UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

DOCTORAL SCHOOL

PhD THESIS ABSTRACT

THE CARDIOPHYSIOLOGICAL CHANGES STUDY IN NONALCOHOLIC CIRRHOTIC PATIENTS

SCIENTIFIC COORDINATOR:

Professor MD PhD Maria IANCĂU

PhD CANDIDATE:

Corina ŞTEFAN (LUNGU)

CRAIOVA

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KEY WORDS: nonalcoholic hepatic cirrhosis, *cirrhotic cardiomyopathy,* QT interval prolongation, beta-blockers

INTRODUCTION

Hepatic cirrhosis is an irreversible and diffuse liver disease characterized by progressive alteration of its functions, including blood flow, initially in the liver, then in other organs, which is a major health problem, both by weight and by complications.

Hepatic cirrhosis is spread across the globe, and in recent decades there has been a tendency of increase of frequency, although the predisposing factors vary from country to country. The specialty literature suggests that about 0,1% of the European population is affected by cirrhosis, which corresponds to 14 to 26 new cases per 100 persons / year or an estimated figure of 170,000 deaths / year (Zatonski et al., 2010). Knowing the prevalence is essential to understand the importance of liver disease in general morbidity. For the Dolj geographical area, statistics show a prevalence of cirrhosis, with increasing values in the past five years, from 2112 cases in 2008 to 2438 cases in 2012 and 3645 illnesses by cirrhosis in 2013.

As a consequence of liver dysfunction in the development of liver cirrhosis effects occur in other organs or apparatus too. The most important concern the cardiovascular system, which raises both diagnostic and treatment issues for the practicing physician. The present paper represents an answer to the need observed through the study of the specialty literature concerning the cardio-vascular anomalies that, during the cirrhosis, are grouped under the hyperdynamic circulatory syndrome (Moller et al., 2009), cirrhotic cardiomyopathy (Seirafi, 2009) or sympathetic hypertonia.

Given that the definition and the mechanisms of producing the cardiovascular changes during cirrhosis are poorly clarified, aspect that gives rise, moreover, to numerous discussions, the aim of our study was to identify the cardiophysiological changes of nonalcoholic cirrhosis and to assess some clinical and laboratory aspects with significant role in influencing these changes. In this regard, we plan to meet several objectives, including the identification of QT interval prolongation at patients with non alcoholic cirrhosis, evidence of arrhythmias at patients with cirrhosis and their association with QT prolongation, assessing the influence of propranolol on the QT interval duration at these patients being in various degrees of severity, assessing the influence of propranolol on cardiac echocardiographically highlighted parameters at a group of non-alcoholic cirrhotic patients.

The practical importance of the research has emerged as a result of the need to monitor cardiac function at nonalcoholic cirrhotics, given that liver cirrhosis involves changes of cardiovascular structure and functions, with a general latent infraclinique evolution, difficult to be clinically recognizable in stages of maximum therapeutic efficacy.

Among the aspects with original behaviour, the correlation of the cardiophysiological changes from non alcoholic liver cirrhosis with multiple parameters (etiology of cirrhosis, evolutionary stage, disease severity) allowed to establish the measure in which a thorough knowledge of the cardiac function changes at cirrhotic patients may contribute to a better prognosis by appropriate therapeutic decisions

The results of our study, the complexity of the issues highlighted, with therapeutic and prognostic implications, are useful for the practicing physician and indicate the need for closer monitoring of the cirrhotic patient.

The thesis includes six chapters, containing 146 pages, 54 tables, 48 figures and a number of 141 references, and is divided into two parts, as follows: a theoretical part consisting of two chapters, and the second part of original contributions, of four chapters, in which the results of personal research are represented.

The partial results of the study conducted during the four years have been presented at scientific meetings and events in the researched field and disseminated by the publication of three articles in relevant journals indexed in international databases, and through the presentation of a number of six communications at national conferences with international participation.

For the support offered in making this thesis, I want to thank the staff of the Medical Clinic III of the Municipal Hospital, Craiova Philanthropy'', which allowed my clinical and paraclinical study of the hospitalized patients.

For the high competent guidance and suggestions that I have received throughout the period of making the research, for the trust and generosity to share from her vast professional and scientific experience as well as for the human and professional model she is, give thanks and my best regards to Mrs. Maria Iancău doctor university professor, the scientific leader of this thesis.

PART I: THE STAGE OF KNOWLEDGE

Chapter I: Cardiovascular changes in cirrhosis

This chapter presents summary data on liver cirrhosis and the cirrhosis specific cardiovascular changes that occur in advanced stages. Hepatic cirrhosis induces cardiovascular changes that include hyperdynamic circulatory syndrome and cirrhotic cardiomyopathy (Lupu, 2010).

Cardiovascular changes are more pronounced the more advanced liver cirrhosis, relating to the increase of the cardiac output the decrease of peripheral vascular resistance and of blood pressure (Liu et al., 2006). At cirrhotic patients, the heart presents both structural and functional changes. These clinical and laboratory changes are integrated into the concept of cirrhotic cardiomyopathy (Wong F, 2009). It is a relatively new concept, for a long time less relevant in the clinical context different from alcoholic cardiomyopathy, and which is a determining factor in morbidity and mortality of the cirrhotic patients (Mooler et al., 2002).

Chapter 2: Beta-blockers in cirrhosis

The chapter exposes modern concepts about treatment with beta-blockers, which has become in past years one of the most effective preventive therapies against variceal bleeding, with beneficial effects on cardiovascular dysfunctions at the patients with cirrhosis too.

The heart rate variability, due to the influence of the autonomic nervous system on the cardiovascular activity in liver cirrhosis has been frequently studied (Nishiyama, 2010), this being able to foresee occurrence of cardiac dysfunction associated with a poor prognosis at patients with advanced cirrhosis (Ates et al ., 2006).

PART II: PERSONAL CONTRIBUTIONS

Purpose of the study. Set objectives

The **purpose** of this study, **motivated** by the fact that cardiac dysfunction in cirrhosis often remains ignored, is to establish, by tracking the cardiophysiological changes at nonalcoholic cirrhotic patients whether the therapeutic balancing both the cirrhosis and of cardiomyopathy can cause improvement thereof.

The set objectives are: the identification of the QT interval prolongation at patients with non alcoholic cirrhosis, the evidence of arrhythmias at patients with cirrhosis and their association with QT prolongation, the assession of the influence of propranolol on the QT interval duration at these patients, in various degrees of severity, the analysis of the relationship of the QT prolongation with the cirrhosis evolution and the discontinuation of the treatment with propranolol, the assession of the influence of propranolol on echocardiographically highlighted cardiac parameters at a group of non-alcoholic cirrhotic patients.

STUDY GROUP. METHODE

In the study there was included a group, statistically significant, initially including 93 subjects, finally, for objective reasons, remaining 90, selected from the hospitalized patients, explored and diagnosed with non alcoholic cirrhosis compared with a control group with the liver and heart function not ok.

The inclusion in the study was made after the full analysis of the clinical and laboratory data (history, physical examination, abdominal ultrasound, electrocardiography, radiologic examination, upper gastrointestinal endoscopy, laboratory tests), which confirmed the diagnosis of cirrhosis.

The exclusion criteria from the study: liver disease of other etiology than the viral one, chronic lung disease, heart failure, ischemic and non ischemic cardiomyopathy, valvular heart disease, cardiac septal defects, intracardiac disturbances of conducting stimuli and of heart rate, hypertension, thyroid disease, diabetes, patients using calcium channel blockers.

RESULTS:

The results represent the highlight of the evolution of non-alcoholic cirrhosis, the weight of the changes cardiophysiological, especially QT interval prolongation at patients with cirrhosis from the Dolj County. Depending on the etiology, there was not identified a significant difference between the average duration of the QT interval measured at cirrhotic patients with C, respectively B viral etiology. It is more common at men the QT interval prolongation, in a significantly higher percentage, but the duration of the QT interval is greater at women.

Chart 1. The distribution of the study group according to gender and QT interval duration

	QT prolonged		*QT normal*		*Total*	
	Number of patients	*%*	*Number of patients*	*%*	*Number of patients*	*%*
Women	*13*	*72.22*	*5*	*27.78*	*18*	*100.00*
Men	*66*	*91.67*	*6*	*8.33*	*72*	*100.00*

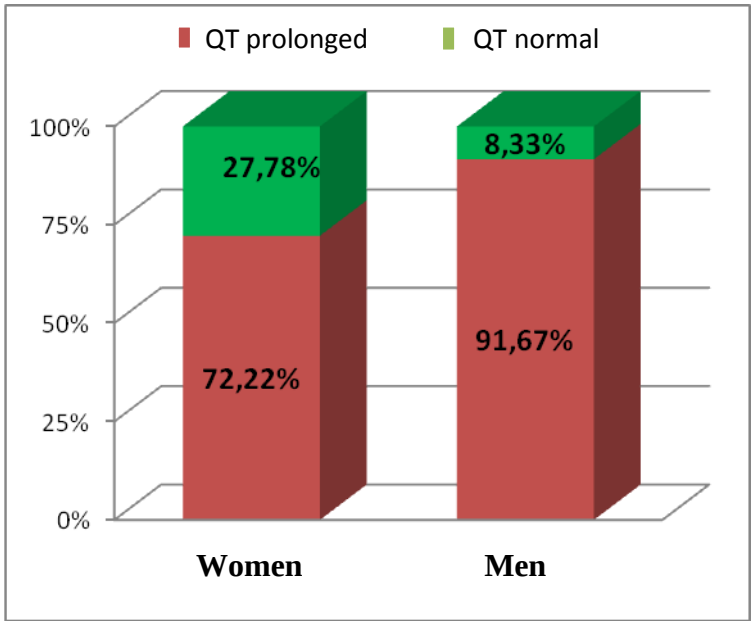

Figure 1. The distribution of the study group according to gender and QT interval duration

QT duration	Men	Women
Number of patients	24	6
Average (seconds)	0.4028	0.4130
Standard deviation	0.0082	0.0045
C.V. (%)	2.03%	1.08%
p test Student	0.006742 Significant difference	

Chart 2. The average value of the QT interval duration (seconds) according to gender, at the control group

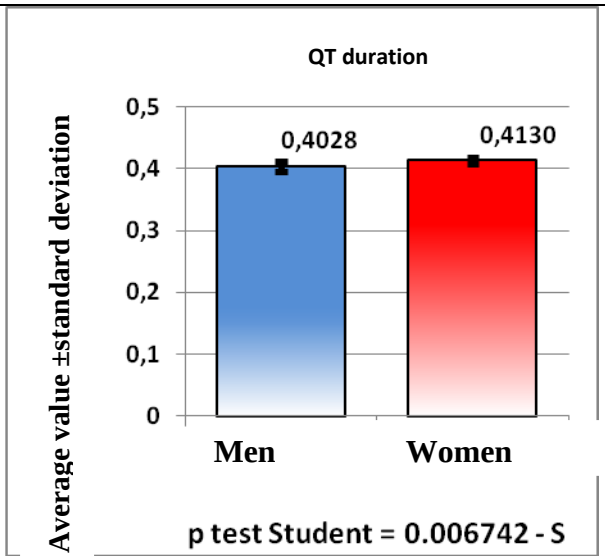

Figure 2. The average value of the QT interval duration (seconds) according to gender, at the control group

There was noted highly significant differences for the 31-50 years age range, and a highly significant difference between the three classes of severity, patients enrolled in severity class C, having the most pronounced elongation of the QT interval.

Age	QT interval duration (seconds)	
	Women	Men
20-30	-	0.5033
31-40	0.4500	0.5125
41-50	0.4614	0.5080
51-60	0.4780	0.4683
61-70	0.5243	0.5200

Chart 3. The QT interval duration (seconds) at representative cases from the studied group according to the decade of age

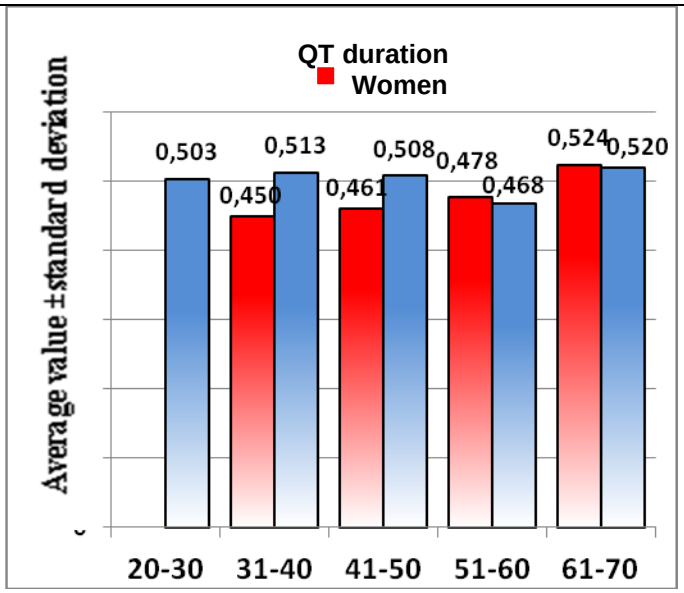

Figura 3. *The QT interval duration (seconds) at representative cases from the studied group according to the decade of age*

Comparing the averages of the QT intervals between the 3 classes of severity of cirrhosis according to the Child-Pugh classification, the lowest values were found at patients enrolled in the A class of severity, the B class patients had intermediate values, and C class patients had the most pronounced prolongation of the QT interval.

Class of severity	*A Class*	*B Class*	*C Class*
Number of patients	*26*	*22*	*31*
Average (seconds)	*0.45*	*0.51*	*0.53*
Standard deviation	*0.006*	*0.025*	*0.020*
C.V. (%)	*1.40%*	*4.94%*	*3.83%*
p test ANOVA	*Highly significant difference*		

Chart 4. The distribution of the patients according to the class of severity and the QT interval duration (seconds)

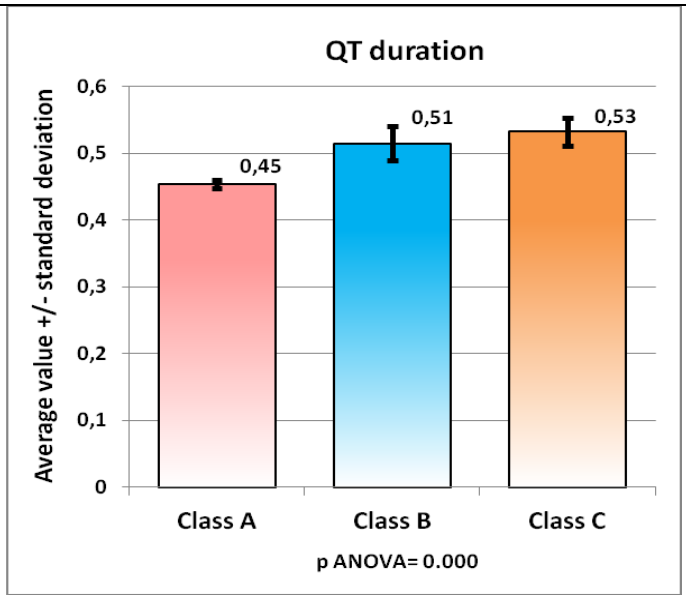

Fig. 4. The distribution of the patients according to the class of severity and the QT interval duration (seconds)

The results of the study point out that there is a significant difference statistically relating to the type of arrhythmias that occur at men and women with cirrhosis and with prolonged QT interval.

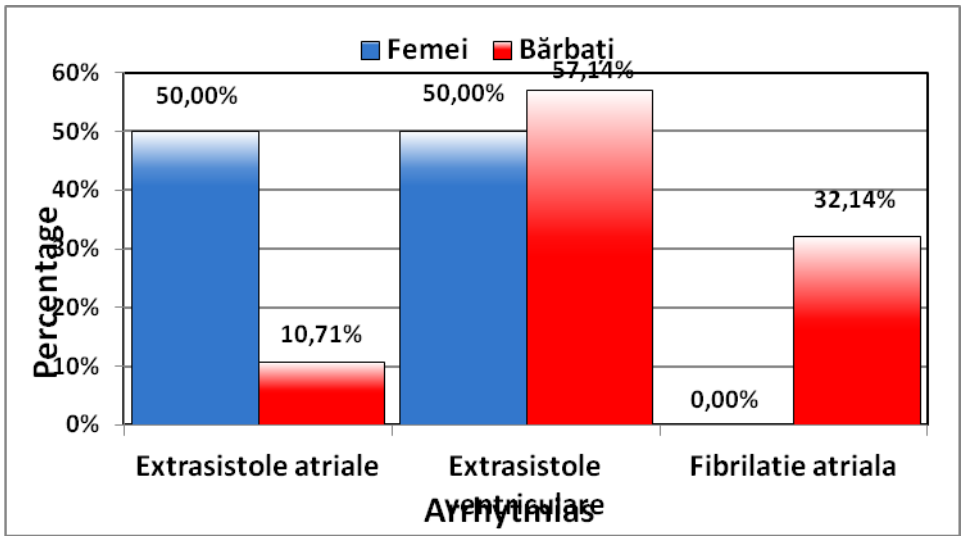

Figure 5. The type of arrhytmias at the patients from the study group according to gender

The study of the influence of propranolol, at cirrhotic patients with QT interval prolonged, identified significant and highly significant decrease of the duration of the QT interval after the treatment with propranolol at both sexes, in both B and C severity classes of cirrhosis. The discontinuation of the treatment with propranolol during the cirrhosis evolution, facilitates the installation of arrhythmias.

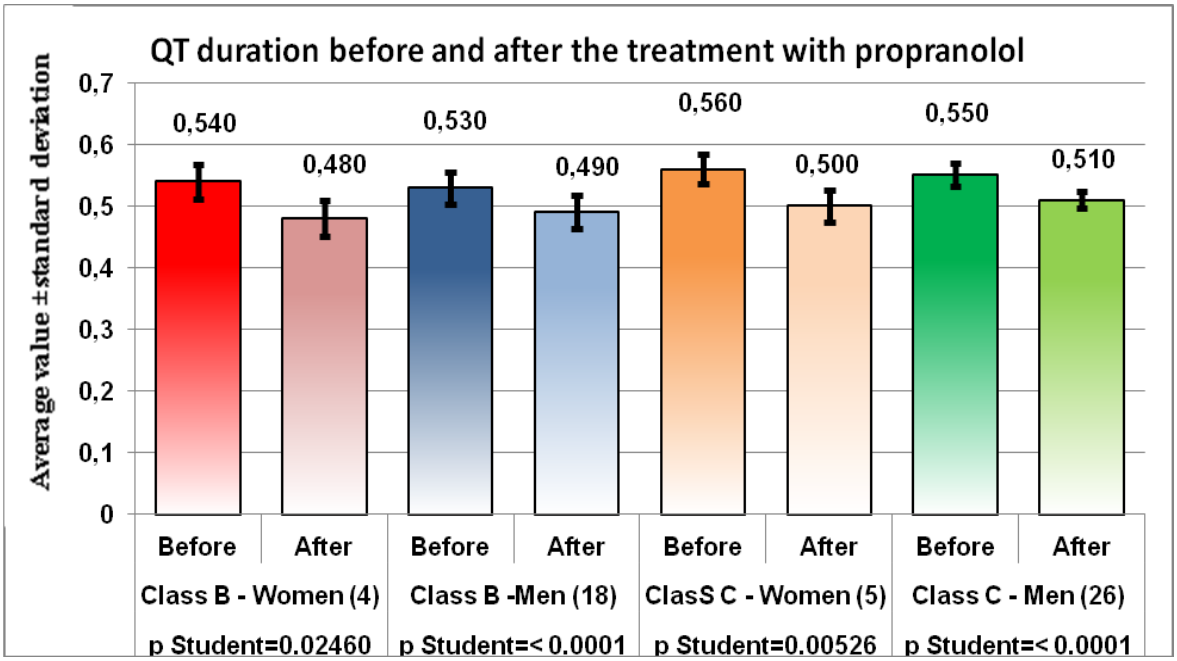

Figure 6. The graphical representation of the QT interval duration (seconds) before and after the treatment with propranolol according to gender and class of severity

DISCUSSIONS:

The patients with non alcoholic cirrhosis presents in its evolution, electrocardiophysiological changes, especially the QT interval prolongation difficult to establish, as being variable because cardiomyopathy evolves many years at subclinical stage. This aspectalso explains the different values of the authors, concerning the corrected QT prolongation at patients with cirrhosis, from 25% in B class and 60% in C class of the Child-Pugh severity, higher than the prevalence of 3 - 5% from the general population (Wong, 2009).

In cirrhosis of viral etiology there was not identified a statistically significant difference between the average duration of the QT interval measured at patients with viral B, respectively C etiology, but it was found that QT interval prolongation is more common

at patients with C virus involved in the proportion of 69.62% in the etiology of cirrhosis, compared to B virus patients 30.32%.

At men it is more common the QT interval prolongation, in a significantly higher percentage (91.67% vs. 72.22%) but the duration of the QT interval is higher at women, aspect concluded in the literature data indicating that women have QT intervals normally longer than men, averagely with 3.8% (Karasu et al., 2004).

In relation to age, there were found highly significant differences for the 31-40 years age ranges respectively 41-50 years.

Considering the average duration of the QT interval in relation with the severity of cirrhosis there was identified a highly significant difference between the three classes of severity, the patients enrolled in C class severity, having the most pronounced prolongation of the QT interval.

In relation with the severity of portal hypertension, the QT duration change is related more to the hepatic dysfunction than to the severity of portal hypertension.

The QT interval calculation and correlation with the heart rate at patients with liver cirrhosis and the patients from the control group showed that the average heart rate and the QT interval was significantly greater at patients with cirrhosis comparatively to the non cirrhotics.

There is a significant difference statistically speaking in terms of the type of arrhythmias that occurr at men and women with cirrhosis, and of the presence of arrhythmias at patients with Long QT interval.

The study of the influence of propranolol, at non-alcoholic cirrhotic patients, identified significant and highly significant decrease of the duration of the QT interval after the treatment with propranolol at both sexes, in both B and C severity classes of cirrhosis and echocardiography there was noted an improvement of ejection fraction.

The relevant aspect of the undertaken study for the opportunity to be used to identify patients at risk, is the early detection of cardiac electrical changes, especially the QT interval prolongation at patients with nonalcoholic cirrhosis in order to draw therapeutic decisions for balancing both liver dysfunction and cardiac functions, thus improving prognosis.

CONCLUSIONS:

From the study on a group of 90 patients with non-alcoholic cirrhosis, both from rural and urban environment, there are the following conclusions:

The patients with nonalcoholic cirrhosis present in its evolution electrocardiophysiological changes, especially the QT interval prolongation (> 0.45 seconds), the average duration of the QT interval is greater than the average for control subjects (0.4079 ± 0.0103 seconds).

A viral etiology cirrhosis there was not identified a significant difference between the average duration of the QT interval measured in patients with viral B respectively C etiology, “p'' resulted from a Student's t test being p = 0.938> 0, 05, and the value p'' obtained from the Fisher's exact test being higher than the maximum admitted level 0.05 (p = 0.376).

In relation to gender, it is more common at men the QT interval prolongation, in a significantly higher procentage (p = 0.032 Fisher exact <0.05), but the duration of the QT interval is higher at women, the value resulted from the t-test value of a Student being p = 0.0406.

In relation to age, I found highly significant differences for the 31-40 years age ranges, respectively 41-50 years (p Student <0.001). The age, because of the difficulties of defense and recovery, is more exposed to the installation of electrocardiophysiological changes.

Considering the average duration of the QT interval in relation to the severity of cirrhosis, I found a highly significant difference (<0.001) between the three classes of severity, the patients enrolled in C severity class having the most pronounced prolongation of the QT interval as a consequence of the emphasized failure that favours the cardiovascular changes.

In relation to the severity of portal hypertension, the QT interval duration is prolonged at over 52% of patients with cirrhosis, the change of the duration of the QT interval is linked more to the hepatic dysfunction than to the severity of portal hypertension.

The calculation and correlation of the QT interval with the heart rate at patients with liver cirrhosis and patients from the control group showed that the average heart rate and QT interval was significantly greater at patients with cirrhosis comparatively to the non cirrhotics (the average rate of the heart rate at the treated cirrhotics was 75.67 strokes/ min, compared to compared to 67 strokes / min at patients of the control group).

The cardiac arrhythmias were present in 85%, the most common being the ventricular premature heart beats, followed by atrial fibrillation, according to the QT prolongation and the severity of liver disease.

In the study group there is statistically a significant difference, p-value = 0.044 <0.05, in terms of type of arrhythmias that occur at men and women with cirrhosis. Statistically I found a significant difference ($p < 0.05$) in the presence of arrhythmias at patients with prolonged QT interval.

The study of the influence of propranolol, at cirrhotic patients with QT intervals prolonged, identified significant and highly significant decrease of the duration of the QT interval after the treatment with propranolol at both sexes, in both B and C severity classes of cirrhosis, $p < 0.05$. The discontinuation of the treatment with propranolol during the cirrhosis evolution, facilitates the installation of arrhythmias.

The treatment with propranolol at cirrhotic patients with cardiovascular events has a meaning that can be double counted because, on one hand, it prevents the variceal bleeding rupture, and on the other hand it prevents the installation of arrhythmias that can be fatal.

By comparing the average of the ejection fraction between the two subgroups and the control group studied from echocardiography, I identified a significant difference ($p = 0.002$), the highest values being found for B group(71.01% average value), treated with propranolol compared with the values observed in the case of the subjects from the control group (66.18%).

It was also noted an increase of the left ventricular diastolic diameter at the two subgroups of cirrhotic patients compared with the controls, of the difference being greater among the control group patients (47.13 mm) and B subgroup patients (52.69 mm), cirrhosis treated with propranolol.

Thus, we support the claim that the use of propranolol is important in relieving symptoms and echocardiography parameters at patients with nonalcoholic cirrhosis.

Highlighting the heart disease signs through echocardiography detection of changes at patients with nonalcoholic cirrhosis can be used to determine the stage of cirrhosis, in combination with other specific methods of heart disease (clinical, electrocardiographic and laboratory), these being necessary to prove the correlation between cirrhosis and cardiac dysfunction too.

The use of propranolol is important in relieving symptoms and echocardiography parameters at patients with nonalcoholic cirrhosis.

The early detection of cardiac electrical changes, especially the QT interval prolongation at patients with liver cirrhosis has special clinical and therapeutic implications:

The association of electrocardiophysiological disorders remains a factor of unfavorable prognosis and can be used to identify patients at risk.

It avoids the administration of drugs that may increase the duration of the QT interval, thus preventing severe arrhythmias.

It can be therapeutic decisions of balancing both liver dysfunction and cardiac functions, thus improving the prognosis and avoiding fatal consequences.

Our study has a highly original approach, representing a contribution to the therapeutic approach in nonalcoholic cirrhosis, draws attention to the importance of pursuing the cardiovascular changes by the practicing physician over the specific therapeutic behavior meant to improve the prognosis of this disease.

REFERENCES:

Ates F, Topal E, Kosar F, et al.: The relationship of heart rate variability with severity and prognosis of cirrhosis. Dig Dis Sci 51:1614, 2006.

Diculescu M, Haret R, Stoicescu A., Cardiomiopatia cirotică. Gastro; 2006:3.

Karasu Z, Mindikoglu AL and Van Thiel DH. Cardiovascular problems in cirrhotic patients. The Turkish Journal of Gastroenterology 2004, Volume 15, No 3: 126-132

Liu H, Gaskari SA, Lee SS, et al. Cardiac and vascular changes in cirrhosis: Pathogenic mechanisms. World J Gastroenterology 2006; 12:837-42.

Lupu DL, Afectarea cardiovasculară la pacienţii cirotici, Revista Medicală Romană, 2010, volLVII, nr.1:36-37.

Moller S, Henriksen JH. Cirrhotic cardiomyopathy:a pathophysiological review of circulatory dysfunction in liver disease. Heart. 2002; 87 (1): 9-15.

Moller S, Henriksen JH. Cirrhotic cadiomyopathy. J Hepatol. 2010 Jul;53(1):179-90

Nishiyama T: Recent advance in patient monitoring. Korean J Anesthesiol 59:144, 2010

Seirafi M, Spahr L, Cirrhotic cardiomyipathy, Rev. Med. Suisse, 2009: 5(215)

Wong F.; Cirrhotic cardiomyopathy. Hepatol Int. 3. 2009: 294-304.

Zatonski WA, Sulkowsi U, Manczuc M, Rehm J, Boffeta P, Lawenfels AB, et al. Liver cirrhosis mortality in Europe, with special attention to Central and Easterr Europe. Eur Addict Res. 2010;16:193-201.