

UNIVERSITY OF MEDICINE AND PHARMACY

CRAIOVA

FACULTY OF MEDICINE

**ARRHYTHMIA RISK IN CHRONIC LIVER
DISEASES**

PHD THESIS

ABSTRACT

PhD COORDINATOR:

Prof.univ. Dr. DAN IONUȚ GHEONEA

PhD Student,

VERONICA CALBOREAN

CRAIOVA

2018

CONTENT

INTRODUCTION	4
GENERAL PART... ..	4
1.CHRONIC HEPATIC BACKGROUND.....	4
1.1. Definition.....	4
1.2. Classification.....	4
1.3. Pathogenesis.....	5
1.4. Clinical picture.....	5
1.5. Paraclinical diagnosis.....	5
1.6. Positive diagnosis.....	5
1.7. Differential diagnosis.....	5
2.CARDIAC ARRHYTHMIAS.....	5
2.1.The excitoconductor system. General notions of anatomy and electrophysiology.....	6
2.2. Cardiac arrhythmias manifestation.....	6
2.3. Classification of cardiac arrhythmias.....	6
2.3.1. Supraventricular arrhythmias.....	6
2.3.2. Ventricular arrhythmias.....	6
SPECIAL PART.....	6
3.1. INTRODUCTION.....	6
3.2. THE AIM OF THE STUDY.....	7
4. STUDY LOT AND WORKING METHOD.....	7
4.1. Tipe of the study.....	7
4.2. Study lot	7
4.3. Working method.....	7
5. STUDY 1 – Corelations between chronic hepatic disease and arrhythmia risk.....	7
5.1. Purpose.....	7
5.2. Material and method.....	7
5.3. Results.....	7
• The relationship between chronic hepatic disease and atrial fibrillation.....	7
• The relationship between chronic hepatic disease and atrial flutter.....	8
• The relationship between chronic hepatic disease and atrial tachycardia.....	8

• The relationship between chronic hepatic disease and sinus bradycardia	8
• The relationship between chronic hepatic disease and atrial extrasystole	8
• The relationship between chronic hepatic disease and ventricular extrasystole.....	8
• The relationship between chronic hepatic disease and atrio-ventricular blocks.....	8
5.4. Discussions.....	9
5.5. Conclusions.....	9
6. STUDY 2 – Study of QT interval duration in patients with chronic hepatic disease	9
6.1. Purpose.....	9
6.2. Material and method.....	9
6.3. Results.....	10
• QT interval and etiology of the chronic hepatic disease.....	10
• The relationship between QT interval and patient sex.....	10
• The relationship between QT interval and the patient’s environment of origin.....	10
• QT interval prolongation according to the age of patients.....	11
• QT interval prolongation according to the CHADSC-VASC score.....	11
• QT interval prolongation according to the NTproBNP value.....	11
6.4. Discussion.....	11
6.5. Conclusions.....	12
7. STUDY 3 – Evaluation of Echocardiographic Parameters in Patients with Rhythm Disorders Associated with Chronic Hepatic Disease	12
7.1. Purpose.....	12
7.2. Material and methods.....	12
7.3. Results.....	12
7.4. Discussions.....	14
7.5. Conclusion.....	14

Key words : chronic hepatic disease, arrhythmias, long QT syndrome

INTRODUCTIONS

Because of the involvement of cardiovascular disorders in the development of chronic hepatic disease, we have proposed to investigate the risk and prevalence of arrhythmias in order to evaluate the various cardiac disturbances and their significance.

Arrhythmias represent a major risk factor with potentially fatal clinical significance. The diagnosis of arrhythmias and the profound understanding of the mechanisms of occurrence and self-maintenance of the causes of occurrence is one of the challenges of the modern pathology that led me to study it in this Phd thesis.

Early detection of cardiac arrhythmias is of great importance in the evolution of the patient with chronic hepatic disease. The diversity of etiologies and varied clinical picture compels us to investigate all aspects of the arrhythmogenic substrate and the triggering and aggravating factors in chronic hepatic disease. At the same time, through our research, we want to draw attention to the importance of following rhythm disorders to improve prognosis and specific therapeutic behavior .

I. GENERAL PART

1. CHRONIC HEPATIC BACKGROUND

The term of chronic hepatic disease describes a frame with a symptomatic content that reflects multiple etiologies such as viral infections (B, C, D), metabolic factors, drug factors, autoimmune diseases. This term is also characterized by a common clinical expression and a non-inflammatory substrate of varying degrees.

1.1. Definition. Chronic hepatic disease is described as an inflammatory liver disease lasting more than 6 months. The clinical symptomatology of chronic hepatic disease may or may not be present and from a biochemical perspective the enzymatic level may oscillate.

1.2. Classification. Classically, chronic hepatic disease has been classified from a descriptive point of view. These lesion categories were structured in persistent, aggressive or active, septal and lobular chronic hepatitis. However, this category is no longer used, and is replaced by a more structured classification based on etiology, necroinflammatory process (grading) or on the basis of scoring systems.

1.3. Pathogenesis. In the pathogenesis of chronic hepatic disease, immunological mechanisms, especially those of the cellular type, caused by different etiological agents, play a major role. The importance of the land, including the genetic pattern and the peculiarities that depend on the trigger agent, vary from case to case.

1.4. Clinical picture. Chronic hepatitis define a framework of a common clinical picture with different traits, depending on etiology. From a subjective point of view, hepatic disease presents a modest clinical picture, barely distinguishable for a long time, or described by an inexplicable asteno-adyamic syndrome. From an objective point of view, hepatomegaly is the most common manifestation, characterized by a smooth and sensitive, sometimes painful surface. Also, the appearance of splenomegaly may be associated. Other manifestations may be: jaundice, vascular stars and in some cases hemorrhagic manifestations.

1.5. Paraclinic diagnosis. In 2014, the American College of Gastroenterology established new evidence-based rules for the diagnosis and management of hepatic lesions. This system is based on the use of more useful methods of objectification of liver lesions. These are: ultrasound, computed tomography and nuclear magnetic resonance that allow the discovery of hepatic lesions of asymptomatic patients.

1.6. Positive diagnosis. Diagnosis of hepatitis involves the research of several stages:

- Identification of liver disease
- Grading and Staging of Chronic Hepatitis
- Determination of etiology
- Establishing the histological substrate
- Appreciation of particular clinical patterns, evaluating extrahepatic manifestations.

1.7. Differential diagnosis. It is fundamental to perform differential diagnoses between different hepatic pathologies, so we can determine if it is a hepatic disease of viral etiology (such as chronic viral hepatitis B or chronic viral hepatitis C), a metabolic toxic disorder, a hemochromatosis, Wilson's disease or a pathology of drug or autoimmune etiology.

2. CARDIAC ARRHYTHMIAS. Cardiac arrhythmias represent a particular importance in terms of the risk of sudden arrhythmic cardiac death, presenting a regional or systemic hemodynamic disorder of varying intensity with progress towards complications or premature death.

2.1. The excitoconductor system. General notions of anatomy and electrophysiology. Initially, the main conducting tissues were described only histologically, and in parallel with the advancement of the research methods of cell physiology, fundamental electrical phenomena were also described. The electrical activity of the heart is the one that determines the contractile response. The heart works on the fundamental principles of cellular depolarization production, conduction and transmission.

2.2. Cardiac arrhythmia manifestation. Cardiac arrhythmias present a wide range of clinical manifestations. From the symptomatology point of view cardiac arrhythmias present a poor clinical picture, sometimes subtle or described by the patient using the word "palpitations." Cardiac and extracardiac manifestations are also associated, such as: precordial pain, syncope or lipotima, dyspnoea, dizziness, anxiety disorder or panic disorder.

Objectively, with the exception of rhythm disorders, no other specific cardiovascular sign appears. Within the heart auscultation, various associated valvulopathies can be associated.

2.3. Classification of cardiac arrhythmias. Classification of cardiac arrhythmias is structured on the basis of several parameters, most frequently using classification according to the location of arrhythmia along with its electrocardiographic appearance.

2.3.1. Supraventricular arrhythmias. Include a spectrum of tachyarrthmia with narrow QRS complex (sinus tachycardia, atrioventricular nodal reentrant tachycardia, atrial tachycardia, atrial fibrillation, atrial flutter).

2.3.2. Ventricular arrhythmias. Ventricular arrhythmias can occur both isolated on an apparently healthy cord and in the context of complications in certain structural cardiac conditions. Ventricular arrhythmias represent an extremely important problem, with vital implications for patients' progression and prognosis given the increased risk of sudden cardiac death.

THE SPECIAL PART

3.1. INTRODUCTION. One of the reasons behind the choice of this topic for my doctoral thesis is that the arrhythmic risk in patients with chronic hepatic disease is most often underestimated. For this, starting from data from the literature, I began studying arrhythmic risk in patients with chronic liver disease. Thus, we have attempted to establish multiple clinical and paraclinical correlations to see if early diagnosis and therapeutic balancing leads to clinical improvement in the context of chronic hepatic disease. At the same time, we have tried to

highlight the importance of the frequency and severity of arrhythmias and the risk of sudden cardiac death in patients with chronic hepatic disease.

3.2. THE AIM OF THE STUDY. Due to the increased frequency of cardiovascular disorders in the evolution of chronic hepatic disease, we have proposed to investigate the arrhythmic risk and the prevalence of arrhythmias in order to evaluate the various cardiac diseases and their significance.

4. STUDY LOT AND WORKING METHOD

In our study, 126 patients were diagnosed based on the clinical and paraclinical examination with chronic hepatic disease and 120 patients without chronic hepatic disease, representing the control group.

The study was conducted over a period of 14 months, from 1.10.2016 to 1.01.2018.

We evaluated patients both from cardiology and hepatology point of view, through anamnesis, clinical examination, abdominal ultrasound, echocardiography, electrocardiogram and laboratory investigations.

5. STUDY 1 - Correlations between chronic hepatic disease and arrhythmia risk

5.1. Purpose. Our goal was to analyze the existing arrhythmic risk in chronic hepatic disease.

5.2. Material and method. For the analysis of electrocardiographic changes, each patient in our group performed an electrocardiographic examination. We analyzed heart rhythm disorders in patients with chronic hepatic disease, according to the etiology.

5.3. Results

The relationship between chronic hepatic disease and atrial fibrillation. Of the 126 patients surveyed in our study 74 of them presented atrial fibrillation. Of these 21 were previously diagnosed with chronic hepatitis B virus infection, 19 with chronic hepatitis C virus infections, 23 patients had a diagnosis of alcoholic cirrhosis and 11 metabolic toxic hepatitis. The total prevalence of atrial fibrillation in subjects with chronic hepatic disease included in our study was 58.73%. The statistical analysis we performed revealed a 1.23-fold greater risk of atrial fibrillation in patients with alcoholic cirrhosis than in patients with chronic hepatic disease of viral etiology. We also analyzed the risk of atrial fibrillation in patients with alcoholic cirrhosis versus patients with chronic hepatitis of metabolic toxic etiology. In this case, although

the value of the Student t test was $p = 0.4962$, the relative risk is 1.1684 times the occurrence of atrial fibrillation in patients with alcoholic cirrhosis.

The relationship between chronic hepatic disease and atrial flutter. The highest proportion of patients with atrial flutter (10.53%) was present in subjects diagnosed with metabolic toxic hepatitis.

The relationship between chronic liver disease and atrial tachycardia. Regarding tachycardia we can state that there is a 5,0667-fold higher risk in patients with metabolic toxic hepatitis than patients with alcoholic cirrhosis. Although the value of the Student t test is 0.1267, the risk of tachycardia is 2, 35 times higher in patients with metabolic toxic hepatitis compared to those diagnosed with hepatic disease of viral etiology.

The relationship between chronic hepatic disease and sinus bradycardia. The statistical analysis we performed revealed a 2.13-fold higher risk of bradycardia in patients with metabolic toxic hepatitis than in patients with alcoholic cirrhosis. We also analyzed the risk of bradycardia in patients with metabolic toxic hepatitis versus patients with chronic hepatitis of viral etiology. In this case, although the value of the Student t test was $p = 0.3125$, the relative risk is 1.88 times the occurrence of bradycardia in patients with metabolic toxic hepatitis.

The relationship between chronic hepatic disease and atrial extrasistole. The relative risk of atrial extrasistoles in patients with chronic viral hepatitis is 5,1233 times higher than those affected by alcoholic cirrhosis and 1.4315 times higher than those with metabolic toxic hepatitis. The exact Fisher test had Positive value of $P = 0.027551$.

The relationship between chronic hepatic disease and ventricular extrasystoles. Statistical analysis confirms correlations between ventricular extrasystoles and hepatic disease of viral etiology, describing a relative risk of 1.9521 times greater in viral pathology than toxic hepatitis pathology. The relative risk of ventricular extrasystoles is 1.3973 times higher in patients with hepatic disease of viral etiology compared to those diagnosed with alcoholic cirrhosis.

The relationship between chronic hepatic disease and atrio-ventricular blocks.

Most cases of atrioventricular blocks occurred in patients diagnosed with chronic hepatitis B virus infection (23.68%). The second position was the diagnosis group of alcoholic cirrhosis (17,65%). The other places were for the patients diagnosed with chronic hepatitis C virus infections (11.43%) and those with metabolic toxic hepatitis (10.53%).

Analyzing the nosological and etiological framework of installation atrioventricular block in patients in the study group, we can see a very close incidence between the viral etiology (17.81%) and that caused by alcoholic cirrhosis (17.65%).

5.4. Discussions.

The high incidence of arrhythmias seen in the patients in our study diagnosed with alcoholic cirrhosis is directly correlated with the literature. Both in the research preceding our study as well as in the present case, the devastating impact of the alcohol consumed over a long period of time and its involvement in the occurrence of rhythm disorders in a diseased organism has been proved.

Data from the literature suggests a higher arrhythmic risk in patients with comorbid hepatic disease compared to the non-hepatic injury population, so it is fundamental to have a complex multidisciplinary approach to patients with chronic hepatic disease.

5.5. Conclusions. 74 out of 126 patients had atrial fibrillation, of which 67.65% had alcoholic cirrhosis, 55.26% chronic hepatitis B virus infection, 54.29% chronic hepatitis virus C infection and 57.89% metabolic toxic hepatitis. The highest incidence of atrial flutter was seen in patients with metabolic toxic hepatitis, but the risk of installing atrial flutter in patients with alcoholic cirrhosis or chronic hepatic disease of viral etiology should not be ignored. 26 subjects experienced changes in heart rate of the type bradycardia and tachycardia, with a correlation between these cardiac changes and metabolic toxic hepatitis. Atrial and ventricular extrasistoles have been identified in a significant number of patients. Most of these patients were diagnosed with chronic hepatic disease of viral etiology. The incidence of the atrioventricular block was the highest in case of chronic hepatitis B virus infection, but the differences are small, which makes us believe that in case of hepatic diseases of ethanolic etiology the risk of atrioventricular block is also high.

6. STUDY 2 - Study of QT interval duration in patients with chronic hepatic disease

6.1. Purpose. The main purpose of our study was to identify the prolongation of QT interval in patients in the present study, thus demonstrating the importance of cardio physiological changes in the evolution of chronic hepatic disease.

6.2. Material and method. Our study included a group of 126 patients with chronic hepatic disease and a control group of 120 patients without hepatic pathology who were

hospitalized from 1.10.2016 to 1.01.2018. We evaluated patients both from cardiological and hepatological point of view through anamnesis, clinical examination, abdominal ultrasound, echocardiography, electrocardiogram and laboratory investigations. The QT interval was performed in all patients by conducting the electrocardiographic examination and its calculation was made using the Bazett formula: $QTc = QT / \text{radical in the range RR}$.

6.3. Results

QT interval and etiology of the chronic hepatic disease. Using the ANOVA test, we found that there was a statistically significant difference between QT mean values based on the underlying etiology, the ANOVA result being $p \text{ ANOVA} = 0.024 < 0.05$. Continuing the analysis by performing Fisher LSD post-hoc tests, we highlighted the fact that the objectionable difference of the ANOVA test occurs between the mean QT interval for patients with chronic hepatitis C virus infection and those with alcoholic cirrhosis. Patients with cirrhosis experienced a longer duration of QT, around 475.15 ms. The alcoholic etiology of cirrhosis results in elevated QT interval in both women and men.

Relationship between QT interval and patient sex.

Lot	Lot witness		Lot of study	
Gender	Women	Men	Women	Men
Nr.	54	66	43	83
Average	411.55	413.40	461.56	461.14
Dev.std.	36.03	39.10	42.03	45.10
C.V. (%)	8.76%	9.46%	9.11%	9.78%
Result	p Student=0.790	0.790	p Student=0.960	0.960

For the study group the value of the statistical indicator p Student was 0.960, while for the control group p Student presented the value of 0.790.

The relationship between the QT interval and the patient's environment of origin.

The distribution of subjects by the environment of origin gives us the following results. Over 42% of the subjects come from rural areas. Of these, more than half (35 out of 53 subjects) experienced QT changes. The percentage of subjects from urban areas was greater than 57%. A

number of 49 patients from urban areas presented QT prolongation compared to only 24 subjects without prolonged QT interval.

Prolonging the QT interval according to the age of the patients. We considered it useful to achieve a distribution of patients in our study over decades of age. Most subjects in our study were in the 60-69 decade (52 subjects). The second place included subjects aged 70-79 years (29 subjects), followed by patients aged 50-59 (20 subjects). A smaller number of patients were enrolled in the 80-89 decade (16 subjects). Only 9 patients in the study group were aged 40-49 years.

Age	Nr. Cases	Average	Standard deviation
40-49	9	462.56	50.29
50-59	20	468.75	44.10
60-69	52	452.98	34.33
70-79	29	455.83	49.24
80-89	16	488.13	50.79

Prolonging the QT interval according to the CHADSC-VASC score. By doing the Student's p test, we could not demonstrate that there was a significant difference between QT interval values and CHADS-VASC score 1 or greater than 2, despite the apparent large numerical difference (470 vs. 456.44) because the variability of the data was very high , exceeding the test error limit (p test Student = 0.426 - NS).

Prolonging the QT interval according to the NTproBNP value. The percentage of those with prolonged QT interval that showed values of NTproBNP over 2000 pg / mL is 85.29%. Only 14.71% of subjects with prolonged QT interval were found negative NTproBNP values.

6.4. Discussions. QT interval analysis correlated with patient sex revealed in the study group a number of 54 men with prolonged QT interval versus only 30 women with this electrocardiographic change. Our data can not be directly correlated with literature data that shows a much higher incidence in women. Statistically, there were no significant differences between the mean values of the QT interval by sex, either in the study group or in the control group. The p Student test values confirms this. The QT interval study based on the age of the

patients shows that the highest percentage was recorded in the 60-69 age group, and the fewest patients were in the 40-49 age group. The presence of such a high number of patients aged 60-69 can be explained by established epidemiological studies reflecting a much higher incidence of cardiovascular disorders in this decade of age.

6.5. Conclusions. Most patients in our study presented high QT interval values (84 subjects-66.67%). The largest proportion of subjects with prolonged QT interval was male (58 men vs 30 women). The majority of patients that we found this cardiophysiological change were from the urban environment (58.33%). The highest proportion of cardiovascular comorbidity was represented by patients with heart disease and chronic hepatitis B virus infection (30.16%). The number of men diagnosed with ethanolic cirrhosis or metabolic toxic hepatitis was clearly superior to women. In contrast, for patients diagnosed with chronic hepatitis B virus infection or C virus infection, the incidence of gender is close.

7. STUDY 3 - Evaluation of Echocardiographic Parameters in Patients with Rhythm Disorders Associated with Chronic Hepatic Disease

7.1. Purpose. The purpose of our study was to evaluate the degree of cardiac affecting in patients with rhythm disorders associated with chronic hepatic disease. We correlated different signs of cardiac involvement, those characteristic of systolic and diastolic dysfunction and echocardiographic parameters with the etiology of chronic hepatic disease. We also looked at the incidence of valvular refluxes correlated with the etiology of chronic hepatic disease.

7.2. Material and methods. To analyze the degree of cardiac affecting of each subject from our research (study lot and witness lot) we performed a complete cardiovascular examination.

7.3. Results. The mean value of left ventricle in diastole (VS(D)) in patients with chronic hepatic disease, depending on etiology was : 53.44 mm for patients diagnosed with chronic hepatitis B virus infection, 47.8 mm for subjects with chronic hepatitis C virus infection, 56,94 mm for patients diagnosed with alcoholic cirrhosis and 50.16 mm for patients with metabolic toxic hepatitis. The mean value of VS(D) on the control group was 42.31 mm. Regarding the left ventricle diameter in systole (VS(S)) we recorded the following data: 41.89 mm - for chronic hepatitis B virus infection, 32.22 mm for chronic hepatitis C virus infection, 45.09 mm for patients with alcoholic cirrhosis respectively 39,26 mm in patients with metabolic toxic hepatitis. To specify that the average diameter of the control group was 21,7 mm, which is

a much lower value than those recorded in the patients from the study group. The significant difference from the control group was high. This was also confirmed by the Student t test results ($p < 0.0001$).

We obtained the following mean values of left atrium: 47.86 mm for patients with chronic hepatitis B virus infection, 45.18 mm for patients with chronic hepatitis C virus infection, 56.47 mm for patients with alcoholic cirrhosis and 43.74 mm for subjects diagnosed with metabolic toxic hepatitis. The analysis with the control group shows significant differences by comparing the recorded value in the control group (28.39mm) versus the mean value of the study group (48.83mm) and through the results of the Student test ($P < 0.0001$).

The mean value of the left ventricular wall reported to the entire nosological palette of our research was 11.80 mm. This was divided into etiologies as follows: 11.93 mm - chronic hepatitis B virus infection, 11.75 mm - chronic hepatitis C virus infection, 11.44 mm - alcoholic cirrhosis and 12.26 mm - metabolic toxic hepatitis. The average diameter of left ventricle walls for the control group was 8, 76 mm.

Interventricular septum mean values were as follows: 12.53 mm for chronic hepatitis B virus infection, 13.03 mm for chronic hepatitis C virus infection, 11.44 mm for alcoholic cirrhosis, and 12.53 mm for metabolic toxic hepatitis. The average value of the interventricular septum diameter for the study group is 12.37 mm, while the average value of the interventricular septum diameter for the control group is 9.18 mm.

Average of right ventricular diameter in patients with chronic hepatitis B virus infection was 40.97 mm, for those with chronic hepatitis C virus infection-33.91 mm, 47.52 for patients with alcoholic cirrhosis and 34.60 mm for those with metabolic toxic hepatitis . We therefore see an average of 39.97 mm for patients in the study group versus an average of 30.29 mm for patients in the control group.

The mean of the study group had a total value of the right atrium of 46.54 mm. For patients with chronic hepatitis B virus infection the average value of the right atrium diameter was 48.33 mm, for those diagnosed with chronic hepatitis C virus infection the value was 38.26 mm, 54,29 mm for patients with alcoholic cirrhosis and 43.33 mm for those with metabolic toxic hepatitis. The average value of the diameter of the right atrium regarding the control group was 33, 07 mm.

7.4. Discussions. These data are consistent with the literature that states that both diastolic and systolic function are altered in the course of liver cirrhosis. Some studies show that diastolic dysfunction is present in all patients diagnosed with chronic hepatic disease. Although these morphological changes are not in a relationship of direct proportionality to diastolic dysfunction, we consider that echocardiography plays a fundamental role in the early detection of systolic and diastolic dysfunctions.

7.5. Conclusions. All of our correlations were reinforced by statistically significant differences between the study group and the control group, confirmed by the study average, standard deviation and the Student t test.