**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA**

**DOCTORAL SCHOOL**

# *Effects of Beta-Blockers Use in Patients with Hepatic Cirrhosis*

## DOCTORAL THESIS

## ABSTRACT

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# I. THE CURRENT STAGE OF KNOWLEDGE

## CHAPTER 1. HEPATIC CIRRHOSIS

Hepatic cirrhosis (HC) is the final stage of chronic hepatopathy, characterized by the appearance of regenerative nodes and extensive fibrosis associated with hepatocyte necrosis but also by the distorsion of hepatic architecture. The word cirrhosis comes from the Greek word "kirrhos" which means yellow-orange [1]. However, the definition of hepatic cirrhosis remains a morphological one, and it is described by the World Health Organization (WHO) in 1978 as "a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules" [2].

The main causes of liver cirrhosis are: alcoholic hepatitis, chronic hepatitis B virus (HVB), chronic hepatitis C virus (HVC), non-alcoholic liver steatosis, hemochromatosis, autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis [3,4]. There is no curable treatment for hepatic cirrhosis, except liver transplantation.

In developing countries, cirrhosis is an important cause of morbidity and mortality, with a strong impact on the quality of life of patients [5]. In many developed countries, death rates in patients with cirrhosis have decreased significantly in recent years [6].

Diagnosis of liver cirrhosis is based on evidence from anamnesis (signs and symptoms of hepatocellular failure and portal hypertension) and is confirmed by paraclinical explorations.

The two major pathophysiological syndromes i.e. hepatocellular failure and portal hypertension lead to clinical manifestations. The latter may vary according to the stage of evolution of liver cirrhosis.

Diagnosis of cirrhosis in the compensated stage is difficult to achieve. Clinical manifestations are uncharacteristic and may include: weight loss, anorexia, osteoporosis due to vitamin D malabsorption and calcium deficiency, and hypotonia. In compensated stage of the disease, clinical data may often be uncharacteristic and patients may present an asymptomatic condition. Subsequently, the more the disease progresses, the symptoms may reveal portal hypertension manifested by abdominal discomfort, bloating, abdominal volume

increase due to ascites fluid or signs of liver failure i.e. physical asthenia, gingivorrhagia, epistaxis.

Due to a positive predictive value, the Child-Pugh-Turcotte score is the most used in the staging of patients with liver cirrhosis [7]. According to this staging, Stage I and II patients correspond to compensated liver cirrhosis and the Stage III and IV patients correspond to decompensated liver cirrhosis. Therefore, the essential factor in differentiating the compensated form from the decompensated form is the ascitic fluid.

## CHAPTER 2. BETA-BLOCKERS IN HEPATIC CIRRHOSIS

Beta-blockers are a class of drugs that are extremely important because of their use in various medical conditions. Their discovery dates back more than 100 years ago, when researchers launched the idea that the pharmacological action of catecholamines consists in the selective binding of certain receptors for which they manifest a high selectivity [8].

In 1981, Lebrec et al. performed the first randomized clinical trial involving 74 patients with cirrhosis with a history of variceal bleeding. This study demonstrated a significant reduction in variceal bleeding relapse in patients who were administered propranolol versus placebo treatment [9,10].

Non-selective beta-blockers (BBNS) are used in primary prophylaxis in patients with small esophageal varices but with increased bleeding risk and those with medium to large esophageal varices; regarding secondary prophylaxis, the current recommendations target endoscopic variceal ligation in addition to the use of BBNS.

It was presumed that the effect of BBNS on the prevention of variceal bleeding episodes is mediated by several mechanisms that act on hemodynamic changes present in patients with cirrhosis [11-13]. Patients with portal hypertension manifest hyperdynamic circulation characterized by increased cardiac output and splenic blood flow and a reduction in peripheral and splanchnic vascular resistance, associated with increased plasma volume. With increased intrahepatic resistance, this hyperdynamic circulatory status plays an important role in the pathogenesis of portal hypertension and the complications thereof [14]. The most important hemodynamic role of BBNS is the decrease in cardiac output through β1

receptors and a splanchnic vasoconstriction achieved through β 2 receptors, leading to a reduction in portal blood flow [15,16].

The positive effects of BBNS, other than hemodynamic ones, are demonstrated in patients who may face a relatively low bleeding risk if they receive BBNS, even when they do not have a clear response and improvement of symptomatology during treatment [17]

Carvedilol is a promising BBNS with a superior vasodilator effect when compared to propranolol due to the former intrinsic anti- Alpha1-adrenergic activity and enhanced delivery capacity of nitric oxide [18]. Thus, carvedilol reduces portal hypertension not only by lowering portal blood flow (as is the case with other BBNS), but also by decreasing hepatic vascular resistance that is usually elevated in patients with liver cirrhosis.

## CHAPTER 3. CARDIOVASCULAR CHANGES IN HEPATIC CIRRHOSIS

Experimental studies and clinical trials have shown that the patients shows a cardiac condition known as cirrhotic cardiomyopathy characterized by reduced cardiac contractility accompanied by diastolic dysfunction and electrophysiological abnormalities.

There have been described several pathophysiological mechanisms involved in decreasing myocardial contractility in patients with cirrhosis, of which we mention deficiencies or dysfunctions in beta-adrenergic receptors, increased fluidity of the plasma membrane, changes in membrane and calcium channels but also the involvement of humoral factors such as nitric oxide, monoxide carbon and various cytokines.

Blood circulation in patients with advanced liver cirrhosis is hyperdynamic, resulting in an increase in cardiac output. Pathogenesis involves marked splanchnic arterial vasodilation and reduced peripheral vascular resistance. In this context, pressures in cardiac chambers are largely normal, at least in part, because reduction of heart post-loading protects systolic function.

Despite increased cardiac output, systolic dysfunction is included in the definition of cirrhotic cardiomyopathy as formulated by the dedicated working groups, and refers to the inability of the heart to meet its requirements in terms of generating adequate blood pressure and optimal cardiac output. This can be evidenced by exercise that increases left ventricular

pressure, left ventricular volume and ejection fraction, and heart rate in patients with cirrhosis [19-22].

Systolic dysfunction, assessed by classical echocardiography methods, may be present in patients with advanced cirrhosis of the liver. At rest, its presence indicates a negative prognostic value and contributes to the development of subsequent complications such as retention of sodium and liquids with ascites fluid formation and kidney failure.

Most patients with liver cirrhosis present different degrees of diastolic dysfunction. Diastolic filling normally consist of two phases: the first is rapid diastolic relaxation (active phase) followed by late diastolic filling (passive phase).

Numerous studies have shown that in most patients with cirrhosis there is a certain level of diastolic dysfunction [23]. Diastolic dysfunction may progress until systolic dysfunction occurs, although this has not been directly demonstrated in these patients. [24]

Electrophysiological disorders in patients with cirrhosis do not depend on and are not in a causal relationship with the etiology of the underlying liver pathology but may worsen in parallel with its increasing severity.

Patients with advanced liver cirrhosis usually have tachycardia. The inability to increase heart rate subsequently contributes to the need to maintain a cardiac output adequate to the needs of systemic circulation when effective vollemia suddenly worsens, as occurs in post-paracentesis induced circulatory dysfunction and in hepatorenal syndrome [25-27].

Dyssynchronous electrical and mechanical systole in patients with liver cirrhosis was confirmed by evaluation of systolic time intervals or by simultaneous measurement of the aortic pressure curve and electrocardiogram recording [28,29].

A long QT interval is frequent in patients with cirrhosis, with a prevalence of over 60% in those in an advanced stage of disease [30]. Variable prevalence may result from different QT interval correction methods with heart rhythm (QTc). Bazett's formula for calculating the heart rate corrected QT interval is widely used, but it does not completely suppress the relationship between QT and heart rhythm. This is relevant in the case of patients with cirrhosis because they may typically have tachycardia.

Administration of beta-blockers in hepatic cirrhosis may shorten the QTc interval, but events such as gastrointestinal bleeding prolong the QTc interval [31].

# II. OWN CONTRIBUTION TO THIS TOPIC

## THESIS OBJECTIVES

***Primary Objectives***

- Assessment of systolic function in patients with cirrhosis by classical 2D transthoracic echocardiography imaging methods (Left Ventricular End-Diastolic Volume – LVEDV, Right Ventricular End-Systolic Volume– RVESV, assessment of the cardiac output - CO through the calculation formula CO = SV x HR, where SV - systolic volume and HR - heart rate, Left Ventricular Ejection Fraction - LVEF, and by modern methods i.e. Speckle Tracking echocardiography (GLS - global longitudinal strain))
- Assessment of diastolic function in patients with liver cirrhosis by classical 2D transthoracic echocardiography (E wave, A wave, E-wave deceleration time) and modern methods i.e. Tissue Doppler imaging (TDI)
- Assessment of hemodynamic and electrophysiological changes in patients with liver cirrhosis (blood pressure measurement, heart rate determination, prolongation of QT interval on electrocardiogram)
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***Secondary objectives***

- Determining favourable prognosis factors by administration of beta-blockers in patients with liver cirrhosis
- Development of algorithms for hemodynamic and echocardiographic assessment of patients with liver cirrhosis
- Quantifying the impact of cardiovascular changes occurring in patients with liver cirrhosis depending on the stage of the disease

## CHAPTER 4. MATERIALS AND METHODS

The study was conducted at the Medical Clinic I - Gastroenterology and Cardiology Clinic of the Craiova County Emergency Clinical Hospital during the period 2014 - 2017. It included 67 patients with a diagnosis of liver cirrhosis (viral, alcoholic, etc.), clinically and hemodynamically stable (not admitted to hospital due to liver cirrhosis or any related complications in the last 6 months) who were benefitting from treatment with beta-blocker (i.e. Propranolol) of their chronic condition or who were requiring treatment after diagnosis. Moreover, 45 patients suffering from B or C virus viral hepatitis were selected in the study among the subjects who had no medical history of cardiovascular disease and who underwent a routine physical 2D echocardiographic examination and EKG with results and parameters within the normal limits.

The patients were clinically evaluated (anamnesis, objective examination) , and an EKG examination was performed to determine heart rate, heart rhythm, electrical axis of the heart, cardiac depolarization waveform morphological templates, and atrial and ventricular repolarization, atrioventricular conduction and QT interval analysis. In terms of medical imaging investigation, patients included in the study were examined with ultrasound (abdominal ultrasound - liver and spleen examination and transthoracic echocardiography by classical methods - 2D ultrasound and new diagnostic methods - Speckle Tracking and Tissue Doppler Imaging - to assess the left ventricular ejection fraction, the systolic and diastolic pressure).

## CHAPTER 5. STATISTICAL DATA PROCESSING

For the data processing we used the following software: Microsoft Excel (Microsoft Corp., Redmond, WA, USA), XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA).

The data thus obtained were stored in Microsoft Excel files, and then processed statistically in order to run a statistical analysis of patients' clinical and paraclinical related data.

The secondary processing of information i.e. the descriptive analysis of the batches of patients according to different parameters, the calculation of the basic statistical parameters, the mean and the standard deviation, the ratio thereof, called the coefficient of variation, the

graphic representation thereof and the calculation of the regression coefficient were carried out with Excel, using Pivot Tables, Functions-Statistical, Chart, and Data Analysis. In order to perform normality tests (Shapiro-Wilks and Anderson-Darling) and complex statistical tests (Chi square test, Mann-Whitney-Wilcoxon test, Kruskal-Wallis test, Z test for proportions) we used XLSTAT modules controls or SPSS.

In order to characterize the numerical data used in the studies performed for this thesis, we used the following statistical parameters: arithmetic mean and standard deviation, the ratio thereof - the coefficient of variation, and the spread indicators, minimum, maximum, median, quartiles (percentiles) values.

# III. DISCUSSION

According to the data published in the literature, the mean age of patients diagnosed with cirrhosis exceeds 55 years, a fact which was also highlighted in our study where the mean age was 59.4 ± 7.34. Regarding age decades, by reviewing the data from the studied group, we noticed that more than half of the patients with liver cirrhosis were aged < 60 (51.67%). Because these patients belong to the young, active population, it results that cirrhosis is an important condition with implications both socially and economically due to the high costs and resources it entails.

From the point of view of gender distribution of patients with liver cirrhosis in our study, we found a higher share of males (56.67%); thus, the male / female ratio was 1.30:1. This result is consistent with the data presented in the studies that have shown a higher prevalence of liver cirrhosis among male patients.

Concerning the residence milieu, the prevalence of liver cirrhosis had slightly increased values among patients living in urban areas (51.67%). The data were not consistent with those in the literature where most patients with cirrhosis commonly come from rural areas due to their low socio-economic status. However, this finding can be explained by the fact that urban populations benefit more frequently from medical check-ups, an improved primary medical care, and a more accurate information through various media that contribute overall to an early diagnosis of liver disease.

The Child-Pugh-Turcotte score for Cirrhosis Mortality has been used for approximately 30 years to diagnose and assess the severity of liver cirrhosis. This is preferred due to a low degree of complexity and a positive predictive value. Among the group of

patients surveyed in our study, we noticed a high prevalence of cirrhosis (approximately half of the patients - 46.67%) in class B, approximately an equal share (43.33%) included in the C class and only a small proportion (10%) in class A.

In our study, most patients diagnosed with liver cirrhosis, regardless of the stage of the disease (Child-Pugh Class A, B or C), benefited from a therapy with beta-blocker. During patients monitoring, no significant differences were found among the mean systolic blood pressure, mean diastolic blood pressure and mean blood pressure between the three categories of patients either after an acute dosing or the 6 months re-evaluation. No patients receiving beta-blocker therapy experienced refractory ascites, severe bradycardia or severe hypotension. Moreover, beta-blocker based treatment could be administered throughout the study, according to the Baveno VI Guidelines, and no patient experienced a systolic blood pressure lower than 100 mmHg or a mean blood pressure lower than 82 mmHg, which would be imposed discontinuation of BBNS administration.

Patients receiving BBNS therapy experienced no major events (death, severe complications of liver cirrhosis) throughout the study, and this finding is consistent with the findings of the studies in specific literature in this field.

The QT interval is prolonged in patients with liver cirrhosis, irrespectively of the disease stage according to the Child-Pugh-Turcotte score (class A, class B or class C) and independent of its aetiology. The reason for this anomaly remains unclear and further studies are required to understand the pathophysiological mechanisms involved in the process. However, the additional risk for the development of severe arrhythmias and sudden death should be carefully assessed prior to any therapeutic intervention in these patients.

In this study, the prevalence of diastolic dysfunction in patients with cirrhosis was high (91.67%), the vast majority consisting in a mild form (i.e. delayed relaxation pattern). We have not identified statistically significant differences in the prevalence of diastolic dysfunction within different Child-Pugh scoring classes. Out of the total patients with liver cirrhosis contained in the study group, 83.33% had diastolic dysfunction, classified as Child-Pugh class A, while in the other two Child-Pugh scoring classes (Child B and Child C) the results were similar (92.86% vs. 92.31%), which is consistent with the data provided in the specific literature.

In our study, we noted also that the LVEF assessed at rest had a normal or slightly increased value in patients with liver cirrhosis without indicating a statistically significant difference from the Control Group. Studies carried out on a large number of animals but also

on human beings regarding systolic pressure in liver disease have shown that this is often normal, sometimes even increased.

# IV. CONCLUSIONS

- The assessment of the degree of severity of liver cirrhosis in patients included in the study, assessed by the Child-Pugh-Turcotte score, indicated that most patients were in advanced stages of liver disease.
- The results obtained in our study show no significant differences in terms of SBP (P = 0.716) and ABP (p = 0.481) between the patients with hepatic cirrhosis treated with beta-blockers and those with chronic viral hepatitis; these differences did not depend either on the degree of severity of liver cirrhosis.
- The results of our study, particularly with regard to electrocardiographic changes that occurred in patients with liver cirrhosis, demonstrated the presence of an prolonged Q-T interval which mean value was significantly higher compared to patients included in the chronic viral hepatitis group (i.e. 0.457s vs. 0.398s – Students's t-test 0.0001 <0.05). Although most patients with cirrhosis had Q-T prolongation, we did not notice a significant difference among the three Child-Pugh severity classes.

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