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Impact of the severity of end-stage liver disease in cardiac structure and function

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ABSTRACT

Background. The impact of end-stage liver disease (ESLD) in cardiac remodeling of patients with cirrhosis is unknown. Our aim was to correlate the severity of ESLD with morphologic and functional heart changes. **Material and methods.** 184 patients underwent a protocol providing data on the severity of ESLD and undergoing echocardiography to assess the diameters of the left atrium and right ventricle; the systolic and diastolic diameters of the left ventricle, interventricular septum, and posterior wall of the left ventricle; systolic pulmonary artery pressure; ejection fraction; and diastolic function. Severity of ESLD was assessed by the Model for End-Stage Liver Disease (MELD) score. **Results.** Left-atrial diameter (r = 0.323; IC 95% 0.190-0.455; p < 0.001), left-ventricular diastolic diameter (r = 0.177; IC 95% 0.033-0.320; p = 0.01) and systolic pulmonary artery pressure (r = 0.185; IC 95% 0.036-0.335; p = 0.02) significantly correlated with MELD score. Patients with MELD ≥ 16 had significantly higher left-atrial diameter and systolic pulmonary artery pressure, compared with patients with MELD scores < 16 points. **Conclusions.** Changes in cardiac structure and function correlate with the severity of ESLD.

Key words. Cirrhosis. Cardiac remodeling. Liver transplantation. MELD score. Cirrhotic cardiomyopathy.

INTRODUCTION

Advanced liver cirrhosis is associated with several cardiovascular and pulmonary abnormalities, including hyperdynamic circulation with decreased effective arterial blood volume, cirrhotic cardiomyopathy and arterial pulmonary hypertension.[1]

High cardiac output and low systemic vascular resistance index are typical features of end-stage liver disease (ESLD), and are related to the common clinical findings of increased heart rate and arterial hypotension.[2]

The pulmonary consequences of the hyperdynamic circulation and portal hypertension are hepatopulmonary syndrome and portopulmonary hypertension. According to the data of the European Respiratory Society Task Force on Pulmonary-Hepatic Vascular Disorders, the prevalence of hepatopulmonary syndrome can approach 20% in some series of patients awaiting liver transplantation, whereas portopulmonary hypertension has its prevalence in the order of 5%.[3] Cirrhotic cardiomyopathy is characterized by an abnormal and blunted response to pathological or pharmacological stress in the absence of any other associated cardiac disease. The combination of features including baseline increased cardiac output, attenuated systolic contraction and diastolic relaxation, electrophysiological repolarization abnormalities and a reduced response to beta-1 adrenergic stimulation are seen in patients with ESLD.[1,4,5]

Structural and functional cardiac abnormalities have been reported in patients with cirrhosis, irrespective of its etiology, including dilation of both heart chambers. In particular, cirrhosis is associated with increase in left atrium and right atrium sizes and in right ventricle diastolic diameter.[6]

The Model for End-Stage Liver Disease (MELD) score provides robust estimates of mortality. It is based upon a logarithmic equation that represents a

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weighted sum of serum values of bilirubin, international normalized ratio (INR) and creatinine.[7]

Collectively, these parameters measure organic dysfunctions in liver cirrhosis and correlate with the severity of ESLD. The liver allocation system for orthotopic liver transplantation (OLT) changed from the classical Child-Pugh system to the MELD score in most of countries of the world after 2002 because direct evidence demonstrated that mortality rates of patients waiting for liver transplantation were lower with the implementation of the MELD scoring system.[8,9] We hypothesized that the severity of ESLD could influence cardiac remodeling in cirrhosis. The aim of this study was to assess the correlation between echocardiographic abnormalities and severity of ESLD (assessed by the MELD score) in patients waiting for liver transplantation.

MATERIAL AND METHODS

Patients

From May 2009 to January 2011, 220 adult patients with liver cirrhosis who presented consecutively to the Department of Gastroenterology of the University of Sao Paulo Hospital were recruited for the current study. The protocol was approved by the Institutional Ethics Board Review. The informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All patients were medically stable and currently listed for liver transplantation. The diagnosis of cirrhosis was established in all patients based on clinical and laboratory data, by imaging methods or by liver biopsy in patients with safe coagulation parameters. The etiology of cirrhosis was hepatitis C virus infection in 81 (44%), hepatitis B in 16 (8.6%), alcohol-induced in 48 (26%), non-alcoholic steatohepatitis in 3 (1.6%), autoimmune hepatitis in 5 (3%), primary biliary cirrhosis in 5 (3%), primary sclerosing cholangitis in 2 (1%) patients and miscellaneous in the remaining 26 patients (14%). All patients with a history of alcohol intake had been abstinent from alcohol for at least 12 months before entering the study.

Twenty eight (12.7%) patients were excluded due to having primary heart disease, of whom 9 had valvar heart disease, 14 coronary artery disease, 3 systolic dysfunction with ejection fraction below 55% (ischemic cardiomyopathy n = 2; hypertensive cardiomiopathy n = 1) and 2 congenital heart disease. Eight patients (3.6%) had well-preserved liver function and concurrent chronic renal failure requiring chronic hemodialysis. Because the MELD calculation is dependent on creatinine levels, patients with chronic renal failure were excluded because high MELD scores in patients under hemodialysis may not correlate to the deterioration of liver function. A total of 184 patients with ESLD remained after exclusions and were the focus of this study.

Esophageal varices at endoscopy were considered a surrogate marker of significant portal hypertension. Functional renal dysfunction in cirrhosis (serum creatinine > 1.5 mg/dL) was diagnosed according to the revised criteria of the International Ascites Club.[10] Out of the 105 patients on propranolol use, 37 (35%) were Child-Pugh A, 53 (51%) were B, and 15 (14%) were C. These patients were found similarly distributed among all three Child-Pugh groups, without a statistically significant difference.

Baseline demographic and clinical features of the included patients are shown in table 1.

Table 1. Baseline demographic and clinical data of 184 patients with cirrhosis waiting for liver transplantation.*

Characteristics	Data
• Age (years)	54.2 ± 11.3
• Gender male/female, n (%)	122 (66)/62 (34)
• BMI (kg/m^2)	26.8 ± 5
• Etiology	
Non-alcoholic, n (%)	136 (74)
Alcohol-related, n (%)	48 (26)
• Ascites, n (%)	64 (34.8)
• Esophageal varices, n (%)	119/172 (69)
• Medical therapy	
Spironolactone, n (%)	76 (41)
Propranolol, n (%)	105 (57)
• Child-Pugh	
A, n (%)	76 (42)
B, n (%)	88 (48)
C, n (%)	20 (10)
• MELD	14.3 ± 5
• Bilirubin (mg/dL)	3.0 ± 3.3
• Creatinine (mg/dL)	1.0 ± 0.5
• Albumin (mg/dL)	3.4 ± 0.6
• INR	1.4 ± 0.4
• Sodium (mEq/L)	139.9 ± 4.4

*Plus-minus values are means ± standard deviation. BMC: body mass index. MELD: model for end-stage liver disease. INR: international normalized ratio.

Cardiac evaluation

A standard protocol, including medical history, physical examination, ECG and chest-X-ray, was performed for all patients by the same cardiologist. All patients underwent two dimensional transthoracic echocardiography with color Doppler according to the recommendations of the American Society of Echocardiography.[11] Measurement of the following parameters were performed: left-atrial and right-ventricular diameters, left-ventricular systolic and diastolic diameters, interventricular septum, left-ventricular posterior wall, ejection fraction and estimated pulmonary artery pressure. This former was determined from the peak tricuspid regurgitation, using the simplified Bernoulli equation and combining the values with an estimate of the right atrial pressure.[12] The E/A ratio (Early maximal ventricular filling velocity/Atrial maximal filling velocity) was used as an index of diastolic function, and was considered abnormal when < 1.0, as reported elsewhere.[13,14] All parameters were recorded in three cardiac cycles, and the mean of the measurements was taken for analysis.

In patients with ascites requiring therapeutic paracentesis with albumin infusion, echocardiography was performed at least two weeks after the procedure to avoid inaccurate measurements due to heart diameters changing transiently in response to volume overload. Therapy with beta-blockers was stopped before echocardiography exam to avoid hypothetical interferences in the measurements.

MELD score

Previous data showed that the MELD score is an accurate predictor of survival in cirrhotic patients on the waiting list for OLT[7] and has been used worldwide as a reliable parameter for liver allocation policies because it correlates with the decline of the liver function.[9] Three easily assessed variables, bilirubin, INR and creatinine, are used to calculate a score that continuously ranges from 6 to a capped value at 40. The score is calculated according to the formula MELD = 9.57 (loge creatinine) + 3.78 (loge bilirubin) + 11.2 (loge INR) + 6.43, as reported elsewhere.[7] We stratified the resulting values as < 16 or ≥ 16 points because this a usual cut off point for considering OLT.[15]

Statistical analysis

Mann-Whitney and Wilcoxon tests were used to compare non-parametric continuous variables. Chi-square and Fisher exact tests were used to compare dichotomous variables when appropriate. P values < 0.05 were considered significant. Spearman rank correlation was used to assess the association between echocardiography parameters and MELD score. All calculations were performed with the PASW statistical package (SPSS version 18.0, Chicago, IL) software. The results were expressed as the mean ± standard deviation and 95% confidence interval when indicated.

RESULTS

Left-atrial diameter, left-ventricular diastolic diameter and systolic pulmonary artery pressure significantly correlated with the MELD score (Figure 1 and Table 2). Patients with more-severe liver disease (MELD ≥ 16) were found to have higher left atrium diameter and higher values of systolic pulmonary artery pressure when compared with patients who

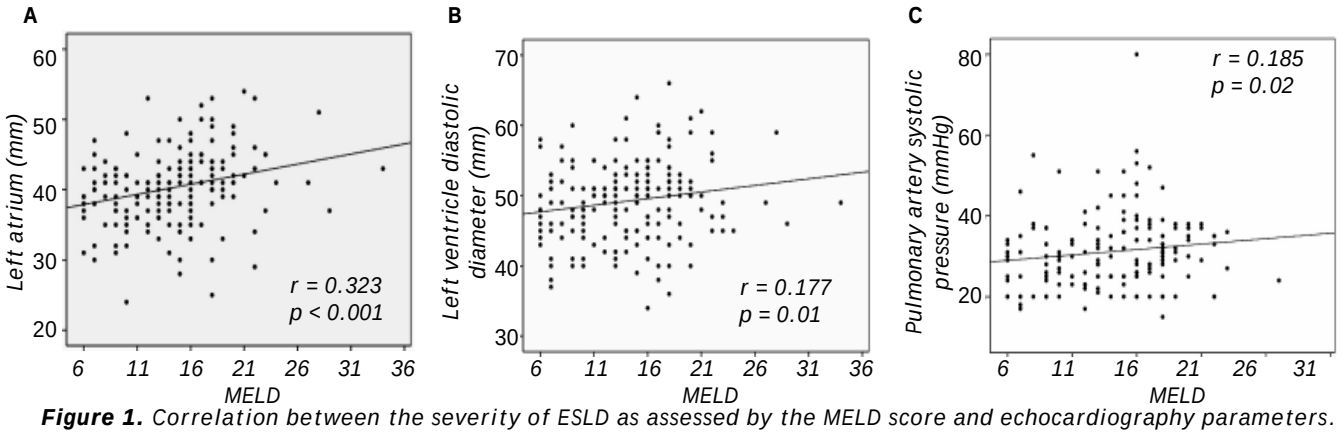

Figure 1. *Correlation between the severity of ESLD as assessed by the MELD score and echocardiography parameters.* ***A.*** *MELD score and left atrium.* ***B.*** *MELD score and left ventricle diastolic diameter.* ***C.*** *MELD score and pulmonary artery systolic pressure. ESLD: end-stage liver disease. MELD: model for end-stage liver disease.*

Table 2. Correlation between echocardiographic parameters and MELD score.*

Parameters	Whole group, n = 184	r value (95% CI)	p value	MELD< 16, n = 105	MELD ≥ 16, n = 79	p value
Left-atrial diameter (mm)	40.29 ± 5.19	0.323 (0.190-0.455)	<0.001	38.96 ± 4.63	42.05 ± 5.40	< 0.001
Right-ventricular diameter (mm)	20.59 ± 3.46	0.074 (-0.089-0.237)	0.2	20.59 ± 2.96	20.59 ± 4.08	0.615
Diastolic left-ventricular diameter (mm)	49.26 ± 5.66	0.177 (0.033-0.320)	0.01	48.59 ± 5.25	50.17 ± 6.07	0.062
Systolic left-ventricular diameter (mm)	31.29 ± 3.95	0.125 (-0.023-0.272)	0.09	30.83 ± 3.57	31.91 ± 4.34	0.067
Interventricular septum (mm)	9.94 ± 1.50	-0.013 (-0.158-0.132)	0.6	9.85 ± 1.49	10.06 ± 1.52	0.249
Left ventricular posterior wall (mm)	9.50 ± 1.38	0.009 (-0.137-0.154)	0.6	9.49 ± 1.46	9.68 ± 1.28	0.210
Pulmonary artery systolic pressure (mmHg)	31.14 ± 9.18	0.185 (0.036-0.335)	0.02	29.84 ± 8.28	32.83 ± 10.06	0.026
Ejection fraction (%)	66.01 ± 4.22	0.040 (-0.105-0.184)	0.6	66.12 ± 3.91	65.85 ± 4.61	0.662
Diastolic dysfunction, n = 77 (%)	-	-	-	51 (53.7)	26 (42.6)	0.193

*Results expressed as mean ± standard deviation (95% IC). MELD: model for end-stage liver disease.

had MELD < 16 points. These results are shown in table 2. 49.3% of patients (77 out of 156) were found to have diastolic dysfunction, which did not correlate with the MELD score (p = 0.193), nor with the Child-Pugh classification (Child-Pugh A and B *vs*. Child-Pugh C, p = 0.806).

Although all patients were abstinent from alcohol, a previous history of alcohol intake was present in 24.5% of patients with MELD < 16 and 17.3% of patients with MELD ≥ 16; this difference was not statistically significant (p = 0.2). Diabetes mellitus and arterial hypertension were diagnosed in 39 (21%) and 36 (19%) patients, respectively. Hepatopulmonary syndrome was diagnosed in 5% out of the 184 patients.

DISCUSSION

Our study shows that echocardiographic abnormalities seen in patients with liver cirrhosis, who are on the waiting list for transplantation, correlate directly with the severity of ESLD assessed by the MELD score. The most striking findings in our studies were an increase in left-atrial and diastolic left-ventricular diameters and an increase in systolic pulmonary artery pressure. Although diastolic dysfunction was seen in 49.3% of the subjects, no correlation was found with the severity of ESLD (MELD score or Child-Pugh class).

The demonstrable morphological and functional heart changes in patients with cirrhosis have been grouped under the term cirrhotic cardiomyopathy,[16] whose underlying physiopathology closely resembles the cardiac remodeling seen in conditions such as volume or pressure overload, myocarditis and myocardial infarction. Although the other conditions are different, they share biochemical and mechanical events that lead to gross changes in the heart, characterized by changes in geometry, mass, function and wall stress. Continuous increased wall stress produces further dilatation by the stimulation of a number of neuro-hormonal pathways, resulting in chronic heart failure.[17]

The mechanisms for the cardiac remodeling observed in patients with cirrhosis are not fully understood, but may be related to the presence of the hyperdynamic circulation, which is a hallmark of cirrhosis, in accordance to forward flow theory and peripheral vasodilatation hypothesis.[18]

In an echocardiography study of 24 patients with alcoholic cirrhosis, the enlarged left ventricular diameter was found both at end diastole and end systole. Increased cardiac output occurred in conjunction with an enlarged ventricle throughout the cardiac

cycle, i.e., the increase in left ventricular end-systolic diameter seems not to be related to the diminished afterload, but determined by an increase in vascular volume.[19]

Recent findings, in accordance with the prevailing hypothesis favoring central hypovolemia and decreased effective arterial blood volume in cirrhosis, have shown that a higher portal pressure and a higher hepatic blood flow independently determines a higher cardiac output.[2]

However, divergent results regarding the morphological changes in the hearts of patients with cirrhosis are reported.[6,20,21] Those differences are probably related to the accuracy of the echocardiographic measurements, differences in patient selection and differences in the etiology and severity of the liver disease. Previous publications have found left-atrial, right-atrial and right-ventricular diastolic diameters to be significantly greater in cirrhotic patients, compared with controls, but parameters concerning left-ventricular systolic dimensions, septal wall and posterior wall thickness did not show significant differences.[6]

Diastolic dysfunction, which is considered a major criterion for cirrhotic cardimiopathy,[1] is highly prevalent among patients with ELVD,[22] but in the current study and previous reports[23] it did not correlate with the severity of liver disease. Furthermore, in a retrospective study of 209 patients, the baseline E/A ratio < 1.0 could not predict the decrease in left ventricle stroke work despite an increase in filling pressure, which was observed in approximately up to a quarter of patients with cirrhosis undergoing liver transplantation.[22]

In the transplant setting, the MELD score is a reliable parameter to assess the deterioration of liver function because it correlates with mortality.[9] In this regard, the current study demonstrates that the MELD scoring system also correlates with heart changes observed in echocardiographic studies.

It is important to mention that several factors have been reported to influence the size of the left atrium.[24] In cardiovascular diseases, particularly arterial hypertension and diabetes mellitus associated with left-ventricular diastolic dysfunction, the higher ventricular filling pressure can increase the size of the left atrium.[25] It is unlikely that the presence of concurrent diabetes mellitus has biased our results because no correlation between left-atrial size and diastolic dysfunction was found. We excluded patients with valvar disease. Thus, the enlargement of the left atrium could not be explained by mitral regurgitation. Hepatopulmonary syndrome, which is defined as an arterial oxygenation defect induced by intrapulmonary vascular dilatations associated with hepatic disease, is well recognized as a cause of left atrium volume increase.[3,26]

Portopulmonary hypertension is a pre-capillary form of pulmonary arterial hypertension (mean arterial pulmonary pressure higher than 25 mmHg at rest and normal pulmonary capillary wedged pressure) associated to portal hypertension in the absence of other causes of pulmonary hypertension.[3] Although it can be a cause of enlargement of the right ventricle and increased atrial volume, there is no published data on the influence of pulmonary artery hypertension on the left-side chambers.[27]

One could argue that a number of patients in this study had previous history of alcohol intake, diabetes and arterial hypertension. However, it is unlikely that this scenario influenced the results because a similar proportion of cases were found in patients with higher or lower MELD scores.

A confounding effect of beta-blockers on the results is also unlikely. These drugs were withdrawn before echocardiography and the proportion of patients on therapy with propranolol was similar in the different Child-Pugh classes. Furthermore, propranolol has not been reported to influence cardiac remodeling, neither in heart failure nor in cirrhosis.

Progressive major cardiac remodeling is considered an ominous sign and usually relates to overt heart failure.[17] Because low peripheral resistance reduces cardiac workload in patients with liver cirrhosis, the clinical consequences of this process may not be evident unless additional volume overload occurs. However, adverse cardiac outcomes may be precipitated by liver transplantation[22] or transjugular intrahepatic portosystemic shunt insertion.[28] Pulmonary congestion after albumin infusion during therapeutic paracentesis has also been associated with cirrhotic cardiomyopathy.[29] Furthermore, as many as 50% of cirrhotic patients undergoing liver transplantation will have cardiac dysfunction, and cardiovascular complications may be implicated in 23.8% of deaths after OLT.[2,30-32]

It is likely that the cardiac remodeling seen in patients with liver cirrhosis is associated with a proportion of cardiovascular morbidity and mortality, because small increases in ventricular volume have been associated with independent risk of mortality in patients with coronary artery disease[33] or heart failure.[34] However, this phenomenon has not yet been demonstrated in patients with cirrhosis.

In addition, cardiac remodeling in cirrhosis may play a role in the pathogenesis of hepatorenal

syndrome. Published data suggest that the decrease in cardiac output that occurs during episodes of bacterial infection reduces renal perfusion pressure and may precipitate the development of hepatorenal syndrome.[35]

A potential limitation of the present study is found in the echocardiography protocol. The estimation of the pulmonary artery pressure was performed by echocardiography and not by right catheterization. In our previous experience, 18% of patients with presinusoidal portal hypertension had elevated systolic pulmonary pressure at echocardiography, but invasive hemodynamics confirmed pulmonary hypertension in 7%.[36]

Another potential limitation is the theoretical influence of the medical therapy with propranolol in reversing cardiac remodeling. However, propranolol induced remodeling was not reported neither in patients with heart failure nor with cirrhosis.

Cardiovascular disease has emerged as a leading cause of perioperative morbidity and mortality in the liver transplant setting. It has been suggested that a number of cardiovascular complications in cirrhotic patients and in liver transplant recipients are not associated with myocardial ischemia.[33] However, it is unclear whether heart remodeling accounts for a proportion of cardiovascular mortality and morbidity in patients with cirrhosis that undergo OLT. A better understanding of this process may aid in assessing the predictive value of echocardiography changes as it relates to prognosis because it is known that the greater the extent of the cardiac remodeling, the poorer the prognosis in other conditions. Future studies are warranted to explore the impact of heart changes seen by echocardiography in cardiac risk stratification and adverse outcomes during OLT.

ABBREVIATIONS

- **ESLD:** end-stage liver disease.
- **MELD:** Model for End-Stage Liver Disease.
- **INR:** international normalized ratio.
- **OLT:** orthotopic liver transplantation.

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