

Cirrhosis-Associated Cardiomyopathy

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Abstract

Liver cirrhosis is the 12th leading cause of death in the US. The heart is one of the most adversely affected organs in liver cirrhosis. Cirrhosis-induced cardiomyopathy describes the cardiac dysfunction in patients with cirrhosis characterized by impaired contractile response to stress and/or altered diastolic relaxation with electrophysiologic abnormalities in the absence of other known cardiac disease. The current definition of cirrhosis-induced cardiomyopathy does not take into account recent evidence of resting contractile and relaxation dysfunction that can be appreciated by advanced imaging tools such as Doppler tissue imaging and cardiac magnetic resonance imaging. Cirrhosis-induced cardiomyopathy is caused by cellular as well as physiological mechanisms including but not limited to: beta adrenergic receptor dysfunction, calcium channelopathy, elevated levels of catecholamines, elevated levels of nitric oxide, carbon monoxide and hydrogen sulphide and stimulation of endogenous cannabinoid pathways capable of producing negative inotropic, relaxation, and electrophysiological defects. Currently there is no specific therapy for cirrhosis-induced cardiomyopathy. There is some evidence that short courses of beta blockers may restore prolonged QT interval to normal values. Also, there is an emerging evidence for a role of aldosterone antagonists in reducing myocardial hypertrophy. Liver transplantation may revert cardiac dysfunction, but surgery and shunt insertion may also aggravate the condition. More standardized tools are needed to screen for and treat cirrhosis-induced cardiomyopathy.

Introduction

Cirrhosis refers to a progressive, diffuse, fibrosing condition that disrupts the normal architecture of the liver, caused by a myriad of conditions with the most common being: alcohol, viral, and non-alcohol fatty hepatitides. Typically, approximately 80-90 percent of the liver parenchyma needs to undergo destruction before liver failure is manifested clinically [1]. Liver cirrhosis is the 12th leading cause of death in the US with a mortality rate of 9.7 per 100,000 persons [2].

Of intrigue, is that the heart is one of the most adversely affected organs in liver cirrhosis. Cardiac dysfunction as a consequence of cirrhosis has been implicated in a host of clinical scenarios that includes but not exclusive to sudden deaths after Orthotopic Liver Transplantation (OLT), Transjugular Intrahepatic Portosystemic Stent Shunt (TIPS), and surgical portocaval shunts [3]. Of concern, these cardiac deaths occur despite exclusion of cardiac disease by routine investigations, underscoring the subtlety and seriousness of this condition.

The spectrum of heart diseases affected by liver cirrhosis includes 3 major groups; underlying heart disease aggravated by cirrhosis, heart disease that is caused by a pathological process that co-affects the heart and liver, and heart disease that is cirrhosis-associated. The latter can further be classified into the following categories: vascular, pericardial and myocardial.

We believe that the term 'cirrhosis-associated cardiomyopathy' is superior to the term 'cirrhotic cardiomyopathy' because it better defines the role of cirrhosis in causing cardiomyopathy. The latter term does not differentiate between cardiomyopathy caused by cirrhosis per se versus cardiomyopathy caused by the underlying cause of cirrhosis. The former term will be used for the rest of this review.

Cirrhosis-Associated Cardiomyopathy (CAC) describes the cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiologic abnormalities in the absence of other known cardiac disease [4]. This syndrome is seen in approximately 40-50% of adult patients with cirrhosis [5], and in children with biliary atresia [6]. The clinical manifestations of this syndrome may correlate with the severity of cirrhosis [7].

This review will discuss the following: historical perspectives, pathogenetic mechanisms, clinical characterization, and treatment options of CAC.

Historical Perspective

The attempts to characterize cardiac dysfunction in hepatic cirrhosis generated three main questions:

- Whether there is a cardiac dysfunction in cirrhosis?
- Whether cardiac dysfunction is caused by cirrhosis per se or by the underlying etiology of cirrhosis (i.e. whether CAC is cirrhosis-induced or an etiologically-linked phenomenon)?
- Whether CAC is a resting or a stress-induced syndrome?

Initially, it was thought that patients suffering from liver cirrhosis were protected from coronary artery thrombosis given the accompanying coagulopathy of advanced liver disease. The initial report of a cardiovascular abnormality in patients suffering from cirrhosis came from a pioneering report by Kowalski et al. [8] of 22 patients with liver cirrhosis secondary to heavy alcohol intake all with an elevated resting cardiac output that was out of proportion to oxygen consumption, had reduced peripheral vascular resistance and a prolonged QT interval. Noteworthy, these hemodynamic changes were the same for patients with ascites compared to those without ascites. Also of importance, these patients did not have any history of baseline cardiac disease. In an attempt to study the cardiac performance in cirrhosis during exercise, Abelmann et al. [9] studied 11 patients with alcohol-induced cirrhosis

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both at rest and during mild exercise. Under resting conditions, a hemodynamic profile similar to that reported by Kowalski et al was observed. During mild exercise, all patients demonstrated an increase in cardiac output that was out of proportion with their increase in oxygen consumption. These findings were observed both in patients with and without ascites. Based on these findings, the authors concluded that patients with advanced alcohol-induced liver disease who were not thiamine-deficient in fact possess adequate cardiac reserve during periods of stress. Answering the question of whether non-cirrhotic alcoholics show the same hemodynamic response to exercise, the same investigators reported a less pronounced increase in cardiac output to exercise (an increase in blood flow of 703 ml/100ml increase in O₂ consumption in non-cirrhotics versus 1318ml/100ml increase in O₂ in non-cirrhotic alcoholics) [10]. This study by Murray and colleagues [11] added more insight into the prevalence of hyperdynamic circulation in non-alcoholic cirrhotic patients. Compared to normal controls and patients with biliary cirrhosis, patients with parenchymal (portal) cirrhosis demonstrated significantly higher resting cardiac output, lower calculated peripheral vascular resistance and hypervolemia. Noteworthy, cirrhosis in the study patients were not exclusively caused by alcoholism. Taken together and using cardiac output as a surrogate of left ventricular contractility, patients without a baseline cardiac disease, and regardless of the underlying etiology of cirrhosis, manifest a profound hyperdynamic circulation under rest and exercise that correlates directly with the severity of disease.

A decade later, growing evidence emerged suggesting an impaired cardiovascular responsiveness of patients suffering from cirrhosis to pharmacologic and physiologic stress. Regan et al. [12] reported the left ventricular response of patients with alcohol-induced cirrhosis without baseline cardiac disease to the vasoconstrictor, angiotensin. Compared with normal controls, patients with cirrhosis demonstrated a significant rise of left ventricular end diastolic pressure with no increase in stroke volume. Normally, angiotensin, an afterload enhancer and potent vasoconstrictor, provokes an increase in stroke work and stroke output as a result of increase in left ventricular contractility. Gould et al. [13], then Limas et al. [14] demonstrated a significant reduction in stroke volume and cardiac output with a concomitant increase in left ventricular end diastolic pressures during both physiologic and pharmacologic stress test, the latter being produced by ouabine, a potent inotrope. This apparent contradiction in exercise response between the Gould's/Limas' and Murray's groups may be attributed to a more severe form of exercise and measurement of left sided filling pressures in the former compared with the latter. As opposed to enhanced insight into the stress response of patients with cirrhosis, these studies resulted in unanswered questions; was this measured response an alcohol-effect or an effect caused by the disease itself, cirrhosis?.

That question remained largely unanswered until Caramelo et al. [15] infused saline into rats with carbon tetrafluoride-induced cirrhosis and observed a 50% reduction in cardiac output along with a 112% increase in peripheral vascular resistance. This study seemed to indicate that cardiac dysfunction acquired during cirrhosis was actually caused as a result of the cirrhosis rather than being a consequence of alcohol. Multiple observational animal and human studies have subsequently followed emphasizing the impairment of stress responsiveness in alcoholic and non-alcoholic cirrhosis patients [16-18]. So in summary, cirrhosis itself is associated with cardiac dysfunction in the form of a hyperdynamic circulation at rest with impaired responsiveness to physiologic and pharmacologic stressors. This picture is reproducible irrespective of the etiology of cirrhosis.

Clinical Characterization of Cirrhosis-Associated Cardiomyopathy

Cardiac dysfunction resulting from cirrhosis can be separated into: systolic dysfunction, diastolic dysfunction, and electrophysiological dysfunction.

Systolic dysfunction

According to the current working definition of cirrhosis-induced cardiomyopathy (Table 1), systolic dysfunction describes a contractile defect that is uncovered by stress. Based on this definition, cardiac output and ejection fraction are used as surrogates of contractility. As well, systolic function is interchangeably used with contractile function. It is not entirely clear from this definition whether the use of more sensitive markers of myocardial contractility would reveal a resting contractile dysfunction in the presence of a high cardiac output.

The high resting cardiac output and lower filling pressures encountered in patients with cirrhosis is partially explained by low systemic vascular resistance and increased arterial compliance [19]. Physical exercise, however, is associated with a significant elevation of left ventricular filling pressures and a relatively smaller increase in cardiac output, ejection fraction and heart rate [20]. A less than optimal exercise-induced increase in ejection fraction in the presence of an exercise-induced lowering of afterload is a sign of left ventricular contractile dysfunction. Similarly, other stresses that increase either the preload (OLT [21], TIPS [22], sodium load [23]), or afterload (angiotensin [14]) have been associated with acute cardiac decompensation. These changes have been shown to be more pronounced in patients with ascites [24].

Recently, cardiac magnetic resonance imaging (CMRI) and advanced echocardiography technologies have uncovered more of the subtleties of CAC. As assessed by CMRI, there is a modest increase in left ventricular mass, left ventricular end-diastolic and left atrial volumes [25]. A recent echocardiographic study using tissue Doppler imaging [26] revealed a significant increase in left ventricular end-

Cardiac dysfunction in patients suffering from cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with associated electrophysiological abnormalities in the absence of other known cardiac disease.

Diagnostic criteria:

Systolic dysfunction

- Blunted increase in cardiac output with exercise, volume challenge or pharmacological stimuli
- Resting EF <55%

Diastolic dysfunction

- E/A < 1
- Prolonged deceleration time (> 200 msec)
- Prolonged isovolumetric relaxation time (< 80 msec)

Supportive criteria

- Electrophysiological abnormalities
- Chronotropic incompetence
- Electromechanical uncoupling
- Prolonged QTc interval
- Enlarged left atrium
- Increased myocardial mass
- Increased BNP, pro-BNP
- Increased Troponin I

Table 1: Working Definition of Cirrhosis-induced Cardiomyopathy.

diastolic diameter and a reduction in peak systolic velocity and systolic strain rate. Peak left ventricular systolic velocity and strain measured by tissue Doppler are considered more sensitive indices of left ventricular contractile function than the ejection fraction and cardiac index [27]. This is because these markers are more indicative of the more vulnerable longitudinally-arranged sub-endocardial fibers [27]. These findings strongly suggest resting structural and contractile changes in patients with cirrhosis that are not included in the current definition. Similar structural changes have been observed in children with biliary atresia scheduled for liver transplantation [6].

Reduced systolic function may have prognostic implications such as the development of ascites and renal dysfunction [4].

Taken together, there is existing evidence showing that contractile dysfunction in cirrhosis takes place under resting conditions and that it has prognostic implications.

Diastolic 'lusitropic' dysfunction

Diastolic or lusitropic dysfunction is a prominent feature of CAC. This describes an impairment of ventricular filling as a result of alterations in the receptive ventricular properties. The term 'lusitropic' dysfunction may be preferred to 'diastolic' since some phases of ventricular filling actually occur during systole [28], and since diastole is an interval and not a property. The term 'lusitropic' dysfunction more specifically describes ventricular relaxation properties.

The underlying mechanism of lusitropic dysfunction in cirrhosis is increased myocardial wall stiffness most likely due to myocardial hypertrophy, fibrosis and sub-endothelial edema [19] resulting in high filling pressures of the left ventricle and atrium and ultimately increasing the risk of pulmonary edema because of the backward failure.

One of the criteria used in the current definition of CAC needs to be interpreted with caution. Normally, the velocity of early rapid ventricular filling (denoted by E) is greater than the late filling phase that is dependent on atrial contraction (denoted by A) [29]. Therefore, E/A less than 1 may denote impaired ventricular relaxation. A low E/A , however, is highly preload-sensitive. Patients with decompensated cirrhosis may retain fluids which may mask the diagnosis of an underlying lusitropic dysfunction. Also, $E/A < 1$ may be a normal age-related variant. Moreover, The American Society of Echocardiography has included tissue Doppler imaging criteria in the diagnosis of lusitropic dysfunction [30]. Doppler tissue imaging measures the slow velocity high amplitude annular tissue motion (denoted by E') which is less affected by preload. An increase in the E'/E ratio has been used as a more sensitive measure of lusitropic dysfunction [31].

Lusitropic dysfunction is more prevalent in patients with ascites, and some have reported that it improves following paracentesis. Most recent evidence, however, did not find a correlation between lusitropic dysfunction and the severity of liver disease [26]. As one might predict, liver transplantation has been shown to reverse lusitropic dysfunction [24].

Electrophysiological dysfunction

Electrophysiological dysfunction includes: prolonged QT interval, chronotropic incompetence and electromechanical dissociation. QT interval prolongation adjusted for heart rate (QTc) is found in approximately 50% of patients with cirrhosis [32]. It has been shown to be significantly related to the severity of liver disease, plasma norepinephrine levels, and the presence of portal hypertension [33].

Prolonged QT interval was independently associated with the risk of sudden death in cirrhosis, although the latter is relatively uncommon [32]. The most likely underlying mechanism is dysfunctional potassium channels prolonging the duration of action potential and QT interval [34]. Studies on the dispersion of QT interval (i.e., difference between the longest and shortest interval) report a normally maintained diurnal variation in patients with liver cirrhosis [35]. A recent retrospective study reported that prolonged QTc (>463 msec) independently predicted mortality from gastrointestinal bleeding [36]. Beta receptor blockade seems to restore a normal QT interval in some individuals [37]. Also, prolonged QTc is partly reversible by liver transplantation, despite being prolonged during the early phase of transplantation [38].

Chronotropic incompetence refers to the inability of the heart rate to respond to physiologic and pharmacologic demands such as exercise, head tilt, inotropes, and a higher than normal increase in plasma norepinephrine concentrations. This has been a consistent finding in alcoholic as well as non-alcoholic cirrhosis [18].

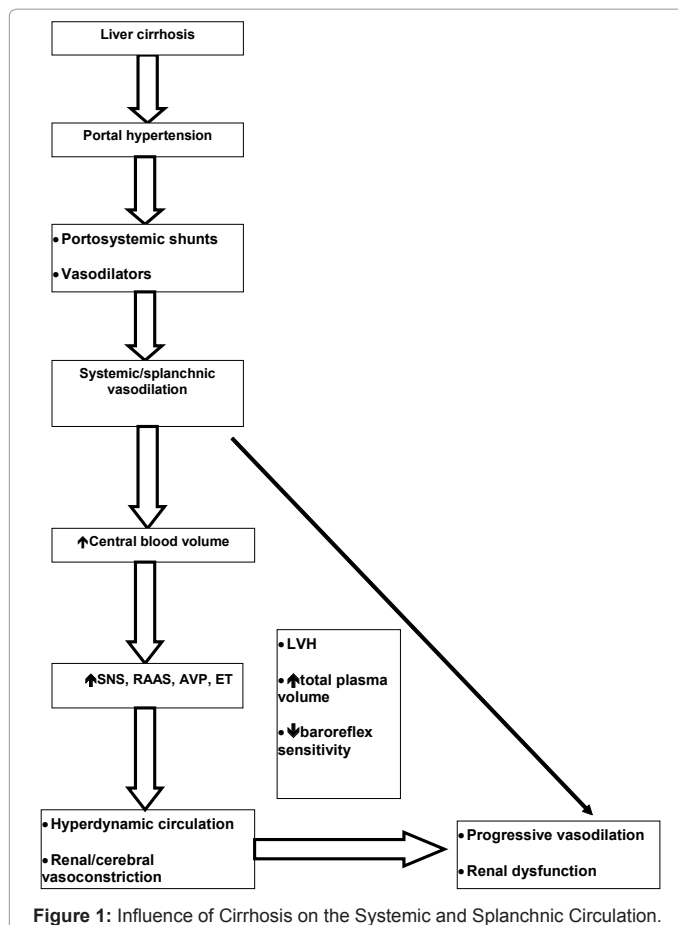
The inability to increase the heart rate in response to demands may partially explain reduced cardiac output under these conditions.

The time between the onset of electrical and mechanical systole is normally tightly controlled and is referred to as electromechanical coupling. A defect in electromechanical coupling leads to the dyssynchrony between electrical and mechanical systole. Bernardi et al. [17] demonstrated prolongation of pre-ejection phase at rest, together with defective shortening with exercise in patients with cirrhosis denoting a defect in electromechanical coupling. Henriksen et al. [37] reported a substantially increased difference between electric and mechanical systole in cirrhotic patients with prolonged QTc interval compared to those with normal QTc interval. The duration of mechanical systole was normal, however. A recent study [39] demonstrated a normal duration of left ventricular mechanical systole in cirrhotic patients with normal ejection fraction.

Physiological Mechanisms

Circulatory disturbances

Circulatory disturbances that occur in cirrhosis play a key role in CAC. The initiation of portal hypertension triggers 'progressive arteriolar vasodilation' of the systemic and splanchnic circulation [40]. It is theorized that this vasodilation is secondary to the escape of systemic and intestinal vasodilators from degradation by the diseased liver, as well as the formation of new blood vessels in the gut. The resulting splanchnic pooling of blood leads to a reduction in the central effective blood volume, and activation of vasoconstrictor systems such as the Sympathetic Nervous System (SNS), the Renin-Angiotensin-Aldosterone System (RAAS), vasopressin, endothelin and neuropeptide Y [41], to increase the cardiac output and restore vascular tone, hence the development of a hyperdynamic state. Because of the surplus of vasodilators, the splanchnic circulation becomes less responsive to the effects of agents such as norepinephrine, angiotensin, and vasopressin [42]. The arterial pressure is thus mainly maintained by renal, cerebral and hepatic vascular vasoconstriction leading to compromise of the blood flow to these organs. This cascade continues until this sustained elevation in cardiac output becomes ineffective to meet the excessive demands of the hyperdynamic circulation. Moreover, vicious activation of the RAAS induces cardiac morphological changes in the form of left ventricular hypertrophy leading to lusitropic dysfunction, preload intolerance and propensity for pulmonary edema formation [43] (Figure 1).



Cardiac autonomic dysfunction

Reduced baroreceptor sensitivity is one of the hallmarks of CAC. In fact, it has been shown that baroreceptor sensitivity is reduced in cirrhosis and that was significantly related to serum sodium, heart rate and central circulation time [44]. Moreover, reduced baroreceptor reflex sensitivity has been shown to inversely correlate with left ventricular mass [45]. These results suggest a link between reduced baroreceptor sensitivity and end organ damage in cirrhosis. Whether this reduction in sensitivity is a marker or a factor in the pathogenesis of CAC remains to be determined.

Biomarkers of cardiac dysfunction

Serum levels of markers of myocardial injury, stretch, and failure were shown to be elevated in patients with cirrhosis irrespective of aetiology. Troponin I, a marker of myocardial injury, was shown to be elevated in some patients with cirrhosis with reduced stroke-volume index and left ventricular mass index. This increase was unrelated to the severity of cirrhosis [46].

Similarly, Brain Natriuretic Peptide (BNP), a marker of left ventricular failure that signals to induce natriuresis, diuresis and vascular tone relaxation, was shown to be elevated in patients with advanced non-alcoholic cirrhosis who also manifested echocardiographic signs of left ventricular hypertrophy [47,48]. With this said, there is a need for more precise markers to assist with enhanced diagnostic, management and prognostic value in the CAC.

Cellular Mechanisms

Beta adrenergic receptor pathway

Cardiomyocyte contractility is primarily mediated via beta adrenergic signaling pathway. In brief, stimulation of β -adrenergic receptors lead to activation of a stimulatory “GS” protein which in turn leads to activation of the membrane-bound enzyme adenylyl cyclase leading to the formation of cyclic Adenosine Monophosphate (cAMP) from Adenosine Triphosphate (ATP). Cyclic AMP activates a protein kinase A which stimulates the release of calcium from the sarcoplasmic reticulum. This in turn mediates actin-myosin fibrillar cross linking leading to cellular contraction.

In cirrhosis, several abnormalities in the β -adrenergic pathway have been identified. For example, there is a reduction in β -adrenergic receptor density [49], GS proteins [50], and adenylyl cyclase activity leading to a reduction in net cAMP generation [51]. In addition, there have been reports of altered membrane fluidity due to changes in the lipid composition of the cardiomyocyte plasma membrane with increased cholesterol/phospholipids ratio resulting in a decreased signaling of β -adrenergic receptors [52]. As part of the plasma membrane abnormalities, multiple investigators have demonstrated abnormalities of L-type calcium channels in the form of decreased receptor density and altered electrophysiological function [53], decreased channel protein expressions, and attenuated response to direct isoproterenol stimulation. Intracellular calcium dynamics were normal compared with controls [53], however, pointing to a cardiomyocyte cell membrane defect rather than intracellular calcium system's defect.

Endogenous cannabinoid signaling pathway

Normally the endogenous cannabinoid signaling pathway is minimally expressed. In cirrhosis, however, there is an up-regulation of this system resulting in negative inotropic effects [54]. These negative inotropic effects are primarily mediated by endocannabinoid subtype-1 (CB-1) receptors via stimulation of the inhibitory G (Gi) protein which inhibits adenylyl cyclase with resultant reductions in cAMP. In a rat model of cirrhosis [55], the contractile response of cardiac papillary muscle to isoproterenol was significantly blunted. Restoration of this response occurred with the administration of a cannabinoid receptor-1 antagonist [55]. In another rat model of cirrhosis, the endogenous CB-1 agonist, anandamide was associated with inhibition of cardiac contractility. Administration of the CB-1 antagonist, AM251 led to recovery of contractility [56].

Evanescent Gases

Nitric oxide and carbon monoxide

Nitric oxide (NO) and Carbon monoxide (CO) pathways have negative inotropic effects. Both NO and CO are produced by inducible NO synthase (iNOS) and hemeoxygenase (HO), respectively. Both gases stimulate guanylate synthase enzyme to generate cyclic guanosine monophosphate (cGMP), which phosphorylates protein kinase G to inhibit calcium influx into the cardiomyocyte. In a rat model of cirrhosis, stimulation of NO pathway by endotoxins or cytokines resulted in a negative inotropic effect that was reversed by incubating rats with the iNOS inhibitor L-NMMA [57]. In a similar rat model of cirrhosis [58], HO gene expression was augmented in cirrhotic rats compared with controls. Also, the use of HO inhibitors reversed blunted contractile properties of isolated cardiac papillary muscles.

Together, these findings suggest a negative inotropic effect of NO and CO in CAC.

Hydrogen sulphide

Recent evidence has emerged on a role for endogenous hydrogen sulphide in the chronotropic incompetence observed in cirrhosis patients. In a rat model of cirrhosis, incubation of isolated atria with inhibitors of hydrogen sulphide synthesis, led to the restoration of chronotropic responsiveness during adrenergic stimulation [59]. This area is intriguing especially since the exogenous administration of these gases is possible, but further studies are needed to explore these pathways.

Role of inflammatory mediators and cytokines and apoptosis

Cirrhosis-associated cardiomyopathy is associated with elevated catecholamine levels as a result of sympathetic over activity. There is a link between sympathetic over activity and the elevation of inflammatory cytokines such as Interleukin-8 (IL-8), Interleukin-6 (IL-6), Interleukin-1b (IL-1b), and tumor necrosis factor- α in CAC. Interestingly enough, transforming growth factor- β (TGF- β), an abundantly elevated cytokine in cirrhosis, is a potent profibrogenic and proapoptotic stimulant [60]. It is theorized that TGF- β stimulates mitogen-activated protein kinases (MAPK), particularly the isoform MAPK/P-38-, in cardiomyofibroblasts. Rat models of ischemia pre [61]- and post-conditioning [62] have shown a strong contributory role of MAPK/P38- α in cardiomyocyte apoptotic cell death reversible by using a specific MAPK/P38- α inhibitor. Activation of MAPK/P38- α by TGF- β highlights apoptosis as a mechanism of CAC. Further studies are needed to characterize the specific apoptotic mechanisms involved in CAC.

Other potential pathways

More evidence is emerging on the role of nuclear factor- κ B [63] and cardiac myofilament proteins titins and collagen and an altered ratio of the stiffer collagen I and the more compliant collagen III [64]. The latter specifically affects the lusitropic properties of the heart.

Aspects of Treatment

To date there are no clinical trials on the management of CIC. Patients in heart failure should be treated following guidelines for non-cirrhosis induced cardiac failure. Noteworthy, the use of afterload reducers may not be well-tolerated given the widespread and progressive vasodilation characteristic of cirrhosis. Short courses of non-selective beta blockers were shown to restore prolonged QT intervals towards normal [37]. No recommendation, however, for the chronic use of beta blockers can be made at the present time. Cardiac glycosides are less effective inotropes. A potential role for the aldosterone antagonist, K-canrenoate exists to reverse the RAAS-induced myocardial fibrosis in pre-ascitic cirrhosis [65]. Despite the theoretic appeal, more studies are needed to further explore this approach.

Liver transplantation is thought to ameliorate both the hyperdynamic and the intrinsic myocardial dysfunction in cirrhosis. The time frame for this improvement to take place is not entirely clear, however. Some studies [66] have shown an immediate amelioration of the hyperdynamic state after OLT, others have demonstrated persistence of hyperdynamic circulation for 2 years after transplantation [67]. A recent study of 40 patients scheduled for liver transplantation has reported amelioration of left ventricular hypertrophy, lusitropic dysfunction as well as normalization of the contractile response to stress

after transplantation [24]. Having said this, OLT as a procedure carries its own challenges to the cirrhotic heart. Some of these challenges are: abrupt decrease in cardiac output due to decreased cardiac preload resulting from clamping of the inferior vena cava, fluid losses and coagulopathy, post reperfusion injury that may lead to further reduction in cardiac contractility and heart rate, and the propensity for development of post-operative hydrostatic pulmonary edema secondary to fluid overload. It is of concern that there are no currently available means of screening for patients prone to the development of cardiac complications in the peri-transplantation period [19]. Cirrhotic patients with concomitant severe cardiomyopathy may benefit from cardiac transplantation [68].

Conclusion

Cirrhosis-associated cardiomyopathy is a cirrhosis-induced structural cardiac disease that is shown to manifest at rest and under stress, and an entity that can be overlooked by conventional investigations that are routinely performed. It is caused by myriad of physiological and cellular mechanisms, with many yet to be totally understood. To date, no specific treatment, other than liver transplantation, exists for this syndrome. Lastly more standardized tools are needed to screen for this disease.

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