

REVIEW ARTICLE

Cirrhotic Cardiomyopathy: The Interplay Between Liver and Cardiac Muscle. How Does the Cardiovascular System React When the Liver is Diseased?

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Abstract: It is widely known that liver cirrhosis, regardless of the etiologies is accompanied by severe hemodynamic changes. The principal pathophysiological mechanisms are the hyperdynamic circulation with increased cardiac output, heart rate along with reduced systemic vascular resistance. Thus, counteractive mechanisms may develop that eventually lead to systolic as well as diastolic dysfunction and rhythm disturbances, in order to keep a steady homeostasis in the human body.

Literally, blunted contractile responsiveness to physical or pharmacological stress, impaired diastolic relaxation and electrophysiological changes, primarily QT interval prolongation, do occur progressively in a cirrhotic patient with no known preexisting cardiac disease. This condition is identified as cirrhotic cardiomyopathy (CCM), an entity different from that seen in alcoholic cardiac muscle disease.

For the past decades, clinicians did study and attempt to understand the pathophysiology and clinical significance of this process. Indeed, various factors have been identified acting at the molecular and cellular level.

Electrocardiography, echocardiography and various serum biomarkers are the main tools that help healthcare practitioners to point to the correct diagnosis.

Noteworthy, the subjects that suffer from cirrhotic cardiomyopathy may progress to heart failure during invasive procedures such as surgery, insertion of a transjugular intrahepatic portosystemic shunting (TIPS) and liver transplantation. Besides, several studies have illustrated that CCM is a contributing factor, or even a precipitant, of hepatorenal syndrome (HRS), a conceivable reversible kidney failure in patients with liver cirrhosis and ascites.

The treatment is the same as it is in the patients with liver cirrhosis and heart failure and there is no particular treatment for cirrhotic cardiomyopathy. Hence, it is of utmost importance to clearly comprehend the pathophysiology of this disease in order to design more accurate diagnostic tools and definitive treatments in a way to prevent the complications of cirrhosis and overt heart failure.

The objective of this review is to describe in a comprehensive way the pathological alterations that occur in the cardiovascular system of cirrhotic patients. It will also point the limitations that remain in the diagnosis and treatment strategies and more importantly, this review will alert the clinicians in the modern era to further observe and record additional pathological changes in this subset of patients.

Keywords: Cirrhosis, cirrhotic cardiomyopathy, systolic dysfunction, diastolic dysfunction, heart failure, TIPS, homeostasis.

1. INTRODUCTION

Cirrhosis is a chronic disease that exclusively affects the liver [1]. Chronic tissue injury causes tissue fibrosis and

regeneration nodules that certainly lead to distortion of the normal hepatic parenchyma and alterations of its vasculature [1, 2]. Cirrhosis consists of two main phases; the compensated phase where the patient is asymptomatic and the decompensated one, where there is systemic symptomatology, involving vital organs such as the cardiac muscle, the lungs, kidneys, adrenal glands, the brain and the immune system [3]. Common causes are mainly chronic alcohol use and

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hepatitis B and C [4], while less usual causes include non-alcoholic steatohepatitis (NASH), Wilson's disease, autoimmune hepatitis and cryptogenic cirrhosis [5].

The correlation that exists between liver cirrhosis and circulatory system has been well established by Kowalski *et al.*, more than 60 years ago [6]. Hemodynamic parameters are affected in such a way that lead to increased cardiac output (CO) and stroke volume (SV) and decreased systemic vascular resistance (SVR). Interestingly, the lessened hepatic function along with portal hypertension and splanchnic vasodilation induce the development of hyperdynamic syndrome [7].

Further studies confirmed that the hemodynamic circuit is disturbed in alcoholic and non-alcoholic cirrhotic patients and this is associated with significant cardiovascular abnormalities, as liver cirrhosis progresses [8, 9]. Impaired myocardial contractility, particularly under stress conditions, insufficient relaxation of the left ventricle during diastole due to the increased thickness of the ventricular wall and electrocardiographic (ECG) abnormalities (characteristically, QT interval prolongation) constitute the term CCM [10, 11]. At the molecular level, it has been described that there is an exhaustion of beta-adrenergic receptors, cytoplasmic impregnation by endocannabinoids, and imbalance between nitric oxide and endothelin [12].

It should be apparent that all these changes do arise in subjects with liver cirrhosis, regardless of the etiologies, and no known pre-existing cardiac disease [8, 9]. It is worthwhile to mention that the clinical phenotype is silent unless a major stressor takes place, where heart failure within its complications may develop [11]. This is attributed to the fact that the left ventricle afterload is significantly reduced due to the peripheral vasodilation, thus masking any sign or symptom of heart failure [13]. As a result, in circumstances where the afterload increases, *e.g.* post liver transplantation period, the cardiac performance may be aggravated postoperatively due to alterations in the cardiovascular system; progressive normalization of the hyperdynamic circulation state, which is accompanied by elevation of the peripheral resistance and arterial pressure and later progresses to heart failure because of the increased afterload [14].

So, the clinician should be suspicious and alert for the development of CCM in this subject population. Resting tachycardia and baseline increased cardiac output [6], reduced myocardial contractility with a blunted systolic-diastolic response to inotropic and chronotropic stimuli [15], increase of brain natriuretic peptide (BNP) [16, 17] and serum troponin levels [18], as well as conduction abnormalities [19] do comprise a constellation of cardiac abnormalities that should be taken under consideration. Signs of any cardiac dysfunction should be monitored and followed by using the available diagnostic tools [20]. Routine screening will unveil that 50% of cirrhosis patients suffer myocardial compromise [17]. Nonetheless, despite the efforts to correlate the cardiovascular findings to the etiology or the severity of the hepatic failure, the results are controversial [21].

Dyspnea, fluid retention and limited exercise capacity due to reduced cardiac contractility and impaired diastolic function may develop [22]. However, the term hepato-

cardiac syndrome contrary to the HRS and hepatopulmonary syndrome respectively (HPPS) is still not acceptable nowadays, since the late recognition of clinical findings leads to misdiagnosis and treatment delay [23]. HRS can be a later complication, especially after infections such as spontaneous bacterial peritonitis. Characteristically, the risk of HRS is increased with the presence of myocardial dysfunction in cirrhosis [24-26].

Once heart failure becomes evident, diuretics as in congestive heart failure patients without cirrhosis are given for symptomatic relief, while intravenous (I/V) human albumin ameliorates cardiac dysfunction by binding cardio-depressant factors [27, 28]. Additional clinical studies targeting vasodilatory substances could be helpful in the future treatment of CCM [29].

2. DEFINITION AND EPIDEMIOLOGY

Until lately, there was no official consensus for the diagnosis of CCM, thus there was an utmost "noise" regarding its identification. Nonetheless, diagnostic and supportive criteria for CCM were proposed by a group of experts at the 2005 World Congress of Gastroenterology at Montreal. These criteria consist of three main parts; (1) systolic dysfunction: blunted increase in cardiac output on exercise, volume challenge or pharmacological stimuli or resting ejection fraction <55%, (2) diastolic dysfunction: the ratio of early to late (atrial) phases of ventricular filling or E/A ratio <1.0 (age-corrected), prolonged deceleration time (>200ms), or prolonged isovolumetric relaxation time (>80ms), (3) supportive criteria: electrophysiological abnormalities, abnormal chronotropic response, electromechanical uncoupling/dyssynchrony, prolonged QTc interval, enlarged left atrium, increased myocardial mass, increased BNP and pro-BNP, or increased Troponin I [10].

Nevertheless, accurate data regarding the prevalence of CCM are limited due to the fact that the disease remains clinically silent until late stages. This is happening primarily because patients with cirrhosis initially have subtle left ventricular diastolic dysfunction (LVDD) with normal systolic function at rest. Rumbustious symptomatology develops when the patients are exposed to a stressor. Interestingly, it has been assessed that as many as 50% of patients undergoing liver transplantation will uncover signs of cardiac dysfunction [11], while 7-21% of patients died from complications of heart failure in the post-liver transplantation period [13]. Still, the majority of patients with advanced cirrhosis (*e.g.* Child-Pugh class B and C) may have either diastolic dysfunction or ECG abnormalities. At this part, the use of accurate diagnostic tools, such as a two-dimensional echocardiogram or dynamic cardiac MRI, is essential as it may detect lesions that otherwise are silent [20].

3. PATHOPHYSIOLOGY

It is of utmost importance to recognize the initial pathophysiological changes that do occur in liver cirrhosis patients in order to understand the subsequent functional changes. Cirrhosis along with portal hypertension leads to splanchnic and systemic vasodilation. It is fascinating the fact that vasodilating substances escape degradation from the fibrotic liver or bypass through portosystemic collaterals, which are gen-

erated from vascular endothelial growth factor (VEGF) to the systemic circulation causing dilatation of the venous system [30-32]. To our knowledge, some of the potent vasodilating agents are; nitric oxide, carbon monoxide, endogenous cannabinoids, brain natriuretic peptide, calcitonin gene-related peptide, and endothelin-3 [11, 33, 34]. Vasodilation is the primary trigger that alters most of the hemodynamic parameters. Specifically, at the initial stages, this dilatation of the blood vessels and drop of peripheral vascular resistance is masked by the formulation of a hyperdynamic circulation. Hallmark of a hyperdynamic state is the increased cardiac output, stroke volume and heart rate. Yet, later on, the disease progression, the plasma volume expands through the activation of renin-angiotensin-aldosterone-system (RAAS), sympathetic nervous system (SNS) and release of antidiuretic hormone (ADH, AVP) [10, 35]. ADH is indirectly measured by its precursor, called copeptin [35]. Despite that plasma volume increases, there is still not equal distribution between central and non-central (splanchnic) vascular areas. Notably, the splanchnic blood volume is increased compared to that of cardiac muscle, lungs and aorta resulting in effective hypovolemia [10, 36]. This redistribution creates a vicious circle, where the central hypovolemia activates further baroreceptors of SNS and RAAS resulting in further fluid retention and redistribution. This cascade in the long term affects the structure and functionality of the cardiac muscle leading to systolic and diastolic dysfunction as well as electrophysiological abnormalities [37, 38].

3.1. Systolic Dysfunction

As has already been stated, systolic dysfunction is one of the criteria that met in CCM. However, it is noteworthy to remark that the left ventricular systolic function of cirrhotic patients is normal and or increased at rest as a consequence of hyperdynamic circulation [39]. A number of studies demonstrated that when this group of patients is exposed to stress, either physiological *e.g.* sepsis, or pharmacological loses its cardiac contractility [40-42]. To be more precise, the systolic dysfunction was already “there” but it was the hyperdynamic state that masked it. There are a number of hypotheses based on observational experiments, regarding the decline of systolic function. These include impairment of b-adrenergic receptor signaling, increase in endogenous cannabinoids and presence of cardio-depressant substances [43-45].

The redistribution of blood volume (more blood volume in the splanchnic area and less blood volume in the central arterial area) and the low arterial blood pressure activates the SNS *via* volume-mediated receptors and baroreceptors, respectively [46]. The repercussion is sympathetic overactivity and increased levels of noradrenaline, which in turn damage the cardiomyocyte and alter the b-adrenergic signaling, either by desensitizing these receptors, altering their function resulting in decreased cyclic adenosine monophosphate (cAMP) production, or downregulating them [47, 48].

In addition, animal studies demonstrated that inflammatory states, such as cirrhosis increase the expression of endogenous cannabinoids (EC), especially anandamide (AEA). Experiments showed that reuptake inhibitors of AEA caused

cardiac hypo-responsiveness through Cannabinoid-1 (CB1) receptor [44].

Moreover, cardio-depressant substances, such as nitric oxide (NO) and carbon monoxide (CO), seem also to play a crucial role in the cirrhotic heart. Inflammatory cytokines promote NO production, which in turn stimulates cyclic guanosine monophosphate (cGMP). As a result, the main mediator of b-adrenergic stimulation, cAMP, is degraded. In addition, through activation of protein kinase G, the sarcolemma L-type calcium channels are inhibited along with the calcium release from the sarcoplasmic reticulum, thus limiting the contractile force of myocardium [49]. At the same way, CO acts on cardiac myocytes through cGMP, like NO [29]. All the antecedent pathophysiological changes produce a blunted cardiac responsiveness to volume, postural changes, exercise or pharmacological stimulus; features that have been recognized in cirrhotic patients.

3.2. Diastolic Dysfunction

Diastolic dysfunction is quite common in patients with liver cirrhosis and is associated with increased mortality [50, 51]. It has been demonstrated that myocardial fibrosis and increased myocardial mass induce increased stiffness of the myocardial wall with subsequent impaired ventricular filling and diastolic dysfunction [52]. Abnormal left ventricular relaxation impedes blood flow through the ventricle, increases left ventricular end-diastolic pressure and increases atrial contribution to late ventricular filling. These abnormalities are delineated by the increased E/A ratio and prolonged deceleration time on the 2-dimensional Doppler echocardiography [53].

It has also been documented that in cirrhotic patients there is increased bacterial translocation and endotoxemia due to decreased intestinal motility as well as increased intestinal permeability that altogether cause an alteration in the local mucosal immune system. Curiously, a recent study showed a marked correlation between the severity of diastolic dysfunction and serum levels of lipopolysaccharide-binding protein (LBP), a marker of exposure to bacterial endotoxin. It was assumed that the bacterial endotoxin heightened the splanchnic vasodilation thus worsening the cardiac load [54, 55]. This alteration of hemodynamic parameters intensifies salt and water retention. Salt loading increases aldosterone production, independently of the circulating RAAS, which contributes to cardiac hypertrophy. Fibrosis of the myocardium is stimulated by the activation of the angiotensin-1 receptor as well as the overexpression of transforming growth factor-b1 (TGF-B1), in the cardiac muscle [56, 57].

The diastolic dysfunction may precede the systolic alterations. Cardiac preload is the variable that plays a critical role in the development of diastolic dysfunction. Variations of pre-load determine the progress of impairment of diastolic compliance. This is why patients with ascites who undergone large-volume paracentesis and are able to increase the blood return to the heart have a substantial amelioration of diastolic dysfunction [43]. A well-known marker that is used for assessing diastolic dysfunction is E/A ratio [58, 59]. However, this marker is neither sensitive nor specific since it is influenced by changes in preload and afterload [60]. Diastolic

dysfunction is not related to the etiology of liver disease and its presence does not depend on the stage of liver disease (compensated vs decompensated cirrhosis). Though, its severity correlates with the degree of liver failure, meaning that there is an association between diastolic dysfunction grade and Child-Pugh score [55]. Importantly, diastolic dysfunction affects the prognosis of patients undergoing TIPS insertion or liver transplantation [61].

3.3. Rhythm Disturbances

The main electrocardiographic lesion of CCM is the prolongation of the QT interval. This finding is detected in 40-50% of cirrhotic patients. Other electrophysiological irregularities involve electromechanical uncoupling as well as chronotropic and inotropic incompetence [19, 62].

-Prolongation of QT interval: Portal hypertension causes prolongation of the QT interval (>440ms) even in the absence of cirrhosis. However, its presence in cirrhotic patients correlates well to the worsening of liver disease [19]. Since the heart rate is a factor that affects QT interval, it is mandatory to use specific formulas to assess for the exact interval, called QT corrected (QTc). Fridericia formula is the one that is applied in cirrhotic patients for calculation of QTc [63]. Different mechanisms have been proposed that eventually lead to prolong QT interval; autonomic dysfunction, exposure of different cytokines through portosystemic shunts to heart, high circulating levels of noradrenalin that cause hyperactivity of sympathoadrenergic discharge [64, 65], loss of K channel on the plasma membrane that is responsible for delayed ventricular repolarization [66-68]. Ventricular repolarization responsible for QT interval varies in its duration to even the slightest change in portal pressure among cirrhotic patients [19]. Concernedly, patients that before liver transplantation found to have prolonged QTc interval, 50% of them normalized it after liver transplantation [69]. On the other hand, chronic b-blocker therapy has shown a reduction in prolonged QT interval [70].

-Chronotropic incompetence: Any incapability of the cardiac muscle to increase its rate in response to metabolic demands and pharmacological stimuli is called chronotropic incompetence [71]. It has been hypothesized that desensitization and downregulation of beta-adrenergic receptors in the sinoatrial node are responsible for chronotropic incompetence, which is proportional to the severity of cirrhosis [72].

4. DIAGNOSIS

As we stated above, CCM is an indolent clinical entity that remains silent until end-stage liver disease, where the cardiac reservoir has obliterated. Hence, a group of experts tried to determine the criteria that define CCM and presented them in 2005, at the World Congress of Gastroenterology in Montreal. These criteria, consist of three major categories; systolic dysfunction, diastolic dysfunction and supportive criteria (laboratory findings, electrocardiographic abnormalities, imaging studies) [12, 73]. Patients with cirrhosis should be evaluated for any abnormalities on a routine basis because most of the times they present no signs from the cardiovascular systems until a stressor applied. Hence, it has been well demonstrated by many studies that procedures such as TIPS and liver transplantation may cause sudden heart failure and

pulmonary edema postoperatively if diastolic and systolic dysfunction is not detected before surgery [74, 75]. In order to detect systolic dysfunction, clinicians should not be based on the conventional echocardiographic assessment of LV systolic function that measures ejection fraction (EF) at rest, because due to hyper-dynamic state it seems that systolic function is normal. Currently, 2D-STE has been suggested as an additional marker for the accurate evaluation systolic function. This method may identify subclinical LV dysfunction at an earlier stage [76].

5. TREATMENT

Until nowadays, there is no established treatment strict for cirrhotic cardiomyopathy. Nonetheless, when CCM progresses into heart failure, patients are treated as those who are not cirrhotic but do have a failure of the cardiac pump. The mainstay of treatment is diuretics [12]. Non-selective b-blockers lessen the hyper-dynamic load in patients with cirrhosis and do cause an improvement in the QT interval. Whether this shortening of the QT interval has any beneficial effect on prognosis, is still questionable [77]. On the other hand, studies have shown that the cardio-depressant effect of b-blockers may increase the mortality rate in subjects with refractory ascites [78]. Likewise, angiotensin-converting enzyme (ACE) inhibitors, are not recommended since they deteriorate the vasodilatation that already characterizes the advanced cirrhosis [10]. Heart failure patients, NYHA class III and or IV, do have a substantial benefit by adding an aldosterone antagonist on their treatment, as studies have demonstrated that there is a significant decrease in hospitalization and mortality by 35% and 30%, respectively. Myocardial fibrosis, activation of the SNS and baroreceptor dysfunction are promoted by aldosterone effects hence, aldosterone antagonists may improve diastolic function by reducing myocardial fibrosis and left ventricular dilatation. Thus, more studies need to be conducted in order to further elucidate the role of aldosterone antagonists in CCM. On top of that, newer pharmacological agents against inflammatory cytokines and NO are under investigation in order to specifically target and battle CCM; for instance, agonists of farnesoid X receptor (a gene involved in intrahepatic generation of vasodilator hydrogen sulfide) and NCX-1000 (a new compound that releases NO in the liver).

CONCLUSION

When the cardiac muscle is diseased, this may have impacts on various other organs, such as the liver, kidneys, lungs, brain, *etc.* Similarly, it has been postulated that advanced liver diseases can lead to myocardial dysfunction. Liver cirrhosis that can be caused by a number of different factors; alcohol, steatosis, viruses, metabolic diseases, is commonly associated with hemodynamic abnormalities. The main culprits are the vasodilatory molecules that “escape” their catabolism by the diseased liver and get into systemic circulation through portosystemic shunts. The net result is increased cardiac output along with normal or decreased blood pressure and decreased systemic vascular resistance. The subsequent activation of SNS, RAAS and release of vasopressin in order to increase the endovascular volume lead to a stiff, hypertrophied and fibrotic ventricle. Diastolic

dysfunction drops into systolic dysfunction and electrophysiological lesions. Patients with a history of cirrhosis and worsening hemodynamics should further be evaluated for cardiomyopathy. Likewise, those who undergo TIPS or liver transplantation needs to be monitored and staged for any decompensation. There is no standard treatment specific for CCM, except this if heart failure. New strategies and treatment approaches need to be further investigated. However, because the prevention is still the most valuable and potential “treatment”, the clinician should be alert for any future complications.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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