Two-dimensional echocardiographic evaluation in liver cirrhosis patients in prediction of cirrhotic cardiomyopathy

Dvodimenzionalna ehokardiografska evaluacija obolelih od ciroze jetre u predviđanju cirotične kardiomiopatije

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Abstract

Background/Aim. Cirrhotic cardiomyopathy (CCM) is a clinical syndrome in liver cirrhosis (LC) patients, which is characterized by the abnormal cardiovascular (CV) response to physiologic, pathologic, or pharmacologic stress provocation, but normal to increased cardiac output and contractility at rest. The aim of the study was to identify the structural and functional myocardial changes in the prediction of CCM in patients with LC of various origins in advanced stages. **Methods.** The research was performed as a prospective, nest case-control study, on carefully selected 40 patients in the advanced stage of LC and negative personal medical history on previous CV disease and 40 healthy subjects as the control, from January 2012–December 2014. Echocardiographic parameters significant for prediction of the development and/or presence of CCM were determined by trans-thoracic two-dimensional Doppler echocardiography imaging. **Results.** Most of the LC patients were alcoholic (80%), dominantly in Child-Pough C stage of the disease (70%). The average value of QT interval in the LC patients was significantly higher (0.44 ± 0.03 ms vs 0.42 ± 0.01 ms; $p < 0.001$), as well as brain natriuretic peptide (BNP) serum level (284.61 ± 181.44 ng/L vs 69.41 ± 31.08 ng/L; $p < 0.001$) compared to those in the healthy subjects. A significant association with serum BNP level in LC patients was shown with left atrial diameter ($p = 0.031$), left ventricular ejection fraction ($p = 0.014$), pulmonary artery systolic pressure (PASP) ($p = 0.000$) and the presence of tricuspid valve regurgitation of 2+ ($p = 0.000$), affecting its change of 41.6%. **Conclusion.** The obtained results suggest that LC patients have significant echocardiographic signs of myocardial dysfunction, as well as the increased BNP serum level. Left atrial diameter, left ventricular ejection fraction, PASP and tricuspid valve regurgitation are valuable echocardiographic predictors of CCM.

Apstrakt

Uvod/Cilj. Cirotična kardiomiopatija predstavlja klinički sindrom obolelih od ciroze jetre, koji karakteriše nenormalno usporen odgovor na fiziološke, patološke, ili farmakološke draži, uz normalno povećan minutni volumen srca i kontraktilnost u mirovanju. Cilj istraživanja je bio identifikacija strukturnih i funkcionalnih promena miokarda, kao prediktora cirotične kardiomiopatije, kod bolesnika sa cirozom jetre različite etiologije u odmaklim fazama bolesti. **Metode.** Istraživanje je sprovedeno po tipu prospektivne studije slučaja, na odabranih 40 bolesnika u odmakloj fazi ciroze jetre sa negativnom ličnom medicinskom istorijom na kardiovaskularne bolesti i 40 zdravih ispitanika kao kontrolom, u periodu od januara 2012. do decembra 2014. godine. Pomoću transtorakalne dvodimenzionalne dopler ehokardiografije određivani su parametri od značaja za razvoj i/ili prisustvo cirotične kardiomiopatije. **Rezultati.** Većina obolelih bila je sa alkoholnom cirozom jetre (80%), dominantno u Child-Pough C stadijumu bolesti (70%). Prosečne vrednosti QT intervala kod obolelih od ciroze bile su značajno više (0,44 ± 0,03 ms vs 0,42 ± 0,01 ms; $p < 0,001$), kao i serumske vrednosti moždanog natriuretskog peptida (BNP) (284,61 ± 181,44 ng/L vs 69,41 ± 31,08 ng/L; $p < 0,001$), u poređenju sa onima kod zdravih ispitanika. Oboleli od ciroze jetre imali su značajnu povezanost između serumskih vrednosti BNP i dijametra leve pretkomore ($p = 0,031$), ejekcione frakcije leve komore ($p = 0,014$), sistolnog pritiska u pulmonalnoj arteriji

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(p = 0,000) i prisustva regurgitacije trikuspidne valvule od 2+ (p = 0,000), koji su uticali na promenu vrednosti BNP za 41,6%. **Zaključak.** Rezultati ovog istraživanja sugerišu da oboleli od ciroze jetre imaju značajne ehokardiografske znake miokardne disfunkcije, uz povećan serumski nivo BNP. Dijametar leve pretkomore, ejekciona frakcija leve komore, pritisak u pulmonalnoj arteriji i prisustvo regurgitacije trikuspi- dalne valvule, predstavljaju važne ehokardiografske prediktore cirotične kardiomiopatije.

Ključne reči:
jetra, ciroza; kardiomiopatije; ehokardiografija, dopler; natriuretski peptid, moždani.

Introduction

The heart and liver may interact in several different ways. Acute or chronic heart failure (HF), especially in case of the right HF, may lead to a spectrum of many liver disorders, including the cardiac cirrhosis, or congestive hepatopathy [1]. On the other hand, chronic liver disease such as cirrhosis may affect the heart and the whole cardiovascular system, leading to a clinical syndrome of cirrhotic cardiomyopathy (CCM) [2].

Cirrhotic cardiomyopathy was first defined in 2005 on the annual expert consensus meeting of the World Gastroenterology Organisation in Montreal as: "a cardiac dysfunction in patients with liver cirrhosis characterised by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease" [3, 4]. Although this term had a significant lack of strict criteria, the prevalence of CCM is reported to be between 40% to 50% in cirrhosis patients, while its development seems to be independent of the etiology of liver disease [5, 6].

The different myocardial adaptations seen in liver cirrhosis (LC) can be classified in structural, electrophysiological and functional changes. Structural changes include enlarged cardiac chambers and increased myocardial mass [7]. A prolonged QT interval and an abnormal chronotropic response to stress, are the main electrophysiological changes. Functional changes mainly consist of an impaired cardiac response to exercise or diastolic dysfunction [1, 7, 8]. The most common cardiac abnormalities on autopsy were left or right ventricular dilatation and left ventricular hypertrophy, which are encountered in more than 30% of the patients [9]. Some echocardiographic studies show conflicting data, but left atrial (LA) dilatation and mild left ventricular (LV) hypertrophy are the most common reported abnormalities [10, 11]. These changes probably reflect a combination of mechanical overload due to hyperdynamic circulation and neurohormonal activation [2, 12, 13].

Diastolic dysfunction is the most prominent functional alteration seen in CCM [3, 4]. It is due to a combination of myocardial hypertrophy, fibrosis due to increased aldosterone levels and subendothelial oedema. The reported prevalence is between 45% and 56% [8]. There are no strict diagnostic criteria but impaired cardiac response to stress, LV diastolic dysfunction, and prolonged QT are the most prominent features [14].

Cirrhotic cardiomyopathy is diagnosed if there is any evidence of systolic or diastolic myocardial dysfunction, along with associated criteria such as electrophysiological abnormalities and/or changes in serum markers levels [4, 14]. Many studies have made the link between the decrease in LV function and increased concentrations of natriuretic peptides in plasma, which opened the possibility of biochemical confirmation of heart failure [15, 16]. The most reliable results are obtained with the N-terminal atrial natriuretic peptide (NT ANP), brain natriuretic peptide (BNP) and its precursor N-terminal pro BNP (NT pro BNP) [13]. Analysis of these peptides is clinically significant as a test to exclude the diagnosis of heart failure due to their high negative predictive value [12].

Data on the clinical significance of CCM are scarce but several publications indicate a poor prognosis for these patients. In patients prior to performing a transjugular portosystemic shunt (TIPS), diastolic dysfunction expressed as an E/A ratio ≤ 1, was a predictor of ascites persistence and death [17]. The presence of the cardiomyopathy should be suspected in patients with worsening hemodynamics. Such patients may benefit from more aggressive monitoring and treatment of the underlying pathology leading to decompensation, and from close monitoring during procedures that could cause decompensation i.e., TIPS, paracentesis, liver transplantation (LT) [18, 19].

The aim of the study was to identify the structural and functional myocardial changes in patients with liver cirrhosis of various origin in advanced stages of the disease, by two-dimensional echocardiographic evaluation, assessing its significance and correlation with serum levels of BNP in the prediction of CCM.

Methods

Patients

The research was performed as a prospective, nest case-control study, in the Clinic for Gastroenterology and Hepatology and Clinic for Cardiovascular Disease, Clinical Center of Niš, on carefully selected 40 patients with verified liver cirrhosis in the advanced stage of the disease (Child-Pough B and C stage) and the negative personal medical history on previous cardiovascular disease, as an experimental group, and 40 healthy subjects as the control one, in the period between January 2012 and December 2014. All the patients gave informed and written consent for the participation in the study, while the ethical approvement for the research was obtained from the Academic Council of Faculty of Medicine, University of Niš (N° 04-828/12).

Diagnosis and staging of liver cirrhosis

The diagnosis of cirrhosis was based on clinical, echocardiographic (Toshiba Ecossee 96, 3.75 MHz convex probe, 1996, Japan) and laboratory parameters of liver damage, and in some

cases histologically by parenchymal biopsy. The severity degree of cirrhosis was evaluated by "scoring" system of functional liver damage by using the Child-Pough classification [20].

Cardiovascular examination

In all of the observed patients was done: a) standard electrocardiogram in 12 leads, b) arterial blood pressure measurement (mmHg), c) heart rate measurement, d) serum values of brain natriuretic peptide (ng/L) (Olympus, AU 400, 2003, Japan) and e) echocardiography examination determining the values of left ventricular end-diastolic and end-systolic diameter, LV ejection fraction and LA diameter, E/A ratio, deceleration time (DT) and isovolumic relaxation time (IVRT), right ventricular diameter, presence of tricuspid valve regurgitation and pulmonary artery systolic pressure (PASP). Echocardiographic study was made in M-mode technique, by two-dimensional Doppler echocardiographic examination (ACUSON X 300, KT-LM 150 HD, Siemens, Germany) [21].

Follow-up of the patients

At the moment of hospitalization, patients underwent a standard clinical, echosonographic and laboratory processing in order to verify the cause and severity of liver cirrhosis, and then performed cardiovascular analysis in accordance with inclusion and exclusion criteria for the entry into the study, whereupon were placed in the experimental subjects group. All subjects of the experimental group were treated by hepatoprotective and substitution therapy in accordance with the stage of liver cirrhosis. The control group subjects made only the cardiovascular analysis.

Statistical analysis

Statistical analysis was performed on the personal computer. Excel program from Microsoft Office 2007 software package was used for entering, ranking, clustering, tabular and graphical display of data. All calculations were performed using SPSS program ver.18.0. In all analysis, the limit of statistical significance as the default error estimates of 0.05.

The mean ($\bar{x}$), standard deviation (SD), structure (%) and 95% confidence interval (95% CI) were shown in the description analysis. Comparison of mean values of numerical characteristics between two examined groups of patients was done by Student's-t test or Mann-Whitney U test in cases where the distribution of values did not meet the requirements of the normal distribution. Comparison of the frequency of attribute characteristics between groups was performed by Mantel-Haenszel χ^2 test or Fisher exact test's probability of the null hypothesis, in cases where some of the features expected frequency was less than five [22].

Analysis of the relationship of investigated factors and indicators of cardiac function were done by the linear regression analysis. There were calculated values of the regression coefficients (β) and the boundaries of their 95% confidence intervals (95% CI). All the examined factors were involved in a univariate model of analysis. Those factors which shown significant association with the dependent variables in univariate models, were included in the multivariate models, and then, applying the backward method of multivariate model, were excluded under the control of the influence of other factors involved, which did not show a significant impact on the dependent variable, as long as the model did not contain only major factors and constant of regression [23].

Results

The observed groups of patients were homogenous in relation to the average distribution of general demographic characteristics (age, gender, social status, living and working place). In relation to ethiology of liver cirrhosis, most of the patients in experimental group were with alcoholic liver cirrhosis (32/80%). According to Child-Pough classification, there was registered a significantly higher number of patients in stage C of disease (28/70%), in relation to those in stage B of disease (12/30%). From typical clinical symptoms and signs of cirrhosis deterioration, which were decisive parameters in the further assessment for the effects on cardiovascular function in observed patients of the experimental group, there were registered: ascites in 29 (72.5%), encephalopathy in 19 (47.5%), jaundice in 21 (52.5%) and the presence of esophageal varices in 30 (75%) of the patients.

Results of examined cardiovascular system parameters in liver cirrhosis patients (experimental group)

The average values of arterial blood pressure in cirrhosis patients were within normal limits and amounted to 113.38 ± 14.82 mmHg for systolic blood pressure, and 70.13 ± 10.03 mmHg for diastolic one. For these subjects, electrocardiogram registered an average moderately elevated heart rate frequency from 86.9 ± 14.45 beats *per* minute, while in 22 (55%) of respondents, the extended value of the QT interval (> 0.44 s) was registered, an average of 0.44 ± 0.03 s. In 34 (85%) patients with cirrhosis, an average increased serum level of BNP of 284.61 ± 181.44 ng/L was registered. The presence of pathologically altered values of echocardiographic parameters in patients with liver cirrhosis is shown in Figure 1.

Only in 5% of cirrhosis patients, a reduced LV ejection fraction (<55%), with average values at the group level of 64.43 ± 4.12% was registered. Increased LA diameter (> 40 mm) was registered in 40% of respondents, the average at the group level of 38.28 ± 6.17 mm. Reduced E/A ratio (< 1 ms), was registered in 29 (72.5%) cirrhosis patients, with mean values at the group level of 0.93 ± 0.28 ms. Extending values of DT (> 200 ms), were registered in 38 (95%) patients, with average values, at the group level of 275.65 ± 71.25 ms, as well as IVRT (> 80 ms) in 30 (75%) with an average value at the group level of 90.52 ± 22.82 ms. Increased right ventricular diameter (RVD) (> 25 mm), was registered in 31 (77.5%) of cirrhosis patients, with average values of 26.63 ± 2.93 mm and tricuspid valve regurgitation was present in 24 (60%), mostly of the first degree (55%). The average value of the inferior vena cava diameter in in-
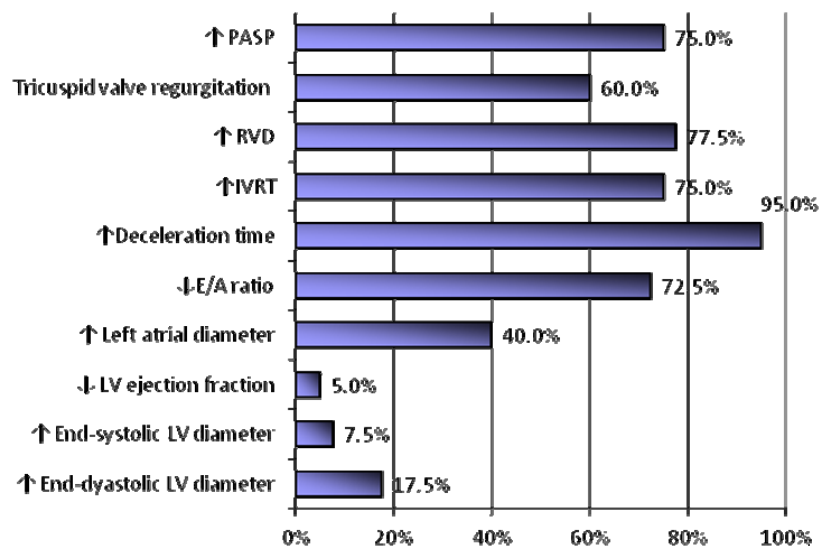
Fig. 1 – The presence of pathologically altered values of echocardiographic parameters in patients with liver cirrhosis
PASP – pulmonary artery systolic pressure; RVD – right ventricular diameter; IVRT – isovolumic relaxation time;
LV – left ventricle.

spirium amounted to 2.27 ± 3.69 cm. In 30 (70%) an increased PASP (>25 mm) was registered, in an average of 31.75 ± 7.89 mm, as shown in Figure 1.

Comparison of the cardiovascular system parameters in the assessment of myocardial functions between two observed groups of patients

The average value of the arterial systolic blood pressure in the cirrhosis patients was 113.38 ± 14.82 mmHg, which was significantly lower compared to the healthy subjects (125.38 ± 8.65 mmHg) ($p < 0.001$). Mean arterial diastolic blood pressure was not significantly different between the observed groups and was within normal range (70.13 ± 10.03 *vs* 72.0 ± 8.83 mmHg; $p = 0.378$). From the examined electrocardiographic parameters, the average value of heart rate was statistically significantly higher in the cirrhosis patients compared to that in healthy subjects (86.9 ± 14.45 *vs* 70.97 ± 6.07 n/min; $p < 0.001$), as well as the average value of QT interval (0.44 ± 0.03 *vs* 0.42 ± 0.01; $p < 0.001$). In patients with liver cirrhosis, the average value of BNP was 284.61 ± 181.44 ng/L, being significantly higher compared to the value of healthy subjects ($p < 0.001$).

Echocardiographic examination of morphological and functional characteristics of the heart cavities, as well as all tested parameters of myocardial dysfunction in patients with liver cirrhosis, verified significant differences in the average values, compared to values in healthy subjects, as shown in Table 1.

Analysis of relationship between the values of echocardiographic characteristics and serum brain natriuretic peptide in cirrhosis patients for predicting cirrhotic cardiomyopathy

Univariate linear regression analysis as significant predictors of serum levels of BNP, among the examined echo-cardiographic characteristics of heart cavities and the parameters of diastolic dysfunction in liver cirrhosis patients, confirmed: LA diameter, LV ejection fraction, DT, RVD, PASP and the presence of tricuspid valve regurgitation, as shown in Table 2.

Multivariate regression analysis as the most important predictors of serum levels of BNP, among the investigated echocardiographic characteristics of the cirrhosis patients, allocated values of : LA diameter, LV ejection fraction, PASP and the presence of tricuspid valve regurgitation of 2+, as shown in Table 3.

These echocardiographic parameters in common analysis model of association with serum levels of BNP, affecting its change of 41.6%.

Discussion

Liver cirrhosis of various etiology manifests as a state of low systemic vascular resistance, high peripheral volume with low central blood volume, precipitating a state of neurohormonal activation and high cardiac output, which may adversely affect cardiac reserve and lead in clinical syndrome of CCM [14]. In its most benign form, CCM manifests as subtle electrocardiographic (ECG) and echocardiographic abnormalities, most commonly as prolonged QT interval and diastolic dysfunction, but typically with preserved systolic function by two-dimensional ultrasound imaging in the resting and pre-transplant vasodilated state [24–25]. At the extreme, CCM progresses to the heart failure under the hemodynamic stress, unmasked by the demands of variceal bleeding, high doses of vasopressors, reversal of low to high afterload, withdrawal of cardioprotective medications used in the treatment of end stage LC (beta-blockers and mineralocorticoid antagonists), worsened by concomitant sepsis or systemic inflammatory response syndrome [24]. Recently, there is increasing data on the role of cardiac biomarkers, such as

Table 1

Comparison of the average echocardiographic parameters values between liver cirrhosis patients (experimental group) and healthy subjects (control group)

Echocardiographic parameters	Cirrhosis patients (n = 40)	Health subjects (n = 40)	Significance (*p*-value)
Left heart cavities			
left atrial diameter (mm), x̄ ± SD	38.28 ± 6.17	34.73 ± 1.91	0.001*
end-systolic left ventricular (LV) diameter (mm) , x̄ ± SD	29.48 ± 5.35	27.33 ± 1.69	0.018*
end-diastolic LV diameter (mm), x̄ ± SD	47.78 ± 5.48	46.68 ± 3.32	0.281
LV ejection fraction (%), x̄ ± SD	64.43 ± 4.12	69.68 ± 3.29	0.001*
Diastolic dysfunction			
E/A ratio (ms), x̄ ± SD	0.93 ± 0.28	1.16 ± 0.07	0.001*
deceleration time (ms), x̄ ± SD	275.65 ± 71.25	185.15 ± 8.34	0.001*
isovolumic relaxation time (ms), x̄ ± SD	90.52 ± 22.82	76.95 ± 2.29	0.001*
Right heart cavities			
right ventricular diameter (mm), x̄ ± SD	26.63 ± 2.93	23.38 ± 3.03	0.001*
pulmonary artery systolic pressure (mm Hg), x̄ ± SD	31.75 ± 7.89	23.35 ± 2.66	0.001*
inferior vena cava diameter in inspirium (cm), x̄ ± SD	2.27 ± 3.69	1.59 ± 0.14	0.253
Tricuspid valve regurgitation, n (%)			
1+	22 (55)	6 (15)	0.001*
2+	2 (5)	0 (0)	0.494

x̄ – arithmetic mean; SD – standard deviation; *statistically significant difference.

Table 2

Correlation between echocardiographic parameters of the liver cirrhosis patients with the values of serum brain natriuretic peptide (results of univariate linear regression analysis)

Echocardiographic parameters	ß	Boundaries of 95% CI for ß lower limit	Boundaries of 95% CI for ß upper limit	Significance (*p*-value)
Left heart cavities				
left atrial diameter (mm)	12.927	5.698	20.156	0.001*
end-systolic left ventricular diameter (mm)	-3.021	-14.41	8.371	0.598
end-diastolic left ventricular diameter (mm)	6.058	-3.997	16.112	0.233
left ventricular ejection fraction (%)	-13.528	-21.30	-5.748	0.001*
Diastolic dysfunction				
E/A ratio (ms)	53.522	-120.0	227.046	0.540
deceleration time (ms)	0.733	0.199	1.268	0.008*
osovolumic relaxation time (ms)	0.996	-1.436	3.428	0.417
Right heart cavities				
right ventricular diameter (mm)	12.998	2.146	23.850	0.020*
pulmonary artery systolic pressure (mm Hg)	11.977	4.631	19.323	0.002*
inferior vena cava diameter (inspirium) (cm)	2.058	-16.03	20.146	0.821
Tricuspid valve regurgitation				
1+	152.444	81.066	223.822	0.000*
2+	404.293	722.3	86.380	0.013

ß – regression coefficient; CI – confidence interval; * statistically significant difference.

Table 3

Correlation between echocardiographic parameters of the liver cirrhosis patients with the values of serum brain natriuretic peptide (results of multivariate regression analysis)

Echocardiographic parameters	ß	Boundaries of 95% CI for ß lower limit	Boundaries of 95% CI for ß upper limit	Significance (*p*-value)
Left atrial diameter (mm)	7.368	0.711	14.025	0.031*
Left ventriculary ejection fraction (%)	-8.752	-15.675	-1.829	0.014*
Pulmonary artery systolic pressure (mm Hg)	12.940	7.405	18.474	0.000*
Tricuspid valve regurgitation 2+	477.794	714.254	241.334	0.000*
Constant of regression	150.344	-424.484	725.172	0.604

ß – regression coefficient; CI – confidence interval; * statistically significant difference.

BNP, and advanced echo imaging techniques using tissue Doppler imaging (TDI) and strain imaging, to advance the better understanding of this clinical entity.

Prolongation of the QT interval is the most common ECG finding in LC, seen in up to 50% of patients and is associated with sudden cardiac death [26]. Chronic hyperactivation of the sympathetic nervous system and delayed repolarization of cardiomyocytes secondary to defects in K^+ channel function, have been observed in cirrhotic patients with the associated QT interval prolongation, which

may reverse after LT, although may persist in up to 50% of patients [27]. On the other hand, the use of beta-blockers for the varices treatment is associated with QT prolongation reduction [28, 29]. There is also a strong evidence of electromechanical uncoupling, with dysregulation in the normal sequence of cardiomyocyte depolarization and contraction [30, 31]. In our study, 55% of LC patients had prolonged QT interval values, significantly higher compared to the healthy subjects on average ($p < 0.001$).

In addition to ECG testing, echocardiography provides more valuable information regarding the development of clinically important systolic and diastolic dysfunction. Two-dimensional transthoracic echocardiography with TDI is an important imaging technique for better understanding of the dynamic myocardial changes that may occur as cirrhosis worsens, while volume overload becomes more severe, developing a hepatorenal syndrome. The American Association for the Study of Liver Diseases recommends this method as part of the evaluation of liver transplantation cirrhosis candidates to assess for systolic and diastolic dysfunction, outflow gradients, hypertrophy, chamber sizes, and non-invasive assessment of pulmonary pressures [32]. Many echo studies in this patient population have been done, demonstrating variable findings, most notably the presence of diastolic dysfunction, using both two-dimensional imaging and TDI assessments, demonstrating the association of diastolic dysfunction with worsening of cirrhosis [4, 8, 18]. In a recent autopsy study of 133 patients with LC, cardiomegaly and left ventricular hypertrophy were found in up to 43% of patients [9].

Diastolic dysfunction is common in LC patients and has been widely reported in many clinical studies, most commonly evaluating abnormalities in E/A ratio [17, 24]. Using basic two-dimensional echocardiography indices of diastolic dysfunction, pulsed-wave Doppler at the mitral valve leaflet tips provide information about early and late diastolic filling in normal sinus rhythm, with rapid passive filling followed by atrial contraction. Measurements of DT, along with measurement of isovolumic relaxation time by pulsed-wave Doppler at the septal insertion of the mitral valve, provide estimates of diastolic parameters and can guide in categorizing patients on the spectrum of diastolic abnormalities using a validated grading system [33]. However, E/A ratio is load-dependent, making its use in cirrhosis problematic, as the fluid shift is a prominent physiologic derangement in this condition. Diastolic dysfunction parameters may change based on weight, whether or not measurements were obtained before or after paracentesis, or whether obtained before or soon after other major interventions such as TIPS, which precipitates a marked increase in preload and can precipitate fulminant heart failure from latent or subclinical CCM. TDI is an increasingly attractive modality to assess diastolic dysfunction in the setting of suspected CCM given both angle-independence and load-independence [34]. In our investigation, reduced E/A ratio (< 1 ms) has been registered in 72.5% cirrhosis patients, significantly lower compared to healthy subjects ($p < 0.001$). Extending values of DT (> 200 ms), were registered in 95% of patients, as well as prolonged

IVRT (> 80 ms) in 75% LC patients, significantly higher compared to values in healthy subjects ($p < 0.001$). On the other hand, we registered a reduced LV ejection fraction (< 55%) in only 5 LC patients, generally significantly lower average values compared to those in the healthy subjects and increased LA diameter (> 40 mm) at 40% of patients. Increased RVD (> 25 mm) was registered in 77.5% of LC patients, while the tricuspid valve regurgitation was present in 60.0%, mostly of the first degree. In 70.0% of investigated LC patients an increased PASP was registered, significantly higher in average compared to values found in the healthy subjects, which is corresponding to the previously mentioned literature data.

Nowadays, a serial use of biomarkers is an increasingly important strategy for the diagnosis and management of patients with CCM. Both BNP and NT-proBNP have been reported to be significantly increased in patients with advanced cirrhosis compared to controls. This increase is probably secondary to increased cardiac production of natriuretic peptides since hepatic degradation does not seem to be affected. Increased BNP and NT-proBNP were associated with the severity of both cirrhosis and cardiac dysfunction [13]. Our investigation showed a significantly higher the average BNP value in LC patients in Child-Pough stage B and C of the disease, compared to values in the healthy subjects ($p < 0.001$). BNP has been studied in cirrhotic patients as a surrogate for cirrhotic cardiomyopathy, with recent predictive data regarding the incidence of renal failure and mortality after liver transplantation, and its association with a model for the end stage liver disease (MELD) and Child-Pough scores, the severity of LC, and diastolic or systolic dysfunction [13, 35, 36]. In our study, the most important predictors of serum levels of BNP, among the investigated echocardiographic characteristics of the LC patients, were values of: LA diameter, LV ejection fraction, PASP and the presence of tricuspid valve regurgitation of 2+. Therefore, an increasing BNP levels in the setting of dyspnea, exertional intolerance, and progressive renal dysfunction in LC patients may alert clinicians to reassess myocardial systolic and diastolic function.

Conclusion

Data obtained in this study indicate that in patients with liver cirrhosis, morphological and functional myocardial damages in the form of cirrhotic cardiomyopathy, are created and developed in the field of the advanced stage of the disease, mostly as a consequence of altered systemic hemodynamics. Patients with liver cirrhosis had significant echocardiographic signs of myocardial dysfunction, as a prolonged deceleration time and isovolumic relaxation time, together with reduced E/A ratio, as well as the increased BNP serum level. Left atrial diameter, LV ejection fraction, pulmonary artery systolic pressure and tricuspid valve regurgitation, were strongly associated with BNP serum levels, which suggests their importance as predictors in the assessment of the origin and development of cirrhotic cardiomyopathy.

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