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Concise Review

Cirrhotic cardiomyopathy

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Abstract

Liver cirrhosis is associated with a wide range of cardiovascular abnormalities. These abnormalities include hyperdynamic circulation characterized by an increase in cardiac output and a decrease in peripheral vascular resistance. Despite the increased cardiac output, impaired ventricular contractility in response to both physiological and pharmacological stimuli has been described. Other cardiac abnormalities include structural changes including enlargement or hypertrophy of different cardiac chambers and electrophysiological changes such as QT prolongation. This constellation of cardiac abnormalities is termed cirrhotic cardiomyopathy. The pathogenic mechanisms of cirrhotic cardiomyopathy are multifactorial and include cardiomyocyte plasma membrane physico-chemical changes, attenuated stimulatory pathways, and enhanced activity of inhibitory systems. Accumulating evidence suggests that cirrhotic cardiomyopathy plays a major role in the pathogenesis of cardiac dysfunction following liver transplantation or transjugular intrahepatic portosystemic shunt placement. Recent research also strongly suggests that cirrhotic cardiomyopathy contributes to the pathogenesis of hepatorenal syndrome, especially following infections such as spontaneous bacterial peritonitis. Treatment of this syndrome remains largely empirical. Successful liver transplantation is thought to improve all the organ-related hemodynamic dysfunctions, including hepatopulmonary syndrome, cerebral hypoperfusion, hepatorenal syndrome, and cirrhotic cardiomyopathy. The prolonged QT interval normalizes following liver transplantation. Thus, liver transplantation appears to be the ultimate treatment for the cardiovascular complications of cirrhosis.

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Introduction

Liver cirrhosis is associated with a wide range of cardiovascular abnormalities. This was first described by Kowalski and Abelmann who noted a higher resting cardiac output an decreased systemic vascular resistance in patients with cirrhosis.[1,2] Following that, numerous studies confirmed the existence of hyperdynamic circulation characterized by peripheral vasodilatation and increased cardiac output. However, despite the hyperdynamic circulation, impaired ventricular contractility in response to stimuli was described in cirrhotic patients.[3-7] These abnormalities were initially thought to be a manifestation of latent alcoholic cardiomyopathy. But in the mid-1980s, studies in nonalcoholic patients and in experimental animal models showed a similar pattern of blunted cardiac contractile responsiveness.[8-10] Thus these cardiovascular changes are now termed 'cirrhotic cardiomyopathy'.[11-14] Overt heart failure is not generally a feature of cirrhotic cardiomyopathy, because the associated marked vasodilatation accompanying the hyperdynamic circulation significantly reduces ventricular afterload. The following is a concise review of the clinical features, pathogenesis and management of cirrhotic cardiomyopathy.

Clinical features

In the absence of specific diagnostic criteria, the exact prevalence of cirrhotic cardiomyopathy remains unclear. At present, cirrhotic cardiomyopathy can be defined as the constellation of one or more of these following factors: 1) normal or increased left ventricular systolic contractility at rest, but attenuated systolic or diastolic responses to stress stimuli, 2) structural or histological changes in cardiac chambers, 3) electrophysiological abnormalities such as prolonged electrocardiographic QT interval, 4) serum markers suggestive of cardiac stress.

1. Systolic/diastolic dysfunction

Despite the increased or normal cardiac output at rest, under physiological stress cirrhotic patients fail to mount an adequate stimulatory cardiac response. Gould et al documented in cirrhotic patients that with exercise the left ven-

tricular end-diastolic and pulmonary arterial pressures increased with no change in the cardiac index. In other words, cardiac output did not increase despite increased ventricular filling pressures, which indicates a highly impaired ventricular response.[6] Similarly Grose et al showed that when cirrhotic patients underwent maximal exercise, cardiac output increased by only 97%; this is considered inadequate when compared to approximately 300% increase in healthy controls.[15] Similar blunted cardiac systolic response to exercise was also demonstrated by Wong et al;[16] moreover patients with ascites showed greater dysfunction than those with preascitic cirrhosis.[16] The cardiac response to different physiological stimuli, including Valsalva's maneuver, ice-cold skin stimulation, and mental stress was investigated by Lunzer et al and found to be inadequate.[17] Lee and colleagues showed an inappropriate decrease in the cardiac output in the postprandial state in cirrhotic patients.[18]

Blunted cardiac responsiveness has been reported in response to other pharmacological agents. Limas et al showed that angiotensin infusion in cirrhotics resulted in an increase in the pulmonary wedge pressure, which reflects left ventricular filling pressure, without any change in the cardiac output.[7] Blunted cardiac responsiveness has also been documented in response to catcholamine infusions.[19,20]

Diastolic dysfunction is thought to be more prevalent in cirrhotic patients.[21-23] This is manifested by a stiff, noncompliant ventricle that impairs diastolic filling. Finucci et al compared the diastolic function in 42 cirrhotic patients with 16 healthy controls. The cirrhotic patients had increased left ventricular end-diastolic and left atrial volumes, stroke volume, and late diastolic flow velocity compared to normal controls; these results indicate an impaired left ventricular relaxation in the cirrhotic patients.[21] A widely-used index of diastolic function is the echocardiographic E/A ratio. This is the velocity of the diastolic early filling wave (E) divided by the velocity of the late (or atrial) filling wave (A). Normally, this ratio is >1. Many studies have demonstrated a low E/A in patients with cirrhosis.[24]

2. *Structural/histological changes*

Multiple studies were conducted to evaluate the heart mass in patients with liver cirrhosis. Most studies did not show any significant structural changes in liver cirrhotic patients.[25,26] However, some have reported changes of left ventricular hypertrophy in both humans and in portal hypertensive rats.[22,27] Studies evaluating the heart mass using echocardiography reported enlarged left atrial volumes with normal ventricular volumes.[28,29] Others however, reported increases in both the end-diastolic and end-systolic volumes of the left ventricle.[26,30-32] Changes involving the right heart chambers are less pronounced and were normal in most studies.[26] These cardiac changes may be related to the hyperdynamic circulation of cirrhosis and were correlated with its severity in some studies.[33] The presence of cardiac histological changes has been described in several autopsy studies. Findings include myocardial hypertrophy, cardiomyocyte edema, fibrosis, nuclear vacuolation, and unusual pigmentation.[12,34-35] However, these changes were reported from studies dating back at least 50 years in patients suffering from alcoholic cirrhosis. Lunseth et al studied the autopsies of 108 patients with cirrhosis from all causes (although most were alcoholic) and demonstrated the same cellular myocardial abnormalities that were described in earlier studies.[36] Other studies conducted on animal models including some of our work on long-term bile duct ligated cirrhotic rats failed to show any histological changes by light microscopy.[8,37] This discrepancy between the histological changes in human and animal studies is probably related to the long disease duration in cirrhotic patients *versus* the much shorter periods needed to induce cirrhosis in animal models.

3. *Electrophysiological abnormalities*

QT prolongation has been described in patients with liver disease and is significantly related to the severity of the underlying liver disease.[38-41] However, significant ventricular arrhythmias and sudden cardiac death remain uncommon. The prolonged QT interval is thought to revert to normal following improvement in liver function and liver transplantation.[40,42] The effect of ! -adrenergic blockade on the prolonged QT interval in cirrhotic patients was also evaluated and was found to reduce the prolonged QT interval towards normal.[43] Henriksen et al examined the temporal relation between electrical and mechanical systole in patients with liver cirrhosis and in addition to the prolonged QT interval in their study population they also showed alteration in the cardiac excitation-contraction temporal relationship.[44] In conclusion the prolonged QT interval is well linked to liver disease and is a feature of cirrhotic cardiomyopathy. Its exact mechanism and its prognostic significance require further study.

4. *Serum markers*

Cardiac troponin I and the family of natriuretic peptides were noted to be elevated in cirrhotic cardiomyopathy, possibly reflecting the underlying myocardial strain. Atrial natriuretic peptides (ANP) is released mainly by the atria in response to stretch, and brain or B-type natriuretic peptide (BNP) by the ventricles.[45] Troponin I increases in conditions leading to ventricular hypertrophy or dilatation. Pateron et al showed an increased serum troponin I level in about 1/3 of cirrhotic patients. Elevated levels correlated with decreased ventricular stroke volume index.[46] In cirrhotic patients, BNP levels correlated significantly with septal thickness and end-diastolic left ventricular diameter.[47] These results suggest the potential role of these markers for screening patients with cirrhosis for the

presence of cirrhotic cardiomyopathy, and thereby identifying such patients for further investigations.

Pathogenic mechanisms

The impaired cardiovascular responsiveness in cirrhosis is likely related to a combination of factors that include cardiomyocyte plasma membrane physicochemical changes, attenuated stimulatory pathways and enhanced activity of inhibitory systems. We will briefly discuss these factors.

Autonomic receptor function

Cardiac responses to catcholamines are known to be attenuated in chronic liver disease.[19,20] The role of ! -adrenergic receptors was elucidated in multiple studies. The ! -adrenergic receptor system is the main stimulant of ventricular contractility.[48] This system consists of the receptor, heterotrimeric guanine nucleotide-binding proteins (G-proteins), and adenylate cyclase. The occupation of the ! -adrenoceptor by an agonist leads to activation of the membrane-bound G-protein which stimulates adenylate cyclase to produce the second messenger, cAMP. cAMP activates cAMP-dependent protein kinase which phosphorylates several other proteins leading to intracellular calcium fluxes and hence cardiac muscle contraction.[49,50] Several studies have shown that ! -adrenergic receptor density is reduced both in cirrhotic patients and animal models.[9] Gerbes et al found that lymphocyte ! -adrenoceptors are significantly reduced in decompensated cirrhotic patients.[51] Although this study did not examine heart tissue, there is generally a good correlation between lymphocyte $!_2$ and cardiac ! -adrenoceptors (mainly $!_1$) in humans. In cirrhotic rat heart, multiple defects in the ! -adrenergic signaling pathway have been demonstrated, including reduced ! -adrenoceptor density, decreased membrane content and function of the stimulatory Gs-protein, uncoupling of the receptor-ligand complex from G-protein, and impaired activity of the adenylate cyclase enzyme itself.[52,53]

Muscarinic receptor stimulation exerts a negative inotropic effect on cardiac muscle, and is considered a physiologic counterbalance to the stimulatory ! -adrenergic system. Thus an enhanced muscarinic tone could contribute to the pathogenesis of negative inotropic effects. However, we did not find any increase in muscarinic receptor activity in cirrhotic rat hearts. On the contrary, muscarinic responsiveness was found to be blunted in cirrhotic hearts.[54] This is not caused by receptor downregulation but is likely a compensatory response to the attenuated ! -adrenergic system.

Membrane physicochemical changes

Membrane fluidity is a term used to describe the degree of motional freedom for lipid moieties in the lipid bilayer of the plasma membrane which is normally a dynamic environment.[55] Membrane fluidity plays a major role in the functions of biomembranes. It has been demonstrated that the fluidity of the plasma membranes from heart cells and other tissues is decreased in cirrhotic patients.[12,52] This appears to be related to an increase in membrane cholesterol content which changes the physicochemical properties of the cell membrane. We demonstrated that cardiomyocyte plasma membrane fluidity plays an important role in ! -adrenoceptor function in cirrhotic rats, translating to a 40% decrease in isoproterenol-stimulated cAMP production in the absence of any changes in ! -adrenoceptor density or binding affinity. Restoration of normal values of membrane fluidity *in vitro* in cirrhotic cardiomyocyte membrane preparations normalizes isoproterenol-stimulated cAMP production, thus confirming the fluidity-dependent function of ! -adrenoceptors.[52]

Alteration in the cardiomyocyte plasma membrane physical properties also affects the function of membrane-bound ion channels.[13] Moreau et al have shown altered control of vascular tone by Ca^{++} and K^+ channels.[56,57] They examined the hemodynamic responses to glibenclamide, an arterial adenosine triphosphate-sensitive potassium (K^{ATP}) channel blocker in cirrhotic rats and showed a significant increase in the vascular tone in cirrhotic rats compared to normal rats.[56] Ward et al have shown a decreased function of two types of K^+ channels in ventricular myocytes from cirrhotic rats, which could potentially explain the prolongation of the QT interval.[58]

Nitric oxide

The effect of nitric oxide has been implicated in the pathogenesis of different cardiac dysfunctions including ischemic heart disease.[59] Our understanding of its role in regulating the myocardial function through both vascular dependent and independent effects has grown significantly in the past few years. NO also plays an important role in regulating the systemic and coronary vascular tone.[60] At high levels NO is known to negatively regulate cardiac function. Balligand et al have reported that the non-selective blockade of nitric oxide synthase (NOS) by N omega-monomethyl-L-arginine (L-NMMA) augments the contractile response of rat ventricular myocytes to the ! -agonist isoproterenol without any effect on the baseline contractility.[61] Whether this effect is mediated by the inhibition of adenyl cyclase activity or through the second messenger cyclic guanosine monophosphate (cGMP) remains unclear.

NO is overproduced in cirrhosis; measured serum levels are significantly elevated in both cirrhotic patients and in animal models.[62-64] This overproduction could be the result of up-regulated endothelial constitutive NOS (eNOS) activity as a result of the increased shear stress caused by the hyperdynamic circulation. Another possible explanation is the augmented inducible NOS (iNOS) activity

stimulated by the increased level of circulating cytokines such as interleukins and TNF∀.[65]

Van Obbergh et al reported that inhibition of NO synthesis with L-NMMA restored the blunted contractility function of isolated hearts from cirrhotic rats while it had no significant effect in control animals.[66] We showed similar results; using several different protocols, we comprehensively demonstrated a role for NO in negative inotropic mechanisms of cirrhotic BDL rat hearts.[67] Moreover, in these hearts, iNOS mRNA transcription and protein expression were increased whereas eNOS mRNA and protein content remained unchanged compared to controls.[67]

Carbon monoxide (CO)

CO is a known vasodilator and similar to NO, it also inhibits cardiac contractility via cGMP.[68,69] It is produced through the breakdown of heme by the enzyme heme oxygenase which exists in two forms, an inducible (HO-1), also known as heat shock protein-32 and a constitutive (HO-2) isoform. Suematsu et al demonstrated an important physiological role for CO as a vasodilator in the hepatic microcirculation.[70] We investigated its role in the pathogenesis of cirrhotic cardiomyopathy. Our study showed that HO-1 mRNA transcription and protein expression are significantly augmented in ventricles of cirrhotic animals compared to controls. Furthermore, the heme oxygenase inhibitor zinc protoporphyrin significantly decreased the elevated cGMP content and reversed the decreased contractility of isolated BDL papillary muscles, but did not affect control muscles.[71] These results suggest that activation of the HO/CO pathway is involved in the pathogenesis of cirrhotic cardiomyopathy.

Endocannabinoids

Endogenous cannabinoids (also called endocannabinoids) exert a negative inotropic effect in both human and animal models through their interaction with the inhibitory G-protein coupled receptors, CBI and CB2.[72,73] The plasma level of the endocannabinoid anandamide is known to be increased in cirrhosis.[74] We showed that the blunted contractile response of isolated left ventricular papillary muscle from cirrhotic rats is restored after preincubation with a CB1 antagonist.[75] These results suggest that endocannabinoids acting through CB1 receptors may contribute to the pathogenesis of cirrhotic cardiomyopathy.

Cellular calcium kinetics

Calcium plays the central role in cardiomyocyte contraction through stimulation of actin-myosin cross-linking. Calcium enters the myocyte through plasma membrane calcium channels and is stored in the sarcoplasmic reticulum. Sarcoplasmic reticulum stores are released when stimulated by ryanodine or caffeine, thus this has been termed the ryanodine-release receptor (RyR). We investigated the status of the cellular Ca^{2+}-regulatory system in a the BDL-cirrhotic rat and demonstrated that the calcium influx through the L-type calcium channel located in the plasma membrane is significantly less than that in control myocytes. Additionally, the receptor density of the calcium channels is decreased in the plasma membrane of cirrhotic hearts compared to controls. On the other hand, all the intracellular calcium-handling functions of the SR and RyR seem to be unimpaired.[76] Protein expression and mRNA transcription for RyR2 and sarcoplasmic reticulum Ca^{2+}-pump ATPase (SERCA2) are similar in BDL and sham controls.[76] These results suggest that the plasma membrane calcium channels are quantitatively reduced and functionally depressed, whereas intracellular systems are intact.

Clinical implications

The effect of liver transplantation on cirrhotic cardiomyopathy remains incompletely clarified. Orthotopic liver transplantation (OLT) induces severe stresses on the cardiovascular system during both intra- and post-operative periods.[14,77] Intraoperatively, cardiac output can be significantly compromised secondary to either reduced preload or to impaired myocardial contractility. Postoperatively hemorrhage, third spaces losses, and ongoing ascites production can cause profound hypovolemia. On the other hand, volume overload from aggressive fluid replacement can also be a strain on the heart. Metabolic derangements in the form of acidosis, hypothermia, and electrolyte disturbance in the immediate postoperative period can also impair the cardiac contractility. Marquez et al demonstrated that the hemodynamic depression caused by hypocalcemia-induced citrate intoxication from massive transfusion was reversed after the administration of $CaCl_2$.[78] The reperfusion syndrome is another factor that may induce hemodynamic instability in the immediate post transplant period. The exact mechanism is unclear, but factors such as hyperkalemia, acidosis, and graft release of cardiodepressant cytokines such as tumour necrosis factor (TNF) ∀ have been hypothesized.[14]

The systemic vasodilatation and the hyperdynamic circulation improve following liver transplantation.[79] This sudden increase in the systemic vascular resistance can be further aggravated by aggressive perioperative fluid replacement and the hypertensive side effects of immunosuppressive medications leading to a significant increase in the afterload and then unmasking the associated cardiomyopathy. The clinical significance of these hemodynamic changes on the cardiac function in the perioperative period has been demonstrated in multiple studies. Cardiac causes account for approximately 7-15% of deaths in the post-operative period, making it an important cause of death following liver transplantation.[14,80,81]

Donovan et al reported in a prospective study of 190 transplanted patients that radiographic evidence of pulmonary edema occurred in about half (56%) during their hospitalization.[82] Fortunately most of these episodes were mild and subclinical. This could be related in part to the careful selection process undertaken by most transplant centers. Nasraway et al found that nonsurvivors of LT have less cardiac reserve pretransplant; postoperatively, they demonstrate early myocardial depression and subsequently lower levels of cardiac index and oxygen delivery.[83] Predicting which patients are at risk of developing cardiac complications following liver transplantation is difficult. Donovan et al investigated the use of 2-dimensional and dobutamine stress echocardiography in predicting adverse cardiovascular events in the post-OLT period. In this study all the patients who developed acute left ventricular failure postoperatively had a normal ventricular function preoperatively.[14,82] This study and others that were done to evaluate the predictive value of echocardiography suggest a low predictive value in predicting cardiac complications.

The increasing use of transjugular intrahepatic portosystemic shunts (TIPS) has led to the recognition that they can be associated with a number of complications, including cardiac-related abnormalities. The presence of congestive heart failure is an absolute contraindication to the insertion of TIPS. The cardiac and hemodynamic effects of TIPS in cirrhotic patients have been evaluated by several groups.[84-87] These studies showed worsening of the hyperdynamic circulation, manifested by an acute increase in the cardiac output and a decrease in the systemic vascular resistance following the insertion of the TIPS. These observations led to the concern of the development of cardiac related complications in the setting of cirrhotic cardiomyopathy. Not surprisingly an increase in the right atrial pressure, pulmonary artery pressure, pulmonary vascular resistance, and pulmonary wedge pressure has been reported, reflecting the common prevalence of diastolic dysfunction in this patient population.[84,86] Cardiac failure, myocardial infarction, and acute pulmonary edema also have been reported following TIPS.[84] A recent study showed that patients with an E/A < 1 had an increased morbidity and mortality following TIPS.[88] This data suggests that the presence of cirrhotic cardiomyopathy plays a prognostic role in patients undergoing procedures which stress the cardiovascular system.

A possible relationship between ventricular dysfunction, peripheral vasodilatation and sodium retention has been postulated. Wong et al assessed the relationship between subtle cardiovascular abnormalities and abnormal sodium handling in cirrhosis. In this study they subjected patients with preascitic cirrhosis to a high sodium diet for 7 days. These patients started retaining sodium and fluids during the follow up period. Healthy controls showed a normal cardiac response with an increase in the slope of the peak systolic pressure to end systolic volume relationship, whereas preascitic cirrhotic patients had an abnormal baseline cardiac contractility that worsened after the sodium challenge, manifested by a reduction of systolic pressure and an increase in the end-systolic volume, implying that inadequate cardiac contractility may contribute to the renal and water retention.[22]

Ruiz-del-Arbol examined the renal and cardiac functions in 23 patients presenting with spontaneous bacterial peritonitis. All 23 patients cleared their infection with the appropriate antibiotics. Eight patients subsequently developed renal failure; these patients had a lower cardiac output at admission that declined further with infection resolution, compared to those that had normal renal function.[89] In this study the systemic vascular resistance, a measure of peripheral vascular tone, remained unchanged in the two groups, whereas mean arterial pressure decreased in the renal failure group indicating that the reduced cardiac output directly translated to decreased renal perfusion. These observations suggest that inadequate ventricular contractility in the face of the cardiovascular-renal stresses imposed by sepsis may contribute to the pathogenesis of hepatorenal syndrome associated with spontaneous bacterial peritonitis.[89-91]

Treatment strategies

Due to the limited number of human studies, the management of cirrhotic cardiomyopathy remains largely empirical. Fortunately, overt heart failure is an uncommon feature of this syndrome. This is likely related to the peripheral vasodilatation of cirrhosis, which decreases the afterload. If overt heart failure develops in these patients, then the same general treatment principles of noncirrhotic congestive heart failure apply, including bed rest, salt restriction, oxygen, diuretics, and careful preload and afterload reduction.[14]

Positive-inotropic drugs based on ! -adrenergic stimulation will probably be ineffective in patients with cirrhotic cardiomyopathy due to the desensitization of ! -adrenergic receptors and multiple defects in the signaling of this system.[9,52,53] This was suggested by study of Mikulic et al which showed insignificant responses to dobutamine infusions in cirrhotic patients.[19] Alternatively phosphodiesterase antagonists such as amrinone which inhibits cAMP degradation might be useful because much of the ! -adrenergic signaling defects are upstream of adenylate cyclase. However, this remains conjectural and untested at present.

The role of cardiac glycosides in cirrhotic cardiomyopathy remains unclear. One study using ouabain, a short acting cardiac glycoside, was ineffective.[7] Henriksen et al have reported that the acute administration of a single doze of propranolol improved the prolonged electrocardiographic QT interval in cirrhotic patients, but whether there is an improvement in contractile dysfunction with chronic dosing remains unknown.[43] More recently Pozzi

et al showed that 24 weeks of treatment using an aldosterone receptor antagonist in cirrhotic patients significantly reduced left ventricular wall thickness, peripheral sympathetic activation, and showed a nonsignificant tendency to improve the diastolic dysfunction.[92] These investigators speculated that a longer period of treatment might have demonstrated significant improvement in contractility.[92]

Liver transplantation is the only curative therapy for cirrhosis and its complications. Successful liver transplantation is thought to improve all the organ-related hemodynamic dysfunctions, including hepatopulmonary syndrome, cerebral hypoperfusion, hepatorenal syndrome, and cirrhotic cardiomyopathy.[93] For example the prolonged QT interval normalizes following liver transplantation.[40,42] Thus, liver transplantation appears to be the ultimate treatment for cardiovascular complications of cirrhosis.

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