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Real Time 3-D Echocardiography for Evaluation of Left Ventricular Systolic Function in Patients with Liver Cirrhosis Caused by Hepatitis C Virus

***Asmaa Ahmed Ali Hasan, *Nessren Mohamed Baha El Deen Mohamed**
Cardiology Department and Tropical Medicine Department – El Zahraa University Hospital,
Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt.
Corresponding author: Asmaa Ahmed Ali Hasan, E-mail: dr.aahmedali@gmail.com, Mobile: 01281253583

ABSTRACT

Background: Cardiovascular changes are associated with Liver cirrhosis so, it is important to assess its function in cirrhotic patients. Child-Pugh scoring system is the simplest clinical method used for classifying liver cirrhosis. 3D echo and 2D speckle tracking echocardiography (2D-STE) are the most recent imaging modalities able to evaluate LV systolic function accurately. **Aim**: To assess LV systolic function in patients with chronic liver cirrhosis caused by HCV by different echocardiographic modalities including 3D and STE and correlation of the results with the severity of cirrhosis based on Child-Pugh score. **Material and methods:** A prospective study was done in Cardiology Department, Al-Zahraa University Hospital including a total of 75 subjects; 45 cirrhotic patients and 30 subjects as a control. 2D, 3D LV volumes and EF and 2D-STE of the LV were measured. Then, the patients' group was divided into 3 subgroups according to Child Pugh score then LV systolic function were assessed with different echo modalities (2D, 3D and MM, TDI (Sm) and, 2D STE). **Results:** The LVEF increased significantly in patient group by M-mode and 2D but decreased by TDI, 3D echo and STE. Increased systolic velocity (Sa) by TDI in group III of cirrhosis but lowered systolic function by using STE. Also, there was a significant correlation between severity of liver cirrhosis and LVEF by 2D STE, 3D and 2D. **Conclusions:** The recent noninvasive 3D echo and 2-D STE techniques are a promising methods for early detection of LV systolic dysfunction in asymptomatic patients with viral liver cirrhosis. Also, the LV systolic dysfunction is related to the extent of severity of liver cirrhosis.

Keywords: Liver cirrhosis – real time 3D - Ventricular function - Speckle tracking echocardiography- Child pugh score.

INTRODUCTION

Echocardiography is considered a noninvasive method to assess cardiac function; however, conventional echo-Doppler technique has some limitations in its accuracy [1]. So, tissue Doppler imaging (TDI), speckle tracking imaging (STI), and real time 3 dimensional echocardiography (RT3DE) can be applied to overcome these limitations for the quantitative assessment of regional myocardial function. The recently developed 2D-STE modality has an angle-independent in evaluation of the LV deformation which was from the spatial gradients of myocardial velocities when using TDI or from the relative position of "speckles" within a myocardial region when using speckle tracking [2]. So, this modality is considered more sensitive and accurate than conventional one in detecting any subtle ventricular changes in function [3].

Heart failure, which related to cirrhotic cardiomyopathy is considered the third leading cause of death [4, 5]. So, it is important to evaluate cardiac function in patients with cirrhosis. Liver cirrhosis is also associated with many cardiovascular changes as hyperdynamic circulation due to increased cardiac output and decreased systemic vascular resistance [6]. Liver cirrhosis also is associated with normal systolic function at rest, systolic dysfunction under special \conditions of stress [7]. The relationship between the severity of liver disease and cirrhotic cardiomyopathy is not proved yet and it is still a matter of debate. The Child-Pugh scoring system is the most common clinical method used for assessing severity of liver cirrhosis. So, we used it in this study [8, 9].

Subjects:

This study enrolled a total of seventy five subjects, forty five clinically stable (i.e. had not been hospitalized or undergone any interventions due to cirrhosis within the previous 6 months), patients with viral cirrhosis caused by HCV who were followed up at the Tropical Department of Al-Zahraa University Hospital, between May 2017 and December 2018 and were referred to our echocardiography laboratory for the assessment of LV systolic function. Thirty healthy persons as a control group, age and sex-matched, selected from individuals who had no history of cardiovascular disease and who underwent a routine physical examination with normal ECG and 2D-TTE findings. The hypertensive or diabetic patients, pre-existing cardiac disease as RHD, congenital heart disease, ischemic heart disease, myocarditis whether due to infection in its etiology or whatever cause, primary heart muscle diseases like cardiomyopathies, poor image quality, any metabolic or systemic diseases

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other than liver disease that might affect cardiac structure were excluded from our study.

Methods:

After giving an informed consent, all the individuals included in this study were subjected to the following: full medical history focused on symptoms related to liver cell failure (jaundice, bleeding tendency and hepatic encephalopathy), general examination with emphasis on blood pressure, heart rate, anthropometric measurements and abdominal examination for detection of organomegaly and or ascites. Laboratory investigations included liver function tests (s. albumin, total bilirubin, prothrombin time, INR, AST and ALT) and abdnominal ultrasonography were performed for all individuals. The diagnosis of liver cirrhosis was depending on the clinical examination, biochemical tests, and also abdnominal U/S in all patients. Two-dimensional transthoracic echocardiographic imaging (2D-TTE) also was done for all individuals in our study for assessment of LV systolic function by its different modalities including M-mode, 2D, 3D, TDI and 2D strain (speckle tracking echo).

The Child-Pugh scoring system, which is the most commonly used clinical method for assessment of severity of liver cirrhosis was evaluated as follows; the least severe one scored 5-6 points (class A), the moderately severe scored 7-9 points (class B) and the most severe liver disease scored 10-15 points (class C). So, patients group were classified into three subgroups, 15 patients were in class A, 15 patients were in class B and 15 patients were in class C.

Ethical approval:

Informed consent forms were signed by every individual in this study and **the study was approved by the Ethics Committee of the Al-Azhar University Faculty of Medicine.**

Echocardiographic examination

Trans-thoracic echocardiography (TTE) study was performed for all individuals included in this study in both supine and left lateral position, all measurements were made by one staff cardiologist over at least three cardiac cycles and the average value for each parameter was calculated. Using GE system Vivid-S3, Matrix probe M3S multi frequency 2.5 MHz and 4V probe for 3D acquisition with the capability of tissue Doppler imaging and three dimensional imaging (3D) capabilities.

Comprehensive TTE M-Mode, 2D, in the standard views (parasternal long axis, parasternal short axis, apical four, three and two chamber views) from all accessible windows were obtained with ECG physio-signal displayed with all detected echo-Doppler study with Loop recording of 2-3 cycles. All images were digitally stored for later off-line analysis at echo Pac work station GE version 201. All parameters were taken according to standards of the American Society of Echocardiography.

1- M-mode measures LV end-diastolic and end-systolic dimensions, LV percent fractional shortening, and LVEF.
2- 2DE measures 2D LV end diastolic and end systolic volumes and 2D-LVEF.
3- 3DE measures LV volumes, EF using 4D autoquantification software.

The TDI was obtained from apical 4-chamber and 2-chamber views. For data acquisition, three complete cardiac cycles were collected and stored in a cine loop format. The image sector width was set as narrow as possible to allow a frame rate acquisition greater than 90 frames/s. Special attentions was paid to the color Doppler velocity range setting to avoid any aliasing within the image. The mitral annular systolic velocity (Sa) by pulsed wave tissue Doppler was obtained at lateral, posteroseptal, inferior and anterior annular positions then average of these four sites were calculated.

The LV longitudinal strain was also assessed using 2D STE analysis with QRS onset as the reference point, applying a commercially available strain software package to the LV on echo Pac version 201. Images were acquired at 70–90 frames per second at end-expiration in the apical 4-chamber, 3-chamber and 2- chamber views. Using the Automated Function Imaging software (AFI), following which the software tracked the endocardial contour. The LV 2D ST GS% was obtained in all study cases automatically for the 6 LV walls in the apical 4-, 2- and 3-chamber views. The averages of these values were used for the comparison of the cirrhotic patients with the control group.

Diagnosis of cirrhosis in patient group was based on clinical grounds (chronic liver disease signs, 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). Severity of cirrhosis was assessed by Child Pugh score. Moreover, correlation between the disease severity and left ventricular functional changes was done.

Statistical analysis

It was performed via SPSS statistics (version 23). The defining statistics were expressed as mean and standard deviation for normally distributed data. Comparison between study groups was done using

unpaired t test when a normal distribution hypothesis was present in the analysis of the differences in certain measurements between the control and patient groups. While, the Mann–Whitney U-test was employed when this hypothesis could not be established. Also, correlation between severities of liver cirrhosis based on child Pugh scoring system and left ventricular systolic function by different echocardiographic modalities. P-value < 0.05 was considered to be significant.

RESULTS

Group (A) represented 45 patients with viral liver cirrhosis caused by hepatitis c virus and group (B) represented 30 age-and sex-matched healthy subjects as a control. When the demographic and clinical data of the groups were compared, the systolic and diastolic blood pressures were observed to be lower in the cirrhotic group. When the biochemical values were evaluated as aspartate transaminase (< 0.005) and alanine transaminase (p = 0.00), values were higher. While, serum albumin (p < 0.01) value were lower in the cirrhotic group. The demographic, clinical and biochemical characteristics of the studied cases were shown in table (1).

Table (1): Baseline demographic, clinical and biochemical characteristics of study population

	Group A (patients)	**Group B (control)**	***p-value***
Numbers	45	30	
Male/Female, %	19(42%)/ 26(58%)	16 (53%)/ 14 (46%)	NS
Age in years	47.13 ± 9.2	46.8 ± 8.9	NS
BMI (kg/m2)	**26.6 ± 3.5**	**26.6 ± 3.9**	**0.95**
HR	77 ± 10	74 ± 10	NS
SBP	113 ± 8	119 ± 9	0.03
DBP	69 ± 6	73 ± 8	0.03
LVMI (g/m2)	**167.17 ± 5.56**	**126.47 ± 3.06**	**<0.001**
Smoking, %	19	22	NS
Biochemical parameters			
ALT	31.7 ± 8.5	21.65 ± 2.6	0.00
AST	37.6 ± 9.7	21.2±4.9	0.00
Serum Albumin	3.2 ± 0.9	4.4 ± 0.4	0.01
TotaL Bilirubin	1.26 ± 0.08	0.46 ± 00.2	0.01
INR	1.4 ± 0.04	0.9 ± 0.05	0.00

Abbreviations: HR, heart rate, SBP, systolic blood pressure; DBP, diastolic blood pressure; mo, month.,ALT,, Alanin transferase, AST, Aspertate transferase,, INR, International Normalizing Ratio.

By conventional echocardiography, although there was significant increase in EF by M-mode (p value <0.01) in cirrhotic group versus control group, there was insignificantly increased LV end diastolic dimensions, LV end diastolic volume and EF by 2D in cirrhotic group versus normal group (Table 2).

Table (2): Baseline LV echocardiographic parameters in patient group versus control group.

	Group A (patients)	**Group B (control)**	***p-value***
IVSd	9.1 ± 1.5	8.4 ± 1.4	0.1
PWDd	9.2 ± 1.2	8.9 ± 1.1	0.3
LVEDd	50.9 ± 6.2	48.5 ± 4.1	0.1
LVESd	29.9 ± 4.5	30 ± 4.2	0.9
FS %	40.7 ± 6.2	37.8 ± 5.4	0.09
EF by M-mode	71 ± 6.9	65.7 ± 5.5	0.004
LVEDV	79.7 ± 30.4	70.8 ± 14.9	0.2
LVESV	30.3 ± 11.2	34.1 ± 6.9	0.1
EF by 2D	60.9 ± 7.3	59.6 ± 3.8	0.2

Abbreviations: IVSd, interventricular septal thickness in diastole; LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; LVPWd, left ventricular posterior wall thickness in diastole; EF, ejection fraction; FS, fraction shortening' .

Importantly, there was a significant lower TDI systolic velocity and LV GLS % for assessment of LV systolic function. Moreover, there was a significantly lower 3D LVEF (p value= 0.001) in the cirrhotic group versus control (Table 3).

Table (3): Comparison LV TDI echocardiographic parameters, 3D and STE in patient group versus control group.

TDI	**Group A (patients)**	**Group B (control)**	***p-value***
Average Sa	6.7 ± 1.4	7.9 ± 1.3	0.00
LV 2D strain (GLS%)	19.5 ± 2.7	20.7 ± 4.3	0.04
3D LVEDV (ml)	57.9 ± 18.2	83.9 ± 20.1	0.000
3D LVESV (ml)	26.2 ± 10.2	32.3 ± 9.1	0.002
3D LVEF (%)	55.3 ± 9.6	61.9 ± 3.3	0.001

Abbreviations: TDI, tissue Doppler imaging; Sa, myocardial systolic excursion velocity; measured by tissue Doppler echocardiography; GLS, global longitudinal strain, 3D LVEDV, LV end diastolic volume by 3D echo, 3D LVESV, LV end systolic volume by 3D echo, 3D LVEF, LV ejection fraction by 3D.

The LV systolic function increased in the diseased group by M-mode and 2D as the hyperdynamic state but decreased when using TDI systolic velocity and STE evidenced that it is not load dependent. Figure (1).

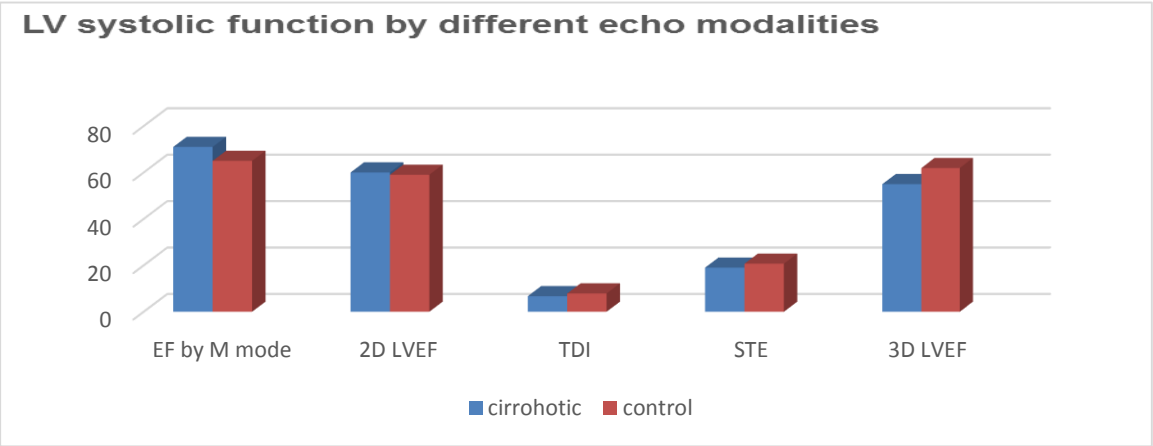

Figure (1): comparison between cirrhosis group and normal one by LV systolic function indices by different echo modalities**.**

In our study, the patient group was divided into three subgroups based on the Child Pugh score indicating the severity of the disease. Group (I): Child A consisted of 15 patients their mean age was 36.7 ± 7.4 years old, group (II): Child B included 15 patients, their mean age was 52.4 ± 4 years and group (III): Child C included 15 patients with decompensated cirrhosis, their mean age was 52.3 ± 4.2 years. All patients were hepatitis C virus, with predominance of female gender (about 58% of the study population) with no statistically significant difference between the 3 groups in regard to risk factors (p-value was 0.5 for smokers). By conventional Echo parameters, there was normal LV dimensions in the 3 groups (LVIDd and LVIDs) but increased (especially LV end diastolic dimension and EF by M-mode) in class C (group III) indicating hyperdynamic function especially in group (III) and by TDI there were increase in Sa in group III but lowered systolic function in STE (Table 4).

Table (4) Baseline echocardiographic parameters in the patients groups according to Chlid Pugh class:

Variables	Group I Child A (n=15)		Group II Child B (n=15)		Group III Child C (n=15)	
	Mean	± SD	Mean	± SD	Mean	± SD
Biochemical Parameters						
ALT	27.4	7.3	31.3	9.1	36.8	9.9
AST	26.3	1.6	44.9	2.9	41.9	1.0
Serum Albumin	4.2	0.5	2.7	0.7	2.4	0.3
Total Bilirubin	0.6	0.2	1.5	0.06	1.8	0.09
INR	1	0.05	1.6	0.03	1.9	0.05
Conventional Echocaradiographic data						
IVSd (mm)	9.2	1.6	9.1	1.02	8.4	1.07
LVIDd (mm)	50.9	5.4	49.8	6.8	52.2	6.9
LVIDs (cm)	31.2	4.1	29.4	4.9	29.2	4.5
LVPWd (cm)	9.2	1.3	8.8	1.1	8.9	1.2
EF-Mmode (%)	68.7	6.4	69.9	8.6	74.4	4.3
%FS	37.7	5.0	40.3	7.9	44	3.6
LVEDV	95	32.9	79	31.9	64.9	19
LVESV	36.9	10.2	31.5	9.9	22.6	8.9
EF by 2D	58.3	5.8	58.9	8.0	65.7	5.9
TDI , 3D and speckle Tracking Echo parameters						
Aver. TDI Sa m/s	6.4	0.7	6.6	0.9	7.2	2.2
Average LV 2D GLS%	19.5	2.9	19.1	3.9	18	1.5
3D LVEF	56.7	14.3	52.5	7.3	56.7	4.9

When we compared laboratory investigation for liver function among 3 patient groups we found significant difference between group I versus II or III as in total bilirubin and INR but no significant difference in laboratory investigation in group II versus III (Table 5).

Table (5) Comparison between the 3 patients groups by Laboratory investigations representing liver function:

Variables	Group I & II	Group I&III	Group II &III
ALT	0.6	0.2	0.5
AST	0.03	0.06	0.7
Serum Albumin	0.00	0.9	0.2
Total Bilirubin	0.003	0.005	0.1
INR	0.01	0.05	0.2

Also, we didn`t find any significant difference between group I and II as regards parameters measured by either conventional Doppler echocardiography, TDI or by 2D STE. However, there was significant differences between group II versus III in LVESV, EF and STE and group I versus III as regards LV volumes, EF by 2D and LV GLS%. So, in the child C group, when the 2D-STE values were compared, values were observed to be significantly lower in the child c group. But no significant difference in 3D LV EF between 3 groups (Table 6).

Table (6): Comparison between patients group according to Child Pugh classification in LV systolic function by different echocardiographic modalities**.**

Variables	Group I & II	Group I & III	Group II & III
IVSd (cm)	NS	0.2	NS
LVIDd (cm)	0.6	0.6	0.4
LVIDs (cm)	0.3	0.3	0.9
LVPWd (cm)	NS	0.6	NS
FS	0.3	0.00	0.2
EF%	0.7	0.03	0.1
LV systolic function by 2D, 3D, TDI & STE			
LVEDV	0.2	0.02	0.2
LVESV	0.2	0.00	0.05
EF by 2D	0.8	0.01	0.04
LV TDI Sa	0.5	0.2	0.4
Lv GLS (STE)	0.7	0.04	0.04
3D LVEF	0.4	1	0.4

By correlation between severity of liver cirrhosis based on Child Pugh scoring system and left ventricular systolic function by different echocardiographic modalities, we found that there was a significant correlation with LV systolic function when measured by global longitudinal strain (2D speckle tracking) (p value = 0.01), 3D EF (p value < 0.001) and 2D EF (p value = 0.01) and not by M-mode EF or EF measured by TVI (p value = 0.35) as shown in table (7).

Table (7): Correlation between Child Pugh score and LV systolic function by different echo modalities

	R	P value
EF by M-mode	0.27	0.14
EF by 2D	0.43	0.01
EF by GLS (2D STE)	0.43	0.01
EF by TVI	0.17	0.35
EF BY 3D	0.01	<0.001

DISCUSSION

Abnormal cardiac changes, which present in those patients are primarily as a result of chronicity of the disease, which is resulting in a compensatory increased cardiac output [10]. Early detection of ventricular dysfunction may be helpful in guiding treatment. Although one would expect an increase in left ventricular ejection fraction (LV EF) in response to high cardiac output, the absence of this response in our study by some echo modalities might reflect that these modality is considered as an early marker of systolic dysfunction. Also, RT3DE showed that LVEF was significantly lower in our studied patient group when compared to controls. So, RT3DE is considered superior to conventional echo in detection of the subtle changes in the LVEF in our studied patients' group compared to control. This might be interpreted by the accuracy of RT3DE, which is limited when using conventional echocardiography due to image position and possibility of errors in boundary tracing [11, 12].

Also, Reduced systolic velocity of mitral annulus displacement (Sm) by TDI is considered also a sensitive marker of early detection of left ventricular systolic dysfunction in individuals with preserved EF by conventional methods. In our study, there was significant decrease in mitral annulus systolic velocity(S wave) in studied patients' group when compared to control. This reflects an impaired contraction and segmental wall motion abnormalities in this group of patients .

Patients with liver cirrhosis are proved to have a hyperdynamic circulation, which is manifested as high cardiac output, resulting in cardiovascular abnormalities and changes in geometry as proved in the previous studies [13, 14].

In our study by conventional echo assessment, there was a significant increase in LVEF and volume especially end diastolic volume in patients with cirrhosis. A probable reason for this might be because of decreased peripheral vascular resistance and increased cardiac output as a result of hyperdynamic circulation. So, recent echocardiographic modalities especially which is not load-dependent is needed and is useful to detect early changes in the left ventricle before its appearance as clinical manifestation of dysfunction. A number of previous studies on cirrhosis showed that systolic function is apparently normal or even increased at rest [15].

Although our small number of patients' group, we found that global longitudinal strain (GLS) was significantly lower in cirrhotic patients than control despite their apparently normal EF by conventional echo measurement (a subclinical impairment in the longitudinal LV systolic function in cirrhotic patients with preserved LV pump function). Our finding is in concordance with a study by **Refik *et al.*** [16] who studied also 75 cases (38 cirrhotic patients and 37 healthy persons) and revealed that in the cirrhotic group, the global longitudinal strain was lower than healthy one (20.57 ± 2.1 vs.28.7 ± 43.1, $p<0.001$) and also agrees with **Francisco *et al.*** [17] who studied total 127 cases (109 hospitalized patients with cirrhosis and 18 healthy controls) and showed that peak systolic longitudinal strain (PLS) was lower in patients than in control, although the ejection fraction was similar in both groups. This might be interpreted by changes in left ventricular mechanics and geometry where during systole the radial muscle fibers thickening is preserved, with an increase in the circumferential shortening and a decrease in the longitudinal fibers shortening. This results in the maintenance of the LV global function. These changes due to what is called "pump dysfunction". So, volume-derived measurements of LV systolic function have limitations in assessing myocardial contractile function. Also, a number of compensatory mechanisms, as increasing in LV end-diastolic volume, can mask these changes in myocardial force development [18, 19]. So, in our study we prefer LV GLS in early detection of the LV systolic dysfunction as it deteriorates early. These results proved that the longitudinal function deteriorates early (i.e. before the onset of the clinical symptoms and the reduction in the global ventricular function) under pathological cardiac conditions.

In our study, when the cirrhotic group was divided into three subgroups according to the Child Pugh scoring system, the longitudinal global strain in assessing LV systolic function was reduced in the group III (Child Pugh C). Also in our study, we found that the conventional echo parameters were within normal range in the 3 groups but were hyperdynamic especially in Child C group. These results are in agreement with a study by **Piyush *et al.*** [20] who depended on conventional echo parameters to compare cardiac status in patients with liver cirrhosis and healthy persons and proved that the conventional echocardiographic parameters of systolic function were not different in cirrhotic patients with different Child-Pugh classes [21].

CONCLUSIONS

The noninvasive recent assessment of the LV systolic function by RT3DE and 2D STE modalities became a promising and accurate methods for early detection of LV systolic dysfunction especially in asymptomatic patients with viral liver cirrhosis. Based on Child Pugh scoring system, there was a significant

correlation between the extent of severity of liver cirrhosis and LV systolic dysfunction.

RECOMMENDATION:

We recommend a future study on a large number of patients and examining patients with liver cirrhosis with STE and RT4DE, which are considered a recent echocardiographic modalities whatever the stage of the disease and to become routinely especially before any invasive procedure.

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