation but normal LV filling pressures. When LAP increases, IVRT shortens, and its duration is inversely related to LV filling pressures in patients with cardiac disease.

***D. Mitral E/é*:** MV E velocity divided by mitral annular é velocity. é velocity can be used to correct for the effect of LV relaxation on mitral E velocity, and the E/é ratio can be used to predict LV filling pressures. (7)

***E. MPI*:** Myocardial performance index (MPI), or Tei index, is a Doppler echocardiographic parameter defined as the sum of the Isovolumic contraction and relaxation times divided by the ejection time. It is considered a reliable parameter for the global left ventricular function.(8)

V. RESULTS

A total of 63 liver disease patients and 63 healthy controls were included in the study. Patients were divided into two groups to be studied: a liver disease without evidence of cirrhosis (22 patients) and liver disease with evidence of cirrhosis (41 patients).

The mean age of all patients was 47.03±11.2 years, and the sex ratio (M: F) was 1.5:1. The mean age and sex ratio of the controls groups were similar to those in the patient's groups.

The most common cause of liver disease in our study was viral hepatitis (Table 1).

Table 1 .Cause of liver disease in patients group in our study

Cause of liver disease	Without cirrhosis (22)	With cirrhosis (41)
HCV	**6 (27.3%)**	**14 (34.2%)**
HBV	**4 (18.2%)**	**13 (31.7%)**
NAFLD	**6 (27.3%)**	**0 (0%)**
Cryptogenic	**0 (0%)**	**13 (31.7%)**
Biliary disease	**1 (4.5%)**	**1 (2.4%)**
HAV	**2 (9.1%)**	**0 (0%)**
Other cause	**3 (13.6%)**	**0 (0%)**

When we studied Electrocardiogram to identify the QT interval, we noticed an increase in QTc in the patient's group compared to the control group, and this increase was statistically significant (P-value=0.0001)(Table 2). We also noticed a statistically significant difference between the two patient groups (P-value= 0.03), also between patients with cirrhosis and without cirrhosis compared to the control group (P-value= 0.005 and 0.04 respectively).

Table 2. QTc differences between liver disease patients and controls in our study

QTc(ms)	Liver disease		Controls	P-Value
	With cirrhosis	Without cirrhosis		
	458.65±40.6	441.22±36.1	425.8±20.8	0.0001

When we studied Myocardial Performance Index (MPI) in patients groups compared to controls, we noticed a statistically significant increase in MPI in liver disease patients compared to controls (P-value=0.01)(Table 3). We also noticed a statistically significant difference between the two patient groups (P-value= 0.01), also between patients with cirrhosis and without cirrhosis compared to the control group (P-value= 0.001 and 0.04 respectively).

Table 3. Myocardial Performance Index (MPI) differences between liver disease patients and controls in our study

MPI	Liver disease		Controls	P-Value
	With cirrhosis	Without cirrhosis		
	0.43±0.1	0.39±0.05	0.33±0.04	0.01

When we studied left systolic ventricle function, we noticed an increase in ejection fraction (EF) in patients with cirrhosis compared to control group which was statistically significant (P-Value=0.03). The difference in the patient's group as a whole was not statistically significant compared to controls (P-Value=0.07)(Table 4).

Table 4. Ejection fraction (EF) differences between liver disease patients and controls in our study

EF(%)	Liver disease		Controls	P-Value
	With cirrhosis	Without cirrhosis		
	65.5±8.8	60.1±7.1	59.3±5.1	0.07

When we studied left ventricle diastolic function in liver disease patients, we noticed statistically significant changes in LV diastolic function in cases compared to controls (Table 5). We also noticed a statistically significant increase in Isovolumic relaxation time IVRT in patients with and without cirrhosis (92.36±12.2 ms and 88.77±13.1 respectively) as compared to controls 73.7±10.2 ms (p-value=0.01), but we did not notice any statistical significance in E/A and E/é parameters between patients and controls (P-Value=0.3 and 0.1 respectively)(Table 6).

Table 5. Left ventricle diastolic function changes in liver disease patients and controls in our study

LV Diastolic function	Liver disease		controls
	With cirrhosis	Without cirrhosis	
Normal	18(43.9%)	14(63.7%)	53(84.1%)
Grade I	15(36.6%)	7(31.8%)	10(15.9%)
Grade II	6(14.6%)	1(4.5%)	0(0%)
Grade III	2(4.9%)	0(0%)	0(0%)

Table 6. Left Ventricle diastolic function differences between liver disease patients and controls in our study

LV Diastolic Function	Liver disease		Controls	P-Value
	With cirrhosis	Without cirrhosis		
E/A	**1.08±0.4**	**1.11±0.4**	**1.19±0.3**	**0.3**
IVRT (ms)	**92.36±12.2**	**88.77±13.1**	**73.7±10.2**	**0.01**
E/e´	**8.27±3.6**	**7.16±1.89**	**6.99±0.9**	**0.1**

VI. DISCUSSION

The liver plays a pivotal role in nutrient metabolism and detoxification of a variety of metabolic products. It is an important organ in the immune system and has many other functions. The defect in these multiple functions prompted us to study the potential effects of liver disease on the heart. What we observed in this study is that liver disease is associated with important cardiovascular changes. The current study is a case-control study with a male predominance of 60.3% in the patient's group, which can be due to the distribution of liver disease between the genders as it is more common in males. (3)

Firstly we studied QTc, our results showed an increase in QTc in the patient's group compared to controls, and this increase was statistically significant (p-value=0.0001). An explanation of these results may be that liver diseases are inflammatory diseases associated with increased levels of proinflammatory cytokines (IL-1B, IL-6, and TNF-a), which can contribute to the prolongation of the cardiac action potential by their effect on cardiac membrane ion channels. (9)(10)(11)When we compared QTc in the two patient groups, we noticed an increase in mean value in cirrhotic patients with a statistically significant difference (p-value=0.03) which, in addition to the effects of inflammatory cytokines, can be due to hyperactivity of sympathetic nervous system (SNS) in cirrhosis. (12)Another explanation of QTc prolongation in cirrhosis may be because of altered plasma membrane fluidity(13)(14), toxic effects of bile acids on ion channels, and hyperinsulinemia seen in cirrhotic patients. (15)

Myocardial Performance Index (MPI) values which reflect both systolic and diastolic function of the left ventricle, showed a statistically significant increase in liver disease patients compared to controls (p-value=0.01). This increase in MPI prompted us to study left ventricle systolic and diastolic function separately.

When we studied left ventricular ejection fraction (LVEF), we noticed an increase in cirrhotic patients compared to controls which were statistically significant (p-value=0.03). The difference between the patient's group as a whole and controls was not statistically significant, and that may be because a relatively long period was needed for LV systolic dysfunction to be developed. The increase in LVEF in cirrhotic patients can be due to the hyperdynamic circulation in cirrhosis in the context of splanchnic vasodilatation and elevated portal vein pressure. (16) In cirrhosis, there is an increased production/activity of vasodilator factors (NO, Endocannabinoids, and CO) and decreased vascular reactivity to vasoconstrictors. (17)In addition, there is a decreased metabolism of potential harmful vasodilators because of loss of functional liver cell mass(18) or because bypass the liver through portosystemic collaterals and escape degradation in the diseased liver. (19)

A study which was done in Australia in 2013 showed an important role of the Renin-Angiotensin system (RAS) in the development of splanchnic vasodilatation. Although RAS contributes to fibrogenesis and increased hepatic resistance in patients with cirrhosis, the increased activity of the alternate system in which Angiotensin II is cleaved by Ang-converting-enzyme-2 to Ang(1-7) leads to activation of Masr and splanchnic vasodilatation. (20)

When we studied left ventricle diastolic function, we noticed a significant increase in detecting LV diastolic dysfunction in the patient's group. We noticed a statistically significant increase in IVRT in patients compared to controls, but we did not notice any statistical significance in E/A and E/é parameters between patients and controls. That may be because most of our patients had grade I diastolic dysfunction, which associates with prolongation of IVRT.

We can explain these changes in diastolic function from a pathophysiological point of view by the contribution of several factors: 1) Liver disease is associated with an inflammatory state that causes endothelial dysfunction and cardiac ischemia, in addition to the toxic effects of cytokines and ROS on the cardiac muscle. (18)2) Altered plasma lipid levels in liver disease suggests a potentially higher risk of CVD in these patients. (9)3) Hyperactivity of SNS in the context of hyperdynamic circulation in cirrhosis with sustained activation of RAAS as Ang II and aldosterone induce cardiac fibrosis and ongoing remodeling. (21)4) Fluid and sodium retention is seen in cirrhosis in the early stages because hemodynamic changes cause volume overload, cardiac hypertrophy, fibrosis, and subendocardial edema. (22) With the progression of the disease, advanced mesenteric vasodilatation leads to accumulation of fluids in the splanchnic circulation with

ascites formation, which causes decreased effective blood volume despite intense activation of compensatory mechanisms in a vicious cycle. (18)

VII. CONCLUSION

In patients with liver disease, the QTc interval, which reflects ventricular action potential was prolonged, left ventricular diastolic function was compromised, and Myocardial Performance Index (MPI), which reflects both systolic and diastolic left ventricular dysfunction, was abnormally increased compared to healthy subjects matched for age, gender, and cardiovascular risk factors. We conclude that cardiovascular abnormalities in liver disease may arise on the basis of combined humoral, nervous, and hemodynamic changes. Our results indicate the importance of collaboration between cardiologists and hepatologists in the follow-up and management of patients with liver disease.

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