Evaluation of Cardiac Systolic Function in Cirrhotic Patients Undergoing Liver Transplantation

Roya Sattarzadeh Badkoubeh[1], Babak Geraiely[1], Mohssen Nassiri Toosi[2], and Ali Jafarian[3]

[1] *Department of Cardiology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Department of Internal Medicine, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[3] *Department of General Surgery, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract- We assessed different systolic cardiac indices to detect left and right ventricular systolic dysfunction in cirrhotic patients before liver transplantation. Between 2010-2011, 81 consecutive individuals with confirmed hepatic cirrhosis who were a candidate for liver transplantation were enrolled in this study. A total of 32 age and sex matched healthy volunteers were also selected as the control group. A detailed two-dimensional, Color Flow Doppler, and Tissue Doppler echocardiography were performed in all patients and control participants. Left atrial diameter and area, right atrial area, left ventricular end-diastolic volume, and basal right ventricular diameter were significantly higher in the cirrhotic group ($P<0.05$). Left ventricular ejection fraction, stroke volume, left ventricular outflow tract velocity time integral and tricuspid annular plane systolic excursion were also higher in the cirrhotic group ($P<0.05$). Peak systolic velocities of tricuspid annulus, basal segment of RV free wall and basal segment of septal wall, peak strains of basal and mid portions of septal wall, mid portion of lateral wall and peak strain rates of basal and mid portions of septal and lateral walls were higher significantly in cirrhotic group, as well ($P<0.05$). Isovolumic contraction time, LV systolic time interval and Tei indexes of left and right ventricles which all are representatives of systolic dysfunction were higher in cirrhosis. Peak systolic velocity of a mid-segment of the lateral wall was lower in the cirrhotic group ($P<0.05$) as well. Most of the cirrhotic patients display signs of cardiovascular disturbances that become more manifest following exposure to stresses such as transplantation. Cardiac failure is an important cause of death following liver transplantation. Because of the load dependency we cannot use most of the cardiac systolic indices for evaluation of systolic function in cirrhotic patients. Thus, we suggest that LV systolic time interval and Tei indices of left and right ventricles might be useful indices in the evaluation of systolic function in cirrhotic patients.

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Introduction

Most of the cirrhotic patients display signs of cardiovascular disturbances that become more manifest following exposure to stress such as transplantation. Cardiac failure is an important cause of death following liver transplantation. It has been revealed that there is an overall association between the severity of the cirrhosis and the degree of cardiac dysfunction (1).

These abnormalities might be manifested by a systolic dysfunction, diastolic dysfunction or electromechanical abnormalities such as prolonged Q–T interval (2-4). Numerous combined neurohumoral and hemodynamic mechanisms have been identified leading to cardiovascular disturbances and affecting the patients' prognosis following advanced cirrhosis (5-7). The increased blood volume in advanced cirrhosis contributes to a persistent increase in cardiac output which may overload the heart and augmented cardiac workload may contribute to cirrhotic cardiomyopathy (8). In other circumstances, increased cardiac output and augmented cardiac work would cause overt heart failure but because of the decreased afterload as reflected by reduced systemic vascular

Corresponding Author: B. Geraiely
Department of Cardiology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 22112017, Fax: +98 21 66939537, E-mail address: babak_geraiely@yahoo.com

resistance, left ventricular failure may be latent in cirrhosis (1).

Other mechanisms underlying cirrhotic cardiomyopathy include abnormal beta-adrenergic signaling, cardiomyocytes membrane fluidity changes, interstitial fibrosis, and myocardial hypertrophy (9, 10). Recent experimental and clinical findings of impaired cardiac function have led to introduction of the cirrhotic cardiomyopathy as a new clinical entity and a few studies delineated the echocardiographic systolic and diastolic characteristics in advanced cirrhosis (1,4,8).

Most of the previous studies have evaluated load-dependent indices of systolic function such as LVEF but because systolic dysfunction in cirrhotic patients seems to be masked with peripheral vasodilatation and volume overload. The present study aimed to assess different systolic cardiac indices that many of them such as strain and strain rate imaging are suggested to be relatively load-independent methods for evaluation of systolic function (11).

Materials and Methods

During June 2010 and December 2011, 81 consecutive individuals (mean age 38.81 ± 13.10 years, 58.0% male) with confirmed hepatic cirrhosis diagnosed by either liver biopsy or laboratory, clinical and ultrasonography findings who were candidates for liver transplantation were enrolled in the study. Patients with serum hemoglobin level < 9 gr/dL and thyroid dysfunction were excluded.

Those with age > 40 or multiple risk factors for coronary artery disease underwent myocardial perfusion scan for assessment of cardiac ischemia. Patients with evidence of ischemia or other concomitant heart diseases such as significant valvular heart disease were excluded. A total of age and sex matched healthy volunteers from the clinical staff of the hospital were also selected as the control participants. Neither patients nor control participants had hypertension, chronic obstructive pulmonary disease, renal failure, tachyarrhythmia, conduction disturbances, or pulmonary hypertension. Written informed consent was obtained from all participants. The current study was approved by the ethics committee of the Tehran University of Medical Sciences.

The baseline variables including age, sex, underlying diseases, and Child-Turcotte-Pugh Score for Cirrhosis were obtained from the patient's recorded files or by face to face interview. A detailed two-dimensional, color flow Doppler and tissue Doppler echocardiography was performed using commercially available ultrasound system Vivid-7(GE) with a 3-MHz transducer. Examinations in all patients and control participants were performed by the same operator using guidelines of American Society of Echocardiography (12).

Two-dimensional (2D) and M-mode echocardiography

Cardiac chamber diameters and volumetric parameters were measured in standard parasternal long axis and apical 4-chamber views. All patients were examined at rest in left lateral decubitus position.

The LV end diastolic and end systolic diameters were obtained at the level of mitral leaflet tips from parasternal long axis window using two-dimensionally guided M-mode echocardiography. Left ventricular ejection fraction (LVEF) was computed from the apical two- and four-chamber views using modified Simpson's method.

Tricuspid Annular Plane Systolic Excursion (TAPSE) was measured to assess RV systolic function, using two-dimensionally guided M-mode in the apical 4-chamber view.

Color doppler echocardiography

Isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT) and ejection time (ET) were measured by obtaining the mitral inflow and LV outflow Doppler profiles simultaneously. The myocardial performance index of LV (Tei Index) was calculated by dividing the sum of IVRT and IVCT by ET (13).LV systolic time interval was calculated by dividing IVCT by ET (14).

Left ventricular outflow tract time velocity integral (TVI) was measured by placing the pulse Doppler sample volume just before the aortic valve.

Stroke volume was derived from the continuity equation (14).

Tissue doppler imaging (TDI)

The pulse-wave TDI was performed by the same machine, using tissue Doppler function. Peak systolic velocity of the mitral annulus was measured with TDI technique, by placing a 4-5 mm sample volume at the septal and lateral mitral annulus. Peak systolic velocity of the tricuspid annulus was measured at the anterior tricuspid annulus using the same method and was used to assess RV function besides TAPSE.

Peak systolic velocities of mid and basal portions of septal and lateral walls and basal RV free wall were measured by an offline method using tissue velocity imaging.Tei index of RV was calculated using TDI of the tricuspid annulus.

Strain and strain rate imaging

Doppler based longitudinal peak strain and strain rates of basal, and mid segments of septal and lateral walls of LV and a basal segment of RV free wall were measured.Strain and strain rate profiles were averaged over three consecutive cardiac cycles. Maximum negative deviations were measured for peak strain and strain rates (15).

For statistical analysis, the comparison between the categorical variables was performed by Chi-square test or Fisher's exact test if required and the quantitative variables by student *t*-test or Mann-Whitney U test. *P* value of less than 0.05 was considered statistically significant. All the statistical analyzes were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

The cirrhotics and control participants were not significantly different in male/female ratio (47/34 and 17/15, respectively; $P = 0.636$) and mean age (38.81 ± 13.1 and 35.4 ± 10.72 years, respectively; $P = 0.194$). Among cirrhotic patients, the most frequent underlying disease was Hepatitis B infection (21.0%) followed by Hepatitis C infection (18.5%), cryptogenic cirrhosis (17.3%), Primary Sclerosing Cholangitis (13.6%), autoimmune hepatitis (12.3%), Wilson's disease (7.4%) and other causes (9.9%). Regarding the Child-Turcotte-Pugh Scoring for Cirrhosis, 48.8% of the cirrhotic patients were stratified in the Child score B, 42.4% of the patients were classified as child score C and 8.8% of them were categorized in the child score A. In physical examination, 29 cirrhotics (36.0%) and 3 of control participants (9.0%) had grade II – III/VI mid systolic murmur in left upper sternal border without any significant valvular heart disease.

Left atrial diameter and area, right atrial area, basal right ventricular diameter and left ventricular end-diastolic volume in the cirrhotic patients were significantly higher than the non-cirrhotic ones. However, left ventricular end-systolic dimensions were not different between the two study groups (Table 1).

Table 1. Baseline measures of the cardiac volumes and diameters

Item	Cirrhotic group (n=81)	Non-cirrhotic group (n=32)	*P*-value
Left atrial diameter (cm)	3.69 ± 0.57*	3.08 ± 0.49	< 0.001
Left atrial area (cm^2)	19.07 ± 4.67	13.03 ± 3.29	< 0.001
Right atrial area (cm^2)	14.54 ± 3.81	11.02 ± 2.91	< 0.001
Left ventricular end-diastolic diameter (cm)	4.82 ± 0.61	4.61 ± 0.45	0.050
Left ventricular end-systolic diameter (cm)	2.98 ± 0.56	2.99 ± 0.49	0.902
Left ventricular end-diastolic volume (cm^3)	98.17 ± 24.17	88.08 ± 22.23	0.038
Left ventricular end-systolic volume (cm^3)	39.54 ± 12.12	38.68 ± 11.44	0.724
Basal right ventricular dimension (cm)	2.86 ± 0.42	2.54 ± 0.27	< 0.001

* All parameters are shown as Mean ± SD

The parameters of left ventricular ejection fraction (LVEF), stroke volume and left ventricular outflow tract velocity time integral were significantly higher in cirrhotic patients. But isovolumic contraction time (IVCT), left ventricular Tei index and systolic time interval which are representative indices of systolic dysfunction were also significantly higher in this patient group.

Peak systolic velocities of tricuspid annulus, basal RV free wall and basal segment of septal wall were significantly higher in cirrhotic patients while peak systolic velocity of mid segment of lateral wall was higher in the control group and other peak systolic velocities were not significantly different between two groups.

Tricuspid Annular Plane Systolic Excursion (TAPSE) which is a quantitative index of RV systolic function was significantly higher in cirrhotics but measured right ventricular Tei index was higher in this patient group also.

Regarding strain and strain rate parameters, peak strain of basal and mid segments of the septal wall and a mid segment of the lateral wall were higher in cirrhotics. Left ventricular peak strain rate in all segments were significantly higher in cirrhotic patients, however right ventricular peak strain and strain rates were not meaningful between cases and controls.

Echocardiographic indices of systolic function are summarized in Table 2.

Table 2. Cardiac indices indicating cardiac systolic function

Item	Cirrhotic group (n=81)	Non-cirrhotic group (n=32)	*P*-value
Left ventricular Outflow Tract Velocity Time Integral (cm)	21.35 ± 4.21*	16.81 ± 2.80	< 0.001
Left ventricular ejection time (ms)	283.45 ± 30.72	288.38 ± 20.84	0.699
Isovolumic contraction time (ms)	68.41 ± 21.33	54.69 ± 16.63	0.001
Isovolumic relaxation time (ms)	84.61 ± 20.18	74.54 ± 14.49	< 0.001
Stroke volume (cm3)	69.56 ± 21.52	52.27 ± 13.84	< 0.001
Left ventricular ejection fraction (%)	59.97 ± 7.40	55.85 ± 6.28	0.007
Peak systolic velocity of tricuspid annulus (cm/s)	16.41 ± 2.71	14.97 ± 1.89	0.002
Peak systolic velocity of basal segment of RV free wall (cm/s)	10.75 ± 1.46	9.80 ± 1.11	0.001
Peak systolic velocity of Mitral annulus (septal) (cm/s)	9.48 ± 1.42	8.94 ±1.48	0.081
Peak systolic velocity of Mitral annulus (lateral) (cm/s)	11.05 ± 2.16	11.63 ± 1.90	0.168
Peak Systolic velocity of basal segment of septal wall (cm/s)	6.55 ± 1.12	5.96 ± 1.26	0.023
Peak systolic velocity of mid segment of septal wall (cm/s)	4.93 ± 0.93	4.56 ± 0.99	0.073
Peak systolic velocity of basal segment of lateral wall (cm/s)	8.07 ± 1.87	8.03 ± 1.73	0.908
Peak systolic velocity of mid segment of lateral wall (cm/s)	5.48 ± 2.14	6.77 ± 1.80	0.003
Peak strain of septal wall (basal segment) (%)	21.76 ± 5.96	18.54 ± 2.89	0.004
Peak strain of septal wall (mid segment) (%)	20.07 ± 6.45	16.23 ± 2.28	0.001
Peak strain of lateral wall (basal segment) (%)	21.08 ± 6.07	19.91 ± 3.86	0.224
Peak strain of lateral wall (mid segment) (%)	18.55 ± 4.62	16.69 ± 2.96	0.037
Peak strain rate of septal wall (basal segment) (s-1)	1.82 ± 0.72	1.36 ± 0.27	0.001
Peak strain rate of septal wall (mid segment) (s-1)	1.55 ± 0.61	1.29 ± 0.34	0.026
Peak strain rate of lateral wall (basal segment) (s-1)	2.13 ± 0.66	1.65 ± 0.34	< 0.001
Peak strain rate of lateral wall (mid segment) (s-1)	1.65 ± 0.60	1.35 ± 0.31	0.008
Peak strain of basal RV free wall (%)	23.89 ± 5.48	23.68 ± 4.13	0.830
Peak strain rate of basal RV free wall (s-1)	1.92 ± 0.70	1.84 ± 0.47	0.471
Tei index (left ventricle)	0.54 ± 0.12	0.43 ± 0.09	< 0.001
Tei index (right ventricle)	0.33 ± 0.12	0.26 ± 0.06	0.001
Systolic time interval	0.24 ± 0.081	0.19 ± 0.060	< 0.001
Tricuspid Annular Plane Systolic Excursion (mm)	27.23 ± 5.06	21.9 ± 3.22	0.001

* All parameters are shown as Mean ± SD

Discussion

Overall, current findings showed chamber enlargement in cirrhotics but most of the evaluated indices were unable to demonstrate systolic dysfunction in these patients.

In the present study, Left atrial diameter, Left the atrial area, Right atrial area, basal right ventricular diameter and Left ventricular end-diastolic volume were increased significantly in cirrhotic patients. Moreover, other echocardiographic diameters were also increased in cirrhotic patients but they did not reach significance. These chamber enlargements are probably due to volume overload in cirrhotic patients. Similar findings were observed in previous studies (1,4,16). The present study demonstrated that Stroke volume and Left ventricular ejection fraction were increased significantly in cirrhotic patients. Since these two indices are load dependent, the underlying volume overload and peripheral vasodilatation could have obscured the concomitant systolic dysfunction.

One study in cirrhotic cardiomyopathy showed that although resting left ventricular ejection fraction (LVEF) is increased after exercise the left ventricular end-diastolic pressure increases and the expected increases in cardiac stroke index and LVEF are absent or subnormal which indicates an inadequate response of the ventricular reserve to a rise in ventricular filling pressure, despite increased resting LVEF (17).

Thus, however, LVEF reflects systolic function, it is very much influenced by preload and afterload and in some studies in cirrhotic patients it has been reported to be even normal or increased at rest (17,18).

Thus we tried to assess indices of systolic function which are supposed to be load independent, such as peak systolic velocities, strain and strain rates of myocardial segments, Tei index and systolic time interval in cirrhotic patients (14).

In present study peak systolic velocity of the basal segment of septal wall, tricuspid annulus, and basal RV free wall were higher in cirrhotic patients but peak systolic velocity of a mid segment of the lateral wall was lower. Other systolic velocities were more in the patients group but without any significant difference. Hence, it seems that systolic velocities are not so useful for unmasking systolic dysfunction in this group of patients.

Tricuspid annular plane systolic excursion (TAPSE)

Corresponding Author: B. Geraiely
Department of Cardiology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 22112017, Fax: +98 21 66939537, E-mail address: babak_geraiely@yahoo.com

was also significantly higher in the patients that accordingly did not show any evidence in favor of RV systolic dysfunction.

In present study, Peak strain of basal and mid segments of septal wall and mid segment of lateral wall, peak strain rates of basal and mid segments of septal and lateral walls were higher in cirrhotic patients significantly. There were no significant differences in RV peak strain and strain rates between two groups. It seems that these findings were not valuable in demonstrating systolic dysfunction in cirrhotic patients.

The present study showed that Tei index of left ventricle was increased in cirrhotic patients significantly which could indicate either systolic or diastolic dysfunction, as the patients group had significantly increased IVRT. But as mentioned, systolic time interval (the systolic component of Tei index) was also significantly increased in cirrhotic patients; so abnormal Tei index could be at least in part attributable to systolic dysfunction. It seems that Tei index and systolic time interval are useful to reveal the obscured LV systolic dysfunction in these patients. Bernardi *et al.,* found similar findings regarding systolic time interval (19).

Increased value of RV Tei index could be due to subtle RV systolic and/or diastolic abnormalities which are revealed only by a highly sensitive and load-independent index of cardiac dysfunction.

There were some limitations in this study, as follow:

Our control group was relatively small sized.

Using Doppler based longitudinal strain and strain rate imaging which is more operator-dependent than the new speckle based method.

It was ideal to evaluate systolic function in patients before and after liver transplantation, especially in those who might develop overt heart failure as a consequence of this stressor but at the time of composing this article a small group of these patients had been transplanted.

Subtle systolic and diastolic cardiac abnormalities are common in cirrhotic patients which are not manifest until exposure to stresses such as transplantation when they can reduce post-transplant survival.

Current results indicated that some of these abnormalities could be detected using sensitive and load independent echocardiographic indices before exposure to stress. In this regard, we suggest that LV systolic time interval and Tei index might be useful indices in the evaluation of systolic function in cirrhotic patients.

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