Review Article

The heart: Pathophysiology and clinical implications of cirrhotic cardiomyopathy

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Received May 8, 2012; accepted June 8, 2012

Abstract

Cirrhosis is associated with hyperdynamic circulation, which consists of peripheral vasodilatation and increased cardiac output. Peripheral vasodilatation is central to hyperdynamic circulation and portal hypertension in cirrhosis. However, those mechanisms underlying hyperdynamic circulation remain elusive, and are not fully understood. Most of the earlier research and attention have been focused on humoral factor abnormalities. Various gut-derived or locally produced humoral factors such as nitric oxide, endotoxin, endocannabinoids, and others have been implicated as possible mediators of hyperdynamic circulation development in cirrhosis. The associated cardiac dysfunction had been termed “cirrhotic cardiomyopathy (CCM),” which is an entity different from that seen in alcoholic heart muscle disease. Clinically, these patients present with sodium fluid retention, and strain often unmasks the presence of latent heart failure. No specific treatment can yet be recommended, but caution should be used with respect to procedures that may stress the heart such as shunt implantation and liver transplantation. Ultimately, additional research will be necessary to more accurately describe the prevalence, impact, and morbidity and survival rates for CCM, and to identify potential treatments.

Keywords: cirrhotic cardiomyopathy; hyperdynamic circulation; portal hypertension

1. Introduction

1.1. Cirrhotic cardiomyopathy

Cirrhosis is a fatal condition. Most diseases that induce cirrhosis eventually progress, at variable rates, to end-stage liver failure. In addition, mortality due to hepatic failure, variceal bleeding, and infection are common in the advanced stages of the condition. In cirrhosis, despite hyperdynamic circulation at rest, the cardiac response to stimuli is blunted, a phenomenon termed cirrhotic cardiomyopathy (CCM).

In 1953, Kowalski and Abelmann described hyperdynamic circulation in patients with cirrhosis. This occurrence is characterized by increased cardiac output, decreased peripheral vascular resistance, and arterial hypotension. Because of the hyperdynamic circulation, it was initially assumed that cardiac function must be normal. However, studies from the late 1960s showed that ventricular contractile responsiveness to various stimuli such as drugs and exercise was blunted, suggesting latent cardiomyopathy. For example, in patients with cirrhosis, Gould et al reported that exercise doubled the left ventricular end-diastolic pressure, but did not change cardiac output, indicating a markedly blunted cardiac response. However, this and essentially all other studies of that era focused on patients with alcoholic cirrhosis, and thus cardiac dysfunction was presumed to reflect latent alcoholic cardiomyopathy. Only in the last 20 years was similar subnormal responsiveness documented in animal models of cirrhosis.
nonalcoholic cirrhosis.\textsuperscript{2–6} In the past several years, however, many studies have been published showing abundant evidence that humans with nonalcoholic cirrhosis also show similar myocardial hyporesponsiveness to stimuli.\textsuperscript{2–6} Indeed, in human nonalcoholic cirrhosis, both systolic and diastolic ventricular dysfunction have been clearly demonstrated.\textsuperscript{2–6}

Specific diagnostic criteria for CCM have recently been formulated by an international expert consensus committee (Table 1). The consensus definition of CCM is “chronic cardiac dysfunction in patients with cirrhosis, characterized by blunted contractile responsiveness to stress, and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease.”

CCM also satisfies the general definition of diastolic heart failure, i.e., prolonged/inadequate diastole in the presence of preserved/normal systole (such as ejection fraction). Certainly, diastolic dysfunction is present in patients and animal models with cirrhosis. Numerous studies have demonstrated that indices of diastolic filling, such as the E/A ratio [usually due to decreased “E” (early) diastolic filling], are often abnormal in patients with cirrhosis, even at rest.\textsuperscript{2–6} Thus in cirrhosis, diastolic dysfunction appears to be more common than systolic dysfunction.\textsuperscript{4–6,8} Indeed, the pioneering description of CCM by Gould and colleagues noted above represents an example of diastolic dysfunction.

### 1.2. Clinical implications of CCM

With the advent of procedures which stress the cardiovascular system, the clinical significance of CCM is being increasingly appreciated by general medical practitioners. In particular, the widespread use of liver transplantation has highlighted the limitation of cardiac reserve. Up to 56% of patients, most of them with no previous history of cardiac disease, develop clinical or radiographic evidence of pulmonary edema during their post-transplantation hospital course.\textsuperscript{9} Cardiac-related causes account for 7–15% of all deaths after transplantation.\textsuperscript{10,11} Moreover, other surgical stresses including transjugular (transjugular intrahepatic portosystemic shunt or TIPS) and surgical portosystemic shunting procedures have also been reported to precipitate overt heart failure.\textsuperscript{3–6,12} For example, in a recent large randomized trial comparing TIPS with large volume paracentesis, 12% of the TIPS group developed overt heart failure, whereas none of the paracentesis group suffered a similar heart-related problem.\textsuperscript{13}

Cazzaniga et al recently examined the predictive risk factors for death after TIPS insertion.\textsuperscript{14} Multivariate analysis showed that only the degree of diastolic dysfunction (E/A ratio) at day 28 after the procedure (but not baseline E/A) was a significant predictor of 1-year mortality. Thus, the diastolic response to the increased preload caused by the TIPS is crucial, as emphasized in our accompanying editorial.\textsuperscript{15}

Moreover, another recent study suggests that insufficient ventricular contractile reserve contributes to the pathogenesis of hepatorenal syndrome (HRS). Ruiz-del-Arbo et al studied 23 patients with cirrhosis who were admitted with spontaneous bacterial peritonitis (SBP).\textsuperscript{16} SBP is a known risk factor for the development of acute HRS. Despite antibiotic treatment and infection resolution, 8 patients developed HRS, whereas 15 had unimpaired renal function. The major difference between these two groups was the cardiac response: the HRS group had a lower baseline cardiac output than the non-HRS group. Moreover, cardiac output actually declined after infection resolution in the HRS group, whereas it remained unchanged in the non-HRS group. A longitudinal study by these authors found that amongst a cohort of 66 patients with severe cirrhosis, 27 who went on to develop HRS had lower cardiac output and elevated serum markers of hyperdynamic circulation.\textsuperscript{17}

The prototypical inflammatory phenotype of cardiac dysfunction is septic cardiodepression, mediated largely through cytokines such as tumor necrosis factor-\textgreek{z} (TNF-\textgreek{z}).\textsuperscript{18} Indeed, it has been suggested that CCM is indistinguishable from septic cardiodepression. However, there are several notable differences between the two syndromes; the most significant among them being the relative electrophysiological changes. The various phenomena found in patients with cirrhosis such as QT prolongation and electromechanical dyssynchrony (abnormally wide dispersion of the normally tightly regulated time interval between the onset of the electrical QRS complex and mechanical systole) have not been observed in septic cardiodepression.\textsuperscript{19,20} Moreover, correction of sepsis rapidly reverses the cardiodepression, whereas liver transplantation takes several months to reverse the functional contractile responses in CCM.

The medical community still has its skeptics regarding the existence of CCM, because overt heart failure is rare in patients with cirrhosis. However there are two important

<table>
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<th>Table 1</th>
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<td>Definition of cirrhotic cardiomyopathy.</td>
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<tr>
<td>General definition:</td>
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<tr>
<td>Cirrhotic cardiomyopathy is defined as chronic cardiac dysfunction in patients with cirrhosis, characterized by blunted contractile responsiveness to stress, and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease.</td>
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<td>Diagnostic criteria:</td>
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<td>1. Abnormal systolic contractile responses to stress.</td>
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<td>2. Diastolic dysfunction at rest.</td>
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<td>3. Absence of clinically significant cardiopulmonary disease.</td>
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<td>Systolic dysfunction (at least one of the following):</td>
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<td>1. Blunted increase in cardiac output with exercise, volume challenge or pharmacological stimuli:</td>
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<tr>
<td>2. Resting LVEF &lt;55%</td>
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<tr>
<td>Diastolic dysfunction (at least one of the following):</td>
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<tr>
<td>1. E/A ratio (age corrected) &lt;1.0</td>
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<td>2. Prolonged deceleration time (&gt;200 ms)</td>
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<td>3. Prolonged isovolumic relaxation time (&gt;80 ms)</td>
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<td>Supportive criteria:</td>
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<td>1. Electrophysiological abnormalities including the following:</td>
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<td>* Abnormal chronotropic response to stress.</td>
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<tr>
<td>* Electromechanical uncoupling/dysynchrony.</td>
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<td>* Prolonged QTc interval.</td>
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<td>2. Heart chamber alterations: enlarged LA, increased LVWT.</td>
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<td>3. Increased pro-BNP and BNP.</td>
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<td>4. Increased troponin I.</td>
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BNP = brain natriuretic peptide; LVEF = left ventricular ejection fraction; LVWT = left ventricular wall thickness.
Cardiac contractility is regulated by several systems including the sympathetic nervous system. The β-adrenergic receptor (β-AR) when occupied by norepinephrine leads to cyclic adenosine monophosphate (cAMP) generation, which then stimulates the protein kinase A-catalyzed (PKA catalyzed) phosphorylation of sarcoplasmic reticulum (SR) proteins [calcium-releasing receptors called ryanodine receptors (RyR)] that ultimately result in calcium transients which induce actin–myosin cross-bridging and thus cell contraction.23–25 PKA also phosphorylates several other key proteins to enhance contractility/relaxation, including phospholamban (which increases Ca\(^{2+}\)-reuptake by SR), troponin I on the thin (actin) filament, and myosin-binding protein-C on the thick (myosin) filament.

The β-AR–ligand complex acts via G proteins to stimulate the adenylate cyclase catalytic unit to generate cAMP.23,24 In the cirrhotic rat heart, it has been previously demonstrated that there are several defects in β-AR-signaling pathways, including decreased β-AR density, reduced Gs- and Gi-protein levels, uncoupling of β-AR–ligand complex from G protein, and reduced generation of cAMP.25–28

2.2. Altered membrane biophysical characteristics

It has also been shown that altered membrane biophysical characteristics, including decreased fluidity, impair cardiomyocyte function.4–6,29,30 However, normalization of fluidity in cardiomyocyte membrane preparations by an in vitro fluidizing fatty acid analog, A2C, only partially restored the cAMP-generating ability, suggesting that other mechanisms play a role in CCM.29,30

2.3. Endogenous cannabinoids

Endogenous cannabinoids such as anandamide are also involved in CCM. Bátkai et al reported increased circulating anandamide and expression of CB1 receptors in vascular endothelial cells of cirrhotic rats and patients with cirrhosis.31 Gaskari et al recently showed that blockade of endocannabinoid signaling improved cardiac contractility in cirrhotic rats both in vitro and in vivo through a CB1-mediated pathway dependent on Gi protein.32,33 The source of endocannabinoids appears to be local cardiac overproduction, stimulated by a stress such as tachycardia. Thus, cannabinoids may contribute to the blunted responsiveness to cardiovascular stimuli, but do not appear to affect baseline contractility. Increased TNF-α levels, acting via nuclear factor-kappa B–inducible nitric oxide synthase and p38MAPK-signaling pathways, play an important role in the pathogenesis of cardiodepression in cirrhotic mice. TNF-α also suppressed contractility by increasing oxidative stress and endocannabinoid activity.35

2.4. SR

The major source of cytosolic calcium transients is the SR. Not only is the flux of intracellular calcium via RyR release critical for systolic contraction, but also is the reuptake of calcium by SR Ca\(^{2+}\)-adenosine triphosphatase (called SERCA-2) significantly affects relaxation rates.36 Phospholamban regulates SERCA-2 by phosphorylation. A previous study showed that SR mechanisms of calcium release and reuptake, including RyR2 (the cardiac isoform) and SERCA protein expression, are intact in the cirrhotic bile duct-ligated rat heart.37 Thus, to date, calcium-cycling abnormalities in CCM seem to be limited to the plasma membrane. Accordingly, the primary focus of the current grant proposal is not SR function.

3. Cardiac function and liver transplantation

When a new liver is implanted, the circulating concentrations of cardiotoxic and vasoactive substances should be reduced; liver transplantation should, therefore, improve circulatory changes including the hyperdynamic circulation. However, some authors have seen a persistent increase in cardiac output for up to 2 years after liver transplantation, whereas others have reported an immediate attenuation of the hyperdynamic circulations.38–40 Therefore, the duration of hyperdynamic adaptation after liver transplantation is not yet completely understood. The events occurring during the intraoperative period should be separated from the immediate postoperative period and more sustained events. The surgical procedures significantly stress the heart by causing a sudden reduction in the cardiac preload, resulting in a decrease in cardiac output.10 Bleeding and fluid losses during the operation can further reduce cardiac output. Pulmonary edema has been observed in a considerable number of patients partly because of excessive fluid administration.9,10 Another critical period during the operation is that of reperfusion of the graft which can, in the occurrence of a postreperfusion syndrome with cardiac instability, reduce arterial blood pressure and heart rate.10 However, currently there is no reliable method to identify patients who are susceptible to developing these cardiac complications. Therapondus et al reported that the serum BNP value ≥ 250 pg/mL as a predictor of cardiac failure in the early post-transplantation period.11 However, Donovan et al identified only a few patients with left ventricular dysfunction postoperatively, and all these patients had normal preoperative cardiac function; therefore, it was not
possible to predict perioperative cardiac failure in this study.\(^9\) Abnormal cardiac responses during transplantation have been related to a longer postoperative incubation period.\(^{43}\) Interestingly, in that study, hyponatremia and indicators of effective hypovolemia predicted an abnormal cardiac response.

Postoperatively, there is a decrease in cardiac output, heart rate, pulmonary artery pressure, and an increase in arterial blood pressure and systemic vascular resistance.\(^{39,42}\) Torregrosa et al noted a significant improvement in cardiac performance and a reduction in myocardial mass between 6 and 12 months after liver transplantation.\(^{43}\) Furthermore, diastolic and systolic function improved significantly during this period.

More than 80% of patients with end-stage liver disease may have a cardiovascular and autonomic dysfunction before liver transplantation.\(^{44,45}\) About two-thirds of the patients with cirrhosis have an autonomic dysfunction before liver transplantation.\(^{41,44,46}\) The prolonged QT interval reverses in about half of the patients after liver transplantation, probably as a result of diminished portosystemic shunting.\(^{43,47,48}\) But in a minority of the patients, the QT interval may worsen after liver transplantation.\(^{46}\)

In conclusion, liver transplantation is the ultimate treatment for patients with end-stage liver disease, but perioperatively it exerts a considerable stress on the cirrhotic heart. However, proper identification of patient at risk of developing cardiac failure is difficult. Dobutamine stress test has been applied to identify patients at risk of developing cardiac complications but at present we need a more sensitive and specific test to identify those patients who will develop cardiac failure after liver transplantation. Postoperatively, cardiac function seems to normalize with improvements in cardiac hypertrophy, diastolic and systolic function, and QT interval, but more studies on the cardiac effects are needed.

In conclusion, the impaired cardiac contractility in CCM is different from that seen in alcoholic heart muscle disease (Table 2). Among the significant pathophysiological mechanisms involved in CCM are reduced β-AR signal transduction and a defective cardiac electromechanical coupling.\(^{48,49}\) The cirrhotic heart may be overloaded with a high-output failure, while being hyperdynamic with a diastolic dysfunction; strain may unmask a latent congestive heart failure. No specific therapy can be recommended for this condition, and management of patients with CCM should be directed to prevent congestive heart failure and include conventional treatment for pulmonary stasis with diuretics. Vasodilators, such as angiotensin-converting enzyme inhibitors, should not be used because they present the risk of further aggravation of the systemic vasodilatory state. Aldosterone antagonists may have beneficial effects in terms of a reduction in left ventricular dilatation and wall thickness as well as improvement of diastolic function. Cardiac glycosides do not seem to improve cardiac contractility in CCM. In addition to their lowering effect on portal pressure, β-blocker may reduce the hyperdynamic load and improve the prolonged QT interval, but future research should elucidate whether they also improve the contractile dysfunction, electromechanical abnormalities, and mortality. In addition, CCM seems to play a role in the development of HRS. Lastly, we conclude that liver transplantation improves most of the cardiac dysfunction.

### References


