

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA**

**DOCTORAL SCHOOL**

**DOCTORAL THESIS**

**CARDIAC CHANGES IN ALCOHOLIC HEPATIC DISEASE**

ABSTRACT

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# I. INTRODUCTION

Excessive alcohol consumption causes multi-organic impairment, most commonly hepatic and / or cardiac impairment. Dilatative cardiomyopathy due strictly to long-term alcohol consumption is called alcoholic cardiomyopathy and has its own characteristics both clinico-biological, physiopathological and morphopathological. Since the heart and liver are organs in close functional relation, the important malfunction of one of it, almost always affects the other.

## II. STATE OF KNOWLEDGE

### II.1 PHYSIOPATHOLOGIC INTERACTIONS BETWEEN THE HEART AND THE LIVER

While congestive hepatopathy and cardiac cirrhosis are caused by right heart failure and are reversible after cardiac transplantation, liver cirrhosis affects cardiac function and electrophysiology in the absence of other cardiac structural diseases. It affects the patient's prognosis and aggravates the evolution in the case of invasive procedures such as insertion and systemic intrahepatic transjugular or orthotopic liver transplantation.

#### *The heart as the cause of liver disease*

The liver is rapidly affected by reduced blood flow and increased blood pressure in the sinusoidal vascular bed by increasing pressure in the vena cava in heart failure. Cardiac hepatopathy is classically described in chronic or acute heart failure, but there are often conditions that affect both the heart and liver so that the limit cannot be traced exactly. There are two important ways of hepatic impairment caused by cardiac impairment, namely the reduction of arterial perfusion and passive congestion due to increased systemic venous pressure.

#### *The liver as the cause for cardiac disease*

The entity called cirrhotic cardiomyopathy comprises systolic and diastolic dysfunction as well as electrophysiological dysfunctions. There are several pathophysiological mechanisms involved for each aspect of heart disease.

Systolic impairment is an integrated part of the definition of cirrhotic cardiomyopathy and is related to the inability of the heart to meet the requirements regarding blood pressure and flow in special stressful situations. It is usually revealed by pharmacological, physical or surgical stress and it is involved in the development of renal failure in advanced stages of the disease.

The systemic circulation is hyperdynamic with increased cardiac output, and the pathognomonic sign is given by visceral arterial vasodilation and reduced peripheral vascular resistance.

Diastolic dysfunction, which has a high prevalence and involves changes in the pattern of ventricular filling through the mitral orifice, is closely related to ventricular pre-load and is associated with the development of ascites, the onset of hepato-renal syndrome and negatively influences the prognosis.

## II.2 ALCOHOLIC CARDIOMYOPATHY

Most patients with stable liver disease have subtle myocardial impairment that is not evident at a routine examination at rest, but with the progression of liver disease or under physiological or pharmacological stress, the manifestations of heart failure are cleared. Cardiac dysfunction in cirrhosis includes impaired systolic or diastolic function, electrophysiological abnormalities that are primarily expressed by increasing the duration of ventricular repolarization (increased QTcorrected interval) and chronotropic incompetence.

Changes in ventricular diastolic function occur more often before systolic dysfunction, according to several studies in the field, but there is possible that they occur simultaneously.

Systolic and diastolic dysfunctions have been shown to have prognostic implications, resulting in heart failure being implicated in the onset of renal vasoconstriction and the development of hepatorenal syndrome. Arterial vasodilation and increased cardiac output, the characteristics of hyperdynamic circulation, are the pathophysiological mechanisms that lead to sodium and water retention in patients with liver cirrhosis.

As the disease progresses, worsening of these hemodynamic changes leads to severe renal vasoconstriction and decreased renal function that characterizes hepato-renal syndrome. Chronotropic incompetence is another feature of cirrhosis, alcoholic and non-alcoholic, and refers to the inability of the sinus node to increase heart rate under physical or pharmacological stress conditions.

Cardiac abnormalities are common in patients with liver cirrhosis, regardless of their etiology and worsen their prognosis. The clinical management of this generic entity called cirrhotic / alcoholic cardiomyopathy remains a challenge because of the paucity of clinical evidence of the difficulty of diagnosis, as there are no standardized methods.

## II.3 ECHOCARDIOGRAPHIC ASPECTS OF CARDIAC CHANGES IN ALCOHOLIC HEPATIC DISEASE

### II.3.1 DIASTOLIC DYSFUNCTION

Diastolic dysfunction (DD) is the most common feature of cardiac cirrhosis, its non-invasive evaluation was based on echocardiographic analysis of mitral flow using pulsed Doppler function, where the E wave of early filling is followed by the atrial filling represented by the wave. A, and the ratio between the two is normally subunit.

Evaluation based on diastolic mitral flow in determining diastolic function has several limitations that should be considered, with different preload conditions and heart rate being able to significantly change the E / A ratio, even in normal subjects.

Diastolic velocities assessed by tissue Doppler at the mitral annulus level play a major role in the evaluation of DD. Early diastolic annular velocity (E ') is a sensitive parameter of myocardial relaxation. A high E / E ratio means that there is a small volume transfer between the two heart cavities despite a high pressure gradient, which reflects diastolic dysfunction and increased left ventricular filling pressures.

As DD appears to have the potential to influence the prognosis of patients with cirrhosis, it becomes obvious that a longer and more careful follow-up period is required in all patients with diastolic dysfunction, with priority in those with low albumin and an elevated E/E" ratio.

The ejection fraction (FE) is the most widely used parameter for global left ventricular systolic function. It is calculated from the end-systolic and end-diastolic volumes, which can be estimated by different methods. Systolic dysfunction is generally manifested as an inadequate increase in cardiac output during physical exertion or pharmacological stress.

## II.4 FUTURE PERSPECTIVES

The clinical management of cirrhotic cardiomyopathy remains uncertain due to the lack of clinical evidence and challenges in diagnosing the disease as well as the lack of standardized criteria. The studies should be designed to examine the interaction between environmental, nutritional, genetic and epigenetic factors in alcoholic cardiomyopathy.

Understanding myocardial expression of micro-RNA patterns and changes in epigenetic factors / mechanisms becomes an increasingly attractive for studying the inner mechanisms and a potential therapeutic target.

The new pharmacological strategies of gene therapy could be the future direction to which the research will move. Gene therapy has already several possible targets including nitric oxide system and oxidative stress.

## III. PERSONAL CONTRIBUTIONS

### III.1 OBJECTIVES AND PURPOSES

The purpose of the research presented in this paper is in line with the researches of the last 30 years in the field and refers to identifying cardiac disorders - systolic and diastolic, subclinical - and establishing early heart failure in patients with hepatic impairment due to alcohol consumption without pre-existing heart disease. One of the purposes is to correlate it with the degree of hepatic impairment in order to highlight the impact on the prognosis of patients and the appropriate time to initiate treatment. Thus, it traces the directions of a proper follow-up of patients with advanced liver disease, awareness of the existence of the links between the hepatic impairment given by alcohol and the cardiac one and not lastly, of establishing the need for early therapeutic interventions in such cases, following the progression of the disease, patients' lives and, indirectly, the reduction of the economic and social burden of these comorbidities.

Among the objectives of the study were the discovery of some direct or indirect correlations between the data related to heart disease and the severity of the hepatic alcoholic disease. The identification of clinical and echocardiographic markers of subclinical diastolic or systolic dysfunction and their correlation with the stage of liver disease, but also with other biological variables such as natriuretic peptide level is one of the initial objectives.

Another objective is to identify changes in myocytes in the context of a severe alcoholic liver disease, this paving the way for the discovery of new therapeutic targets at the molecular and cellular level.

### III.2 METHODS

The personal research was divided into two parts:

In the first part - the study included 50 patients enrolled in the period 01.01.2016 - 01.08.2017, selected from the patients admitted to the Gastroenterology Clinic and Medical Clinic II of the County Clinical Hospital of Craiova. Criteria for inclusion in the study were:

- patients with diagnosed alcoholic liver disease - alcoholic steatohepatitis, hepatosteatosi or hepatic cirrhosis of alcoholic etiology,
- without a history of pre-existing cardiac disease, namely: significant hemodynamic valvulopathies, ischemic heart disease, dilatative cardiomyopathy with a different etiology other than ethanol;

The group of 50 patients with liver disease of alcoholic origin in various stages of evolution were divided into subgroups according to the Child-Pugh score, in class A of which 10% belonged, class B represented by 54% of patients with cirrhosis and class C with 36% of patients. The control group was represented by the normal reference values for the biological samples collected and for the investigations used.

Regarding the second part of the research, we carried out in collaboration with the Department of Morphopathology of UMF Craiova a morphopathological and immunohistochemical study in order to identify the intensity of the expression of desmin - by quantitative and semiquantitative measurements in the myocardium affected by comparison with normal myocardium. For this purpose, 36 left ventricular fragments were collected from deceased and autopsied patients in the Morphopathology Department of the Craiova Emergency County Clinical Hospital, with the diagnosis of dilative cardiomyopathy of alcoholic etiology.

Patient data and variables collected through the paraclinical investigations used were recorded in Microsoft Excel files, then processed statistically, in order to analyze the relationships and correlations between the demographic, clinical and paraclinical information of the patients.

### III.3.1 RESULTS – PART 1

The distribution by province of origin reveals that the percentage of patients from the rural area is significantly higher than their share in the population of the county.

The distribution of patients according to the Child-Pugh class shows that the predominant percentage is for the Child-Pugh B class - 54%, but the patients in Child-Pugh C are found in an important percentage in the studied group - 36%.

From the point of view of the electrocardiographic characteristics, it was demonstrated that there is a significant difference between the average duration of the QT interval depending on the severity class, those in the Child C group having a mean QT interval duration significantly longer than the others.

Regarding the biological characteristics, significant differences of hemostasis markers - spontaneous INR and prothrombin time - were identified between the two Child classes, the hemostasis being significantly modified in the Child C class compared to the Child B class.

Also, a decrease in liver synthesis function was identified by the significantly lower difference in mean value of albumin for subjects in Child C class, compared with those in Child B class.

The mean value of NTproBNP for the subjects in the Child B class, respectively Child C, is significantly different, those in the Child B group having a mean value higher than the others.

Another measured biological constant that is different between Child Pugh classes, with a significantly higher Student t test, is the hemoglobin value, which has a much lower mean value in patients in Child C class.

The ultrasound results show that, although we did not identify a significant difference in the diastolic E / A ratio, there is nevertheless a significant difference between the value of the average E / E 'ratio of the subjects in the Child B and Child C class, patients

in Child C group having a higher mean value than the others, revealing a more advanced diastolic dysfunction. A significant difference was revealed by the Student t test, as expected, and between the values of the septal E / E' and lateral E / E' ratios of the studied subjects, those of the Child B class had lower mean values of both ratios ( $p = 0.038 < 0.05$ , respectively  $p = 0$ ). For the echocardiographic parameters represented by the index volume of the left atrium (AS), the mean end-diastolic volumes of the VS and the average end-diastolic volumes of the VS were not identified significant differences between the two Child groups, but the average volumes of the end-diastolic VS are above the normal limit according to the document. European consensus.

According to the correlations identified, a lesser-known, but undoubtedly important, correlation is observed between the velocities of the septal and lateral systolic waves measured by tissue Doppler and the value of creatinine - inverse correlation, as well as between them and creatinine clearance - direct correlation. Therefore, subclinical systolic dysfunction is in direct correlation with renal dysfunction ( $p = 0.039 < 0.05$ ).

NTproBNP is directly correlated with diastolic dysfunction - the higher the NTproBNP, the higher the septal I / E ratio and the mean E / E' reflecting diastolic dysfunction with increased filling pressures.

The telediastolic volume of the left ventricle is inversely correlated with the myocardial systolic wave measured by tissue Doppler - S lateral, and the telesystolic volume of the VS is inversely correlated with the septal S wave, both volumes being directly correlated with pressure in the pulmonary artery.

The ejection fraction of the left ventricle is directly correlated with the septal and lateral velocities measured at tissue Doppler (S septal and S lateral), but is also directly correlated with systolic function of the right ventricle (VD) measured by TAPSE and systolic wall velocity measured by tissue Doppler. Therefore, left ventricular systolic dysfunction is directly correlated with right ventricle systolic dysfunction.

### III.3.2 RESULTS – PART 2

Histopathological analysis of the 36 cases selected from patients deceased with the diagnosis of dilated cardiomyopathy of alcoholic etiology, revealed changes in the cardiomyocyte structure and in the extracellular matrix structure. The investigated cases revealed heterogeneity in the immunosuppression of desmin.

We identified a significant decrease in the numerical density of the dark discs in the case of dilated cardiomyopathy compared to the control cases,  $p < 0.05$ . A significant difference was found between the selected cases ( $1.94 \pm 0.31$ ) and controls ( $1.824 \pm 0.13$ ) and regarding the ratio of the measured cell surface to the total length of the dark disks ( $p = 0.041$ ).

We also analyzed the dependence between the number of dark disks and their average length, and identified that there is a strong correlation for controls ( $r = 0.67$ ,  $p < 0.0001$ ) but there was no correlation for cases with dilatative cardiomyopathy.

## IV. CONCLUSIONS

The diseases caused by the excessive alcohol consumption, of which the most frequent is the alcoholic liver disease, produce important costs of the health systems worldwide, both with diagnostic investigations, but especially with the treatment of complications. Therefore, the scientific information regarding the diagnosis and treatment of the complications of the disease has an important impact on the evolution and survival of the patients.

The following conclusions are highlighted from the present study:

- Most patients affected by alcoholic liver disease are men and come from rural areas;
- The corrected QT interval is longer in patients in the Child C class, placing them in an area with a higher risk of ventricular arrhythmias;
- We identified increased mean values of atrial natriuretic peptide / N-terminal end of atrial natriuretic peptide (BNP / NTproBNP) in patients with cirrhosis;

The values of this biomarker were above normal in both Child B and Child C cirrhosis patients. The mean values were significantly higher for the patients in the Child B class, so latent cardiac dysfunction is common in these patients, but it is often underdiagnosed;

Early investigation of cardiac dysfunction is important for the evolution and prognosis of patients, and its identification can be easily obtained by dosing BNP / NTproBNP;

- We identified that the mean volume of the left atrium was increased in the patients in the studied group. Also, there is a directly proportional correlation between the left atrial volume and the parameters of diastolic dysfunction, and this is in accordance with the recent data in the literature.

We did not identify a statistically significant difference between Child B and C classes in terms of mean indexed left atrial volume;

- Mean atrial volumes were directly correlated with pulmonary artery pressure, which argues that identifying their growth should lead to the investigation of coexisting diastolic dysfunction;
- Renal dysfunction is associated in the present study with subclinical systolic dysfunction detected by measuring tissue velocities by tissue Doppler, so identifying a low glomerular filtration rate should lead to the search for a subclinical systolic

dysfunction that may influence the prognosis of patients especially major interventions such as liver transplantation;

- There is an abnormal pattern of expression of desmin identified by the study of immunohistochemistry in cardiac muscle cells in most cases of dilative cardiomyopathy;
- This pattern has been correlated with the survival rate in the literature and represents an independent prognostic factor for patients with this condition. Based on the information given by the immunohistochemical study of desmin in myocardial cells, prognostic and evolution models can be created.

These findings contribute to international research on heart disease associated with severe alcohol-induced liver disease and create the prerequisites for further studies that could have a significant impact on the diagnosis and prognosis of these patients.