Cirrhotic cardiomyopathy; Pathophysiology and clinical approach

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Cardiac dysfunction is considerably discovered in patients with liver cirrhosis. Cirrhotic cardiomyopathy (CCM) has newly been assigned to as an entity separate of the cirrhosis etiology. Increased cardiac output due to hyperdynamic circulation, left ventricular dysfunction (systolic and diastolic) and certain electro-physiological abnormal findings are pathophysiological features of the disease. The main underlying mechanisms are complex, including the impaired β-receptor and calcium signaling, altered cardiomyocyte membrane physiology, elevated sympathetic nervous tone and increased activity of vasodilatory pathways. CCM character is impaired cardiac response to stress (physical, physiological and pharmacological). Currently, no specific therapy has proved effective yet. Echocardiography and electrocardiography are the corner stones for diagnosis. In this review, we discuss in brief the pathophysiological background and clinical features of cirrhotic cardiomyopathy, diagnosis and the currently available treatment options.

Keywords: Cirrhosis; Cardiomyopathy; Pathogenesis; Hyperdynamic circulation; Systolic dysfunction; Diastolic dysfunction


Introduction

The heart and liver may interact in several different ways [1]. First, acute or chronic heart failure (HF) and especially right HF may lead to a spectrum of several liver manifestations, including cardiac cirrhosis or congestive liver disease. Second, chronic liver disease such as cirrhosis may affect the heart and the whole cardiovascular system, leading to a syndrome named Cirrhotic Cardiomyopathy (CCM) [2].

Kowalski et al., 1953 reported hyperdynamic circulation in cirrhotic patients [3], but a definition was only proposed in 2005 by an expert consensus during the annual meeting of the World Gastroenterology Organisation in Montreal [4]. The definition of CCM was “a cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress (physiologic, pathologic, or pharmacologic) but normal to increased cardiac output and contractility at rest and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease” [4, 5, 6].

The diagnosis of CCM is by exclusion of other causes of cardiac dysfunction including "valvular heart disease, congenital heart disease, ischemic heart disease, conduction abnormalities, and hypertrophic cardiomyopathy” [7, 8].

The prevalence is reported to be between 40 to 50% in cirrhotic patients independent of liver disease aetiology [9]. Former studies on candidates with liver transplantation; features of cardiac dysfunction were reported in 50% of advanced cirrhosis patients and heart failure reported in 7% - 21% of post-operative deaths [7, 8].
CCM; epidemiology and natural history is not fully defined, as the onset is insidious, long latency time, and it is frequently undiagnosed, or the diagnosis is late in disease course\citep{10,13}.

Regardless the etiology; symptoms are: mild diastolic dysfunction with gradual exercise restriction, paroxysmal atrial fibrillation, ventricular arrhythmias, fulminant heart failure with dilatation of both ventricles, and ventricular hypokinesis which is manifest with more circulatory activity\citep{11,14}.

Volume overload is induced via: the increased cardiac output and volume of intravascular plasma and the hyperdynamic condition of cirrhosis, all of these subsequently participate to: myocardial hypertrophy, enlargement of left atrium, prolongation of isovolumic relaxation time and a decreased early to late ratio of diastolic flow (E/A). While, the decrease in left ventricular afterload, due to peripheral vasodilation, conceals the systolic dysfunction, at rest: it remains normal and only during stress: becomes evident, diagnosed as an impaired inotropic and chronotropic response\citep{11,14}.

Present treatment recommendations of CCM include any supportive deals, pharmacological drugs and liver transplantation. Generally the severity of CCM correlates to the severity of liver disease. Nearly hemodynamic and humoral alterations related to advanced liver disease are restored with time following liver transplantation. Yet, the precise prognosis still unclear\citep{10,15-21}.

**Pathophysiology**

Cardiac dysfunction is considered to be multifactorial in chronic liver disease patients\citep{22}.

Liver cirrhosis is characterised by increased intrahepatic vascular resistance consecutive to fibrosis development and regeneration nodules formation, which result in "portal hypertension"\citep{23}. Portal hypertension, in turn, is correlated to the production of vasodilators including carbon monoxide, nitric oxide, and tumor necrosis factor. In parallel, there is also a reduced degradation of these substances due to the metabolic hepatic dysfunction and portosystemic shunt\citep{9,23}

This contributes to splanchnic vasodilatation, which not only decreases global systemic vascular resistance but also creates splanchnic blood pooling. All these factors result in hyperdynamic circulation and effective hypovolaemia that induces baroreceptor and volume receptor activation of both (renin-angiotensin-aldosterone system and the sympathetic nervous system) with an increased secretion of antidiuretic hormone contributing to the development of cirrhotic cardiomyopathy\citep{24}.

**Vascular tone and the genesis of cirrhotic cardiomyopathy**

Altered liver function and portal hypertension including Variceal bleeding, concomitant anemia and ascites are among the most important factors that contribute to the decreased right and left ventricular preload and afterload\citep{25-27}.

Reduction of central and arterial blood volumes and arterial hypotension can lead to activation of volume receptors and baroreceptors resulting in sodium-water retention\citep{28}.

Cardiac dysfunction (systolic and diastolic), hyperdynamic circulation and abnormal electrophysiological findings are main clinical features triad of CCM. Vasodilatation appears in the splanchnic area while vasoconstriction appears in the kidneys. These conditions are responsible for the decreased effective central blood volume\citep{26,29}.

High level of vasodilators and low vasoconstrictors sensitivity, Tumor Necrosis Factor Alpha (TNF-α), Nitric Oxide (NO), endocannabinoids, adrenomedullin, Calcitonin Gene Related Peptide (CGRP), and Carbon Monoxide (CO) are the most important mediators in this field\citep{30,31}. On the contrary, a concomitant activation of both (RAAS and sympathetic nervous system) including (noradrenaline, neuropeptide-Y, endothelin-1, angiotensin II, and vasopressin) has been observed\citep{32,33}.

**Mechanism for altered myocardial function**

**Systolic function**

In cirrhosis, myocardial dysfunction was associated with the progression of liver disease. Systolic dysfunction, however, is mostly latent. Hyperdynamic unloaded heart failure is the main feature and cardiac output proves to be normal or increased at rest in most cases\citep{34}.

Reduction in myocardial function becomes overt under conditions of pharmacological or physical stress\citep{35}. Hidden systolic dysfunction becomes manifest during the normalization of arterial blood pressure\citep{36}. Accordingly, clinical symptoms of systolic heart failure may evolve after liver transplantation or a Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement\citep{37-39}.

Cirrhotic patients with systolic dysfunction is affected by several molecular abnormalities: (1) Alterations in
beta-adrenergic signaling pathway result in decrease in the density of β-receptors, reduction in G-proteins and consequently a decrease in Cyclic Adenosine Monophosphate (cAMP) production. (2) Increased cholesterol content of the myocardial cell membrane may alter and can impair the ion channel functions. (3) Enhanced endocannabinoid signaling has a negative inotropic effect. (4) NO overproduction exerts a toxic effect on the myocardium due to suppressed contractility and induced apoptosis. As TNF-α is a major trigger mechanism of NO production, high level of this cytokine worsens the pathophysiological and clinical status.

Diastolic function

Decreased left ventricular relaxation is characterized by abnormal trans-mitral ventricular filling, increased atrial pressure and prolonged isovolumic relaxation.

The background of pathophysiology among cirrhotic patients with diastolic dysfunction: (1) The increase in the myocardial wall stiffness, which is often caused by myocardial hypertrophy and fibrosis due to activation of the RAAS. (2) Subendothelial edema and increased interstitial collagen deposition play a further role in the decreased ability for relaxation.

The underlying factor in the development of atrial fibrillation is diastolic dysfunction due to the increase in atrial volume load.

Though, in both symptomatic and asymptomatic patients, diastolic heart failure is an independent risk factor for cardiovascular mortality.

Electrophysiological abnormalities in cirrhotic cardiomyopathy

Electrophysiological abnormalities occurring in cirrhosis comprise: 1-chronotropic incompetence 2-electromechanical uncoupling and 3-prolonged QT interval.

1-Chronotropic incompetence

This phenomenon may appear independent of the liver disease aetiology and correlates with the severity of cirrhosis. In this case the sinus mode is irresponsive to physiological and pharmacological stimuli.

2-Electromechanical uncoupling

There is an asynchrony between electrical and mechanical systole that can lead to an altered contractile function of the ventricular myocardium resulting in congestive heart failure. This phenomenon is related to liver disease severity, also may be caused by defects (receptor and post-receptor).

3-QT interval and dispersion

QT interval is the electrical depolarization and repolarization of ventricular myocardium and it depends on the ventricular rate (the faster the heart rate the shorter it is).

Determination of the QT interval can help identification of the patient with high risk for the emergence of ventricular dysrhythmias. The QT interval duration varies between leads on the standard surface electrocardiogram.

The interlead difference of QT intervals is defined as QT dispersion, it can distinguish between myocardium that is homogeneous from myocardium that displays increased prolongation of repolarization. Since these electrocardiographic markers can predict ventricular arrhythmias together with sudden cardiac death they are considered to be among the most significant noninvasive parameters.

In cirrhotic patients, the prevalence of prolonged QT interval increases with the progression of the liver disease and occurs irrespective of cirrhosis aetiology. At least 60% of end stage liver disease patients show this electrocardiographic abnormality. On the contrary, Baik et al reported that sudden cardiac death is uncommon in cirrhosis. Thus, the QT prolongation clinical significance in cirrhosis still needs clearance.

Also the QT Prolongation interval may worsen after TIPS in patients with portal hypertension (cirrhotic and non-cirrhotic), TIPS was related to the increase in the risk of heart failure.

These electrophysiological changes appeared as a result of a combination of ion-channel dysfunction, plasma membrane abnormalities and β-adrenoceptor and post-receptor pathway defects.

The electrical properties of the myocardial cells largely depend on the duration of the monophasic action potentials; the generation of which is depending on special types of voltage gated ion channels placed in the myocardial cells’ plasma membrane. The function impairment of potassium channels in cirrhotic animal models has been recorded resulting in a prolongation of the action potential, suggesting an increase in transmural heterogeneity of repolarization.

Bacterial infections commonly appear in patients with...
cirrhosis. As the inflammation progresses cardiodepressant substances as (cytokines, endogenous cannabinoids, and nitric oxide) are released [60].

The urokinase type plasminogen activator receptor (suPAR) has recently been suggested to bear prognostic information [67]. These mediators may influence the activation of the inward calcium current leading to increased duration of monophasic action potential.

Moreover, endothelin (which is elevated in cirrhosis) was shown to induce alterations in ion currents of myocardial cell preparations [68]. Also, increased levels of bile acid (biliary cirrhosis) may modulate fluidity of the membrane causing the changes in ion channel activity and the alterations of β-adrenoceptor and G-protein function. Increased activity of sympathetic nervous system together with potassium channel defects may have a role in the genesis of inhomogeneous repolarization. Non-selective β-blockade may have a favorable effect on QT interval duration among cirrhotic patients, probably secondary to the improvement in hyperdynamic circulation and decreased portal pressure. A direct correlation was found between QT and plasma norepinephrine which was absent during β-adrenergic blockade [50, 69]. On the other hand, Zambruni and coauthors reported that the chronic administration of a non-selective β-blocker proved efficacy in the reduction of the QT interval in patients with a prolonged value at the baseline only [70].

**Diagnosis of cirrhotic cardiomyopathy**

**Clinical symptoms**

The diagnosis is difficult as cardiac function is nearly normal at rest. In most cases this condition is well tolerated and may be asymptomatic for a long period of time, and it is often impossible to distinguish the clinical signs and complaints from those of the underlying disease. Most of the patients are diagnosed during the worsening of the liver disease when the main clinical characteristics of heart failure (diastolic and high-output) usually appear. The decrease of systolic ventricular competence may enhance the occurrence of complications, including (sodium and water retention, ascites and worsening of the kidney function) [71].

**Laboratory markers**

Atrial Natriuretic Peptide (ANP): is released from the atrial myocardium due to intracardiac volume overload. Consequently, atrial wall stretch is augmented resulting in higher serum levels of this biomarker which is the case in decompensated cirrhosis [72,73].

Brain Natriuretic Peptide (BNP): with its pro-hormone (pro BNP) are useful in the diagnosis of myocardial injury, and also are elevated in cirrhotic patients [74-76].

Troponin I seems valuable in the determination of risk in patients undergoing transjugular intrahepatic portosystemic shunts [77].

Galectin-3 has been shown to mediate myocardial fibrosis and to be expressed in cirrhosis. Furthermore, galectin-3 binding protein concentrations have also been found to be increased in patients with cirrhosis [78].

**Echocardiography**

Assessment of systolic function: The left ventricular systolic performance highly depends upon its contractility. Additionally, ventricular pre- and afterload, and heart rate have an influence on the myocardial contractile power. The ejection fraction (EF) is known to be the best marker of the left ventricular systolic function. It is known to be a predictor of cardiovascular outcomes, including sudden cardiac death in patients with symptomatic heart failure [79]. For the evaluation of ejection fraction linear measurements (Teicholz or Quinones) can be performed by means of a two-dimensional echocardiography [80]. These methods require certain geometric assumptions, therefore they are not recommended to be used in the everyday clinical practice. Instead, the ejection fraction can be calculated more exactly from the difference between the end-diastolic and the end-systolic left ventricular volume, divided by the end diastolic volume (Simpson’s method) [81]. Finally, speckle tracking, another echocardiographic method evaluates the frame-to-frame tracking of the ventricular myocardium in radial, circumferential and longitudinal axis. This can provide a sensitive description of left ventricular systolic function [82]. Finally, radionuclide scintigraphy (MUGA - Multi Gated AcquisitionScan) can provide highly reliable values of left ventricular ejection fraction when echocardiography is uncertain [83].

Evaluation of diastolic function: Even the asymptomatic diastolic dysfunction can be recognized at an early disease stage and early therapy can be started. Moreover, another echocardiographic entity, isolated diastolic dysfunction (heart failure with normal ejection fraction) can be recognized. For the evaluation of diastolic function the transmitral flow velocities are measured in early diastole and late diastole (presystole) with the help of a pulsed wave Doppler technique. [84, 85, 86] The diastolic dysfunction in cirrhosis is most pronounced in patients with ascites [71].

**Electrocardiography**
Electrocardiography is useful in the recognition of pulse generation and/or conduction disturbances, and cardiac arrhythmia markers can also be examined. The QT interval is one of the most important electrocardiographic parameters for the description of ventricular repolarization in patients with cirrhosis, which may be affected by several disease (amyloidosis, sarcoidosis, carcinoid, hemochromatosis, diabetes mellitus, thyroid dysfunction or Parkinson’s disease) [87, 88]. Genetic causes (long QT syndrome, short QT syndrome), drug interaction (e.g. haloperidol, methadone, amiodarone, sotalol, selective serotonin reuptake inhibitors, macrolide antibiotics, antifungal agents) [89]. So patient’s history is one of the key points in the arrhythmia risk determination.

The QT interval depends on the ventricular rate. Therefore it should be corrected to the heart rate (QTc). There are several methods that may provide the correction of this parameter [90, 91]. Bazett’s formula is one of the most important in this field (QTc= QT/√RR) [92]. The QTc>450 msec value shows an increased risk of ventricular arrhythmias [93]. Interestingly, in patients with cirrhosis this formula does not clearly describe the relationship between the QT and heart rate. Therefore a specific ‘cirrhosis formula’ has been derived, which is similar to the Friderica’s, and can be confidently used in this setting [94]. In order to eliminate the inter-observer variability, during the manual measurements values may be calculated with calipers by one examiner [58].

Cardiac magnetic resonance

Cardiovascular magnetic resonance (CMR) is considered the gold standard for the assessment of cardiac morphology and function in various cardiomyopathies. Omran et al reported that severe liver cirrhosis secondary to HCV causes systolic functional and morphological changes within the myocardium which could be accurately evaluated by CMR [95]. On their study on 84 patients with HCV related end stage liver disease, they found variable degrees of delayed myocardial enhancement (DME) in 83.3% of patients examined. DME ranged from 4-52 with a mean of 19.5 ±16% of myocardial mass. Another study showed DME in all patients with alcoholic cirrhosis ESLD. In that study, DME was detected with a mean of 27% of myocardial mass (range: 2-62%) [96]. It is known that alcoholic liver cirrhosis which is known to be associated with myocardial fibrosis [97, 98].

Treatment approach

Impaired cardiac output in patients with CCM may result in the pathogenesis of hepatorenal syndrome through alteration in renal blood perfusion. In addition, as a result of decreased cardiac output, the sympathetic tone increases contriburesulting in activation of renal sodium and retention of water, and the RAAS. Diastolic myocardial dysfunction can contribute to an elevated ventricular pressure. The consequently decreased circulatory volume can cause more sodium retention. Therefore, the increased excretion of sodium mainly through aldosterone blockers and diuretics can result in an improved cardiac function. As till now, no specific therapy for CCM is available. So, the treatment guidelines should be as for non-cirrhosis with heart dysfunction [99].

Angiotensin Converting Enzyme (ACE) inhibitors:

Cirrhotic patients on ACE inhibitor therapy could attain long term clinical benefits, but currently no studies are available to prove their efficacy in CCM. According to the latest guideline, ACE inhibitor drugs should be administered in heart failure patients, if not contraindicated, in order to decrease the morbidity and the mortality. Data obtained from previous clinical investigations have shown no differences regarding clinical symptoms and survival among available ACE inhibitors. Management must be started with low doses then gradual increase in the doses. Kidney function and serum level of potassium must be monitored periodically especially in patients with renal impairment. It is also important to know that ACE inhibitor administration is safe in cirrhotic patients with (Child Pugh A), but it is not in more advanced stages, as there is decrease in glomerular filtration rate [100,101].

Angiotensin-II receptor blockers

Though Angiotensin Receptor Blockers (ARB) have been shown to increase sodium excretion without significantly affecting renal and systemic hemodynamics, without beneficial clinical effects in long-term treatment of patients with cirrhosis [102].

Loop and thiazide diuretics

Only diuretics can effectively control the retention of fluid among patients suffering from cardiac failure. Therefore, the appropriate administration of these drugs is one of the key elements of the treatment of these individuals, while improper low doses resulting in retention of fluid. Otherwise, the incautious high doses can result in hypovolemia, hypotension and kidney failure. Loop diuretics (e.g. furosemide) are considered to be the commonly used agent in heart failure patients. Thiazide diuretics, may be useful in patients with hypertension showing symptoms of moderate fluid retention since their administration results in a more
pronounced antihypertensive effect [100].

**Aldosterone receptor antagonists**

Hyperaldosteronism is detected in almost cirrhotic patients and heart failure. Aldosterone may have various harmful effects on the myocardium and the cardiovascular system. So, antagonists to mineralocorticoid receptor may be among the first choices of therapy [103]. They can improve the hemodynamic properties of patients with cirrhosis and may decrease the severe symptoms of heart failure [104]. According to the data obtained from the Randomized Aldactone Evaluation Study (RALES) trial, a 30% mortality reduction and a decreased risk of sudden cardiac death can be reached with spironolactone treatment in patients with chronic heart failure (left ventricular EF <35%) [105]. The selective aldosterone blocker (eplerenone) has offer reduction in cardiovascular death rates and hospitalizations due to heart failure [106]. Therefore, aldosterone receptor blockers are useful in the treatment of patients with decreased left ventricular ejection fraction and symptomatic heart failure. Importantly, the accurate monitoring of serum potassium and kidney function can help to avoid the development risk of hyperkalemia and renal insufficiency [100].

**Beta-receptor blockers:**

The beta-adrenoceptor blockers, especially the nonselective ones (propranolol, nadolol) are effective in reducing portal hypertension and thus in the prevention of the gastroesophageal bleeding. More recently (carvedilol), a vasodilator, Non Selective Beta Blocker (NSBB) has intrinsic anti-alfa adrenergic activity - has been reported to have more effect on reducing portal hypertension than nadolol or propranolol. Also, beta-blockers can improve the cardiac contractile function [107,108]. At the same time, no studies on beta-blockers for CCM are available till now.

Beta-receptor blockers showed their effectiveness in mortality reduction in patients with systolic heart dysfunction so can be one of the treatment choices [106]. Bisoprolol, metoprolol succinate and carvedilol have been proven to be the most effective in this field. Due to the beneficial effect of carvedilol on portal hypertension, this agent could be the first consideration in CCM [100].

Furthermore, long term therapy with beta blockers can decrease heart failure symptoms, and better clinical status. Management with beta-blockers should be started with low dose, and careful monitoring of patients, since therapy may result in retention of fluid and heart failure worsening, bradycardia, hypotension and pulse conduction abnormalities. Even without symptoms improvement, long term therapy should be applied to decrease cardiovascular mortality [100, 110].

In addition, NSBBs have been proven to return lengthened QT intervals to normal in patients with cirrhosis [69]. Despite all these beneficial clinical data currently no definitive recommendation can be given for chronic administration of beta blockers in cirrhotic patients.

**Transjugular Intrahepatic Portosystemic Shunt (TIPS)**

Since TIPS can rapidly shift a significant amount of blood from the splanchnic circulation to the cardiac circulation, it may result in a sudden worsening of the cardiac function among cirrhotic patients, mainly in individuals with diastolic dysfunction [111].

Liver transplantation is known to be a solution for liver failure due to cirrhosis. Interestingly, it seems to cure the associated cardiomyopathy as well [37]. Previously, amelioration of left ventricular hypertrophy, diastolic (lusitropic) dysfunction and normalization of the contractile function after transplantation have been reported. Prolonged QTc has also been shown to be reversible by liver transplantation, despite remaining lengthened right after the surgery [111]. On the contrary, orthotropic liver transplantation may cause severe hemodynamic consequences, since it can result in an abrupt decrease in cardiac output due to the inferior vena cava clamping. Moreover, a post reperfusion injury, secondary coagulopathy, and post-operative hydrostatic pulmonary edema may worsen the clinical outcome [113]. In addition, cirrhotic patients with concomitant severe cardiomyopathy may benefit from cardiac transplantation [114].

**Farnesoid X receptor agonists**

Novel therapeutic attempts are aiming to increase the intrahepatic concentration of vasodilators. Farnesoid X receptor agonists are responsible for hydrogen sulfide production; moreover, NCX-1000 may release NO in the liver [115]. These agents are promising for future therapeutic regimens but their exact role in CCM is not yet identified.

**Conclusion**

Cirrhotic Cardiomyopathy is a frequently occurring in almost half of cirrhotic patients with advanced disease, regardless of the etiology. The most diagnostic criteria are impaired cardiac stress response, LV diastolic dysfunction and prolonged QT interval. It is important for the clinician to be aware of this syndrome. Up to now, no proven therapies however cirrhotic cardiomyopathy is almost completely reversible after liver transplantation.
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