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Cardiovascular impairment in liver cirrhosis

Cardiovascular impairment in hepatic cirrhosis

SUMMARY

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BRAȘOV, 2024

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LIST OF ABBREVIATIONS AND SYMBOLS

A - DIASTOLIC VELOCITY OF ATRIAL CONTRACTION

AST - ASPARTATE AMINO TRANSFERASE

ALT - ALANINE AMINO TRANSFERASE

ATP - ADENOSINE TRIPHOSPHATE

ASE - AMERICAN SOCIETY OF ECHOCARDIOGRAPHY

BNP - B-TYPE NATRIURETIC PEPTIDE

CCM - CIRRHOTIC CARDIOMYOPATHY

CH - CIRRHOSIS OF THE LIVER

CES - SINUSOIDAL ENDOTHELIAL CELLS

cGMP - CICLIC GUANOZIN MONOPHOSPHATE

CK - KUPFFER CELLS

CT - COMPUTERIZED TOMOGRAPHY

cAMP - CYCYCLIC ADENOZIN MONO PHOSPHATE

CO - CARBON MONOXIDE

EACVI - EUROPEAN ASSOCIATION OF CARDIOVASCULAR IMAGING

e^{l} - PROTODIASTOLIC MITRAL RING PROTODIASTOLIC VELOCITY

E - EARLY DIASTOLIC VELOCITY OF MITRAL INFLOW

ECG - ELECTROCARDIOGRAM

EDS - UPPER DIGESTIVE ENDOSCOPY

EH - HEPATIC ENCEPHALOPATHY

eNOS - NO ENDOTELIAL SYNTHASE

EF - LEFT VENTRICULAR EJECTION FRACTION

ET1 - ENDOTHELIN 1

E/A - THE RATIO OF THE PEAK VELOCITY OF EARLY DIASTOLIC FILLING TO THAT OF ATRIAL CONTRACTION

FA - ALKALINE PHOSPHATASE

FGNA - NON-ALCOHOLIC FATTY LIVER

GGT - GAMMA GLUTAMYL TRANSFERASE

GLS - GLOBAL LONGITUDINAL STRAIN

HSC - HEPATIC STELLATE CELLS

HRV - HEART RATE VARIABILITY

HSC - HEPATIC STELLATE CELLS

HPP - PORTOPULMONARY HYPERTENSION

HPS - HEPATOPULMONARY SYNDROME

iNOS - NO INDUCTIBLE SYNTASE

LA - LEFT ATRIUM

LBF - LOWER LIMB BLOOD FLOW

LV - LEFT VENTRICLE

LVC - LOWER LIMB VASCULAR CONDUCTANCE

L-NMMA - N OMEGA MONOMETHYL L ARGININE

mmHG - MILLIMETERS PER CENT CENT CENT OF MERCURY

MAPK - MITOGEN-ACTIVATED PROTEIN KINASES

nNOS - NO NEURONAL SYNTETATION

NO - NITRIC OXIDE

PBS - SPONTANEOUS BACTERIAL PERITONITIS

PMVH - MEAN HEPATIC VEIN PRESSURE

PT - PROTHROMBIN TIME

RAAS - RENIN ANGIOTENSIN ALDOSTERONE SYSTEM

RyR2 - RIANODIN RECEPTOR TYPE 2

RR - DISTANCE BETWEEN TWO R WAVES MEASURED ECG

RMN - NUCLEAR MAGNETIC RESONANCE

RT - TRICUSPID REGURGITATION

SHR - HEPATORENAL SYNDROME

STROKE - CEREBROVASCULAR ACCIDENT

sPLM - PASSIVE MOVEMENT OF A LOWER LIMIT MEMBER

TDI - TISSUE DOPPLER ULTRASOUND

TIPS - TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

TNFα - TUMOR NECROSIS FACTOR ALPHA

VIAS - INDEXED VOLUME OF THE LEFT ATRIUM

SUMMARY

Introduction: Due to the increasing prevalence of cirrhosis of the liver globally, there is a need for a better understanding of its repercussions on the cardiovascular system. Although there are numerous studies in the literature addressing this topic, there is a need for a better understanding of the damage to the heart as well as the damage to the peripheral vascular system in patients with end-stage liver disease. Cirrhotic cardiomyopathy is most recently defined by the presence of exertional systolic dysfunction, diastolic dysfunction and electrophysiologic changes. The impact of these conditions is unfavorable for the patient, especially in the post liver transplantation period. Thus, a more accurate and earlier diagnosis of cirrhotic cardiomyopathy as well as vascular endothelial dysfunction could play an important role in the evaluation of cirrhotic cardiomyopathy with potential prognostic implications for patients and possible public health policy implications.

Objectives: The PhD thesis aims to better understand cirrhotic cardiomyopathy by defining and comparing different parameters of systolic and diastolic dysfunction and assessing autonomic dysfunction by different parameters. It also aims to study in depth the peripheral vascular endothelial dysfunction by using elements with increased accuracy in its estimation

Materials and Methods: The PhD work comprised three separate research studies. Data collection had ethics committee approval and was performed between November 2019 and March 2024. The first study evaluated various parameters of systolic and diastolic dysfunction on exercise in a group of 70 patients with liver cirrhosis .The parameters used were compared and their accuracy and their correlation with the severity of liver disease were statistically analyzed. In the second study, the focus was on the evaluation of electrophysiologic alterations in a sample of 60 patients with liver cirrhosis and comparison with a control group of 50 patients with no known pathology. For a better understanding, different variables were used to follow patients in different situations (rest, parasympathetic stimulation maneuvers, during exercise and post-exercise but also with 24-hour monitoring). The third study evaluated vascular endothelial dysfunction by various methods (LBF - lower limb blood flow and LVC - lower limb vascular conductance), at rest and during exercise, in a group of 78 patients with liver cirrhosis and compared them with a control group of 30 patients as well as comparisons between subgroups according to the etiology of cirrhosis and APRI score. Study results were statistically analyzed by various specific methods.

Results: The results of the first study showed that the TEI index is a sensitive and specific method in detecting systolic dysfunction compared to left ventricular ejection fraction and that it correlates with the degree of liver damage. Also E/Vp is a superior parameter compared to E/A in the diagnosis of diastolic dysfunction and that this parameter also correlates with the degree of liver damage. The second study showed low values of Valsalva index, 24-hour heart rate variability expressed as SDNN(standard deviation of N-N intervals) and post-exercise heart rate in patients with cirrhosis compared to healthy patients. No statistically significant differences were noted between QTc intervals in the two groups. There were also no statistically significant differences in the comparative analysis of toxic and non-toxic etiology subgroups. The results of the third study showed higher resting LBF and LVC values at rest only when comparing the ethanolic etiology subgroup with the control group, with no significant difference when comparing the two main groups. On effort, statistical significance was also found when comparing the main group with the control group as well as when comparing all subgroups of cirrhotic patients with the control group. Patients with APRI score above 1.5 had higher LBF and LVC values compared to the control group and also when comparing with those with APRI score below 1.5. LVC results were in agreement with LBF.

Discussion: The present work provides a comprehensive investigation of the diagnosis of cirrhotic cardiomyopathy and vascular endothelial dysfunction by multiple methods. The first study showed that both systolic dysfunction parameters (EF and TEI index) had normal values at rest. This finding is consistent with existing data in the literature and can be partly explained by the ubiquitous systemic vasodilatation in liver cirrhosis, which generates a decreased postsarcine. This is further evidence that the diagnosis of cirrhotic cardiomyopathy is extremely difficult based strictly on resting echographic determinations. On statistical analysis of the TEI index, a positive correlation between systolic dysfunction and severity of liver disease was noted, a finding supported by the statistical significance found. This result is consistent with data from previous studies that assessed systolic function by GLS. E/Vp where a directly proportional correlation was demonstrated between the degree of liver damage and the severity of diastolic dysfunction assessed by this highly specific parameter. These data confirm once again, as well as pre-existing data in the literature, that this parameter is a faithful indicator of diastolic function, its correlation with the severity of CH having clear pathophysiologic explanations by worsening biohumoral changes and worsening cardiac receptor function with worsening liver disease. The TEI has been shown to be a much more sensitive parameter than EF in detecting systolic dysfunction. Based on these results, its use in patients with suspected CMC with preserved EF is recommended. Widespread use of this parameter could lead to an increase in the sensitivity of the diagnosis of cirrhotic cardiomyopathy with improved prognosis of these patients in various conditions, either without liver transplantation, post liver transplantation or post SPTI implantation. In the second study, the Valsalva Index was found to be a very good indicator of autonomic nervous system status. In the present study, the statistical significance was met, confirming once again the predominant parasympathetic nervous system involvement in patients with liver cirrhosis, regardless of etiology, with no additional involvement in patients with ethanolic etiology. Heart rate variability is a proven marker of autonomic dysfunction and its assessment by the SDNN parameter has been shown to have high specificity and sensitivity. The presence of autonomic dysfunction was present in this study by low, statistically significant values found in cirrhotic patients, with no notable differences between different etiologies of cirrhosis. The persistence of post-exertional tachycardia in cirrhotic patients, a sign of parasympathetic nervous system alteration, was also evidenced, without any statistical difference in maximal heart rate during exercise.In the third study, the only statistically significant difference at rest was observed when comparing the subgroup of patients with liver cirrhosis of ethanolic etiology with the control group. The mechanisms underlying this finding are unknown but may be partly explained by direct alcohol-induced vasodilation of the vascular endothelium.During exercise, the direct comparison between the two main groups was statistically significant confirming the hypothesis that patients with liver cirrhosis show increased systemic vasodilation induced by nitric oxide in contrast to endothelial dysfunction in the hepatic portal vessels manifested by vasoconstriction. In our case, the physical stressor used - passive lower limb passive motion (sPLM) - led to an increase in nitric oxide production with the direct effect of greater vasodilation than in the control group, with the greatest increase in vasodilation again being noted in the ethanolic subgroup. Regarding the subgroups according to APRI score, only those in the subgroup with APRI over 1.5 showed a statistically significant increase in the measured vasodilation parameters, a finding that suggests the correlation of the degree of fibrosis with the degree of systemic vasodilation, as reported in the literature.

Conclusions: The combined results from all three PhD thesis studies show that the scaled application of the two proposed parameters (TEI index and E/Vp ratio) could lead to a better diagnosis of systolic and diastolic dysfunction in cirrhotic patients, respectively, with positive effects on the prognosis of these patients, that sPLM proved to be a reliable parameter in the estimation of systemic vasodilatation in liver cirrhosis, demonstrating supliemoratory increases in patients with ethanolic etiology, and that the Valsalva index, and SDNN and AV at 2 minutes post exercise were sensitive indicators of autonomic dysfunction in cirrhotic patients and the Valsalva index particularly demonstrated alterations in parasympathetic response. Research results were disseminated through two ISI and two BDI articles.

1. INTRODUCTION. MOTIVATION FOR CHOOSING THE TOPIC

The approximate prevalence of clinically manifest cirrhosis of the liver in adults is 1 in 1000, but the strictly histologic prevalence without clinical manifestation is close to 1 in 100 adults. According to data published by the WHO, one million deaths from this disease are reported annually worldwide. In our country are estimated around 70,000 new cases annually, of which one third are in the severe stage of the disease. The average age at diagnosis is 50 years. The average survival in patients with compensated disease is 12 years but in patients with repeated decompensations it drops dramatically to less than 2 years. characterized by an increased cardiac output associated with a decrease in systemic vascular resistance but also the presence of systolic and diastolic dysfunction of varying degrees.

Cardiovascular disease is divided into :

- cirrhotic cardiomyopathy with specific symptoms and reduced systolic as well as diastolic function
- alteration of electrophysiologic parameters (autonomic dysfunction and prolongation of the corrected QT interval)
- alteration of normal vascular endothelial function (mediated mainly by nitric oxide but also by other parameters)
- fibrinous pericarditis (fibrin buildup in the pericardial space)

Cardiovascular involvement is present in about half of cirrhotic patients, regardless of etiology. Various articles have reported that CMC is more common in male patients, in those over 50 years of age and in those with liver cirrhosis of ethanolic etiology, but without clear evidence.

The present work aims to evaluate systolic and diastolic dysfunction in cirrhotic patients by using more reliable parameters for early detection of systolic and diastolic performance reduction compared to the classical parameters used in daily practice.

In this context, we studied various parameters of cardiovascular impairment in a group of 70 patients with different stages and etiologies of liver cirrhosis.

The thesis is composed of two parts: the general part, which summarizes the current knowledge of liver cirrhosis and the alterations of cardiovascular function in these patients, and the special part, which is the personal research.

The special part is divided into 3 subcategories:

- Determination of the presence of cirrhotic cardiomyopathy and its evaluation by reliable ultrasound parameters in the measurement of cardiac systolic and diastolic function
- Assessment of alterations in various electrophysiologic parameters in cirrhotic patients
- Vascular endothelial dysfunction assessed by Doppler ultrasound and comparison with a control group of patients without existing disease

The results of the three studies contribute to a better understanding of cardiovascular impairment in liver cirrhosis, more accurate and earlier diagnosis of MCC and peripheral vascular changes in these patients.

2.STATE OF THE ART

2.1.LIVER CIRRHOSIS

2.1.1. GENERAL ASPECTS

Cirrhosis of the liver is defined by altered lobular organization of the liver due to fibrosis of liver tissue and nodular formation, changes due to chronic injury (1).

The main causes are viral infections, toxins, autoimmune diseases, congenital diseases and idiopathic causes. As a result of these injuries, the liver tissue forms fibrotic tissue, initially without repercussions on liver function, then, with increasing degree of fibrosis, evolving with loss of liver function and the onset of liver cirrhosis.

The exact incidence worldwide is not known, but the prevalence is estimated to be increasing compared to the 1990s, with an estimated 5.2 million new cases per year (2).

2.1.2. MORPHOPATHOLOGIC ASPECTS

Liver tissue fibrosis leads to the development of portal hypertension, hyperdynamic circulation and collateral circulation, which are major causes of morbidity and mortality in cirrhotic patients. Intrahepatically, at the sinusoidal level, there is an increase in vasoconstriction and vascular resistance due to increased secretion of endothelin 1 (ET 1) and decreased secretion of nitric oxide (NO). Subsequent to these changes, a process of vascular remodeling and further increase in vascular pressure at this level occurs

As a consequence of these increased pressures collateral circulation is formed. (3)

At the systemic level, however, there are opposite changes, with increased NO secretion and systemic and splahnic vasodilatation, leading to decreased systemic vascular resistance. Consecutively there is activation of the renin-angiotensin-aldosterone system with water and sodium retention. (4,5)

2.1.3 CLINICAL ASPECTS

Cirrhosis of the liver is often completely asymptomatic and the diagnosis is made when a complication occurs or by chance following laboratory tests or an abdominal ultrasound that raises the suspicion. Knowing that patients with chronic viral hepatitis C as well as those with NAFLD have a predisposition of about 20% , respectively 10% to develop liver cirrhosis, liver biopsies are more often indicated in these subgroups,increasing diagnostic accuracy. (6,7)

The characteristic clinical signs are : Jaundice (occurs when serum bilirubin is above 2 mg/dl) ,ascites (clinically manifested in accumulations greater than 1.5 liters), collateral circulation in "jellyfish head" , stellate angiomas (especially on face and trunk) and palmar erythema - both due to reduced degradation of estradiol in the liver and consequent increased serum estradiol, splenomegaly, small liver and liver nodules on palpation of the liver , flapping tremor (sign of hepatic encephalopathy), ecchymoses, gynecomastia, hypogonadism. (8,9)

2.1.4. PARACLINICAL ASPECTS

Liver biopsy is the paraclinical investigation defined as the gold standard in the diagnosis of CH but it has the disadvantage of requiring an invasive, painful maneuver with potential complications such as bleeding or infection.

Abdominal ultrasonography, computed tomography (CT) and nuclear magnetic resonance (MRI), although not of definite diagnostic value, are of important diagnostic value and may raise the suspicion of CH (10,11).

In terms of laboratory tests, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are usually slightly elevated but can also be within normal limits despite advanced CH.

Gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) and bilirubin are elevated in CH, especially in the presence of cholestasis. Prothrombin time (PT) is increased due to coagulation factor deficiency.

Serum albumin is low due to deficient synthesis in the liver. Mild normochromic, normocytic mild anemia is present, and macrocytic anemia is common in cirrhosis of ethanolic etiology. Leukopenia and thrombocytopenia are due to sequestration in the enlarged spleen but also to the suppressive effect of alcohol on the hematogenous bone marrow.

Immunoglobulins, especially the gamma fraction are increased due to decreased hepatic clearance (12).

2.1.4. STAGING AND PROGNOSIS

Survival of patients with compensated CH at 10 years is reported to be 47% but this decreases to 10% with the onset of the first decompensation.

Staging of CH is most often performed in practice using the Child-Pugh scoring system and is divided into three categories (A, B and C).

2.1.5. TREATMENT

General measures are avoidance of alcohol and hepatotoxic drugs, a low-salt diet, vitamin and mineral supplementation, and anti-pneumonic and anti-hepatitis B and C viral vaccines

Specific measures are mainly targeted at the etiology of CH. Thus, antiviral therapy is recommended in patients with post-viral CH, immunosuppressive medication is recommended in patients with autoimmune CH, ursodeoxycholic acid and obeticholic acid in patients with post-primary biliary cholangitis, copper chelating drugs in Wilson's disease, and iron chelation and phlebotomies in patients with hemochromatosis.

In patients with NAFLD, weight loss of at least 7% has been shown to have clinical and prognostic benefits (13)

The only proven effective treatment in CH is liver transplantation. It is indicated in CH that does not respond to drug treatment. Survival at one year after transplantation is 85% and at 5 years 72%.

2.1.6. EXTRAHEPATIC DAMAGE AND COMPLICATIONS

CH can remain compensated for a long period of time until complications develop, but with these complications the prognosis of patients decreases dramatically. The complications of CH are jaundice, ascites, hyponatremia, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome and bleeding from esophageal varices.

2.2. CIRRHOTIC CARDIOMYOPATHY

2.2.1. GENERAL DATA

As early as 70 years ago, the first cardiovascular changes in patients with end-stage liver disease were described. Mortopathologically, dilatation of the cardiac cavities, cardiomyocyte edema, myocardial fibrosis, all in the absence of ischemic coronary artery disease or valvular heart disease or hypertension, were described.

Patients with CH have been found to have increased cardiac output, peripheral vascular resistance and consequently low blood pressure. Despite an increased cardiac output, the cardiac response to physiologic and pharmacologic stimuli is abnormal. These cariac changes have been termed cirrhotic cardiomyopathy (CMC) as early as three decades ago (14,15).

In the absence of a clear diagnostic protocol consensus, the term "cirrhotic cardiomyopathy" is currently defined by :

- Increased resting cardiac output with altered ventricular contractile response to various stimuli
- Systolic and diastolic dysfunction
- Absence of ventricular dysfunction at rest
- Electrophysiologic changes (chronotropic incompetence and corrected QT prolongation) (16,17)

Without clear diagnostic guidelines or protocols, the exact prevalence of CMC remains unknown. Even estimating it is difficult because the disease is generally latent and only becomes symptomatic when the patient is subjected to an external stimulus, such as physical exertion, change in body position, certain medications, or events such as bleeding or surgery. (18)

2.2.2. PATHOPHYSIOLOGICAL MECHANISMS

The mechanisms responsible for the development of CMC are only partially elucidated, despite numerous studies in animals and humans. These mechanisms are diverse and complex, including neurological, humoral and vascular disorders.

2.2.3 DIAGNOSTIC

There is currently no single diagnostic test that confirms the presence of CMC in CH patients.

Although the pathophysiologic mechanisms underlying the development of CMC have been elucidated in animal studies, there is no universally accepted diagnostic protocol worldwide. At the World Congress of Gastroenterology in Montreal in 2005, a panel of experts proposed preliminary criteria for the diagnosis of CMC.

Given the advances in the last decade in the determination of systolic and diastolic function, as well as in electrophysiology and laboratory analysis, the need to improve these criteria has been recognized.

Asftel, by bringing together several specialists internists, hepatologists, cardiologists and anesthesiologists, the Consortium of Cirrhotic Cardiomyopathy was formed in 2019, with the aim of proposing improved criteria for the diagnosis of CMC based on the latest findings.

2.2.3.1 SYSTOLIC DYSFUNCTION

Although EF has been considered the classic parameter in the estimation of systolic function, it has many limitations, being dependent on pre and post pregnancy, the vasodilator state in CH generates a low postsarginin which should achieve an increase in EF. Thus, although EF remains an important measure of global systolic function, additional parameters are needed for this purpose.

Strain ultrasound technique, also known as myocardial strain imaging, has gained ground in recent years as a useful and reliable method for quantifying myocardial contractile function. Strain is divided into several categories (circumferential, longitudinal, radial, and transverse), allowing a more comprehensive assessment of systolic function, more powerful than FE which basically measures mainly radial constrictive function.

Clinical data regarding the use of GLS in the detection of CMC in patients with normal EF are limited and conflicting, with three studies showing normal GLS(19-21) and a 4th study where GLS was found to be decreased. (22)

In another study, the TEI index (sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time) was used to estimate systolic function in cirrhotic patients and was found to have a significant impact on patient prognosis(23).

Cardiac MRI is a noninvasive method for the estimation of SV function and myocardial strain. The T1 images obtained provide diagnostic as well as prognostic value of the degree of myocardial fibrosis and has an extremely useful role in specifying diastolic dysfunction. T2 images are a marker of acute myocardial inflammation, and the use of contrast is useful in detecting cardiac edema and subclinical SV dysfunction.

The 2019 CMC Consortium recommends the use of GLS to detect systolic dysfunction in patients with CH who have preserved EF (>50%) . Low EF or decreased GLS (> -18) in the absence of any pre-existing heart disease are diagnostic for CMC.

2.2.3.2. DIASTOLIC DYSFUNCTION

In 2016, the ESA published new guidelines for the assessment of diastolic VS diastolic dysfunction, an examination that is a routine part of any echocardiographic evaluation. These guidelines recommend screening for elevated VS filling pressures using 4 criteria :

- The protodiastolic velocity of the septal part of the mitral annulus (e^{l}) < 7 cm/s and < 10 cm/s for the lateral part of the mitral annulus, respectively
- Ratio of mitral inflow early diastolic velocity (E) to e^{l} (measured by tissue Doppler) > 14
- Left atrial indexaxt volume > 34 ml/m^2
- Tricuspid regurgitation velocity > 2.8 m/s

Diastolic dysfunction is relatively common in elderly, hypertensive, coronary or diabetic patients. Thus, in the diagnosis of CMC it is of utmost importance to exclude existing comorbidities that could explain diastolic dysfunction.

In conclusion, implementation of the ASE and EACVI guidelines for the determination of diastolic function in patients with CH is recommended.

2.2.3.3. ELECTROPHYSIOLOGICAL CHANGES

Electrophysiological changes in CMC are divided into two broad categories: autonomic dysfunction and changes in ventricular repolarization (prolongation of the corrected QT interval).

Autonom autonomic dysfunction is considered an autonomic imbalance secondary to relatively low parasympathetic tone and increased sympathetic tone. (24,25)

Fleisher et al showed that cirrhotic patients with vagal neuropathy have a 5-fold increased risk of death compared with patients without the disorder (26).

Also, QTc prolongation has been described as part of the constellation of changes in CMC, representing a manifestation of electrophysiologic disturbances and autonomic dysfunction. Unfortunately, only few studies have been able to demonstrate the relationship between these electrocardiographic changes and the prognosis of CH patients (27).

One method of assessing cardiac autonomic function is the measurement of heart rate variability (HRV), which involves the analysis of consecutive R-R intervals over a period of time. HRV reflects the ability of the heart to adapt the heart rate to different circumstances by sensing and responding rapidly to varying stimuli(28).(28)

2.2.3.4. BIOMARKERS

Currently, there is a great interest in researching non-invasively determined biomarkers with diagnostic and prognostic accuracy in heart failure patients. Whether this research will also be applicable to patients with CMC remains to be determined by specific research in this cohort.

The heart produces and releases peptide hormones known as natriuretic peptides, and in pathological conditions of cardiac stress the levels of these hormones increase. For example, B-type natriuretic peptide (BNP) levels increase in systolic and diastolic dysfunction, ventricular hypertrophy and myocardial ischemia (29,30).(29,30)

Also, troponin I, a troponin isoform that is elevated in myocardial injury, has been elevated in ethanolic CH patients in various studies (198). Elevated troponin I levels have been associated with cardiovascular events and with significance in predicting cardiovascular mortality in patients with CH and in those with CH post liver transplantation (31-33).(31-33)

2.2.4. VASCULAR ABNORMALITIES IN LIVER CIRRHOSIS

It is known that CH patients develop a hyperdynamic circulation, an increase in heart rate and a decrease in central blood volume by mechanisms described in detail in the above chapters. In addition to the changes in the intrahepatic vessels, as well as those in the portal circulation, ,changes discussed above, vascular alterations are also described at 2 levels: the splahnic circulation and the systemic circulation

In conclusion, in patients with CH the potent vasoconstrictive mechanisms are less effective in increasing systemic pressure leading to increased blood volume, sodium retention with exacerbation of ascites and at the same time a potent systemic arterial vasodilation is observed but with poor perfusion of vital organs. (34)

The pronounced splahnic vasodilation leads to a progressive reduction in systemic vascular resistance that cannot be counterbalanced by increased cardiac output. Thus an effective arterial hypovolemia develops, with blood flow reducing effects in the kidneys, brain and muscles (35-37)

The more the liver disease progresses, the more the splahnic and systemic vasodilatation is exacerbated with progressive reduction of blood flow to the organs with negative effects.

2.2.5. TREATMENT

CMC is often asymptomatic and thus goes unrecognized until the onset of acute heart failure, usually following decompensation of CH, liver transplantation or after TIPS implantation. Moreover, a specific pharmacologic therapy for CMC does not currently exist and the only proven effective treatment remains liver transplantation. (38-39)

However, recommendations have been made to counteract the various mechanisms involved. Thus, as soon as symptoms of heart failure appear, specific treatment is recommended as recommended by the European and American cardiology societies.

Sodium restriction is recommended as well as its elimination by diuretics. Andosterone antagonists, e.g. spironolactone, are also indicated, since in addition to its diuretic effect, it inhibits myocardial fibrosis and activation of the sympathetic nervous system. A study conducted by Pozzi et al in 2005 determined the effect of long-term treatment with aldosterone antagonists in 22 patients and concluded a significant reduction in ventricular wall thickness, LV telediastolic diameter and hepatic venous gradient. They also found that there is a possible additional role for the use of beta blockers in addition to aldosterone inhibitors in improving cardiac dysfunction in cirrhotic patients (40).

Angiotensin-converting enzyme inhibitors are in principle limited in use because of possible exacerbation of systemic vasodilation in an already vasodilated vascular bed, and although they promote sodium excretion, they have not demonstrated long-term beneficial effects (41).

Non-selective beta-blockers are one of the primary options in the treatment of portal hypertension and in the prevention of variceal bleeding. However, these drugs have also been shown to correct QTc prolongation and improve electromechanical dyssynchronism(42).(42)

Liver transplantation corrects metabolic dysfunction and increases systemic vascular resistance. These effects led to an initial decrease in EF, probably due to cardiac dysfunction exacerbated by a sudden increase in postsarcinosis, with subsequent full recovery(43).(43)

Liver transplantation is the only effective treatment with clear evidence of improvement in systolic and diastolic dysfunction and normalization of the QTc interval (in about half of patients) (44).

3. PERSONAL CONTRIBUTION

3.1.1. STUDY 1 - CARDIAC IMPAIRMENT IN PATIENTS WITH LIVER CIRRHOSIS ESTIMATED BY ECHOCARDIOGRAPHIC PARAMETERS OF SYSTOLIC AND DIASTOLIC DYSFUNCTION. A COMPARISON BETWEEN CLASSICAL AND NEW PARAMETERS.

3.1.1.1.1. INTRODUCTION AND WORKING HYPOTHESIS

Cirrhotic cardiomyopathy is classically defined by the altered systolic response to stress, either physical or pharmacologic, the presence of diastolic dysfunction as well as the presence of electrophysiologic alterations (45).(45)

Traditionally, the parameter used to assess systolic dysfunction has been ejection fraction (EF), with normal values between 50% and 60%, with decreases below 50% indicating the presence of systolic dysfunction.

Diastolic dysfunction is a complex and multifactorial process that combines the pressure gradient between the left atrium and the left ventricle, passive and active relaxation of the ventricles as well as the telediastolic compliance of the left ventricle. The classic E/A ratio and E wave deceleration time were used to assess diastolic dysfunction.
However, there are limitations of these ultrasound parameters used for both systolic and diastolic dysfunction parameters.

Failure to adequately detect systolic and diastolic dysfunction in these patients may have adverse clinical consequences, therefore early detection may help to improve the prognosis of patients(46).
The present work aims to evaluate systolic dysfunction in cirrhotic patients by estimating the TEI post exercise index, a more reliable parameter for early detection of systolic performance reduction compared to the classic parameter used, namely EF. For the detection of diastolic dysfunction with increased accuracy compared to the classic parameter E/A, the E/Vp ratio was used.

3.1.1.2. OBJECTIVES OF THE STUDY :

- Comparison between EF and TEI index in predicting the presence of systolic dysfunction at rest and then during exercise
- whether or not the TEI index can detect the presence of systolic dysfunction in patients with preserved EF
- comparison between E/a and E/Vp in the estimation of the presence of diastolic dysfunction at rest and then during exercise
- the positive or not correlation of tei and E/Vp values in relation to the severity of liver disease
- assessing differences in the values obtained in relation to the age and sex of patients
- assessment of the correlation between the thei index and E/Vp ratio as markers of cirrhotic cardiomyopathy

3.1.1.3. MATERIAL AND METHOD

We conducted an analytic, observational, prospective study, including 70 patients who were evaluated between November 2022 and March 2024 in the outpatient clinic of the Cardiology Hospital ClinICCO Brasov. Each patient signed an informed consent form to participate, and the research was carried out with the approval of the Ethics Committee of ClinICCO Hospital Brasov.

Patients with the following conditions were excluded from the study:

- Heart failure from any cause other than CMC
- Persistent or permanent atrial fibrillation
- Significant ventricular arrhythmia
- Uncontrolled high blood pressure
- Ischemic coronary artery disease
- Chronic kidney disease on hemodialysis
- Ischemic or hemorrhagic stroke
- Inability to exercise
- Difficult ultrasound window that does not allow for proper measurements

They were submitted to a physical effort represented by 10 genoflexions and then immediately assessed echocardiographically, where the systolic function was evaluated on the one hand by measuring the ejection fraction by the Simpson method (normal values above 50%) and on the other hand by measuring the TEI index using Doppler echocardiography and calculated as the sum of the isovolumetric contraction time and the isovolumetric relaxation time divided by the ejection time.

The diastolic dysfunction was then assessed by measuring E/A by pulsed Doppler ultrasound in the mitral valve and E/Vp by measuring Vp by color M-mode ultrasound.

The echocardiograph used was a General Electric Vivid E9 with a 4.2 MHZ heart transducer. Physical effort was supervised by medical staff and echocardiography was performed both at rest and immediately after exercise.

The percentage of patients with systolic dysfunction as assessed by ejection fraction and the percentage of patients with systolic dysfunction as assessed by TEI index were noted and a comparison between the two methods was performed. The presence of diastolic dysfunction was also assessed by E/A ratio and E/Vp ratio**.** The two methods were then compared.

3.1.1.4. RESULTS

- Measurement of resting FE showed that all patients had values above 50%, with an average of 55%, thus indicating the absence of systolic dysfunction at rest
- FE measurements after physical exertion showed values between 40% and 60% with an average of 58%.
- The TEI had values below 0.5 at rest in all patients in the group
- After exercise, values between 0.37 and 0.79 were obtained with a mean of 0.57.
- In terms of post-exertional diastolic dysfunction parameters, 64 of the 70 patients had E/A less than 1
- E/Vp ratio values averaged 2.02 with a range between 1.5 and 2.6
- In terms of post-exertional diastolic dysfunction parameters, 64 of the 70 patients had E/A less than 1
- E/Vp ratio values averaged 2.02 with a range between 1.5 and 2.6
- The TEI showed almost identical mean values between women and men, with a slightly higher variation for women
- Similarly, gender variability in the E/VP and E/A ratio is small
- Ejection fraction had very similar mean values between the Child classes, with a slight variation.
- The TEI index shows an increase in the mean from class A to class C, suggesting progressive cardiac damage with the severity of cirrhosis (p=0.030)
- E/VP ratio has mean values progressively increasing from class A to class C, suggesting worsening diastolic dysfunction with worsening cirrhosis (p=0.022).(p=0.022)
- The results of the correlation analysis between ejection fraction and TEI indicate a very weak correlation (Pearson correlation coefficient of 0.04)
- Not statistically significant (p-value of 0.772)

- This suggests that there is no significant linear relationship between the two variables in this data set
- Finally, the correlation between the E/A ratio and the E/VP ratio is weak and negative (coefficient of -0.19)
- Statistically insignificant (p-value of 0.114)
- This suggests that there is no significant linear relationship between these two variables

3.1.1.5. DISCUSSIONS

Both systolic dysfunction parameters (EF and TEI index) had normal values at rest. This is a finding consistent with existing data in the literature and can be partly explained by the systemic vasodilatation ubiquitous in liver cirrhosis, which generates a low postsarginin . This is further evidence that the diagnosis of cirrhotic cardiomyopathy is an extremely difficult one based strictly on resting echographic determinations. (47,48)

On statistical analysis of the TEI index, a positive correlation between systolic dysfunction and severity of liver disease was noted, a finding supported by statistical significance. This result is consistent with data from previous studies that assessed systolic function by GLS (49-51).(49-51)

E/Vp where a directly proportional correlation was demonstrated between the degree of liver damage and the severity of diastolic dysfunction assessed by this parameter with high specificity.

These data confirm once again, as well as pre-existing data in the literature, that this parameter is a faithful indicator of diastolic function, its correlation with the severity of CH having clear pathophysiologic explanations by worsening biohumoral changes and worsening cardiac receptor function with worsening liver disease (52-55).

TEI has been shown to be a much more sensitive parameter than EF in detecting systolic dysfunction

Based on these results, it is recommended for use in patients suspected of CMC with preserved EF.

Widespread use of this parameter could lead to an increase in the diagnostic sensitivity of cirrhotic cardiomyopathy with improved prognosis of these patients in various conditions, either without liver transplantation, post liver transplantation or post TIPS implantation.

Regarding the accuracy of detection of systolic dysfunction by the two methods, it has been established that the TEI index is a much more sensitive parameter than EF.

Widespread use of this parameter would increase the diagnostic sensitivity of cirrhotic cardiomyopathy

When analyzing the association between the results of the TEI and FE, no positive correlation was found.

3.1.1.6. CONCLUSIONS

These results suggest that the combined use of these parameters (EF, TEI, E/A and E/VP) may provide a more comprehensive picture of the presence and severity of cardiomyopathy, with each parameter contributing unique information on cardiac function.

Using multiple criteria can help to more accurately identify affected patients and avoid the high rates of false-positive or false-negative results associated with the use of a single criterion.

Also, the results obtained encourage the use of the TEI index as a superior FE parameter in terms of accuracy in detecting systolic dysfunction in patients with liver cirrhosis, and confirm its directly proportional relationship with the degree of liver damage.

On the basis of our research, on the one hand, the accuracy of the E/Vp parameter in the diagnosis of diastolic dysfunction and its correlation with the degree of liver damage, and on the other hand, the lack of specificity of the E/A parameter.

Scaling the two proposed parameters (TEI index and E/Vp ratio) would lead to a better diagnosis of systolic and diastolic dysfunction in cirrhotic patients, respectively, with positive effects on the prognosis of these patients.

3.1.1.7. LIMITATIONS OF THE STUDY

- Relatively small sample of patients
- Lack of a gold standard of systolic and diastolic dysfunction (e.g. cardiac MRI) against which both EF and TEI could be compared
- Lack of comparison of the E/Vp ratio with a more accurate index of diastolic dysfunction, e.g. e^{l} , E/e^{l} or indexed AS volume

3.2. STUDY 2 - ASSESSMENT OF AUTONOMIC DYSFUNCTION IN CIRRHOTIC PATIENTS BY VARIOUS ELECTROPHYSIOLOGICAL PARAMETERS

3.2.1. INTRODUCTION

In patients with liver cirrhosis, various changes in electrophysiologic parameters are described in the literature. The main change is autonomic dysfunction. Data in the literature mention a prevalence of parasympathetic neuropathy in about 30-77% of patients and of sympathetic neuropathy in 12-37% of patients(56). Autonomic dysfunction correlates directly proportionally with cardiac output and peripheral vascular resistance. Although there are several theories that may explain the occurrence of these changes, the exact mechanism is still unknown.

It was also found that there was a 70% improvement in autonomic dysfunction after liver transplantation(57).(57)

This paper aims to better understand these changes using different assessment methods and different parameters. Patients included in the study were examined by three main methods : Simple electrocardiography at rest and Valsalva maneuver , ambulatory HOLTER ECG ambulatory monitoring and pathophysiological response to standardized exercise stress test.

3.2.2. STUDY OBJECTIVES

- Assessment of autonomic dysfunction through parameters that follow the patient in different states: at rest, at Valsalva maneuver, on exertion and over 24 hours
- Comparison of these parameters between a group of CH patients and a group of healthy patients
- Comparison of the parameters described above between the subgroup of patients with ethanolic and non-ethanolic CH
- Determination of sympathetic nervous system activation in patients with CH at rest
- Determining the presence of an altered parasympathetic response in cirrhotics

3.2.3. MATERIAL AND METHOD

We evaluated 60 patients with liver cirrhosis by resting ECG, Valsalva ECG, Holter ECG/24 hours and standardized exercise ECG test on cycle ergometer or treadmill (according to patient's preference) and compared with a control group of 50 patients without liver cirrhosis and without other known significant pathologies.

Out of the 60 patients in the liver cirrhosis group, 44 were included in the ethanolic and 16 in the non-ethanolic subgroup.

As resting ECG parameters were used: ventricular allure (AV), the response to the Valsalva maneuver, measured and interpreted using the Valsalva index (highest RR: lowest RR during the maneuver) - normal values >1.20, and the corrected QT interval (QTc) (normal values <460 ms)

The Valsalva maneuver was performed with the patient in a sitting position on the bed, ECG monitored throughout the Valsalva maneuver and 30 seconds after.

As Holter ECG parameters : Heart rate variability expressed by SDNN (standard deviation of NN intervals) and QTc interval . Normal values for SDNN were considered those above 40 and for mean QTc below 460 ms.

Exercise ECG test parameters: the maximum frequency reached by the patient (Fmax) and the frequency at 2 minutes post exercise (FPE) were followed. It should be noted that the exercise test could only be performed in 42 patients, the remaining 18 were unable to perform this investigation.

Patients were divided into two subgroups according to etiology: ethanolic and non-ethanolic.

Thus, the following comparisons were made: between patients with liver cirrhosis and the control group and between patients with ethanolic and non-ethanolic cirrhosis.

The following patients were excluded as exclusion criteria
- Liver cirrhosis Child Class C
- Heart failure of any etiology
- Atrial fibrillation
- Atrial flutter
- Significant driving disorders
- Ventricular arrhythmias
- Chronic kidney disease on hemodialysis
- Ischemic or hemorrhagic stroke
- Vertiginous Syndrome
- Inability to exercise

The results were statistically analyzed.

Resting VA, Valsalva Index as well as Fmax and FPE parameters were interpreted using the Student't test.

Resting QTc intervals and Holter monitored mean QTc intervals were compared using one-way ANOVA test (SAS software). For SDNN results the Fisher test was used.

3.2.4. RESULTS

A) ELECTROCARDIOGRAPHIC PARAMETERS

- At rest

-Resting heart rates (HR) were between 48 and 110 beats per minute in patients in the cirrhotic group and between 55 and 90 in patients in the control group, with no statistically significant differences ($p>0.05$)

-There were also no statistically significant differences between toxic and non-toxic patient groups.

- During and after the Valsalva maneuver
  In the whole group of cirrhotic patients the mean Valsalva index value was 1.18 compared to 1.34 in the control group ($p<0.05$).
- QTc interval
  - In the cirrhotic patients as well as in the control group no resting QTc values above 500 ms were recorded.
  - The mean QTc value in the cirrhotic patients was 437 ms and 440 ms in the control group, with no statistical significance between the two groups
  - The same situation was observed in the comparison between subgroups with values of 438 ms in ethanolics and 440 ms in non-ethanolics
  - When comparing the two subgroups (toxic and non-toxic) the values were 1.17 and 1.19 respectively, $p>0.05$.

B) ECG HOLTER PARAMETERS

- SDNN
- Standard deviation values of 24 h N-N intervals were statistically significantly reduced in cirrhotic patients (SDNN=34) compared to non-cirrhotic patients (SDNN=55), $p<0.05$
- When comparing the subgroups there was no statistically significant difference $p>0.05$
- QTc interval
- The mean QTc value in cirrhotic patients was 431 ms and in control patients 442 ms ($p>0.05$).
- The same situation was observed in the comparison between subgroups with values of 435 ms in ethanolics and 444 ms in non-ethanolics ($p>0.05$)
-

C) PARAMETERS ASSESSED BY EXERCISE TESTING

- Maximum Heart Rate and Post Heart Rate

- In patients with liver cirrhosis, the maximum HR during exercise (154 beats/minute) was not statistically different from the control group (165 beats/minute), the same for the comparison between subgroups ($p>0.05$)
- In cirrhotic patients the mean post-exertional HR was 114 beats/minute and in control patients 73 beats/minute ($p<0.05$). There were no differences between subgroups ($p>0.05$)

3.2.5. DISCUSSIONS

A) ELECTROCARDIOGRAPHIC PARAMETERS

- Resting frequency

Although described in the literature, and with demonstrated pathophysiologic mechanisms, the activation of the sympathetic nervous system in cirrhotic patients manifested by an increased resting heart rate (58) , did not reach statistical significance in the patients included in the study when compared with the control group.
A possible explanation for this finding could be the activation of the sympathetic nervous system in the control patients due to their presence in the medical environment or anxiety about medical examinations.

- Valsalva Index

In previous studies this parameter has been shown to be a very good indicator of autonomic nervous system status. Previous research has demonstrated altered response to the Valsalva maneuver as well as to other parasympathetic challenge tests such as deep inspiration or the patient position shift test (59-63)

In the present study, the statistical significance was met, with cirrhotic patients having a reduced Valsava index compared to the control group, confirming once again the predominant parasympathetic nervous system involvement in CH patients.

B) HOLTER ECG PARAMETERS

In some studies in the literature, prolongation of ventricular repolarization manifested by prolongation of the corrected QT interval has been described in patients with liver cirrhosis (64-67). This change has been described especially in patients classified as Child Pugh C.(68)

In our study, although there was a trend of increased QTc interval in cirrhotic patients, statistical significance was not reached, thus there was no difference between the two groups.

Of note is a study by Koshy et al which demonstrated that there is no correlation between QTc prolongation and the diagnostic criteria for CMC established at the 2005 World Congress of Gastroenterology and the Cirrhotic Cardiomyopathy Consortium, concluding that QTc prolongation and CMC are two separate and unrelated entities. Of course, this conclusion is controversial, with other studies concluding that QTc prolongation is a consequence of CMC and that it poses a significant risk for malignant arrhythmias. (69-73)

Knowing from previous studies that disease severity correlates with QTc elongation, this could be explained by the exclusion of Child Pugh C patients from the study.

Heart rate variability is a proven marker of autonomic dysfunction and its assessment by the SDNN parameter has been shown to have high specificity and sensitivity. (74-76)
The presence of autonomic dysfunction was present in this study, with reduced SDNN values in patients with CH compared to the control group, these results being statistically significant. Thus, the clear presence of autonomic dysfunction in those with end-stage liver disease can also be confirmed by this parameter. It is known from previous studies that this parameter is of prognostic importance, with values above 100 ms having a 5-fold lower risk of mortality and morbidity than those with values below 50 ms(77).(77)
This finding is in agreement with the majority of previous studies by various mechanisms. One possible explanation could be, the release of angiotensin II secondary to mainly NO-mediated systemic

vasodilation. This hormone has been shown to cause a significant interaction with bagal tone, reducing its action. Furthermore, ACEI administration has been shown to improve heart rate variability.

Comparison of the two subgroups of patients showed no notable differences between the different etiologies of cirrhosis.

A) PARAMETERS ASSESSED BY EXERCISE TESTING

Physiologically, exercise testing involves a stimulation of the sympathetic nervous system with an acceleration of the heart rate, and after cessation of exercise with a progressive reduction in adrenergic tone and an increase in parasympathetic tone activity. (78)

In our study, the following was revealed: there was no statistically significant difference between the maximal exercise heart rate results, contrary to the hypothesis that there is an overstimulation of the sympathetic nervous system in CH patients, without a clear explanation for this result.

However, the persistence of post-exertional tachycardia in cirrhotic patients can be considered as a sign of parasympathetic nervous system alteration. The obtained results showed that CH patients have higher post-exertional heart rate values compared to the control group, these results being statistically significant.

Again, there were no statistically significant differences between subgroups of cirrhotic patients.

3.2.6. CONCLUSIONS

Although the resting heart rate was similar between the two groups, measurement of the Valsalva index showed an altered response in the cirrhotic patients, thus demonstrating altered parasympathetic response in these patients.

The same response, with the same significance was also found when examining and statistically analyzing the heart rate parameter at two minutes post exercise.

Heart rate variability was also altered in cirrhotic patients, all 3 parameters demonstrating the presence of autonomic dysfunction in patients with cirrhosis.

There were no statistically significant differences in the subgroups of cirrhotic patients for all parameters assessed.

3.2.7. LIMITATIONS OF THE STUDY

- Relatively small number of patients included
- Limitations related to variation in individual response to the Valsalva maneuver and physical exertion, unrelated to pathology
- Exclusion from the study of patients in Child-Pugh class C, where the highest prevalence of electrophysiologic disorders is reported

3.3. STUDY 3 - VASCULAR ENDOTHELIAL DYSFUNCTION ASSESSED BY VASCULAR DOPPLER ECHOGRAPHY: A COMPARISON BETWEEN PATIENTS WITH LIVER CIRRHOSIS AND A CONTROL GROUP

3.3.1. INTRODUCTION

Traditionally it is considered that a pathology such as liver cirrhosis is accompanied by systemic and splahnic vasodilatation produced by various mediators. A major role is played by nitric oxide (NO), a vasodilator substance released by the endothelium (79,80).(79,80)

Important emphasis has been placed in recent years on the clinical consequences of alteration of normal endothelial function. (81-83)

Previous studies have concluded that there is a decrease in nitric oxide production in the hepatic vascular endothelium as well as an increase in nitric oxide production in systemic vessels.

Numerous previous studies have used flow-mediated dilation (FMD) as a parameter to estimate endothelial function, a traditional parameter with limitations in accurately assessing NO-mediated vasodilation (84,85).

In this work, the estimation of endothelial function was done using a more accurate parameter, namely lower limb passive motion (sPLM) - a parameter considered to be more accurate than other parameters in the estimation of endothelial function (86-89).(86-89)

3.3.2. STUDY OBJECTIVES

- Determining the correlation between LBF and LVC
- Assessment of endothelial dysfunction parameters
- Comparison of endothelial dysfunction parameters between cirrhotics and a resting control group
- Comparison of parameters between etiologic subgroups of cirrhosis at rest
- Comparison of parameters between the different etiologic subgroups and the resting control group
- Comparison between different APRI scores and the control group at rest
- Making the above comparisons after 2 minutes of sPLM

3.3.3. MATERIAL AND METHOD

Follow-up of patients was performed between November 2019 and June 2021 in the outpatient clinic of St. Constantine Hospital in Brasov. Two groups were included in the research.

The first group included 78 patients aged between 44 and 75 years with a diagnosis of cirrhosis of the liver. 70% were men and 30% women. In the second group, 30 patients with no known pathology were included. The APRI (platelet-related TGP Index) score was also calculated and 60 patients (76%) had a value greater than 1, 49 patients (62%) greater than 1.5 and 18 patients (24%) less than 1.

We used the following protocol: patients were supine, we placed a linear transducer with a frequency between 3.5-10 MHz (General Electric Vivid S6) at the level of the common femoral artery while an assistant performed passive calf extensions on the thigh for 3 minutes.

Limb blood flow (LBF) and limb vascular conductance (LVC) (calculated as LBF divided by mean arterial pressure) were measured in ml/min, respectively ml/min x mmHg, using Doppler parameters. Mean arterial pressure was calculated using the formula : MAP = PD = PD + 1/3(PS - PD) (PD = diastolic pressure; PS = systolic pressure)

In the group with cirrhotic patients there were 75% patients treated with non-selective beta blockers. In the control group patients had no medication. All patients taking medication were advised to discontinue 24 hours before measurements. The patients were also advised not to smoke and not to drink alcohol for at least 24 hours before as well as not to eat six hours before the determination of the parameters.

Exclusion criteria were :

- Lower limb arterial disease
- Acute or chronic deep vein thrombosis in the lower limbs
- Postthrombotic lower limb thrombotic syndrome
- Heart failure of any etiology
- Atrial fibrillation
- Atrial flutter
- Significant driving disorders
- Ventricular arrhythmias
- Chronic kidney disease on hemodialysis
- Ischemic or hemorrhagic stroke

The statistical analysis was done using the Mann-Whitney U Test Calculator. Comparisons were made between the two main groups then between subgroups - as etiology (ethanolic, viral, other etiologies) and APRI score (below 1, 1-1.5 , above 1), and finally between subgroups and the control group

3.3.4. RESULTS

THE REPAYMENT:

- LVC results were in line with those of LBF
- When comparing the two main groups, there was no statistically significant difference ($p>0.05$), the same for the comparison of the subgroups of post-viral cirrhosis and cirrhosis of other etiologies with the control group ($p>0.05$)
- When comparing the ethanolic subgroup with the control group the differences were found to be statistically significant $p<0.01$
- Also when comparing the ethanolic subgroup with the viral subgroup no statistically significant difference was found ($p>0.05$)
- No comparison was made with the subgroup of patients with cirrhosis of other etiologies due to the small number of patients in this category.
- The only statistically significant difference was noted when comparing the control group with the subgroup of patients with APRI score above 1.5 ($p<0.01$).
- When comparing the three subgroups of APRI score, no statistically significant difference ($p>0.05$) was observed.

- LVC was 2.2 ml/min/mmHg in the cirrhotic group and 2.1 ml/min/mmHg in the control group. ($p>0.05$).

AFTER THE EFFORT :

- Statistical significance was achieved when comparing the main group with the control group ($p<0.01$)
- When comparing all subgroups of cirrhotic patients with the control group, significant differences ($p < 0.001$) were observed
- No statistically significant differences were obtained when comparing the different etiologies
- In subgroups of patients according to APRI score the mean LBF value was 1150 ml/min in those with APRI score below 1, 1100 ml/min in those with APRI score between 1 and 1.5 and 1400 ml/min in those with APRI score >1.5.
- Patients with an APRI score above 1.5 had higher LBF values compared to the control group and also compared to those with an APRI score below 1.5 ($p<0.01$).
- LVC results were in line with LBF results

3.3.5. DISCUSSIONS

A) Rest

Studies in the literature have shown that liver cirrhosis induces vasoconstriction in the intrahepatic endothelium and NO-mediated vasodilation in the endothelium of systemic vessels including the lower limbs. (90-95)

Under resting conditions, when comparing the two main groups, no statistically significant differences were observed, contrary to the hypothesis that there is an increased secretion of vasodilator mediators in CH patients (95-97).

However, an interesting, statistically significant difference was observed when comparing the subgroup of patients with ethanolic liver cirrhosis with the control group. These results were similar for both parameters used (LBF and LVC). In support of this result comes the study by Coli et al where additional arterial vasodilation was found in ethanolics without a clear explanation. (98)

In previous articles there have been several disputes related to the effect of chronic alcohol consumption on the endothelium and on nitric oxide (NO) production.(99) In contrast to our result , in various studies it has been hypothesized that ethanol inhibits nitric oxide synthesis by different mechanisms including inhibition of NO synthase.(100,101)

One thing to note is that these patients were no longer active drinkers either, so there is no clear explanation for this result.

Also patients with ARPI score <1 showed more vasodilation at rest compared to the control group. This finding could be partly explained by lower oxidative stress in this subgroup with less existing fibrosis.

B) After three minutes of sPLM

The direct comparison between the two main groups was found to be statistically significant confirming the hypothesis that patients with cirrhosis of the liver show increased nitric oxide-induced systemic vasodilation in contrast to endothelial dysfunction in hepatic porto vessels manifested by vasoconstriction.(335-339) In our study both parameters used were concordant.

The mechanism involved is described in the literature and involves increased secretion of vasoactive molecules such as adrenomedullin, vascular endothelial growth factor, carbon monoxide, tumor necrosis factor alpha, prostacyclin (PGI2)(102,103).(102,103)

In our case the physical stressor used - passive lower limb passive motion (sPLM) - led to an increase in nitric oxide production with the direct effect of greater vasodilation than in the control group.

The greatest increase in vasodilation was noted in the ethanolic subgroup.

Regarding the subgroups according to the APRI score, only those in the subgroup with APRI over 1.5 showed a statistically significant increase in the measured vasodilation parameters, a result possibly explained by the increased degree of fibrosis in this subgroup, with increased release of vasodilation mediators (345-350). It is noteworthy that 62 percent of the total number of patients were in this category.

3.3.6. CONCLUSIONS

The existing hypothesis that a pathology such as liver cirrhosis manifests nitric oxide-mediated systemic vasodilation was proven by our study but only after performing a maneuver that increases nitric oxide production, namely sPLM.

Another remarkable finding is the additional vasodilatation manifested both at rest and during exercise in patients in the subgroup with ethanolic liver cirrhosis.

Also, an increased vasodilation was found in patients with APRI score below 1 at rest and in those with APRI above 1.5 at exercise by mechanisms that require better understanding.

4. FINAL CONCLUSIONS

1. The results of our research show that the combined use of the parameters used (EF, TEI, E/A and E/Vp) provides a more comprehensive picture of the presence and severity of cirrhotic cardiomyopathy, better delineating the degrees of systolic and diastolic dysfunction
2. The use of the TEI is encouraged as a parameter with increased accuracy in determining the presence of systolic dysfunction in patients with cirrhotic cardiomyopathy and its use is recommended in the evaluation of all cirrhotic patients, especially in post-transplant patients where there is a significant risk of cardiac decompensation
3. The TEI has been shown to be superior in the diagnosis of systolic dysfunction in cirrhotic cardiomyopathy compared to EF, leading to its recommended use in cirrhotic patients with preserved EF
4. Our study demonstrated a directly proportional correlation between changes in TEI and the degree of liver damage, which was not found in the FE analysis.
5. The accuracy of the E/Vp parameter in the diagnosis of diastolic dysfunction in patients with end-stage liver disease has been demonstrated
6. The parameter E/Vp is superior in terms of accuracy in the assessment of diastolic function compared with the E/A ratio, a conclusion in agreement with the literature.
7. The E/Vp parameter has been shown to correlate directly proportional to the degree of liver damage
8. We note the low specificity of the E/A parameter in the assessment of diastolic dysfunction, with a U-type relationship with diastolic function, so that healthy patients and those with significant diastolic dysfunction have the same values.
9. Based on the results of our research, and the statistical analysis performed, it is proposed to widely use the two proposed parameters (TEI index and E/Vp ratio) in the evaluation of patients with liver cirrhosis. This could lead to a better diagnosis of systolic and diastolic dysfunction in cirrhotic patients, respectively, with positive effects on the prognosis of these patients.
10. The resting heart rate was found to be statistically similar between the group of cirrhotic patients and the group of control patients with no known pathology
11. The results obtained from the statistical analysis of the Valsalva index demonstrated altered parasympathetic response in cirrhotic patients compared to healthy patients
12. The heart rate variability expressed by SDNN, a parameter with an important prognostic value, showed significantly lower values in cirrhotic patients compared to the control group. Thus, this conclusion places cirrhotic patients at increased arrhythmic risk compared to healthy patients.
13. There was no statistically significant difference in SDNN between the various subgroups of cirrhotic patients.
14. Post-exertional heart rate was significantly increased in cirrhotic patients, manifested by persistent tachycardia, reflecting the predominant alteration of parasympathetic tone in this group.
15. The results obtained at Valsalva index (response to a forced breathing maneuver against a closed glottis), and those obtained at SDNN analysis (heart rate monitoring continuously over a 24-hour period), as well as the persistence of post-exertional tachycardia (response to physical

exertion) lead to the conclusion that there is an alteration of vagal tone in cirrhotic patients in different stages and moments of the life of patients with cirrhosis of the liver.

16. No significant prolongation of the corrected QT interval was found in cirrhotics, neither at rest nor on 24-hour Holter ECG monitoring
17. The existing hypothesis that a pathology such as liver cirrhosis manifests nitric oxide-mediated systemic vasodilation was proven by our study but only after performing a maneuver that increases nitric oxide production.
18. Our research found that there is an additional vasodilatation manifested both at rest and on exercise in patients in the subgroup with ethanolic liver cirrhosis
19. Increased vasodilatation was found in patients with APRI score above 1.5 (representing increased fibrotic load) on exercise by mechanisms that require better understanding

5. ORIGINAL CONTRIBUTIONS

1. First of all, the originality of this work is given by the subject investigated, cirrhotic cardiomyopathy and systemic vascular endothelial damage being pathologies with completely unknown pathophysiology, heterogeneous clinical presentations and implicitly a diagnostic algorithm still unstandardized.
2. Our study is the only study in the literature that assessed systolic dysfunction by TEI index and diastolic dysfunction by E/Vp ratio in cirrhotic patients, these parameters being used in several previous studies but in groups of patients with cardiac and not liver pathology
3. Our study is original in determining the correlation between TEI and EF in cirrhotic patients
4. This is the first research in the literature to demonstrate a positive correlation between increased TEI values and severity of liver disease
5. The first use of a parameter combining pulsed Doppler cardiac ultrasound and M-Mode cardiac ultrasound to assess diastolic function in cirrhotics, namely E/Vp
6. The importance of these findings is that a more accurate diagnosis of cardiomyopathy in cirrhotics may improve the prognosis of these patients.
7. Another original element is the follow-up of autonomic dysfunction in an exhaustive way, at different moments of the life of cirrhotic patients (at the doctor's visit, at rest, 24-hour monitoring, during and after exercise)
8. Positive correlation between Valsalva index, SDNN and post-exertional heart rate in cirrhotic patients.
9. The determination of the degree of systemic vasodilation by sPLM and its correlation with APRI score and Child-Pugh classes at rest and exercise is an original research with applicable results in practice.
10. Using the APRI score as a surrogate for liver biopsy to estimate the degree of fibrosis and using this parameter to analyze the degree of peripheral vasodilation is a noninvasive, rapid, practical and non-invasive method, free of possible complications of liver puncture.
11. The elements used in the research as well as their estimation by multiple parameters contribute to a better understanding of cirrhotic cardiomyopathy, the presence and severity of autonomic dysfunction in patients with end-stage liver disease, and a better definition of the relationship between liver cirrhosis and vascular endothelial damage.
12. The tests used in the presented studies are non-invasive, have a high applicability and are easy to use, thus giving our studies a significant clinical relevance.

13. LIMIT

In all of the studies conducted, an obvious limitation is the relatively small sample of patients followed up, with a larger number having higher statistical power.

As for the disruptive factors, their influence was minimized by strict inclusion and exclusion criteria.

In the first study, the lack of comparison of the values obtained with a "gold standard" such as, for example, the comparison of TEI, FE, E/A and E/Vp index values with cardiac MRI data, this comparison adding to the statistical significance of the results.

The use of the comparison between the TEI and GLS index, as well as their correlation, would have represented a better definition of the diagnostic algorithm in CMC. Also, the comparison of the E/Vp

ratio would have been more representative of the tissue velocity of the mitral annulus in diastole (e^{l}) than the E/A ratio, given the higher diagnostic accuracy of e^{l}, and its use in the most recent diagnostic algorithm for diastolic dysfunction in cirrhotics.

The presence of cardiac dysfunction was not correlated with the presence of elevated values of heart failure biomarkers (BNP, NT-pro BNP)

In the second study, only patients with compensated liver cirrhosis were evaluated. As it is known that autonomic nervous system impairment is more prevalent in liver decompensation, a possible underestimation of autonomic nervous system impairment in our study can be concluded.

No specific tests have been performed to assess sympathetic nervous system response.

In the third study, the fact that the assessment of the degree of liver fibrosis was based on the APRI score and not on liver biopsy, the gold standard in fibrosis diagnosis, represents a limitation in the analysis of the presented conclusions. It is also worth mentioning that the usability of the Fibroscan device was limited by its high cost and low availability.

There is also a lack of comparison of the parameters used with classical parameters in the estimation of endothelial dysfunction, such as flow-mediated dilation (FMD). Another limitation is the very small number of patients categorized in the non-viral, non-ethanolic subcategory, making it practically impossible to perform statistical analysis on this subgroup.

6. FUTURE DIRECTIONS

Performing these studies on a larger sample of patients with larger subgroups would allow a better estimation of cirrhotic cardiomyopathy, autonomic dysfunction and endothelial dysfunction, with better analysis of the differences between the different subgroups of patients.

In relation to systolic function in cirrhotic cardiomyopathy, it is proposed to compare the TEI index with the GLS and to compare these parameters with the systolic and diastolic function obtained by cardiac MRI, which would be of particular diagnostic and therefore prognostic importance. Similarly, a comparison between the E/Vp ratio and e^{l} or left atrial indexed volume could represent an interesting research target.

Correlation of cardiac dysfunction parameters with heart failure biomarker values would constitute a hypothesis with scientific potential.

Related to electrophysiologic impairment in liver cirrhosis, it could be investigated using other parameters, such as RMSSD (square root of the successive differences between normal heart beats), pNN50 (percentage of adjacent NN intervals that differ by more than 50 ms) or the triangular index of heart rate variability. Another possible research direction would be the use of electrophysiologic studies, which, although invasive, have the property of providing extremely important details, impossible to assess by non-invasive methods, which could provide new information with diagnostic and especially prognostic potential. It should be noted that there is currently no research in the literature using electrophysiologic studies in patients with liver cirrhosis.

It is proposed to use the above mentioned parameters also in patients with decompensated cirrhosis of the liver, in order to better assess autonomic dysfunction in this high-risk subgroup.

Also, for the comparison between different grades of liver fibrosis, a more eloquent parameter than the APRI score would be the liver biopsy, so it is worthwhile to investigate the systolic and diastolic dysfunction parameters, the autonomic dysfunction parameters, but also the degree of peripheral vasodilatation in accordance with the degree of liver fibrosis obtained by liver biopsy. It should also be

noted that liver biopsy may also give false results due to inaccuracies in the pre-washing process and is encumbered by a potential risk of complications.

Given the pathophysiology of liver cirrhosis, the possibility of estimating the parameters of endothelial dysfunction by pharmacologic stress tests is observed.

SELECTIVE BIBLIOGRAPHY

1. Lyssy LA, Soos MP. Cirrhotic Cardiomyopathy. [In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.
2. Ruiz-del-Árbol L, Serradilla R. Cirrhotic cardiomyopathy. World J Gastroenterol. 2015 Nov 07;21(41):11502-21.
3. Mocarzel LOC, Rossi MM, Rossi MM, Miliosse BM, Lanzieri PG, Gismondi RA. Cirrhotic Cardiomyopathy: A New Clinical Phenotype. Arq Bras Cardiol. 2017 Jun;108(6):564-568
4. Carvalho MVH, Kroll PC, Kroll RTM, Carvalho VN. Cirrhotic cardiomyopathy: the liver affects the heart. Braz J Med Biol Res. 2019 Feb 14;52(2):e7809
5. Chayanupatkul M, Liangpunsakul S. Cirrhotic cardiomyopathy: review of pathophysiology and treatment. Hepatol Int. 2014 Jul;8(3):308-15.
6. Bokarvadia R, Jain M, Kedarisetty C, Varghese J, Venkataraman J. Prevalence and clinical presentation of cirrhotic cardiomyopathy: A single center experience from southern India. Indian J Gastroenterol. 2019 Apr;38(2):150-157
7. Sharma B, John S. Hepatic Cirrhosis. [In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.
8. Liu YB, Chen MK. Epidemiology of liver cirrhosis and associated complications: Current knowledge and future directions. World J Gastroenterol. 2022 Nov 7;28(41):5910-5930. doi: 10.3748/wjg.v28.i41.5910. PMID: 36405106; PMCID: PMC9669831.
9. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. J Hepatol. 2023 Aug;79(2):516-537. doi: 10.1016/j.jhep.2023.03.017. Epub 2023 Mar 27. PMID: 36990226.
10. Dodd GD 3rd, Baron RL, Oliver JH 3rd, Federle MP (1999) Spectrum of imaging findings of the liver in end-stage cirrhosis: part I, gross morphology and diffuse abnormalities. Am J Roentgenol 173(4):1031-1036
11. Harbin WP, Robert NJ, Ferrucci JT Jr (1980) Diagnosis of cirrhosis based on regional changes in hepatic morphology: a radiologic and pathologic analysis. Radiology 135(2):273-283
12. Deaciuc IV, D'Souza NB, Fortunato F, Hill DB, Sarphie TG, McClain CJ. Alcohol-induced sinusoidal endothelial cell dysfunction in the mouse is associated with exacerbated liver apoptosis and can be reversed by caspase inhibition. Hepatol Res. 2001 Jan 01;19(1):85-97.
13. Maher JJ. Hepatic fibrosis caused by alcohol. Semin Liver Dis. 1990 Feb;10(1):66-74. doi: 10.1055/s-2008-1040458. PMID: 2186489.
14. Ozaki K, Matsui O, Kobayashi S, Minami T, Kitao A, Gabata T. Morphometric changes in liver cirrhosis: aetiological differences correlated with progression. Br J Radiol. 2016;89(1059):20150896. doi: 10.1259/bjr.20150896. Epub 2016 Jan 14. PMID: 26765832; PMCID: PMC4986502.
15. Kim MY, Baik SK, Lee SS. Hemodynamic alterations in cirrhosis and portal hypertension. Korean J Hepatol. 2010 Dec;16(4):347-52
16. Lee SS: Cardiac abnormalities in liver cirrhosis. West J Med 1989, 151:530-535.
17. Liu H, Song D, Lee SS: Cirrhotic cardiomyopathy. Gastroenterol Clin Biol 2002, 26:842-847.
18. Zardi, E, Abbate, A, Zardi, D, et al. Cirrhotic Cardiomyopathy. JACC. 2010 Aug, 56 (7) 539-549.https://doi.org/10.1016/j.jacc.2009.12.075

19. Chen , Chan AC, Chan SC, Chok SH, Chok SH, Sharr W, Fung J, et al. A detailed evaluation of cardiac function in cirrhotic patients and its alteration with or without liver transplantation. J Cardiol 2016;67:140-146.
20. Sampaio F, Pimenta J, Bettencourt N, Fontes-Carvalho R, Silva AP, Valente J, et al. Systolic and diastolic dysfunction in cirrhosis: a tissue-Doppler and speckle tracking echocardiography study. Liver Int 2013;33:1158-1165.
21. Rimbas RC, Baldea SM, Guerra R, Visolu SI, Rimbas M, Pop CS, et al. New definition criteria of myocardial dysfunction in patients with liver cirrhosis: a speckle tracking and tissue Doppler imaging study. Ultrasound Med Biol 2018;44:562-574.

22. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, et al. The clinical use of stress echocardiography in non-ischemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30:101-138

23. Tei index is associated with survival in cirrhosis patients treated with transjugular intrahepatic intrahepatic portosystemic shunt Yan Song MD, Weizhi Li MD, Hui Xue MD, Litao Ruan MD, PhD First published: 01 December 2018 https://doi.org/10.1111/echo.14201
24. Lunzer MR, Newman SP, Bernard AG, et al. Impaired cardiovascular responsiveness in liver disease. Lancet. 1975;2(7931):382-5. doi: 10.1016/S0140-6736(75)92896-2.
25. Hendrickse MT, Thuluvath PJ, Triger DR. Natural history of autonomic neuropathy in chronic liver disease. Lancet. 1992;339(8807):1462-4. doi: 10.1016/0140-6736(92)92042-E.
26. Fleisher LA, Fleckenstein JF, Frank SM, Thuluvath PJ. Heart rate variability as a predictor of autonomic dysfunction in patients awaiting liver transplantation. Dig Dis Sci. 2000;45(2):340-4. doi: 10.1023/A:1005468711494
27. Bal JS, Thuluvath PJ. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. Liver Int. 2003;23(4):243-8. doi: 10.1034/j.1600-0676.2003.00833.x.
28. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Med Biol Eng Comput. 2006;44(12):1031-51. doi: 10.1007/s11517-006-0119-0

29. Yamamoto K, Burnett JC JC Jr, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, Nakao K, Redfield MM: Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hyperten- sion 1996, 28:988-994.
30. Motwani JG, McAlpine H, Kennedy N, Kennedy N, Struthers AD: Plasma brain natriuretic peptide as an indicator for angiotensin-convert- ing-enzyme inhibition after myocardial infarction. Lancet 1993, 341:1109-1110.
31. Coss E, Watt KD, Pedersen R, Dierkhising R, Heimbach JK, Charlton MR. Predictors of cardiovascular events after liver transplantation: a role for pretransplant serum troponin levels. Liver Transpl 2011;17:23-31
32. Safadi A, Homsi M, Maskoun W, Lane KA, Singh I, Sawada SG, et al. Perioperative risk predictors of cardiac outcomes in patients undergoing liver transplantation surgery. Circulation 2009;120:1189–1194.
33. Watt KD, Coss E, Pedersen RA, Pedersen RA, Dierkhising R, Heimbach JK, Charlton MR. Pretransplant serum troponin levels are highly predictive of patient and graft survival following liver transplantation. Liver Transpl 2010;16:990-998
34. Newby DE, Hayes PC. Hyperdynamic circulation in liver cir- rhosis: not peripheral vasodilatation but 'splanchnic steal'. QJM. 2002;95:827-30.
35. Merkel C, Gatta A, Milani L, et al. Intrarenal blood flow, circula- tion time, and cortical vascular volume in patients with cirrhosis. Scand J Gastroenterol. 1981;16:775-80.

36. Almdal T, Schroeder T, Ranek L. Cerebral blood flow and liver function in patients with encephalopathy due to acute and chronic liver diseases. Scand J Gastroenterol. 1989;24:299-303.
37. Maroto A, Gines P, Arroyo V, et al. Brachial and femoral artery blood flow in cirrhosis: relationship to kidney dysfunction. Hepa- tology. 1993;17:788-93.
38. Torregrosa M, Aguade S, Dos L, Segura R, Gonzalez A, Evangelista A, et al. Cardiac alterations in cirrhosis: reversibility after liver transplantation. J Hepatol. 2005;42(1):68-74. First study examining cardiac function and reversibility after liver transplantation.
39. Sonny A, Ibrahim A, Schuster A, Jaber WA, Cywinski JB. Impact and persistence of cirrhotic cardiomyopathy after liver transplantation. Clin Transpl. 2016;30(9):986-93.
40. Pozzi, Massimo, et al. "Cardiac, neuroadrenergic, and portal hemodynamic effects of prolonged aldosterone blockade in postviral child A cirrhosis." Official journal of the American College of Gastroenterology| ACG 100.5 (2005): 1110-1116.
41. Hsu, Wei-Fan, et al. "Renal effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with liver cirrhosis: a nationwide cohort study." Gastroenterology Research and Practice 2019.1 (2019): 1743290
42. Henriksen JH, Bendtsen F, Hansen EF, Moller S. Acute non-selective beta-adrenergic blockade reduces prolonged frequency- adjusted Q-T interval (QTc) in patients with cirrhosis. J Hepatol. 2004;40(2):239-46. 90 min beta-blockade corrected the prolonged QTc.
43. Torregrosa M, Aguade S, Dos L, Segura R, Gonzalez A, Evangelista A, et al. Cardiac alterations in cirrhosis: reversibility after liver transplantation. J Hepatol. 2005;42(1):68-74.
44. Koshy AN, Gow PJ, Han HC, Teh AW, Jones R, Testro A, et al. Cardiovascular mortality following liver transplantation: predictors and temporal trends over 30 years. Eur Heart J Qual Care Qual Care Clin Outcomes. 2020
45. Poojary MS, Samanth J, Nayak K, Shetty S, Nayak SK, Rao MS. Evaluation of subclinical left ventricular systolic dysfunction using two-dimensional speckle-tracking speckle-tracking echocardiography in patients with Child-Pugh A and B cirrhosis: A case-control study. Indian J Gastroenterol. 2022 Dec;41(6):567-575. doi: 10.1007/s12664-022-01277-w. Epub 2022 Dec 28. PMID: 36576699.
46. Abd-El-Aziz TA, Abdou M, Fathy A, Wafaie M. Evaluation of cardiac function in patients with liver cirrhosis. Intern Med. 2010;49:2547-52.
47. Friedman HS, Fernando H. Ascites as a marker for the hyperdynamic heart of Laennec's cirrhosis. Alcohol Clin Exp Res. 1992;16:968-970. doi: 10.1111/j.1530-0277.1992.tb01902.x.
48. M. Cazzaniga, F. Salerno, G. Pagnozzi, *et al.* Diastolic dysfunction is associated with poor survival in patients with cirrhosis with transjugular intrahepatic intrahepatic portosystemic shunt Gut, 56 (2007), pp. 869-875
49. Cardiac dysfunction during liver transplantation: incidence and preoperative predictors Transplantation, 85 (2008), pp. 1766-1772
50. Hongqun Liu, Jwan A. Naser, Grace Lin, Samuel S. Lee,Cardiomyopathy in cirrhosis: From pathophysiology to clinical care,JHEP Reports,Volume 6, Issue 1,2024,100911,ISSN 2589-5559,https://doi.org/10.1016/j.jhepr.2023.100911.(https://www.sciencedirect.com/science/article/pii/S2589555923002422)
51. Poojary MS, Samanth J, Nayak K, Shetty S, Nayak SK, Rao MS. Evaluation of subclinical left ventricular systolic dysfunction using two-dimensional speckle-tracking speckle-tracking echocardiography in patients with Child-Pugh A and B cirrhosis: A case-control study. Indian J Gastroenterol. 2022 Dec;41(6):567-575. doi: 10.1007/s12664-022-01277-w. Epub 2022 Dec 28. PMID: 36576699.
52. Abd-El-Aziz TA, Abdou M, Fathy A, Wafaie M. Evaluation of cardiac function in patients with liver cirrhosis. Intern Med. 2010;49:2547-52.
53. Anish, P. G., et al. "Echocardiographic abnormalities in patients with cirrhosis and relation to disease severity." Heart India 7.1 (2019): 26-30.
54. Naqvi I, Mahmood K, Naeem M, Vashwani A, Ziaullah S. The heart matters when the liver shatters! Cirrhotic cardiomyopathy: frequency, comparison, and correlation with severity of

disease. Gastroenterology Review/Przegląd Gastroenterologiczny. 2016;11(4):247-256. doi:10.5114/pg.2016.57962. doi:10.5114/pg.2016.57962.
55. Shaikh S, Abro M, Qazi I, Qazi I, Yousfani A. Frequency of cirrhotic car- diomyopathy in patients with cirrhosis of liver: a tertiary care hospital experience. Pak J Med Sci 2011; 27: 744-8.
56. The role of autonomic dysfunction in cirrhotic patients before and after liver transplantation. Review of literature. Di Stefano et al. DOI: 10.1111/liv 13126 Liver International 2016
57. Waddell-Smith, K.E.; Chaptynova, A.A.; Li, J.; Crawford, J.R.; Hinds, H.; Skinner, J.R. Holter Recordings at Initial Assessment for Long QT Syndrome: Relationship to Genotype Status and Cardiac Events. J. Cardiovasc. Dev. Dis. 2022, 9, 164. https://doi.org/10.3390/jcdd9050164 https://doi.org/10.3390/jcdd9050164
58. alcoholic chronic liver disease. J Hepatol 1997; 26: 1242-8.
59. Fleckenstein JF, Frank S, Thuluvath PJ. Presence of auto- nomic neuropathy is a poor prognostic indicator in patients with advanced liver disease. Hepatology 1996; 23: 471-5.
60. Mohamed R, Forsey PR, Davies MK, Neuberger JM. Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease. Hepatol- ogy 1996; 23: 1128-34.
61. Thuluvath PJ, Triger DR. Autonomic neuropathy and chronic liver disease. Q J Med 1989; 72: 737-47.
62. Johnson RH, Robinson BJ. Mortality in alcoholics with autonomic neuropathy. J Neurol Neurosurg Psychiatry 1988; 51: 476-80.
63. Chaudhry V, Corse AM, Corse AM, O'Brian R, et al. Autonomic and peripheral (sensorimotor) neuropathy in chronic liver dis- ease: a clinical and electrophysiologic study. Hepatology
64. Lee W, Vandenberk B, Raj SR, Lee SS. Prolonged QT Interval in Cirrhosis: Twisting Time? Gut Liver. 2022 Nov 15;16(6):849-860. doi: 10.5009/gnl210537. Epub 2022 Jul 22. PMID: 35864808; PMCID: PMC9668500.
65. Bernardi M, Calandra S, Colantoni A, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. Hepatology. 1998;27:28-34. doi: 10.1002/hep.510270106.
66. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings:a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation. 2010;121:1047-1060. doi: 10.1161/CIRCULATIONAHA.109.192704
67. Garson A., Jr How to measure the QT interval: what is normal? Am J Cardiol. 1993;72:14B-16B. doi: 10.1016/0002-9149(93)90034-A.
68. Koshy AN, Gow PJ, Testro A, et al. Relationship between QT interval prolongation and structural abnormalities in cirrhotic cardiomyopathy: a change in the current paradigm. Am J Transplant. 2021;21:2240-2245. doi: 10.1111/ajt.16500
69. Bernardi M, Maggioli C, Dibra V, Zaccherini G. QT interval prolongation in liver cirrhosis: innocent bystander or serious threat? Expert Rev Gastroenterol Hepatol. 2012;6:57-66. doi: 10.1586/egh.11.86
70. Zhao J, Qi X, Hou F, et al. Prevalence, risk factors and in-hospital outcomes of QTc interval prolongation in liver cirrhosis. Am J Med Sci. 2016;352:285-295. doi: 10.1016/j.amjms.2016.06.012.012.
71. Kim SM, George B, Alcivar-Franco D, et al. QT prolongation is associated with increased mortality in end stage liver disease. World J Cardiol. 2017;9:347-354. doi: 10.4330/wjc.v9.i4.347.
72. Biselli M, Gramenzi A, Lenzi B, et al. Development and validation of a scoring system that includes corrected QT interval for risk analysis of patients with cirrhosis and gastrointestinal bleeding. Clin Gastroenterol Hepatol. 2019;17:1388-1397. doi: 10.1016/j.cgh.2018.12.006.006.

73. Pickham D, Helfenbein E, Shinn JA, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: results of the QT in Practice (QTIP) Study. Crit Care Med. 2012;40:394-399.
74. Mani AR, Montagnese S, Jackson CD, Jenkins CW, Jenkins CW, Head IM, Stephens RC, Moore KP, Morgan MY. Decreased heart rate variability in patients with cirrhosis relates to the presence and degree of hepatic encephalopathy. Am J Physiol Gastrointest Liver Physiol. 2009 Feb;296(2):G330-8. doi: 10.1152/ajpgi.90488.2008. Epub 2008 Nov 20. PMID: 19023029; PMCID: PMC2643913.
75. Altimiras J Understanding autonomic sympathovagal autonomic balance from short-term heart rate variations. Are we analyzing noise? Comp Biochem Physiol A Mol Integr Physiol 124: 447-460, 1999
76. Aronson D, Mittleman MA, Burger AJ. Interleukin-6 levels are inversely correlated with heart rate variability in patients with decompensated heart failure. J Cardiovasc Electrophysiol 12: 294-300, 2001
77. Coelho L, Saraiva S, Guimaraes H, Feitas D, Providencia LA. Autonomic function in chronic liver disease assessed by heart rate variability study. Rev Port Cardiol 20: 25-36, 2001
78. Dillon JF, Nolan J, Thomas H, et al. The correction of autonomic dysfunction in cirrhosis by captopril. J Hepatol 1997; 26: 331-5.
79. Luft, Caroline Di Bernardi, Emilio Takase, and David Darby. "Heart rate variability and cognitive function: Effects of physical exertion." Biological psychology 82.2 (2009): 186-191.
80. Gifford JR, Richardson RS. CORP: Ultrasound assessment of vascular function with the passive leg movement technique. J Appl Physiol (1985). 2017 Dec 1;123(6):1708-1720. doi: 10.1152/japplphysiol.00557.2017. Epub 2017 Sep 7. PMID: 28883048; PMCID: PMC5814681
81. Yasuko Iwakiri, Roberto J. Groszmann. Vascular endothelial dysfunction in cirrhosis Published: March 05, 2007DOI:https://doi.org/10.1016/j.jhep.2007.02.006
82. Luk, Ting-Hin, et al. "Effect of exercise training on vascular endothelial function in patients with stable coronary artery disease: a randomized controlled trial." European journal of preventive cardiology 19.4 (2012): 830-839.
83. Heinisch, B. B., et al. "Alpha-lipoic acid improves vascular endothelial function in patients with type 2 diabetes: a placebo-controlled randomized randomized trial." European Journal of Clinical Investigation 40.2 (2010): 148-154.
84. Xin, Wei, Shuhua Mi, and Zhiqin Lin. "Allopurinol therapy improves vascular endothelial function in subjects at risk for cardiovascular diseases: a meta-analysis of randomized controlled trials." Cardiovascular therapeutics 34.6 (2016): 441-449.
85. Vairappan B. Endothelial dysfunction in cirrhosis: Role of inflammation and oxidative stress. World J Hepatol. 2015 Mar 27;7(3):443-59. doi: 10.4254/wjhh.v7.i3.443. PMID: 25848469; PMCID: PMC4381168.
86. Tousoulis, Dimitris, et al. "Novel therapies targeting vascular endothelium." Endothelium 13.6 (2006): 411-421.
87. Limberg JK, Casey DP, Trinity JD, et al. Assessment of resistance vessel function in human skeletal muscle: guidelines for experimental design, Doppler ultrasound, and pharmacology. Am J Physiol Heart Cir Circ Physiol. 2020;318(2):H301-H325. doi:10.1152/ajpheart.00649.2019
88. Zytoon AA, Allah AN, Faisal A. The prediction of liver disease status using Doppler observations of the hepatic and portal venous system compared with liver biopsy in patients with chronic hepatitiC. Research and Reports in Focused Ultrasound. 2014;2:1-11 https://doi.org/10.2147/RRFU.S57202 https://doi.org/10.2147/RRFU.S57202
89. Shields KL, Broxterman RM, Jarrett CL, Bisconti AV, Park SH, Richardson RS. The passive leg movement technique for assessing vascular function: defining the distribution of blood flow and the impact of occluding the lower leg. Exp Physiol. 2019;104(10):1575-1584. doi:10.1113/EP087845
90. Colak Y, Senates E, Yesil A, Yilmaz Y, Ozturk O, Doganay L, Coskunpinar E, Kahraman OT, Mesci B, Ulasoglu C, Tuncer I. Assessment of endothelial function in patients with

nonalcoholic fatty liver disease. Endocrine. 2013 Feb;43(1):100-7. doi: 10.1007/s12020-012-9712-1. Epub 2012 Jun 3. PMID: 22661277.

91. Paul A Cahill, Eileen M Redmond, James V Sitzmann, Endothelial dysfunction in cirrhosis and portal hypertension,Pharmacology &Therapeutics,Volume 89, Issue 3,2001,Pages 273-293,ISSN 0163-7258,
92. Rasaratnam B, Connelly N, Chin-Dusting J. Nitric oxide and the hyperdynamic circulation in cirrhosis: is there a role for selective intestinal decontamination? Clin Sci (Lond). 2004 Nov;107(5):425-34. doi: 10.1042/CS20040157. PMID: 15270715.
93. Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. Hepatology. 2002 Feb;35(2):478-91. doi: 10.1053/jhep.2002.31432. PMID: 11826425.
94. Rodrigo R, Felipo V. Brain regional alterations in the modulation of the glutamate-nitric oxide-cGMP pathway in liver cirrhosis. Role of hyperammonemia and cell types involved. Neurochem Int. 2006 May-Jun;48(6-7):472-7. doi: 10.1016/j.neuint.2005.10.014. Epub 2006 Mar 6. PMID: 16517021.
95. Martin PY, Ginès P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. N Engl J Med. 1998 Aug 20;339(8):533-41. doi: 10.1056/NEJM199808202033390807. PMID: 970909047.
96. Atucha NM, Nadal FJ, Iyú D, Alcaraz A, Rodríguez-Barbero A, Ortiz MC, López-Novoa JM, García-Estañ J. Role of vascular nitric oxide in experimental liver cirrhosis. Curr Vasc Pharmacol. 2005 Jan;3(1):81-5. doi: 10.2174/1570161052773889. PMID: 15638785.
97. Atucha NM, Nadal FJ, Nadal FJ, Iyu D, García-Estañ J. Role of vascular nitric oxide in experimental liver cirrhosis. Nephrology. 2002;22 Suppl 5:25-8. English. PMID: 12107913.
98. Schrier RW, Niederberger M, Weigert A, Ginès P. Peripheral arterial vasodilatation: determinant of functional spectrum of cirrhosis. Semin Liver Dis. 1994 Feb;14(1):14-22. doi: 10.1055/s-2007-1007294. PMID: 8016658.
99. Møller S, Bendtsen F. The pathophysiology of arterial vasodilatation and hyperdynamic circulation in cirrhosis. Liver Int. 2018 Apr;38(4):570-580. doi: 10.1111/liv.13589. Epub 2018 Jan 15. PMID: 28921803.
100. Fede G, Privitera G, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in patients with liver cirrhosis. Ann Gastroenterol. 2015 Jan-Mar;28(1):31-40. PMID: 25608575; PMCID: PMC4290002.
101. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol. 2015 Nov;63(5):1272-84. doi: 10.1016/j.jhep.2015.07.004.004. Epub 2015 Jul 17. PMID: 26192220.
102. Fernández-Rodriguez CM, Prada IR, Prieto J, Montuenga LM, Elssasser T, Quiroga J, Moreiras M, Andrade A, Cuttitta F. Circulating adrenomedullin in cirrhosis: relationship to hyperdynamic circulation. J Hepatol. 1998 Aug;29(2):250-6. doi: 10.1016/s0168-8278(98)80010-x. PMID: 9722206.
103. Kakihara S, Matsuda Y, Hirabayashi K, Imai A, Iesato Y, Sakurai T, Kamiyoshi A, Tanaka M, Ichikawa-Shindo Y, Kawate H, Zhao Y, Zhang Y, Guo Q, Li P, Onishi N, Murata T, Shindo T. Role of Adrenomedullin 2/Intermedin in the Pathogenesis of Neovascular Age-Related Macular Degeneration. Lab Invest. 2023 Apr;103(4):100038. doi: 10.1016/j.labinv.2022.100038. Epub 2023 Jan 10. PMID: 36870288.

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