Correlations Between Biochemical Profile and Echocardiographic Parameters in Patients with Cirrhosis of the Liver Without Previous Cardiovascular Abnormalities

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The role of cardiac imaging in the management of non-cardiovascular diseases has been continuously increased. Most studies suggest the utility of echocardiography examination in the evaluation of left ventricular function in cirrhotic patients, being well-known that cirrhosis of the liver is associated with cardiovascular abnormalities which include especially left ventricle diastolic dysfunction and left ventricular hypertrophy. Cardiac dysfunction contributes to morbidity and mortality associated with liver transplantation. The aim of this study was to emphasize the role of echocardiography in assessing left ventricular systolic and diastolic function in cirrhotic patients in order to establish a correlation between echocardiography parameters and biochemical variables in patients with end-stage cirrhosis. The study was conducted as a cross-sectional analysis over a two-year period (2016-2018). 41 patients with cirrhotic liver from the departments of Gastroenterology and Cardiology from St Spiridon Emergency Hospital of Ia'i were included in the study, after a written informed consent was obtained. Patients with any previous cardiovascular (CV) abnormalities, other causes of pulmonary hypertension and endocrinopathies were excluded from the study. Using transthoracic echocardiography left ventricle dimensions and wall thickness (left ventricle posterior wall thickness + interventricular septum thickness) and also diastolic function (E wave, A wave, E/A ratio, deceleration time of E wave) and systolic function (ejection fraction) were determined along with biochemical variables. In conclusion, no significant association was obtained between echocardiographic changes and biochemical profile in patients with cirrhosis of liver.

Keywords: echocardiography, cirrhosis, diastolic function, systolic function, biochemical parameters

It is well-known that cirrhosis of the liver is associated with cardiovascular abnormalities which include especially left ventricle diastolic dysfunction and left ventricular hypertrophy. Cardiovascular dysfunction in patients with cirrhosis has been recognized for more than sixty years [1-3]. These abnormalities were initially attributed exclusively to the effects of alcohol, but different authors concluded that these abnormalities may be present irrespective of the etiology [2]. Since 2005, cirrhotic cardiomyopathy was defined as a *chronic cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease.* Several criteria for diagnosing this entity were proposed, based mostly on non-invasive assessment of myocardial function among which echocardiography is at the forefront [2, 4, 5].

Cardiac dysfunction contributes to morbidity and mortality associated with liver transplantation. Cardiovascular events are the third leading cause of death in liver recipients. In the end-stage of cirrhosis cardiac abnormalities are usually subclinical and may be missed because latent myocardial dysfunction may be masked by the marked peripheral vasodilatation. Post-transplant prognosis depends on the identification of cirrhotic patients with cardiomyopathy in the pre-transplant phase because an early diagnosis of cirrhotic cardiomyopathy in the pre-transplant phase may avoid an acute cardiac failure after liver transplantation [2, 4-6].

The aim of the study was to investigate the left ventricle dimensions, wall thickness (left ventricle posterior wall thickness + interventricular septum thickness) and also diastolic function (E wave, A wave, E/A ratio, deceleration time of E wave) and systolic function (ejection fraction) by using transthoracic echocardiography along with biochemical variables in patients previously diagnosed with end-stage liver disease in order to establish a possible correlation between these parameters.

Experimental part

Material and methods

The study was conducted as a cross-sectional analysis over a two-year period (2016-2018). Patients with cirrhotic liver from the departments of Gastroenterology and Cardiology from St Spiridon Emergency Hospital of Iasi were selected for the study. Patients with any pre-existing cardiovascular (CV) abnormalities, other causes of pulmonary hypertension (such as chronic obstructive pulmonary disease, pulmonary embolism, idiopathic), and endocrinopathies were excluded from the study. A total of 41 patients (33 males) aged between 26-62 years were included in the study. A written informed consent was obtained from all the patients. The majority of patients were on a waiting list for liver transplantation having end-stage liver disease.

The history of patients, clinical examination and laboratory details were obtained from the medical records. Biochemical investigations included serum bilirubin, albumin, total protein, prothrombin time/international normalized ratio, liver enzymes (alkaline phosphatase, aspartate transaminase, alanine transaminase). Transthoracic echocardiography, ultrasonography abdomen and upper gastrointestinal (UGI) endoscopy were

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performed. Child - Pugh (CPS) and MELDS score were calculated in order to appreciate the severity of cirrhosis.

Echocardiography was the most commonly used modality for assessing systolic and diastolic function of left ventricle in cirrhotic patients [6-8]. Measurements were made in M mode. The following parameters were determined: diastolic diameter (Dd), systolic diameter (Ds), thickness of the walls, left ventricle volume using the formula: end diastolic volume (EDV) = Dd^3, end systolic volume (ESV) = Ds^3. Ejection fraction (EF) was the most widely used parameter of global left ventricular systolic function. It was calculated using end-systolic and end-diastolic volumes, by the formula: EF = (Dd^3 –Ds^3) x 100/ Dd^3 and we considered normal value EF = 60-80%. Shortening fraction (SF) was also appreciated using a formula: (Dd-Ds) x 100/Dd; normal range between 20-40%. The visual estimation of the EF (eye balling) was used in parallel with the determinations using the diameters without significant differences.

Diastolic dysfunction (DD) has been reported as a common finding in patients with cirrhosis. Abnormalities in membrane receptor function and intracellular signaling pathways and changes in contractile proteins and extracellular matrix composition were involved in the pathogenesis of DD in cirrhosis [9-13].

Diastolic function was appreciated in our study in 2D Echo (dimensions and function of left atrium -LA and left ventricle -LV), in M Mode (dimensions of LA, LV, LV - Wall thickness, the pattern of the interventricular septum (IVS) movement). Non-invasive assessment of DD was classically based on the echocardiographic analysis of mitral inflow pattern using pulsed-wave Doppler. In the presence of DD, early diastolic filling is decreased as a consequence of delayed LV relaxation and atrial contraction becomes a more important contributor to left ventricular filling. This impaired relaxation pattern is characterized by a decrease in E wave velocity, prolongation of E-wave deceleration time, and an increase in A wave velocity resulting in an inverted E/A ratio (< 1) [9-13].

Statistical analysis

Statistical analysis was performed using IBM SPSS 20.0 software (Statistical Package for the Social Sciences, Chicago, Illinois). Data were expressed as mean ± standard deviation or number of cases with percentage, for continuous and ordinal variables. Cross-tabulation and Pearson Chi-Square test were used for describing the relationship between two categorical variables. The one-way analysis of variance (ANOVA) was used to determine the significant differences between the means of continuous variables and an independent categorical variable. For all data, a two-sided p value < 0.05 was considered statistically significant.

Results and discussions

In the study, the majority of patients were males (33 patients), 20 of them in the age group of >50 years, which was consistent with other studies that showed incidence of cirrhosis to be higher among men [2, 4]. The etiology for cirrhosis in our study was predominantly viral (virus B - 4 patients; virus C - 10 patients, virus B+D - 13 patients) and alcoholic (5 patients, alcoholic + virus C - 4 patients), autoimmune 4 patients, cryptogenic - 1 patient, compared with other studies that showed alcoholic fatty liver disease having a higher prevalence and a worse survival compared to other etiological factors [2]. Descriptive data is presented in table 1.

Table 1
DESCRIPTIVE DATA OF THE STUDY POPULATION

Parameter	Value
Age (years)	51.20 ± 8.02
MELD Score	17.58 ± 5.71
AST (U/L)	84.39 ± 60.43
ALT (U/L)	59.86 ± 55.00
GGT (U/L)	84.05 ± 70.07
Total bilirubin (mg/dl)	3.43 ± 3.58
Total cholesterol (mg/dl)	127.63 ± 38.05
Seric albumin (g/l)	3.23 ± 0.70
Urea (mg/dl)	54.07 ± 48.78
Creatinine (mg/dl)	1.02 ± 0.62
EF LV (%)	62.93 ± 5.35

The most common presenting symptom was abdominal distension (in 35 patients, 85%), which might be secondary to ascites that was present in 33 patients (80.48%), exercise intolerance, fatigue, dyspnea and jaundice (28 patients, 68.29%). 12 patients (29.26%) had CPS Grade C, 14 patients (34.14%) had Grade B and 15 patients (36.58%) – Grade A. MELD score was between 7-30 (in 28 patients ≥10).

UGI endoscopy was performed in 90% of cases and 75% of these patients had esophageal varices, but no correlation was found with LV function.

Left ventricular hypertrophy was found during the echocardiographical examination in 15 patients with a moderate degree (left ventricular posterior wall between 12-13 mm and interventricular septum between 12-14 mm). Echocardiographic changes of the left ventricular hypertrophy were correlated with electrocardiographic changes in only 10 patients. In most cases the electrocardiogram had a normal morphology. Only 4 patients with alcoholic cirrhosis showed ectopic ventricular beats on the electrocardiogram and left bundle branch block was present in 2 male patients who associated dilated cardiomyopathy having the same alcoholic etiology. [20-22].

According to the current consensus, using 2D echocardiography, an EF of less than 52% in men and 54% in women, suggests systolic dysfunction. Reference values for 3D may be different since there is less published data on normal subjects [11]. Only 2 male patients from the group previously diagnosed with alcoholic dilatative cardiomyopathy had EF 40-45%. The rest of the patients presented high values of EF (values between 68-75%) caused by the hyperdynamic status described in cirrhosis.

In the 2005 World Congress of Gastroenterology, proposed as a diagnostic criteria for systolic dysfunction a resting EF < 55%. As we know, EF is highly dependent on loading conditions, a higher cut-off value may need to be considered in patients with cirrhosis of the liver due to the peripheral vasodilatation and decreased afterload. This may explain the finding of normal resting ejection fraction in the majority of the studies in cirrhosis [5, 18, 19, 23-25].

Diastolic dysfunction, as defined in the 2005 World Congress of Gastroenterology (E/A ratio < 1.0, deceleration time > 200 ms and isovolumetric relaxation time > 80 ms), is highly prevalent in patients with cirrhosis [10-16]. An association between liver disease severity and DD and an improvement in DD after paracentesis has also been reported. Earlier studies also suggested that DD was related

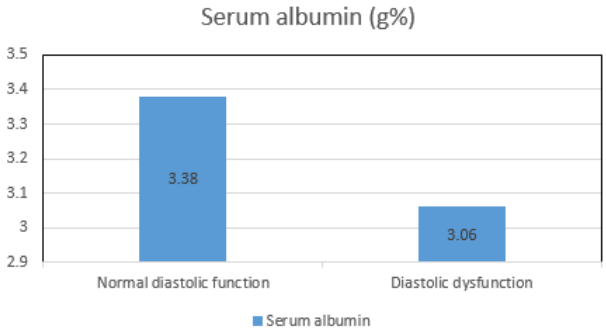

Fig. 1. Diastolic function difference according to serum albumin

to the liver disease severity and improved after paracentesis [10-17].

In our study, diastolic dysfunction was found in 15 patients (36.58%). Of these 15, 7 were CPS Grade B and 6 were Grade C.

In our study patients with diastolic dysfunction had more diminished values of serum albumin ($p = 0.156$) (fig. 1) and diastolic dysfunction was not significantly different depending on the Child class ($p = 0.637$).

Different studies did not show significant difference in echocardiographic parameters among the subgroups of CPS10, which was in agreement with our results ([11-16]. Echocardiographic parameters may be significant in determining prognosis in cirrhosis and help in early diagnosis and treatment of co-existing cardiac abnormalities. Subclinical diastolic and systolic impairments that are missed by conventional echocardiography may be picked up by echo parameters such as strain, strain rate from tissue-Doppler and speckle tracking echocardiography [12-18]. Thus, future studies are needed to appreciate the subclinical cardiovascular involvement among patients with cirrhosis.

Depending on the etiology, only the MELD score was significantly different ($p = 0.006$), while the other parameters did not reach the statistical significance. Based on gender, no echocardiographic parameter was statistically significant. Only the MELD score has been associated with some biochemical parameters (bilirubin, albumin, urea, creatinine) (table 2).

Table 2

ASSOCIATIONS OF MELD SCORE WITH BIOCHEMICAL PARAMETERS

Parameter	r	p
AST	0.130	0.424
ALT	0.039	0.813
GGT	0.021	0.900
Total bilirubin	**0.438**	**0.005**
Total cholesterol	-0.150	0.357
Triglycerides	-0.110	0.499
Total proteins	-0.224	0.164
Seric albumine	**-0.497**	**0.001**
Urea	**0.377**	**0.016**
Creatinine	**0.411**	**0.008**

No significant association was found between echocardiographic changes and CPS in patients with cirrhosis of liver. However, advising an echocardiogram for patients with cirrhosis (CPS - B and C) may prove beneficial for early screening. This needs further evaluation by larger studies, with echocardiographic modalities that can detect subclinical changes in left ventricular function. The correlation between DD and the prognosis of cirrhotic patients also remains controversial, with conflicting results reported in different studies [18, 23-25].

Conclusions

A large number of parameters derived from different imaging modalities are currently available for the assessment of left ventricular function but echocardiography is a widely available method allowing a rapid and detailed evaluation of myocardial function, improving the diagnostic accuracy in patients with different comorbidities. Echocardiography parameters are needed to evaluate cardiac performance in patients with cirrhosis of the liver and, more important, to orientate the clinical management of this specific group of patients. In our study no significant association was found between echocardiographic changes and biochemical parameters in patients with cirrhosis of liver.

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