NT-proBNP and Cardiovascular Dysfunction in Chronic Liver Disease

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Plasma NT-proBNP levels are elevated in heart disease, especially in the presence of ascites-edema syndrome and left ventricular overload. Previous studies have reported cardiovascular dysfunction correlated with the severity of liver damage. This prospective study enrolled 65 subjects with the diagnosis of liver cirrhosis, 82 with chronic hepatitis and 65 healthy subjects in the control group. In chronic hepatitis, NT-proBNP has been shown to be an early marker of diastolic dysfunction and left ventricular remodeling, while in liver cirrhosis it also correlated with portopulmonary hypertension.

Keywords: NT-proBNP, cardiovascular dysfunction, liver cirrhosis, chronic hepatitis

Natriuretic peptides have been identified as biomarkers with diagnostic and prognostic potential in several categories of patients. Brain natriuretic peptide (BNP) is a member of the natriuretic peptide family, structurally characterized by a 17 peptide ring, along with atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP) and D-type natriuretic peptide. Structurally, BNP consists of a biologically inactive portion of 76 amino acids, and an active component of 32 amino acids. BNP and NT-proBNP are secreted in plasma in equimolar amounts, being used in the diagnosis of congestive heart failure and in the differentiation of acute dyspnea of cardiac or pulmonary origin [1]. BNP is released at atrial and ventricular levels, and CNP is secreted by the vascular endothelium and has vasodilator properties [1-3]. These new biomarkers have been also used for screening of asymptomatic subjects. Wang and the investigators from the Framingham Offspring Study reported the long-term prognosis of natriuretic peptide levels in middle-aged population. Over a 5-year follow-up period, BNP level was an independent predictor of heart failure, atrial fibrillation or stroke [4, 5]. Natriuretic peptides contribute to the regulation of blood pressure and the regression of left ventricular hypertrophy.

Liver cirrhosis has been associated with hemodynamic changes and myocardial dysfunctions which make up cirrhotic cardiomyopathy. Patients with liver cirrhosis may have both systolic and diastolic dysfunctions, electro-mechanical disorders, chronotropic incompetence, and various arrhythmias. Although cardiac output is initially normal or increased, the diastolic and systolic function will be gradually affected. The left ventricular filling pressures will be increased, resulting in hypertrophy and myocardial fibrosis. Some patients with cirrhosis or hepatitis may experience dyspnea, fluid retention, and decreased physical effort tolerance. Although all these changes are not fully categorized yet, their diagnosis and assessment as early as possible is essential [6, 7].

Measurement of natriuretic peptides plays a very important role in the diagnosis of heart failure and in assessing other conditions in which intracardiac pressure and volumes can be modified. In particular, the hemodynamic changes encountered in patients with cirrhosis were associated with variations of ANP and proBNP. Also, high sensitive troponin I may be useful in risk stratification in patients undergoing transjugular intrahepatic portosystemic shunt [8]. A disturbed myocardial function may lead to a faster degradation of kidney processes and precipitation of hepatorenal syndrome. For this reason, the establishment of some noninvasive subclinical biomarkers is useful for monitoring patients with chronic liver disease. The present study assessed comparatively NT-proBNP and the cardiovascular function parameters in patients with cirrhosis or chronic hepatitis versus a control group.

Experimental part

Material and methods

This prospective study enrolled 212 subjects (mean age 54.33 ± 8.99, 43.9% men) divided into 3 groups: 65 subjects with liver cirrhosis diagnosis, 82 diagnosed with chronic hepatitis and a control group of 65 healthy subjects. The patients with liver disorders were enrolled after their presentation to the clinic based on clinical and biological criteria, the morphopathological examination being available in 20 cases with cirrhosis and 24 cases with chronic hepatitis. Liver diseases were of viral, metabolic or mixed etiology. Acceptance to participate in the study was given by signing the informed consent approved by the local ethics committee. The cases with cardiovascular disease of other etiologies (myocardial infarction and angina pectoris, cardiomyopathy, congenital heart disease, history of stroke, arrhythmias, heart failure, hypertension), systemic diseases (diabetes, neoplasia, bronchial asthma, mental disorders), chronic ethanol or drug use were excluded. The control group consisted of healthy volunteers in which the investigations excluded the presence of chronic conditions. In the controls the biological samples were normal and the HBsAg and anti-HCV markers were negative. After physical examination and collection of biological samples, the subjects with liver disorder underwent electrocardiogram, abdominal and cardiac ultrasound. Esogastroduodenal radioscopy and endoscopy

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Characteristics	Control (Mean±SD)	Hepatic cirrhosis (Mean±SD)	Chronic hepatitis (Mean±SD)
Age (years)	54.91±8.58	55.17±9.21	53.21±9.12
BMI (kg/m^2)	26.66±4.43	23.12±3.94	26.53±4.77
HR (b/min)	68.35±5.84	85.34±14.99*	76.44±11.89*
SBP (mmHg)	123.69±10.35	121.20±21.79	133.35±17.01*
DBP (mmHg)	72.48±7.18	72.23±11.04	78.84±12.5*
Albumins (%)	56±2,61	45.17±7.2*	52.7±6.39
Gamma-globulins (%)	19.49±2.24	29.56±7.41*	21.32±3.83
Prothrombine index (%)	87.28±6.36	54.86±18.73*	83.96±10
ALAT (U/L)	20.6±6.11	104.31±121.72*	114.51±113.55*
ASAT (U/L)	22.35±6.12	103.8±10.7*	123.57±14.28*
NT-proBNP (pg/mL)	25.33±7.79	423.04±287.37*	142.44±135.08*

Table 1
CLINICAL AND BIOLOGICAL CHARACTERISTICS OF THE STUDIED POPULATION (* - $p < 0.05$ vs control)

were performed to detect the presence and degree of esophageal varices.

Systolic (SBP) and diastolic (DBP) blood pressure was determined with the help of a brachial sphygmomanometer by making two successive measurements with the patient in sitting position. The electrocardiogram was recorded with a conventional, non-computerized electrocardiograph (Siemens, Germany).

The biological samples were determined after collection of peripheral venous blood using standard methods. Plasma NT-proBNP level was determined by ELISA technique using a kit from Biomedica Medizinprodukte & Co KG Austria. After collection, the blood samples were centrifuged and the plasma was stored in the freezer at -20° C until the measurements were performed. Levels lower than 125 μg/mL were considered normal.

M-mode, 2D and Doppler abdominal ultrasound were performed using a convex transducer and the diameters of the liver, spleen, portal vein (PV), splenic vein (SV) and flow velocity in the portal vein were measured. For the echocardiographic examination, the device from Esaote Biomedica AU3 Partner was used. Determinations were made in M-mode, 2D, pulsed, continuous and color Doppler with the 2.5/3.5 Mhz transducer. The size of the right (RV) and left ventricles (LV), left ventricular ejection fraction (EF), left ventricular diastolic function parameters (isovolumic relaxation time - IVRT, E-wave deceleration time - EDT and E/A ratio) were determined and systolic pressure in the pulmonary artery was estimated.

Statistical analysis

The statistical interpretation of data was performed using SPSS version 13.0 and Excel. From the point of view of descriptive statistics, average and standard deviation were calculated. To show significant differences between numerical variables, the t test was used. In case of non-normal distribution of values, the differences were verified using the Mann-Whitney and Kruskal-Wallis tests. Statistical significance was established for $p < 0.05$. Correlation coefficients R and R^2 and regression line coefficients for the relationship of NT-proBNP with the other variables were calculated.

Results and discussion

In total 119 female (56.1%) and 93 male patients (43.9%) were studied, women being predominant in all three groups: 56.9% in the cirrhosis group, 58.5% in the chronic hepatitis group, and 52.3% in the control group. The mean age was 54.33 ± 8.99 years, minimum age 32 years and maximum age 74 years. For patients with cirrhosis, mean age was 55.17 ± 9.21 years, and for those with hepatitis 53.21 ± 9.12 years. Most patients were from urban areas: 60% of those with cirrhosis, 73% of those with hepatitis and 66% of the control group. Screening for viral markers (HBsAg, anti-HCV) was performed in all study patients. Hepatitis B virus (HBV) was present in 25 patients with liver cirrhosis (38.5%) and 21 patients with hepatitis (25.6%). Hepatitis C virus (HCV) was present in 24 with cirrhosis cases (36.9%) and 22 hepatitis cases (26.8%). Most of the studied subjects were non-smokers: 49 in the cirrhosis group (75.4%), 59 in the hepatitis group (72%) and 45 in the control group (69.2%).

Physical examination identified a decrease in body mass index (BMI) in the patients with cirrhosis compared with the control group, and also in the chronic hepatitis group. SBP and DBP were significantly lower in the control subjects and in patients with liver cirrhosis than in patients with chronic hepatitis (table 1). The tendency to hypotension is more pronounced in patients with cirrhosis, especially in orthostatic position. In a study comparing hemodynamic data obtained from patients with liver cirrhosis by two different methods (radionuclide angiography and thoracic electrical bioimpedance), the decrease in SBP and DBP and peripheral vascular resistance was shown to be constant in liver cirrhosis; in some patients blood pressure is normal in supine position and decreases in orthostatic position. Decreased vascular smooth muscle response to endogenous vasoconstrictor action is a feature reported in several studies in portal hypertension patients [9]. Along with a decreasing arterial tone, there is a tendency to tachycardia, noticed by us in our liver cirrhosis group. The increase in sympathetic nerve activity contributing to tachycardia can also be observed in patients with chronic hepatitis [10]. In our study, ascitis was present in 33 of the patients with liver cirrhosis.

From a biological point of view, ALAT and ASAT were significantly elevated in patients with cirrhosis and chronic hepatitis versus the control group. Only in the liver cirrhosis group there was a significant decrease in albumin levels and prothrombin index and a significant increase in gamma globulins. Patients with cirrhosis and chronic hepatitis had significantly higher mean NT-proBNP levels than the control group subjects (423.04 ± 287.37 pg/mL, 142.44 ± 135.08 pg/mL vs 25.33 ± 7.79 pg/mL, $p < 0.05$).

The ultrasound parameters of the studied subjects are presented in table 2. The measurements indicated significantly higher values for the left atrium and ventricle in both types of chronic liver disease. The right atrial diameter was significantly higher in patients with liver cirrhosis, but not in those with hepatitis, the same being true for the estimated systolic pressure in the pulmonary artery. All patients with liver disease presented alterations in left ventricular diastolic function, while left ventricular ejection fraction showed no significant group differences. The echocardiographic changes occurred in parallel with the aspects suggestive of portal hypertension seen on abdominal ultrasound; in patients with liver cirrhosis the diameters of the spleen, portal vein and splenic vein were

Characteristics	Control (Mean±SD)	Hepatic cirrhosis (Mean±SD)	Chronic hepatitis (Mean±SD)
LA (mm)	32.85±4.23	43.6±5.16*	39.89±7.32*
IVS (mm)	8.85±0.96	11.38±1.61*	10.44±1.29*
LVPW (mm)	8.89±0.75	11.32±1.67*	10.49±1.41*
LV mass (g)	169.6±35.65	237.42±85.18*	224.77±73.65*
EF (%)	63.44±4.68	59.26±4.75	59.39±6.09
RA (mm)	34.31±3.24	44.02±6.20*	39.98±5.08
RV (mm)	27.51±2.94	33.38±6.09	30.71±4.33
SPAP (mmHg)	19±6.64	40.52±21.82*	25.02±11.66
E/A	1.27±0.22	0.9±0.27*	1,01±0.34*
IVRT (ms)	80.32±7.26	105.58±15.26*	98.72±8.73*
EDT (ms)	187.75±15.48	257.86±46.82*	237,29±40,11*
Spleen longitudinal diameter (mm)	92.52±5	163.45±26.44*	127.12±18.31*
PV (mm)	9.93±1.16	14.43±1.51*	11.02±1.91
SV (mm)	7.54±0.7	11.43±1.87*	8.69±1,14
Flow velocity in portal vein (cm/s)	18.84±3.87	6.79±1.54*	15.98±2.57

Table 2
ECOGRAPHIC CHARACTERISTICS OF THE STUDIED POPULATION (* - $p < 0.05$ vs control)

significantly higher, while flow velocity in the portal vein decreased.

The correlations of NT-proBNP with the selected biochemical and ultrasound parameters are shown in table 3. NT-proBNP levels correlated with prothrombin index and E/A ratio in patients with chronic hepatitis. In patients with liver cirrhosis, correlations were found with prothrombin index, ALAT, ASAT, E/A ratio, estimated pulmonary artery systolic pressure and flow velocity in the portal vein. No significant correlations with the parameters of left ventricular systolic function were found in the study patients. At the same time, left ventricular systolic function was slightly diminished in patients with liver disease, but the variations were not significant in relation to the control group. These findings are in agreement with those reported in the study by Poliwczak et al. stating that classical echocardiographic assessment is not reliable enough to detect incipient contractile changes to be correlated with NT-proBNP levels [6].

Our study highlights a wide range of clinical and ultrasound cardiovascular changes in patients with chronic hepatic diseases. At the same time, NT-proBNP level was higher, being correlated with cardiovascular changes both in patients with cirrhosis and in those with chronic hepatitis. BNP and NT-proBNP were initially known as biomarkers of heart failure, with persistent elevations following chronic left ventricular volume overload. The biological effects of ANP and BNP are diuresis with natriuresis and vascular relaxation, but many patients with advanced liver disease are resistant to these effects. The pro-BNP fragment is considered a more accurate marker of left ventricular dysfunction due to a more stable structure and longer half-life. In the study by Henriksen et al., BNP and pro-BNP were elevated in patients with liver cirrhosis and correlated with disease severity. According to their research, increased natriuretic peptide levels are mainly due to increased cardiac synthesis, and not to defective use in the liver [11-13].

In a study published in 2013, Licata et al. reported the change in atrial volume, left ventricular mass and pulmonary arterial pressure in patients with cirrhosis, using comparatively a group of hypertensive patients [14]. The changes are related to NT-proBNP and are considered to be the expression of the hyperdynamic syndrome characterized by increased heart rate, high cardiac output, reduced total systemic vascular resistance, and normal or decreased blood pressure. NT-proBNP is considered a marker of clinical and subclinical cardiac dysfunction, mediating the vasodilator syndrome associated with cirrhotic cardiomyopathy [14-16]. Vascular changes are quoted in liver cirrhosis and digestive tumor pathology [17]. Compared with other studies in literature, our study differs by choosing the groups to be compared with the patients with liver cirrhosis. Previously published studies have shown cardiovascular dysfunction and NT-proBNP changes in patients with liver cirrhosis with or without ascites. In our study, the assessment of patients with chronic hepatitis revealed changes of diastolic dysfunction and left ventricular hypertrophy without signs of pulmonary hypertension or right cavity involvement. These data suggest the presence of very early subclinical changes of

Table 3
ANALYSIS OF PEARSON CORRELATION BETWEEN NT-PROBNP AND THE BIOCHEMICAL AND ULTRASOUND PARAMETERS

NT-proBNP	Control (Pearson correlation coefficients)			Hepatic cirrhosis (Pearson correlation coefficients)			Chronic hepatitis (Pearson correlation coefficients)		
	R	R^2	p	R	R^2	p	R	R^2	p
ALAT	0.746	0.556	**0.026**	0.376	0.331	**0.013**	0.216	0.046	0.361
ASAT	0.917	0.842	**0.0001**	0.374	0.140	**0.042**	0.109	0.012	0.648
Prothrombine index	0.621	0.385	0.055	0.451	0.203	**0.012**	0.546	0.298	**0.013**
SPAP	0.464	0.215	0.177	0.547	0.299	**0.002**	0.085	0.007	0.72
E/A	0.436	0.190	0.207	0.428	0.183	**0.018**	0.476	0.226	**0.034**
Spleen longitudinal diameter (mm)	0.695	0.482	0.026	0.025	0.001	0.895	0.121	0.015	0.611
PV	0.205	0.042	0.569	0.086	0.007	0.652	0.193	0.037	0.415
SV	0.202	0.041	0.576	0.184	0.034	0.331	0.015	0.001	0.949
Flow velocity in portal vein (cm/s)	0.464	0.215	0.177	0.547	0.299	**0.002**	0.085	0.007	0.720

cardiomyopathy even in the absence of marked vasodilation in cirrhosis and portopulmonary hypertension. In chronic liver diseases heart failure is latent for a long time and may be due to complex pathophysiological conditions. The occurrence of systolic cardiac dysfunction is related to advanced liver disease and development of renal complications [18-20].

Conclusions

Our study has demonstrated that patients with chronic hepatitis or liver cirrhosis have clinical and echo-ardiographic cardiovascular changes that correlate with NT-proBNP levels. NT-proBNP increases proportionally to the severity of liver lesions and is an early marker of diastolic dysfunction and left atrial and left ventricular remodeling. In advanced liver disease stages, NT-proBNP levels are even higher and correlate with clinical-biochemical severity and signs of portopulmonary hypertension. NT-proBNP has the potential to become a useful marker in the follow-up of cardiovascular dysfunction in chronic liver disease.

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