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Original Article

Cirrhosis-related changes in left ventricular function and correlation with the model for end-stage liver disease score

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Abstract: Objective: The purpose of our study is to investigate cirrhosis-related left ventricular remodeling and functional changes, further to analyze the correlations with model for end-stage liver disease (MELD) score. Methods: A total of 89 cirrhotic patients were enrolled for study and subgrouped according to MELD score: ≤ 9, 10-19, and ≥ 20. Thirty healthy individuals were enrolled as controls. All study participants underwent cardiac assessment of the left ventricle with Doppler echocardiography; the parameters assessed included left ventricular-end systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left atrial diameter (LAD), left ventricular ejection fraction (LVEF), cardiac output (CO), mitral flow velocity (VE/VA ratio), and E-wave deceleration time (DT). Results: The cirrhotic patients had significantly higher LVESD, LVEDD, IVST, LAD, CO and DT than the control group, but significantly lower VE/VA ratio (all $P < 0.05$). Subgroup analysis showed that the higher the MELD score, the greater the increase in LVESD, LVEDD, IVST, LAD and DT (all $P < 0.05$). Nearly one-half of the cirrhotic patients showed left atrial enlargement and a VE/VA ratio ≤ 1, and these features were more common in patients with MELD score ≥ 20. LAD, LVEDD and DT were positively correlated with MELD score (r = 0.208, 0.319 and 0.197, respectively; all $P < 0.05$). Conclusions: Patients with cirrhosis had impaired cardiac function, mainly present as left ventricular diastolic dysfunction, and the extent of dysfunction was correlated with the MELD score. Left atrial enlargement and VE/VA ratio ≤ 1 may serve as useful diagnostic indexes for cirrhotic cardiomyopathy.

Keywords: Liver cirrhosis, cardiac function, left, echocardiography, cirrhotic cardiomyopathy

Introduction

The pathogenic processes of liver cirrhosis lead to changes in cardiac structure and function. In these patients, the clinical manifestation of increased cardiac output and visceral blood flow, decreased systemic vascular resistance and mean arterial blood pressure, dysfunctional ventricular diastolic and/or systolic dysfunction, and mild tachycardia, as well as electromechanical abnormalities with prolonged QT interval without other known causes of cardiac disease, is defined as cirrhotic cardiomyopathy (CCM) [1]. The potential for missed diagnosis of CCM in cirrhotic patients remains a particular concern in clinical practice since cardiac dysfunction in whom is associated with worse prognosis and higher risk of death [1, 2].

The relationship between the severity of liver disease and cirrhotic cardiomyopathy is controversial. Although some studies have shown no direct relationship between the degree of liver dysfunction and extent of changes in cardiac function, others reported the most pronounced cardiac dysfunction in patients with higher model for end-stage liver disease (MELD) score [3-6]. The Child-Pugh scoring system is the most commonly used clinical method for classifying liver cirrhosis. Unfortunately, some of the indexes of this system may be influenced by subjective factors, such as ascites and hepatic

Table 1. The clinical characteristics of different cirrhotic groups and control group

Groups	n	LVESD	LVEDD	IVST	LVPWT	LAD	LVEF	CO	VE/VA	DT
control	30	28.90 ± 3.61	46.54 ± 5.67	8.62 ± 1.12	8.46 ± 0.93	29.15 ± 2.87	62.43 ± 5.33	4.46 ± 1.40	1.26 ± 0.34	160 ± 22
cirrhosis	89	30.54 ± 3.12	48.65 ± 6.23	9.43 ± 1.23	8.85 ± 0.88	33.29 ± 4.18	61.52 ± 5.72	5.54 ± 1.29	1.05 ± 0.31	181 ± 23
t value		2.437	3.015	2.821	1.714	5.322	0.938	2.913	2.246	6.124
P value		0.016	0.002	0.007	0.092	0.000	0.376	0.006	0.024	0.000

LVESD: left ventricular end systolic diameter; LVEDD: left ventricular end diastolic diameter; IVST: interventricular septal thickness; LVPWT: left ventricular posterior wall thickness; LAD: left atrial diameter; LVEF: ejection fraction; CO: cardiac output; DT: deceleration time.

encephalopathy. The MELD scoring system was designed to provide a more accurate assessment of liver disease and takes into account renal insufficiency, the etiology of cirrhosis, etc [7, 8]. In this study, we applied the MELD scoring system to assess the severity of liver disease in patients with cirrhosis and used echocardiography to assess these patients' cardiac structure and function, moreover, to analyze the potential correlation between the disease severity and cirrhosis-related left ventricular remodeling and functional changes.

Subjects and methods

Patient selection

Patients with a liver cirrhosis diagnosis who were hospitalized for treatment at the Second Affiliated Hospital, Xi'an Jiaotong University School of Medicine (Shaanxi, China) between June 2012 and June 2014 were considered for study enrollment. The cirrhosis diagnosis was based on accumulated findings for patient medical record, clinical manifestations, laboratory findings, liver B-ultrasound and/or computed tomography (CT) scan, or liver biopsy. All 138 patients with cirrhosis diagnosis underwent cardiac assessment with continuous-wave Doppler echocardiography and were recruited for study. However, patients were excluded if any of the following potential confounding or complicating factors were present: previous heart disease (i.e. hypertension, coronary heart disease, congestive heart failure, valvular heart disease); chronic kidney disease; chronic respiratory disease; thyroid disease; anemia (hemoglobin < 9 g/dL); diabetes or hyperlipidemia; history of gastrointestinal bleeding within one month. A total of 89 cirrhotic patients, of various etiology, met the criteria for study enrollment, including 64 males and 25 females, with an average age of 51.2 ± 8.9 years-old.

A healthy control group without liver disease was selected from our hospital's population of patients visiting for routine health check-ups. Individuals were offered enrollment according to: normal findings from tests of blood pressure, blood lipids, blood glucose, and liver and kidney function; lack of behavioral/mental, liver, kidney, lung and any other major organ disease; no recent history of drugs that can affect heart function. A total of 30 healthy controls were enrolled for study, including 22 males and 8 females, with a mean age of 49.4 ± 9.2 years-old.

MELD scoring

All cirrhotic patients underwent routine tests of liver function, kidney function, and blood clotting function. The MELD score was calculated as follows: 3.8 × ln TBIL (mg/dL) + 11.2 × ln (INR) + 9.6 × ln Cr (mg/dL) + 6.4 × etiology value [3, 7, 9], where TBIL is total bilirubin, INR is the international normalized ratio, Cr is serum creatinine, and the etiology value is 0 for biliary or alcoholic cirrhosis or 1 for all others. The patients were divided into three subgroups according to MELD score: ≤ 9, 10-19, and ≥ 20.

Continuous-wave Doppler echocardiography

All study participants (cases and controls) underwent two cardiac examinations using the Aplio XG color Doppler ultrasonogram system (Toshiba Medical Systems Corp., Otawara-shi, Tochigi-ken, Japan) with a probe frequency of 3.0-3.5 MHz; two examinations were conducted by two ultrasound practitioners working independently, and the results of each measured parameter were averaged for each patient.

For the examinations, each patient was placed in the left lateral decubitus position to obtain M-mode, two-dimensional, Doppler (pulsed and color) views and measure the left ventricu-

Table 2. Echocardiography parameters in patients with cirrhosis and control groups

	Control group (n = 30)	MELD ≤ 9 (n = 32)	MELD 10-19 (n = 34)	MELD ≥ 20 (n = 23)
Age (years)	49.4 ± 9.2	51.3 ± 8.3	50.3 ± 9.2	52.1 ± 8.9
Gender: male (%)	22 (73%)	21 (66%)	26 (76%)	17 (74%)
Etiology of cirrhosis: (n)				
HBV	--	20	21	15
HCV	--	4	4	2
HBV/HCV	--	2	1	1
Alcohol	--	3	4	2
Cholestasis	--	2	3	3
Cryptogenic	--	1	1	0

lar-end systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST), left ventricular wall thickness (LVPWT), left atrial diameter (LAD), left ventricular ejection fraction (LVEF), and cardiac output (CO). The apical four-chamber view was recorded to determine the diastolic mitral flow spectrum, the peak early (VE) and late (VA) diastolic velocity, the VE/VA ratio, and the E-wave deceleration time (DT).

Statistical analysis

All statistical analyses were carried out with SPSS Statistics for Windows software package, version 17.0 (SPSS Inc., Chicago, IL, USA). Categorical data were analyzed by the χ^2 test and Fisher's exact test. Measurement data were calculated as mean ± standard deviation. Intergroup differences were assessed by univariate analysis of variance (ANOVA). Pairwise group comparisons were conducted using *t*-test. The correlation between the various parameters of left ventricular structure and function and MELD scores was assessed by Pearson's correlation coefficient (*r*). A *P* value of less than 0.05 was considered statistically significant.

Results

Patient characteristics and MELD scores

The average MELD score of the 89 cases of liver cirrhosis in this study was 13.9 ± 5.6, with 32 (36.0%) of the patients having a score of ≤ 9, 34 (38.2%) having scores of 10-19, and 23 (25.8%) having scores of ≥ 20. The most common cause of cirrhosis was chronic viral infection (70/89, 78.7%), with 56 patients having hepatitis B virus (HBV) infection, 10 patients having hepatitis C virus (HCV) infection and 4 patients having HBV/HCV co-infection. Other etiologies were alcoholic liver disease (9 patients, 10.2%) and cholestatic liver disease (8 patients, 9.0%); for two cases (2.3%) the cause was unidentified (cryptogenic cirrhosis). As shown in **Table 1**, there were no significant differences among control and different MELD scores' case groups in age, gender and etiology of cirrhosis.

Correlations between changes in left ventricular structure/function and MELD score in patients with cirrhosis

Compared with the control group, the cirrhosis case group had significantly higher LVESD, LVEDD, IVST, and LAD (all $P < 0.05$), as well as significantly increased CO, decreased VE/VA ratio and prolonged DT (all $P < 0.05$) (**Table 2**). The control and cirrhosis groups had similar LVPWT and LVEF. MELD subgroup comparisons showed that patients with higher MELD score had higher LVESD, LVEDD, IVST and LAD and more prolonged DT than patients with lower MELD scores (all $P < 0.05$) (**Table 3**). However, the patients in the MELD 10-19 subgroup had the higher VE/VA ratio than patients in either the MELD ≤ 9 subgroup or the MELD ≥ 20 subgroup, with the latter showing lowest value (**Table 3**). The three subgroups showed similar LVPWT and LVEF.

Examination of the left arterial structure showed that 49 (55.0%) of the cirrhotic patients had enlargement. Analysis by MELD subgroups showed that the proportion of left atrial enlargement represented in the MELD ≥ 20 subgroup (18/23) was significantly higher than that in the other two subgroups of combined (31/66) ($P < 0.05$). Among the total cirrhotic patients, 39 (43.8%) had a VE/VA ratio ≤ 1; again, the MELD ≥ 20 subgroup had a signifi-

Table 3. Echocardiography parameters in cirrhotic patients with different MELD score

MELD score	n	LVESD	LVEDD	IVST	LVPWT	LAD	LVEF	CO	VE/VA	DT
≤ 9 group	32	29.83 ± 3.46	47.26 ± 4.84	9.06 ± 1.14	8.35 ± 1.02	31.16 ± 3.94	61.92 ± 4.76	5.06 ± 1.36	1.06 ± 0.28	176 ± 22
10-19 group	34	30.65 ± 3.29	49.32 ± 5.12	9.34 ± 1.20	8.62 ± 1.04	33.34 ± 4.37	60.84 ± 5.87	5.93 ± 1.83	1.11 ± 0.35	179 ± 24
≥ 20 group	23	31.44 ± 4.02	50.63 ± 5.90	10.01 ± 1.39	8.97 ± 0.92	34.91 ± 4.89	60.38 ± 5.18	5.32 ± 2.18	0.94 ± 0.33	183 ± 23
F value		3.643	4.221	5.906	2.364	7.546	1.263	3.482	3.311	8.324
P value		0.029	0.011	0.004	0.086	0.000	0.459	0.031	0.037	0.000

LVESD: left ventricular end systolic diameter; LVEDD: left ventricular end diastolic diameter; IVST: interventricular septal thickness; LVPWT: left ventricular posterior wall thickness; LAD: left atrial diameter; LVEF: left ventricular ejection fraction; CO: cardiac output; DT: deceleration time.

Table 4. Correlation between echocardiographic parameters and MELD score

Parameter	*r* value	95% confidence interval	*P* value
LVESD	0.136	-0.023-0.272	0.081
LVEDD	0.208	0.063-0.320	0.009
IVST	0.113	-0.156-0.212	0.121
LVPWT	0.012	-0.132-0.184	0.527
LAD	0.319	0.182-0.443	0.001
LVEF	0.006	-0.114-0.179	0.635
CO	0.107	-0.183-0.216	0.203
VE/VA	-0.089	-0.261-0.165	0.156
DT	0.197	0.051-0.288	0.013

LVESD: left ventricular end systolic diameter; LVEDD: left ventricular end diastolic diameter; IVST: interventricular septal thickness; LVPWT: left ventricular posterior wall thickness; LAD: left atrial diameter; LVEF: left ventricular ejection fraction; CO: cardiac output; DT: decele.

cantly higher number of VE/VA ≤ 1 cases (16/23) than the other two groups combined (23/66) ($P < 0.05$).

The LAD, LVEDD, and DT results were positively correlated with MELD scores in patients with cirrhosis ($r = 0.208$, 0.319 and 0.197 respectively; all $P < 0.05$); Although the results for LVESD, IVST, CO, VE/VA ratio were significantly different between the cirrhosis cases and controls, there was no significant correlation with MELD score found for any of these parameters ($P > 0.05$) (**Table 4**).

Discussion

Patients with cirrhosis suffer from hydrodynamic circulation including increased cardiac output and blood volume, as well as decreased arterial pressure and peripheral vascular resistance [1]. The pathologic processes underlying CCM remain to be fully elucidated, but recent studies have begun to define the molecular pathways involved. In particular, studies in mouse models have shown that tumor necrosis factor-alpha (TNF-α)-induced activation of nuclear factor-KB signaling and oxidative stress-induced changes in the β-adrenergic receptor signaling pathway may promote CCM [1]. While defining the molecular mechanisms of CCM development and progression may provide useful insights into therapeutic approaches, the issue of prompt and accurate clinical diagnosis remains unresolved.

Studies had shown that cirrhotic patients are prone to cardiac dysfunction and related death in stress conditions, such as improper exercise, use of certain drugs, and surgery [3, 9-11]. Occult disease progression and atypical clinical manifestations complicate the diagnosis of CCM. Therefore, it is important to define the clinical signs of CCM to improve positive diagnosis at the earliest possible stage, or to identify patients at risk of developing CCM. The MELD score was originally designed to assess the severity of liver disease. And it had been reported to predict risk of cardiac complications for surgical intervention in patients, such as those receiving liver transplantation, transjugular intrahepatic portosystemic shunt (TIPSS), and splenectomy portosystemic shunt [9-11]. As such, we designed the current study to evaluate the correlation between MELD score and CCM, using echocardiography to assess and analyze structural and functional abnormalities in cirrhotic patients.

Patients with end-stage liver disease have shown cardiac remodeling in the left ventricular cavity; the morphological changes include myocardial hypertrophy, proliferation interstitial cells, and intracellular edema, and the structural changes include left atrial enlargement, left ventricular hypertrophy, dilation and wall thickening of the left ventricle, especially changes in IVST [12]. Left ventricular diastolic

dysfunction is the main cardiac change observed in patients with cirrhosis, and it is also one of the main diagnostic criteria of CCM. Disruptions in systolic function are harder to detect, as they are subtle in the resting state and may only be detectable upon aggravation under physiological stress or in response to drugs [1]. In current study, we observed that for cirrhotic patients, by increases in MELD score was accompanied by an increase in LVESD, LVEDD and IVST, with no significant changes being observed in the LVPWT and LVEF regardless of MELD score classification; correlation analysis showed that the LVEDD was positively correlated with MELD score, which is consistent to the findings from previous studies [3, 4].

Left ventricular diastolic dysfunction can lead to an elevation in left ventricular filling pressure, resulting in increased preload in the left atrium after left ventricle relaxation. The left ventricular filling pressure must be adjusted to meet the needs of increased atrial wall tension (resulting from increased thickness); moreover, the increases in left ventricular filling pressure may promote myocardial hypertrophy and result in left atrial enlargement [13]. In our current study, 55% of the cirrhotic patients presented with left atrial enlargement, and the patients with MELD scores ≥ 20 showed significantly greater extent of enlargement (vs. patients with MELD scores < 20); further analysis showed that LAD was positively correlated with MELD scores. Although left atrial enlargement also occurs under conditions of hypertension, long-term alcohol consumption, and diabetes-related left ventricular diastolic dysfunction [4]. Our patient selection process for this study prohibited inclusion of any patients with heart disease, such as hypertension. In addition, the proportions of patients with alcoholic liver cirrhosis or diabetes mellitus in our study were not significantly different among the three MELD groups. Therefore, the left atrial enlargement that was observed in our patients likely reflects CCM-related left ventricular diastolic dysfunction and disruptions of left ventricular filling pressures, which strengthens our finding of a correlation with the severity of these patients' MELD scores.

The mitral Doppler spectrum encompasses the time from early diastolic filling (represented by the E wave) and to late diastolic filling (represented by the A-wave) during atrial contraction. Normal peak early diastolic filling velocity (VE) is faster than the atrial filling peak systolic velocity (VA), and the VE/VA ratio is a simple, reproducible, and high-sensitivity representation of left ventricular diastolic function [3, 5, 6, 14]. The decrease in the VE/VA ratio reflects reduced pre-load or increased post-load volume and reduced ventricular compliance. In conditions of cirrhosis, the hyperdynamic circulation of patients present as the characteristics of increased circulating blood volume, increased pre-load volume and reduced peripheral arterial resistance. Therefore, we theorize that patients with cirrhosis will have decreased VE/VA ratio and, indeed, nearly one-half of the cirrhotic patients in our study cohort had VE/VA ratios of ≤ 1, with a particularly high representation by the patients with MELD scores ≥ 20; these results suggest that left ventricular diastolic dysfunction may be common in patients with end-stage liver disease. E-wave DT is also one of the indicators of left ventricular diastolic function, and our previous studies have shown that this parameter was significantly prolonged in small sample patients with HBV-related cirrhosis [6, 15]. In this study, the cirrhotic patients showing increases in E-wave DT also had higher MELD scores; moreover, there was a positive correlation between the two parameters, further supporting the likelihood of left ventricular diastolic dysfunction in patients with end-stage liver disease.

Our study also found that the cirrhotic patients with MELD scores in 10-19 had higher CO than the patients with MELD scores ≥ 20, but this finding did not agree with results reported from others [3]. The possible explanations for reduced CO in the patients with MELD scores ≥ 20 (compared to patients with MELD scores in 10-19) may be that these patients showed obvious hypoalbuminemia and reduced colloid osmotic pressure, resulting in decreased volume of circulating blood. Furthermore, it is possible that this group of patients with more advanced liver disease, a condition which is associated with hepatorenal syndrome, were experiencing renal failure and had elevated levels of renin in serum which would be expected to perturb (or accompany disruption of) the renin-angiotensin signaling mechanism, thereby leading to reduced CO [16]. In addition, patients with decompensated cirrhosis showed lower heart rate due to decreased response to the sympathetic nerve activity [17]. Since no

significant change in LVEF [1, 3, 5, 6, 17], lower heart rate in patients with severe liver disease may be explain the reduced CO.

In conclusion, our study of cirrhotic cases showed increased cardiac involvement with increases in MELD severity, particularly involving left ventricular diastolic dysfunction. Patients presented as increased CO and decreased VE/VA ratio. Furthermore, as the MELD score increased, there were significant increases in LVESD, LVEDD, IVST and LAD, as well as prolongation of DT; the LAD, LVEDD and DT parameters were found to have a positive statistical correlation with the MELD score. The higher risk of postoperative cardiac complications in patients with more severe MELD scores may be associated with an increased risk of more severe, possibly unrecognized, preoperative CCM. Therefore, cirrhotic patients with high MELD scores should undergo a comprehensive assessment of cardiac structure and function prior to any surgical intervention. Echocardiography is a non-invasive, real-time, rapid imaging technology with a high accuracy for diagnosing cardiac abnormalities, such as those indicative of CCM. Echocardiography may be particularly useful for obtaining a timely diagnosis of CCM and for assessing the disease severity so that appropriate clinical management may be designed and initiated. And left atrial enlargement and VE/VA ratio ≤ 1 may be useful diagnostic indexes for cirrhotic cardiomyopathy.

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Disclosure of conflict of interest

None.

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