Cardiac Changes in Cirrhotic Patients

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Background and study aim: Cardiac dysfunction in cirrhotic patients presented by imperfect cardiac contractility in response to stress and/or change in the diastolic relaxation of the heart with electrophysiological changes in lack of other recognized cardiac disease. The study aimed to assess the cardiac changes in cirrhotic patients.

Patients and Methods: our study was conducted on 100 adult cirrhotic patients who were divided according to the Child Pugh score into 3 groups: G1: comprised 30 Child A patients. G2: comprised 30 Child B patients. G3: comprised 40 Child C patients. Full history, clinical examination, laboratory (CBC, liver and kidney function tests, viral markers and FBS), ECG and cardiac echo-doppler were done for all patients.

Results: Out of 100 cirrhotic patients, QTC interval was found to be prolonged in 70 cirrhotic patients. Echo-cardiographic abnormalities were found in Child B and C group patients more than in Child A patients. There was significant increase in Echo parameters as (IVRT and PAP) with liver disease deterioration from Child A to Child C. There was no significant difference regarding left and right ventricular end diastolic diameter among the studied groups.

Conclusion: 70% of cirrhotic patients had cardiac changes and there is positive correlation between severity of liver cirrhosis and cardiac changes.

INTRODUCTION

Liver cirrhosis is associated with a wide range of cardiovascular changes including hyper dynamic circulation, pulmonary vascular abnormalities, and cirrhotic cardiomyopathy. The pathogenesis of these cardiovascular changes is multifactorial and includes neuro-humoral and vascular dysregulations. Cirrhosis-related cardiovascular changes are considered the major pathogenic factor of several serious conditions including ascites, hepatorenal syndrome, gastroesophageal varices, and hepatopulmonary syndrome **[1]**. Although the specific cardiovascular conditions related to liver cirrhosis are known, its true prevalence remains unknown, perhaps because it was only observed in patients with advanced liver disease **[2]**. Prolongation of the QTC interval at electrocardiography is the main electrophysiological changes in patients with liver cirrhosis **[3]**.

Our study aimed to assess the cardiac changes in cirrhotic patients.

.PATIENTS AND METHODS

This cross sectional study was carried out in Tropical Medicine Department, Zagazig University Hospitals, during the period from March 2018 to October 2018. The study comprised 100 cirrhotic patients who were attending the outpatient clinics or admitted to Tropical Medicine Department, Zagazig University Hospitals, during this period. They were 58 males and 42 females. Their age ranged from 32 to 75 years.

Cirrhotic patients were divided according to the Child Pugh score into 3 groups:

G1: comprised 30 Child A cirrhotic patients.

G2: comprised 30 Child B cirrhotic patients.

G3: comprised 40 Child C cirrhotic patients.

Inclusion criteria: Patients with established liver cirrhosis, according to clinical, biochemical and imaging study were included in the study.

Exclusion criteria: Patients who had cardiovascular disease, HTN, DM, metabolic syndrome, thyroid disease, active alcohol abuse, hepatocellular carcinoma, active GIT bleeding and any drug history or other causes of prolonged QTC interval were excluded from the study.

Methods:

All participants were subjected to:

I- Detailed history taking with stress on symptoms that reflect cardiac affection.

II- Thorough clinical examination including: pulse rate, blood pressure, local cardiac examination to exclude concomitant heart disease as well as abdominal examination to detect signs of liver cirrhosis.

III- Lab Investigations:

1. Viral markers: HBs-Ag (hepatitis B virus surface antigen) & HCV-Ab (Anti-hepatitis C virus antibody).
2. Complete blood count by using (system xkx21 from roche diagnosis).
3. Liver function tests by using (Dimension Rxl Autoanalyser from Siemens).
4. Kidney function tests by using (Dimension Rxl Autoanalyser from Siemens).
5. Serum sodium and potassium.
6. Fasting blood sugar and post-prandial blood sugar.
7. Lipid profile to exclude hyperlipidemia.
8. Homeostatic Model Assessment (HOMA IR): calculated by using the following formula:
   - Fasting glucose (mg/dL) X fasting insulin (µU/mL) / 405 (for SI units: fasting glucose (mmol/L) X fasting insulin (µU/L) / 22.5).
   - a value greater than 2 indicates insulin resistance
9. TSH, Free T3, T4 by using ELISA kits.

IV- Fib4 was estimated for each patient [25].

FIB 4 = Age (years) x AST level (IU/L)/ Platelet count ($(10^9$/L) x √ALT (IU/L)

V-Abdominal Ultrasound **(using TOSHIBA Apolio 50 SSA-700A Device).**

VI-**Electrocardiogram:** The longest and shortest QT intervals were determined. Correction of the QT interval (QTc) was calculated using the followig formula: [26]

$$QTc = \frac{QT\ interval}{\sqrt{R-R\ interval}}$$

VII- **Echodoppler:** The machine used was **(**Siemens**AcusonX 300 Device)**; Patients were studied in long axis parasternal, short axis parasternal, apical four chambers, apical five chambers, and apical two chambers views to measure the following parameters:

- LV systolic diameter in mm.
- LV diastolic diameter in mm.
- LV volume in systole in ml.
- LV volume in diastole in ml.
- RVdiastolic diameter in mm.
- Pulmonary artery pressure (PAP) in mmHg.
- Peak E velocity in cm/sec.
- Peak A velocity in cm/sec.
- E/A ratio.
- Isovolumetric relaxation time (IVRT) in msec.
- Ejection Fraction (E.F.) [27].

It is calculated from the formula:

$$EF = \frac{EDV - ESV}{EDV} X\,100\%$$

Where EDV (End Diastolic volume) = $(EDD)^3$, ESV (End systolic Volume) = $(ESD)^3$.

Normally it is 50 -70%**.**

Statistical analysis

Collection of data was done, entered and analyzed using Microsoft Excel software. Then all data collected was imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(Statistical Package for the Social Sciences)** software for analysis. Qualitative data represent as number and percentage, quantitative data represent by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X^2). Differences between parametric quantitative multiple groups by ANOVA or Kruskal Walis test, correlation by Pearson's or Spearman's correlation, P value was set at <0.05 for significant results &<0.001 for

high significant result. Data were collected and submitted to statistical analysis.

RESULTS

There was no significant difference among the studied groups as regard age, sex and residence. (table 1)

Systolic blood pressure and diastolic blood pressure were significantly lower among Child B and Child C patients when compared to Child A patients. (table 2)

Signs of LCF as (ascites, L.L. edema, jaundice and hepatic encephalopathy) were more prevalent in patients with advanced liver cirrhosis (Child B and C). (table 3)

There was significant decrease in hemoglobin level, WBcs count, platelets, MCV and MCH with the progression of liver disease from Child A to Child C. (table 4)

There was significant increase in bilirubin, creatinine, PT and INR with the progression of liver disease from Child A to Child C while there was significant decrease in serum albumin with the progression of liver disease. (table 5)

Out of 100 cirrhotic patients, QTC interval was found to be prolonged in 70 cirrhotic patients, who had also echo-cardiographic abnormalities. QTC was recorded to be (0.42 in G1, 0.46 in G2 and 0.48 in G3) with significant difference between the studied groups. There was significant increase in Echo parameters as (IVRT and PAP) with the progression of liver disease from Child A to Child C. There was no significant difference regarding left and right ventricular end diastolic diameter among the studied groups. (table 6)

QTC, EF, IVRT, E\A ratio, LVESV, LVEDV and LVESD were correlated with total bilirubin & INR while QTC was correlated with albumin., EF was correlated with total bilirubin & INR, IVRT was correlated with albumin.(table 7)

Table (1): Demographic data of the studied groups.

Data		Group 1 (N=30)		Group 2 (N=30)		Group 3 (N=40)		F	P
Age(Mean±SD)		53.60±10.31		52.66±11.8		57.70±10.03		2.254	0.11
		No	**%**	**No**	**%**	**No**	**%**	**X^2**	**P**
Sex	**Male**	14	46.7	16	53.3	28	70.0	4.21	0.12
	Female	16	53.3	14	46.7	12	30.0		
Residence	**Urban**	10	33.3	6	20	10	25	0.71	0.7
	Rural	20	66.7	24	80	30	75		

Table (2): Blood pressure of the studied groups.

Variable	G1 (N=30)	G 2 (N=30)	G 3 (N=40)	F	P
SBP	111.40±2.77 (106-115)	94.67±4.272 (90-100)	92.90±3.55 (85-100)	259.52	**0.00****
DBP	71.53±3.339 (67-80)	54.67±2.916 (50-60)	54.00±3.038 (50-60)	326.14	**0.00****

Table (3): Clinical data of the studied groups.

Clinical Data		Group 1 (N=30)		Group 2 (N=30)		Group 3 (N=40)		X^2	P
		No	%	No	%	No	%		
Encephalopathy	**Absent**	30	100.0	12	40.0	0	0.0	96.9	**0.00****
	Grade I&II	0	0.0	18	60.0	14	35.0		
	Grade III&IV	0	0.0	0	0.0	26	65.0		
Jaundice	**Absent**	30	100.0	0	0.0	2	5.0	94.53	**0.00****
	Present	0	100.0	30	100.0	38	95.0		
LL edema	**Absent**	30	100.0	0	0.0	0	0.0	81.57	**0.00****
	Present	0	0.0	30	100.0	40	100.0		
Dyspnea	**Absent**	30	100.0	0	0.0	0	0.0	81.57	**0.00****
	present	0	0.0	30	100.0	40	100.0		
Ascites	**Absent**	30	100	0	0.0	0	0.0	81.57	**0.00****
	Mild	0	0.0	26	86.7	0	0.0		
	Moderate	0	0.0	4	13.3	8	20.0		
	Tense	0	0.0	0	0.0	32	80.0		

Table (4): CBC findings of the studied groups.

Variable	G1(N=30)	G2(N=30)	G3(N=40)	F	P
	Mean±SD	Mean±SD	Mean±SD		
HB(gm/dl)	10.89±1.342	10.21±1.445	9.092±0.794	20.412	**0.00****
WBC ($x10^3$/uL)	7.753±3.215	5.606±2.422	4.997±5.276	4.214	**0.017***
PLT($x10^3$/uL)	83.30±9.717	63.16±9.403	63.53±17.10	24.12	**0.00****
MCV(fL/red cell)	81.53±3.377	74.26±2.711	71.45±3.316	46.754	**0.00****
MCH(pg/red cell)	28.13±2.386	23.86±1.684	22.60±1.957	33.412	**0.00****

Table (5): Kidney and liver function tests of the studied groups.

Variable	G1(N=30)	G2(N=30)	G3(N=40)	F	P
	Mean±SD	Mean±SD	Mean±SD		
Creatinine(mg/dl)	1.006±0.086	1.184±0.324	1.198±0.378	3.982	**0.022***
BUN(mg/dl)	46.62±23.90	46.17±23.41	53.44±30.56	0.840	0.435
Total serum bilirubin(mg/dl)	0.834±0.185	2.262±0.470	4.255±4.110	15.031	**0.00****
Direct serum bilirubin(mg/dl)	0.435±0.175	1.466±0.836	3.030±3.254	13.879	**0.00****
Total protein(g/dl)	7.60±0.2491	6.542±0.480	6.320±1.695	12.184	**0.00****
Albumin(g/dl)	3.79±0.1666	2.932±0.070	2.317±0.224	626.99	**0.00****
ALT(unit/liter)	48.33±23.85	47.53±17.36	52.0±15.248	0.575	0.565
AST (unit/liter)	57.73±27.12	61.73±13.57	69.65±16.96	3.770	**0.026***
PT(second)	12.86±1.341	17.30±1.668	20.09±3.055	87.580	**0.00****
INR	1.28±0.0735	1.716±0.211	1.975±0.315	75.608	**0.00****

Table (6): ECG and Echo parameters of the studied groups.

Variable	G1(N=30)	G2(N=30)	G3(N=40)	F	P
	Mean±SD	Mean±SD	Mean±SD		
QTC(0.36-0.44sec)	0.42±0.006	0.46±0.004	0.48± 0.005	968.06	**0.00****
EF(52-72%)	74.60±2.027	62.93±3.26	60.00±2.754	259.94	**0.00****
IVRT(60-80msec)	68.20±1.972	91.00±3.76	94.25±9.006	170.26	**0.00****
E/A ratio(1-1.1)	1.02±0.0439	0.87±0.044	0.737±0.050	326.37	**0.00****
LVE Systolic Volume (21-61ml)	25.40±0.813	29.26±0.69	29.80±1.742	118.56	**0.00****
LVE Diastolic Volume (62-150ml)	80.73±2.148	88.80±3.52	98.85±10.41	58.845	**0.00****
LVE Systolic Diameter (25-40mm)	27.06±0.784	29.8±0.973	32.65±2.567	86.214	**0.00****
LVE Diastolic Diameter (42-58mm)	45.66±1.917	50.73±2.61	54.90±3.136	103.07	**0.00****
RVE Diastolic Diameter(10-24mm)	22.83±2.870	23.00±1.69	23.35±2.089	2.421	0.121
PAP(16-25mmhg)	17.78±1.678	22.46±1.64	27.50±2.328	122.07	**0.00****

EF Ejection Fraction**, IVRT** Isovolumetric relaxation time, **PAP** Pulmonary artery pressure, **LVE** left veventricle, **RVE** right ventricle, **E/A** Early to late atrial phases of ventricular filling.

Table (7): Correlation between laboratory parameters and detected cardiac abnormalities of the studied groups.

Variable		QTC (msec)	EF (%)	IVRT (msec)	E\A ratio	LVE Systolic Volume (ml)	LVE Diastolic Volume (ml)	LVE Systolic Diameter (mm)	LVE Diastolic Diameter (mm)
Total serum bilirubin (mg/dl)	**r**	0.406**	-.453-**	0.444**	-.442-**	0.256*	0.510**	0.506**	0.462**
	P	0.000	0.000	0.000	0.000	0.010	0.000	0.000	0.000
Direct serum bilirubin (mg/dl)	**r**	0.380**	-.418-**	.424**	-.443-**	0.222*	0.528**	0.498**	0.445**
	P	0.000	0.000	0.000	0.000	0.027	0.000	0.000	0.000
Total protein (g/dl)	**r**	-.476-**	.459**	-.494-**	.386**	-.434-**	-.240-*	-.360-**	-.407-**
	P	0.000	0.000	0.000	0.000	0.000	0.016	0.000	0.000
Albumin (g/dl)	**r**	-.935-**	.880**	-.798-**	.901**	-.785-**	-.681-**	-.805-**	-.791-**
	P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
ALT (unit/liter)	**r**	0.039	0.029	-.003-	-.144-	-.113-	0.174	0.196	0.089
	P	0.697	0.775	0.975	0.153	0.262	0.083	0.051	0.376
AST (unit/liter)	**r**	0.216*	-.183-	0.118	-.292-**	0.087	0.314**	.301**	.168
	P	0.031	0.069	0.240	0.003	0.392	0.001	0.002	.094
PT(second)	**r**	.757**	-.742-**	.667**	-.696-**	.786**	.576**	.644**	.720**
	P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
INR	**r**	.731**	-.735-**	.654**	-.682-**	.643**	.645**	.661**	.671**
	P	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

DISCUSSION

Hyperdynamic circulation is one of many cardiovascular abnormalities that occur in patients with liver cirrhosis **[4].** Cirrhotic Cardiomyopathy describes the impairment of cardiac contraction in response to stress, diastolic dysfunction and electrophysiological changes in the absence of any cardiac disease in cirrhotic patients **[5]**.

Our study revealed that the blood pressure was significantly lower among Child B and Child C group cirrhotic patients compared to Child A

cirrhotic patients. This comes in agreement with the result of Baik et al. **[6]**. Low blood pressure is probably attributed to arterial vasodilatation that commonly found in cirrhosis **[7].**

QTC interval was found to be prolonged in 70% of our cirrhotic patients. QTC interval was significantly prolonged with the progression of liver disease. This prolongation may be due to alterations of ion channel activity in cardiomyocyte plasma membranes **[8]**. Previous studies revealed that QTC interval correlated well with the severity of the liver disease. Fourlas and Alex Poulou **[9]** and Baik et al. **[6]** found that 30–60% of cirrhotic patients had a prolonged QT interval. Also, Zambruni et al. **[10]** found that QTC interval was prolonged in patients with advanced liver disease. Accordingly, about 60% of patients with advanced liver cirrhosis have this electrocardiographic changes and QTC interval prolongation is the most frequent abnormality **[11].**

This study revealed that pulmonary artery pressure (PAP) was increased in Child B and C patients when compared to Child A patients. This result agrees with that of Silvestre et al. **[12]** who found significant correlation between Child score and PAP. Increasing the levels of vasoactive substances circulating in the pulmonary circulation leads to pulmonary hypertension. These substances possibly induce vasoconstriction, with a possible toxic effect on endothelial cells **[13].**

This study revealed that there was no statistically significant difference regarding right ventricular end diastolic diameter among the studied groups. This result was going parallel to that of Soyoral et al. **[14]** who found that there was no change in right ventricular diameters, but it disagrees with that of YanChen et al. **[15]** who demonstrated that the right ventricular dimension is significantly increased in patients with cirrhosis. This could be explained by an increased venous return to the right side of the heart caused by the development of portosystemic collaterals **[16].**

On the other hand, left ventricular end diastolic volume, left ventricular end systolic volume, LV end systolic diameter and LV end diastolic diameter increased in (Child B and C patients) when compared to (Child A patients) but not statistically significant. These abnormal structural findings in cirrhotic patients seem to be an adaptation of cardiac hemodynamics to changes in peripheral circulation with diastole **[17]**.

These results agree with the results of Myers and Lee **[18]** and Li et al. **[19]** who observed that, increasing in Child score was accompanied by an increase in LV end systolic diameter, LV end diastolic diameter, but our results disagree with the results of Soyoral, et al. **[14]** who found no changes in the ventricular diameters and it explained by impairment of the left ventricle performance due to decreased peripheral vascular resistance**.**

Our study revealed that EF was decreased in Child B and C patients compared to Child A patients but not statistically significant and this agrees with the results found by **Salari et al. [20].** This could be explained by that in advanced cirrhosis, there is an increase in blood volume that leads to a constant increase in cardiac output, which may cause cardiac overload, with impaired cardiac contractility and insufficient ventricular reserve response to an increase in ventricular filling pressure **[21].**

In this study, left ventricular diastolic function was assessed by Doppler indices (i.e. E/A ratio, and isovolumic relaxation time). Abnormalities in left ventricular diastolic function in the form of decrease of E/A (E\A ratio <1) but not statistically significant and significant increase of IVRT (IVRT >80) were reported in this study. This result agrees with that of Wong et al. **[22]** who reported that some degree of diastolic dysfunction was nearly present in every patient with liver cirrhosis**.** Diastolic dysfunction in cirrhotic patients has been linked with increased left ventricular wall thickness, subendocardial oedema, fibrosis and distorted collagen composition, ultimately leading to altered relaxation **[23]**.

This study reveals that there is positive correlation between severity of liver cirrhosis and cardiac changes**.** This result agrees with that of Salari et al. **[20]** and Stundiene et al. **[24]**, on the other hand these findings disagree with that of Merli et al. **[11]**, and with the publication of Silvestre et al. **[12].**This disagreement could be due to the small number of the studied population in their studies, the prevalence of cirrhotic cardiomyopathy varies widely because of the lack of a clear definition, the variability of the tools used to assess this entity, and finally ,the variability of inclusion criteria **[12].**

CONCLUSION

This study demonstrates that 70% of the studied patients with liver cirrhosis have cardiac dysfunction in the absence of other risk factors for cardiac diseases. In addition; the degree of cardiac dysfunction is correlated with the severity of liver disease of cirrhotic patients.

Conflict of interest: NO

Funding: NO

Ethical consideration: After approval of ethical committees, Faculty of Medicine Zagazig University. Informed consents were taken from patients included in the study.

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