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Cardiac dysfunction in cirrhosis

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Cirrhosis is known to be associated with numerous cardiovascular abnormalities. These include increased cardiac output and decreased arterial pressure and total peripheral resistance. Despite this increased baseline cardiac output, patients with cirrhosis show an attenuated systolic and diastolic function in the face of pharmacological, physiological and surgical stresses, as well as cardiac electrical abnormalities such as QT prolongation. These abnormalities have been termed cirrhotic cardiomyopathy. The pathogenic mechanisms that underlie this syndrome include impairment of the β-adrenergic receptor signalling, cardiomyocyte plasma membrane function, intracellular calcium kinetics, and humoral factors such as endogenous cannabinoids, nitric oxide and carbon monoxide. Cirrhotic cardiomyopathy is believed to contribute to the cardiac dysfunction that can be observed in patients with transjugular intrahepatic portosystemic stent-shunt insertion and liver transplantation. Insufficient cardiac contractile function may also play a role in the pathogenesis of hepatorenal syndrome precipitated by spontaneous bacterial peritonitis. In this review, the clinical features, pathogenic mechanisms, clinical consequences and management options for cirrhotic cardiomyopathy are discussed.

Key words: cirrhotic cardiomyopathy; cirrhosis; cardiac; ventricular; heart failure; β-adrenergic; membrane fluidity; nitric oxide; endocannabinoid; carbon monoxide; QT interval.

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INTRODUCTION

That cirrhosis is associated with cardiovascular abnormalities has been part of clinical lore for centuries, but only until relatively recently did the development of techniques for precisely measuring cardiovascular variables allow determination of the extent of these anomalies. Before then, clinicians observed the tachycardia and bounding pulses of patients with cirrhosis and surmised that the circulation was hyperdynamic. In 1953 a seminal study by Kowalski and Abelmann determined that patients with alcoholic cirrhosis do indeed have increased cardiac output and decreased arterial pressure and total peripheral resistance, i.e., hyperdynamic circulation.[1] As for the heart, it was assumed that since basal cardiac output is increased, contractile function should, intuitively, be normal as well. Cardiac output is the product of heart rate and the volume of blood expelled with each contraction, or stroke volume (SV). Blood pressure is calculated by multiplying cardiac output by the total peripheral resistance. By this logic, then, an increase in vascular resistance should therefore be able to correct the hypotension secondary to hyperdynamic circulation. However, beginning in the late 1960s, evidence arose that showed this was not the case. Regan et al studied ten alcoholics with no clinical evidence of cardiac disease, along with eight healthy controls, and intravenously infused both groups with angiotensin. Angiotensin is an eight-amino acid oligopeptide which is produced in the body as part of the renin-angiotensin-aldosterone system. Among other roles, it acts on receptors in vascular tissue causing systemic arteriolar vasoconstriction, leading to increased vascular resistance and thereby elevating cardiac afterload. After angiotensin infusion, it was observed that although the left ventricular end diastolic pressure of the alcoholic group increased significantly more than the control group, the corresponding rise in stroke output and work was significantly less than the controls. This suggested a significantly attenuated ventricular contractile response to diastolic filling. At the time, however, this was merely attributed to the chronic effects of alcohol toxicity on the myocardium.[2] A similar result was noted shortly afterwards by Gould et al, who examined the cardiac response to exercise of ten male subjects with evidence of chronic liver disease. At rest, increases in stroke index and cardiac output of all participants were observed. With exercise, however, stroke index declined despite elevations in left ventricular end diastolic pressure, which represents a highly abnormal cardiac response.[3] Approximately five years later, Limas et al also infused angiotensin into ten patients with alcoholic cirrhosis, with no resultant increase in cardiac output. Subsequent administration of the cardiac glycoside ouabain yielded no rise in cardiac output.[4] Under normal conditions, glycosides should increase intracellular calcium through sodium–calcium exchange mechanisms, promoting contractility. This blunted cardiac response to both pharmacological and physiological stress was observed in several studies over the next decade and was always attributed to mild or latent alcohol-induced cardiomyopathy. It was not until 1986 when Caramelo and colleagues infused saline into rats with carbon tetrachloride-induced cirrhosis and noted a 50% decrease in their cardiac output, despite a 112% increase in total peripheral resistance. This landmark study indicated that the impaired cardiac contractile response was associated with cirrhosis *per se*, rather than a direct, adverse effect of alcohol.[5] This has since been confirmed by many studies in both humans and experimental animal models.[6–12] In 1989, this phenomenon was labelled as 'cirrhotic cardiomyopathy'.[6] In summation, it represents a syndrome in cirrhotic patients where cardiac output and contractility are normal or increased at rest, but abnormal in the presence of physiologic, pharmacologic or surgical stresses.

Examples of such stresses include eating, exercise, body position changes, intravascular volume alterations, insertion of transjugular intrahepatic portosystemic stent shunts and liver transplants.[6,11,13]

CLINICAL FEATURES

An expert working group is currently formulating a consensus definition of cirrhotic cardiomyopathy, with the results to be released in late 2006. At present, in the absence of the consensus definition, cirrhotic cardiomyopathy is generally defined by the following clinical criteria: (1) normal or increased left ventricular systolic contractility at rest, (2) attenuated systolic contraction or diastolic relaxation in the face of pharmacologic, physiologic and surgical stresses, and (3) cardiac electrical abnormalities. We will discuss each in turn.

Systolic and diastolic responses

Ventricular systolic function is determined by three main components: preload, afterload and contractility. Ventricular preload is governed by the Frank–Starling relationship; the greater the preload, the greater the end-diastolic volume of the ventricle and, hence, greater the stretch of the cardiac muscle fibres. This translates into an increased force of contraction and a larger volume of blood ejected in systole. Afterload represents the resistance that the ventricle must overcome in order to eject its volume into the peripheral circulation. A lower afterload allows more vigorous cardiac muscle fibre shortening and thus more forceful contraction. Contractility is an intrinsic property of the cardiac muscle fibre itself. At fixed values of preload and afterload, increases in contractility result in greater cardiac output.

Increased cardiac output is part of the hyperdynamic circulation of cirrhosis, and is thought to be secondary to augmentation of both heart rate and ventricular stroke volume. This elevation in cardiac output could mistakenly lead one to assume that cardiac function is intact or enhanced in cirrhotic patients and that the observed arterial hypotension is merely a function of marked peripheral vasodilatation. However, over the last four decades, multiple studies have proven this assumption incorrect. Rather, it is the cardiac response to stress that is markedly abnormal.

Blunted cardiac reactions to physiologic stresses have been confirmed in cirrhotic patients by numerous investigations. As mentioned earlier, Gould et al noted decreases in cardiac stroke index with exercise.[3] Similarly, Kelbaek and colleagues examined 15 patients with biopsy-proven cirrhosis using exercise testing, echocardiography, measured systolic time intervals and left ventricular radionuclide ejection fractions (LVEF). With submaximal exercise, it was observed that the median LVEF in cirrhotics increased by only 6% versus 14% in controls ($p < 0.05$).[13] Grose et al used supine exercise radionuclide ventriculography to assess the cardiac response to exercise. Compared to normal subjects, cirrhotic patients exhibited no increase in LVEF.[14] Attenuated cardiovascular responses (such as decreased heart rate and forearm blood flow) to other physiologic stresses including eating, the Valsalva manoeuvre, ice-cold skin stimulation and mental stress have also been demonstrated.[6,15–17]

Patients with cirrhosis also exhibit this blunted response in the face of pharmacologic stressors. Drugs such as angiotensin, ouabain, isoproterenol and dobutamine have all produced an attenuated cardiac response.[2–4,6,11–16]

In healthy subjects, stimulation of β-adrenergic receptors in myocardium should produce both chronotropic and inotropic augmentation. The effects, however, are blunted in patients with cirrhosis. A diminished inotropic effect was demonstrated by Mikulic et al, who studied the effects of the β_1-adrenergic agonist dobutamine on cardiac output in 14 patients with alcoholic cirrhosis. Although an increase in cardiac output was observed (5.8 ± 1.2 L/min $\rightarrow$ 7.1 ± 1.5 L/min), this was noted to be secondary to increases in heart rate; stroke volume did not change significantly.[18] Reduced chronotropic responses were demonstrated by Ramond et al in 1986. They administered the β-adrenergic agonist isoproterenol to 13 patients with alcoholic cirrhosis and five controls. The dose required to increase the resting heart rate by 25 beats/min (bpm) was significantly higher in cirrhotic patients (median 4.47 μg) than controls (median 1.34 μg). This suggested that cirrhotic patients had a markedly desensitized β-adrenoceptor chronotropic response.[19] Chronotropic desensitization was further explored in mechanistic detail by Lee et al in a rat model of cirrhosis due to chronic bile duct ligation. Compared to controls, cirrhotic rats required a significantly higher dose of isoproterenol to achieve an increase in basal heart rate of 50 bpm (102 ± 19 vs. 28 ± 11 ng/kg). Cirrhotic rats also exhibited a lower maximal heart rate response (104 ± 29 vs. 158 ± 61 bpm in controls) and had significantly lower (−29%) myocardial β_1 receptor density.[20] This study demonstrated that the blunted chronotropic response to β-adrenergic stimulation is due to downregulation of myocardial β-adrenoceptor density.

Diastolic relaxation is also impaired in cirrhosis. Diastolic filling is normally comprised of two parts: rapid, early diastolic (active) relaxation and late diastolic (passive) filling. The early phase relies on the rate of ventricular relaxation, elastic ventricular recoil, the atrioventricular pressure gradient and the passive elastic characteristics of the left atrium and ventricle.[21] The late phase depends on the strength of left atrial contraction and the stiffness of the left ventricle. Diastolic dysfunction occurs when the passive elastic properties of the myocardium are reduced secondary to increased myocardial mass and changes in the extracellular collagen.[22] This leads to stiffening and hypertrophy of the left ventricle with decreased compliance and higher diastolic pressures at each diastolic volume. Hence, relatively small increases in intravascular volume translate into significant elevations in diastolic pressures. Retrograde transmission of this pressure into the left atrium and pulmonary venous system can result in pulmonary oedema.[22]

Several studies to date have demonstrated stiffening and hypertrophy of the left ventricle in cirrhosis. In 1958, Lunseth et al autopsied 108 patients with cirrhosis. Thirty-seven had no historical or pathological indications of hypertension, coronary artery disease or valvular disease. Approximately one-third of these patients, however, had cardiac hypertrophy. Subsequent histological investigation revealed evidence of cardiomyocyte oedema, exudation, fibrosis, altered pigmentation and nuclear vacuolation. Others studies around that time demonstrated similar findings.[6,11,13–16]

Using Doppler echocardiography, ventricular diastolic compliance and corresponding diastolic function can be assessed by measuring the velocity of blood flow from the left atrium to the left ventricle during early diastole (the E wave) and late diastole (the A wave) and calculating the E/A ratio. In other words, a low E/A ratio would be seen in a stiffened, non-compliant ventricle. In this regard, several studies have demonstrated decreased E/A ratios in cirrhotics. Finucci et al evaluated diastolic dysfunction in 42 cirrhotic patients and 16 healthy controls using Doppler echocardiography. Compared to controls, cirrhotic patients exhibited higher late diastolic flow velocities (71 ± 17 vs. 56 ± 18 cm/s; $p < 0.01$) and, subsequently, decreased E/A ratios (1.02 ± 0.35 vs. 1.22 ± 0.25; $p < 0.02$).[23] Similarly, Pozzi et al examined left ventricular diastolic function in 27 cirrhotics with tense ascites, 17 cirrhotics with previous ascites and

11 controls, before and after paracentesis. A significantly decreased E/A ratio was observed in cirrhotics, in general, vs. controls. Paracentesis also improved diastolic function.[24] Those with tense ascites showed the greatest degree of diastolic dysfunction. Such a correlation between extent of systolic and diastolic contractile dysfunction and degree of liver failure has been noted in many other studies, and thus suggests that the extent of cirrhotic cardiomyopathy tends to worsen in concert with advancing degrees of cirrhosis.

These and many other studies suggest that some level of diastolic dysfunction exists in most patients with cirrhosis. In many cases, diastolic dysfunction is detectable at baseline, and thus precedes systolic dysfunction, which tends to manifest only under conditions of stress.

Electrical conductance abnormalities

Various rhythm disturbances have been described in cirrhotic patients over the years including atrial fibrillation, atrial flutter, atrial and ventricular ectopy and ventricular arrythmias. Yet, whether these conductance abnormalities are due to cirrhosis in general or secondary to the arrhythmogenic properties of alcohol remains an issue of contention. Three electrophysiological abnormalities have been observed in cirrhotics of all causes. These include: (1) QT interval prolongation, (2) chronotropic incompetence, and (3) electromechanical dyssynchrony.

Prolonged QT intervals are a result of abnormal myocardial repolarization and are occasionally associated with a higher risk of *torsade de pointes*; a life-threatening ventricular tachyarrhythmia.[25] In the aforementioned 1953 study by Kowalski and Abelmann, eight of the 22 patients with alcoholic cirrhosis exhibited prolonged QT intervals,[1] but this observation was overshadowed by the other novelties contained in the paper, and generally forgotten. Four decades later, Kempler and colleagues 'rediscovered' QT prolongation in patients with a variety of aetiologies of cirrhosis.[26] A few years after that, this issue was examined in detail by Bernardi et al[27] who documented a significant correlation between the severity of liver disease (as indicated by Child–Pugh scores) and rate-corrected QT interval (QT_C) ($r = 0.53$; $p < 0.001$). Furthermore, no link was found between the aetiology of cirrhosis and QT_C length.[27] Many other studies have confirmed QT_C prolongation in cirrhosis[11,13,16,28,29] and have also demonstrated reversibility of this electrical phenomenon following liver transplantation.

As discussed earlier, cirrhotics exhibit blunted cardiac responses to numerous physiological and pharmacological stimuli. The heart's inability to meet these stimuli with an appropriate tachycardiac response is termed chronotropic incompetence. Numerous studies, including those of Kelbaek et al and Grose et al demonstrated this phenomenon.[13,14] Its significance becomes apparent in situations where tachycardia is required including the sympathetic 'fight or flight' response, exercise or haemorrhage.[7–12]

The third electrical conductance abnormality noted in cirrhosis is dyssynchrony of electrical and mechanical systole or, in simpler terms, the difference in time between ECG evidence of systole and haemodynamic/physical evidence of systole. Using Swan–Ganz catheterization and simultaneous ECG monitoring, Henriksen et al found a direct correlation between the times of electrical (represented by the QT interval) and mechanical systole (time from beginning of systolic increase in pressure to the closure of the aortic valve).[30] Moreover, the difference in time between electrical and mechanical systole was significantly greater in those with a prolonged QT_C interval than those with a normal QT_C interval (0.078 vs. 0.031 s, $p < 0.005$). Finally, the time

difference between length of electrical events (QT interval) and the length of mechanical systole (as defined above), which in the controls was a tightly-regulated 6–14 ms, was widely dispersed in the cirrhotic patients (ranging from −120 to 158 ms), suggesting a curious dyssynchrony or disconnection between excitation–contraction coupling in the cirrhotic heart. The clinical significance of these findings remains unclear.

PATHOGENIC MECHANISMS

β-Adrenergic receptor signalling

The β-adrenergic receptor system is one of the main regulators of cardiac contractility. A schematic representation of the β-adrenergic signal transduction pathway is illustrated in Figure 1. Signalling by this system involves the activation of adenylyl cyclase via membrane-bound heterotrimeric G-protein, specifically the stimulatory G_s subunit. This activation results in an increased expression of the second messenger cAMP. cAMP then stimulates protein kinase A to phosphorylate several intracellular proteins such as L-type calcium channels, phospholamban, troponin I, ryanodine receptors, myosin binding protein-C and protein phosphatase inhibitor-1 that are essential for cardiac function. This results in increased intracellular calcium fluxes and subsequent cardiac contraction.[29]

In view of the relationship between the β-adrenergic receptor and cardiac contractility, this system has been subjected to detailed study in cirrhotic cardiomyopathy. In

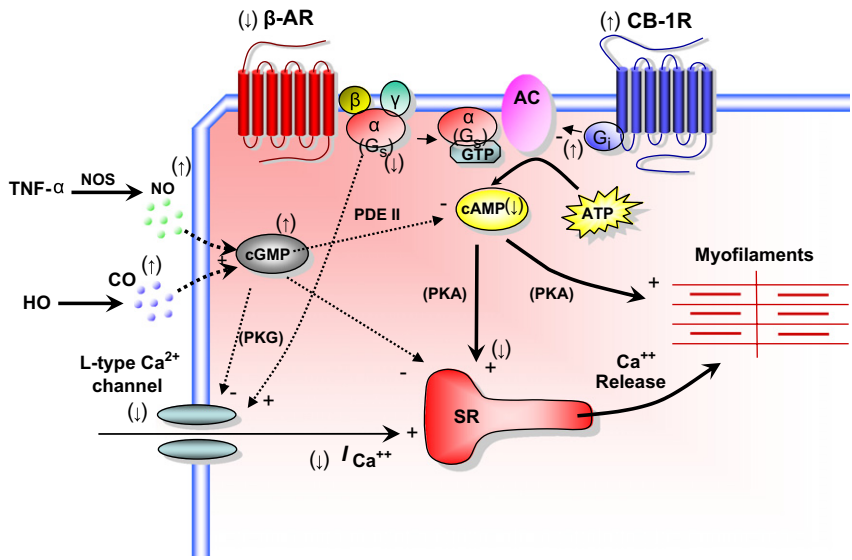

Figure 1. Schematic representation of the β-adrenergic signal transduction pathway and the influence of endocannabinoids, nitric oxide (NO) and carbon monoxide (CO) in the cardiomyocyte. β-AR, β-adrenergic receptor; AC, adenylyl cyclase; α, β and γ represent the heterotrimeric components of G-protein; Gs, stimulatory G-protein complex; Gi, inhibitory G-protein complex; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PKG, protein kinase G; PDE II, phosphodiesterase II; CB-1R, cannabinoid receptor 1; HO, heme oxygenase; NOS, nitric oxide synthase; TNF-α, tumour necrosis factor; SR, sarcoplasmic reticulum. See text for detailed explanation of the signal transduction process. +, stimulatory influence; −, inhibitory influence.

the bile duct-ligated (BDL) rat heart, we have demonstrated a host of abnormalities in the β-adrenergic receptor signalling pathway.[31,32] The G-protein subunits, G_s and $G_{i2\alpha}$, are significantly decreased, in both content and function, without any change to the G_β subunit. cAMP generation was also shown to be attenuated in BDL. This decrease of cAMP is due to impairment of adenylyl cyclase activity, which is partly secondary to decreased G-protein stimulation of the catalytic subunit of the enzyme, and also due in part to an inhibitory effect of jaundice.[32]

Due to the relationship that is known to exist between the stimulatory effects of the β-adrenergic system and the inhibitory effects of the muscarinic cholinergic system, it was important to determine if the contractile impairment results from overactivity of muscarinic M_2 receptors. We demonstrated that M_2 receptor density and binding in cirrhotic rat hearts are unchanged in comparison to controls, but muscarinic responsiveness is blunted in cirrhotic myocardium.[33] However, this attenuated response was not caused by receptor down-regulation, suggesting that the changes observed in muscarinic function are likely compensatory in response to the impaired β-adrenergic stimulatory system.

Membrane fluidity

Membrane fluidity represents the freedom with which lipid and protein molecules are able to move in the plasma membrane lipid bilayer. It has been well established that a normal biochemical and biophysical membrane environment is critical to the proper functioning of many membrane receptors, including the β-adrenergic receptors.[34] Several studies have demonstrated that in cirrhosis, the plasma membrane fluidity in cells from the heart,[35] erythrocytes,[36] kidneys[37] and liver[38] is abnormal, and in some cases have reduced fluidity due to an increase in membrane cholesterol content. Furthermore, our studies in the BDL cirrhotic cardiomyocyte have not only demonstrated this decrease in plasma membrane fluidity and its associated lipid composition changes, but also that these changes play an integral role in diminished β-adrenergic receptor functioning through interference with G-protein coupling[39] and cAMP production.[35] When membrane fluidity was increased to normal levels *in vitro* by a fatty acid fluidizing agent, isoproterenol-stimulated adenylate cyclase activity and cAMP production were also restored to normal.[35,39] This suggests that alterations in plasma membrane fluidity play an important role in the β-adrenergic receptor dysfunction and thus in the pathogenesis of cardiac contractility in cirrhosis.

Endocannabinoids

By definition, endogenous cannabinoids or endocannabinoids are endogenous ligands capable of binding to and functionally activating cannabinoid receptors, CB_1 and CB_2. Cannabinoid receptors are seven-transmembrane-domain proteins coupled to G-proteins of the $G_{i/o}$ type. The endocannabinoid mediated activation of these receptors results in intracellular signalling events that are coupled to the $G_{i/o}$ proteins. The endocannabinoids that are known to bind to these receptors include anandamide, 2-arachidonoylglycerol, and more recent candidates- 2-arachidonyl-glyceryl ether, *O*-arachidonoyl-ethanolamine (virhodamine) and *N*-arachidonoyl-dopamine.[40]

Since their discovery, anandamide and 2-arachidonoylglycerol have been implicated in a variety of physiological and pathological processes. Batkai et al and Ros et al documented the mediatory effect of increased expression of anandamide and CB_1 on the

pathogenesis of arterial hypotension observed in cirrhotic rat models.[41,42] More recently, Domenicali et al showed anandamide as a selective splanchnic vasodilator in cirrhosis acting predominately through two receptors- one of which is CB_1.[43] Given the similarities that exist between mechanisms in peripheral vessels and cardiac tissues, we were interested in a possible role of the endocannabinoid system in the pathogenesis of cirrhotic cardiomyopathy in BDL rats.[44] Our study demonstrated a negative inotropic effect of anandamide in left ventricular papillary muscles of cirrhotic rats. This inhibitory effect on contractility was completely blocked by incubation with AM251, a known CB_1 antagonist, thus confirming that the effect of anandamide is mediated by CB_1 receptors. Force–frequency relationship studies showed that at higher frequencies of contraction, anandamide reuptake blockers (VDM11 and AM404) enhanced cirrhotic papillary muscle relaxation. This effect was blocked by AM251 and pertussis toxin treatment, suggesting that not only are the effects of anandamide CB_1 receptor mediated but more specifically that the effects are mediated by an inhibitory Gi-protein-dependent CB_1 responsive pathway (Figure 1).[44]

Calcium kinetics

Stimulation of the β-adrenergic pathway leads to the activation of numerous calcium related systems, that are crucial for cardiac contraction. In cardiac myocytes, the influx of Ca^{2+} from the extracellular space of the cell occurs via L-type Ca^{2+} channels ($I_{Ca,L}$). Ca^{2+} influx is stored in the sarcoplasmic reticulum, and when released it directly leads to actin-myosin cross-linking and thus cell contraction. Release of intracellular Ca^{2+} is regulated by sarcoplasmic reticulum Ca^{2+} pump adenosine triphosphatase (SERCA2) and Ca^{2+} release channels ryanodine receptor 2 (RyR2).[45] A defect in either the initial entry of Ca^{2+} or the ability to trigger release of Ca^{2+} from its intracellular storage may explain the attenuated contractile responsiveness observed in the cirrhotic myocardium.

Studies performed on the cellular calcium dynamic in our BDL cardiomyocytes showed a significant decrease in receptor density and electrophysiologic function of voltage-gated $I_{Ca,L}$ compared to control myoctes.[46] L-type calcium channel protein expression is quantitatively decreased in BDL cardiomyocytes. Furthermore, isoproterenol stimulation of $I_{Ca,L}$ is also decreased in BDL while the proportional response to forskolin, a direct stimulator of adenylate cyclase, is the same between BDL and sham controls. These results point to an alteration in the β-adrenergic signalling pathway upstream of adenylyl cyclase.[46] In terms of the intracellular calcium kinetics, molecular analysis of SERCA2 and RyR2 showed no difference in either mRNA transcription or expressed protein levels in the BDL compared with the sham controls. RyR2 receptor binding characteristics were also unaltered between the two groups.[46] These findings suggest that the primary defect of the calcium delivery system, and thus impaired contraction, lies in the cardiomyocyte plasma membrane, including $I_{Ca,L,}$ whereas the intracellular calcium systems are intact.

Nitric oxide

Over the past decade, a large number of studies have provided great insights into the multitude of functions and roles of nitric oxide (NO) in normal physiology and disease states. NO, a known vasodilator is synthesized from L-arginine via the catalytic action of NO synthase (NOS). There are three known isoforms of NOS: neuronal (nNOS or NOS1), inducible (iNOS or NOS2) and endothelial (eNOS or NOS3).

It had been hypothesized by Vallance and Moncada that cirrhosis resulted in augmented levels of cytokines, which in turn led to the induction of iNOS to overproduce NO.[47] The use of NOS inhibitors, such as *N* omega-monomethyl-L-arginine (L-NMMA), has been able to provide further insight into the pathophysiological role of NO in cirrhosis. Balligand et al found that the inhibition of NOS synthesis by L-NMMA significantly increased the contractile response of rat ventricular myocytes to the β-agonist isoproterenol without affecting baseline contractility.[48] In terms of a cirrhotic model, van Obbergh et al reported on the role of NO in BDL-cirrhotic rat.[49] They showed that the non-specific NOS inhibitor L-NMMA significantly increased contractile function in isolated working cirrhotic hearts but had no effect on controls. We examined the NO system in detail in the BDL-cirrhotic rat heart.[50] In the cirrhotic rats, baseline isoproterenol-stimulated papillary muscle contractile force was shown to be lower than in the control groups. But when the papillary muscles were preincubated with the NOS inhibitor L-NAME, contractile force increased significantly in the cirrhotic rats, whereas control muscles were unaffected. We also found that cirrhotic cardiomyocytes showed an increase iNOS mRNA and protein expression, whereas eNOS showed no significant difference in expression between the BDL and the sham control hearts. Moreover, the NO donor *S*-nitroso-*N*-acetyl penicillamine inhibited papillary muscle contractility. Whether the effects of NO are mediated by inhibition of adenylyl cyclase activity or through cGMP remains to be further clarified. However, we were able to show that cytokine, TNF-α, and cGMP content in cardiac homogenates showed a significant increase in BDL rats;[50] suggesting a possible cytokine-iNOS-cGMP mediated pathway of action for NO in the pathogenesis of cirrhotic cardiomyopathy (Figure 1).

Carbon monoxide

Carbon monoxide (CO) is produced in the body mainly through the enzymatic actions of heme oxygenase (HO), which is known to exist as inducible (HO-1, also known as heat shock protein 32) and constitutive (HO-2) isoforms. HO catalyses the oxidation of heme to iron, biliverdin and CO. Over the years, the physiological roles of CO have been elucidated in the cardiovascular, nervous and immune systems.[51] Increasing levels of cGMP through activation of guanylyl cyclase have also been linked to the actions of CO.[52] We have previously reported on the role of the HO−CO pathway in the pathogenesis of cardiac contractility in cirrhotic cardiomyopathy.[53] In our BDL rats, a significant increase was observed for HO-1 mRNA and protein expression, whereas neither HO-2 mRNA nor protein content differed between the BDL and control hearts. The ventricular concentration of cGMP was also shown to be higher in cirrhotic rats. However, treatment with HO inhibitor zinc protoporphyrin IX restored the cGMP level and increased the contractile force of isoproterenol-stimulated papillary muscles. These findings suggest that activation of the HO−CO pathway in cirrhosis involves the catalytic action of HO-1, with the cardiodepressant effects of increasing levels of CO occurring via stimulation of cGMP (Figure 1).

CLINICAL CONSEQUENCES OF CIRRHOTIC CARDIOMYOPATHY

Transjugular intrahepatic portosystemic stent-shunts (TIPSS)

TIPSS can place a significant amount of stress on the heart. TIPSS are currently used for indications ranging from refractory ascites to recurrent variceal bleeding. The

device decompresses portal pressure by redirecting portal blood volume into the systemic venous circulation. This results in a marked increase in ventricular preload which could potentially precipitate cardiac dysfunction. Huonker et al performed echocardiographic studies and invasive haemodynamic monitoring in 17 consecutive patients with alcoholic cirrhosis, before and after TIPSS insertion. Post-procedure, they noted increases in left atrial diameter, pulmonary capillary wedge pressure and total pulmonary resistance; thus, indicating diastolic dysfunction.[54] In a study of 70 patients with refractory ascites, half treated with TIPSS and the other half with repeated large volume paracentesis, four (12%) patients in the former group developed cardiac failure, compared to none in the latter group.[55] Likewise, in Schwartz et al reported that 13% of patients developed symptoms and signs of congestive heart failure post-TIPSS insertion.[56] On the other hand, two other large controlled studies of TIPSS did not report any cases of heart failure post-insertion.[57,58] We conclude that although it seems clear that the TIPSS procedure can unmask the impaired ventricular contractility and precipitate overt heart failure in a minority of patients, just how frequently this occurs remains unclear at present.

Hepatorenal syndrome

Hepatorenal syndrome is a form of functional renal failure secondary to intense renal vasoconstriction that develops in patients with cirrhosis or ascites. Two types exist: Type I involves a rapidly progressive renal failure (CrCl $<$ 20 mL/min) and usually results from an inciting event such as infection or alcoholic hepatitis. The associated survival is short. Type II is associated with a more moderate, steady and insidious renal failure (CrCl $<$ 40 mL/min), with a longer survival.[59] It usually presents with advanced cirrhosis and ascites that is often refractory to management. Survival is usually longer.

The pathophysiology of hepatorenal syndrome is not well understood, but current concepts are based on the peripheral arterial vasodilation hypothesis. Here, portal hypertension in cirrhotics leads to vasodilation of the splanchnic arterial bed. This decreases cardiac afterload, which induces a compensatory increase in cardiac and sympathetic output. However, with progressive liver disease and portal hypertension, splanchnic and systemic arterial vasodilation worsens to an extent that cardiac output is unable to compensate and arterial hypotension is the end result. This decrease in blood pressure is detected by baroreceptors, leading to marked increases in sympathetic output, activity of the renin-angiotensin-aldosterone system, antidiuretic hormone levels and, subsequent, salt and water retention. Hepatorenal syndrome develops from the ensuing renal vasoconstriction.[59]

So how is cirrhotic cardiomyopathy involved in hepatorenal syndrome? Ruiz-del-Arbol and colleagues studied 23 patients with confirmed spontaneous bacterial peritonitis (SBP) and recorded various laboratory and haemodynamic parameters both at the time of diagnosis and after treatment and resolution of the SBP. Eight of these patients developed renal failure after resolution of the infection. In addition, the cardiac output and systemic vascular resistance of this group *at diagnosis* were noted to be lower and higher, respectively, than the 15 other patients without renal failure. Moreover, with treatment, cardiac output further dropped significantly in the renal failure patients, but remained unchanged in those without renal failure. Systemic vascular resistance did not change in either group, but the mean arterial pressure significantly decreased in the renal failure group. Since arterial

pressure is the product of cardiac output and total peripheral resistance, it followed that the arterial hypotension observed was secondary to decreased cardiac output. This drop in cardiac output was suggested to be the result of underlying cirrhotic cardiomyopathy leading to renal hypoperfusion, renal arteriolar vasoconstriction and ensuing hepatorenal syndrome.[59,60]

In a related study, this same group sequentially studied haemodynamic and neurohormonal parameters in 27 cirrhotics with tense ascites and initially normal serum creatinine levels, before and after the development of hepatorenal syndrome. The investigators noted lower baseline cardiac outputs in the patients who would eventually develop hepatorenal syndrome and observed significant reductions in mean arterial pressure and cardiac output after renal dysfunction occurred. Significant stimulation of the renin-angiotensin-aldosterone and sympathetic nervous systems were also observed. According to the peripheral arterial vasodilation hypothesis, however, cardiac output should increase in the face of worsening splanchnic arterial vasodilation. These findings further support the role of decreased cardiac output in the development of hepatorenal syndrome and, hence, the possible contribution of cirrhotic cardiomyopathy to this process.[60,61]

Liver transplantation

Liver transplantation exerts enormous stresses on the heart. This topic has been recently reviewed extensively.[17,62] Heart-related complications that can occur in the post-operative period include reperfusion syndrome, arrhythmias, sudden cardiac death, myocardial infarction and heart failure.[17,62,63]

Haemodynamic and metabolic changes occurring intra- and post-operatively can explain many of these problems. Fluid losses (including haemorrhage, third-space losses and continual ascites formation) and operative clamping of major vessels, during the transplantation, can contribute to decreased venous return and, consequently, reduced ventricular preload. Ventricular overload can be induced by aggressive intra-operative fluid administration. Cardiac contractility can be hindered by metabolic abnormalities including acidosis, hypocalcaemia, hypokalaemia and hypothermia.[11,17] Reperfusion of the graft can be associated with hyperkalaemia, acidosis and the release of myocardially depressing mediators, which can lead to clinically significant hypotension and bradycardia.

Post-operatively, restoration of normal portal pressures and liver function, along with hypertensive effects of some of the immunosuppressive medications, can instigate marked increases in SVR. This can result in arterial hypertension and significant elevations in cardiac afterload.[11,62–65] A latent or clinically unapparent cirrhotic cardiomyopathy may then be unmasked, precipitating acute left ventricular failure and subsequent pulmonary oedema.

In fact, studies have shown that pulmonary oedema affects anywhere from 12 to 56% of patients in the peri-operative period.[17,62–67] Donovan et al also observed global left ventricular (LV) dysfunction (mean EF = 20%) in four of their 71 transplant patients (5.6%), all of whom had normal, preoperative cardiac function.[67] Overall, congestive heart failure and other cardiac complications significantly contribute to perioperative mortality, leading to 7–21% of the deaths associated with liver transplantation.[17] Subsequent studies have identified cardiovascular failure as an independent, post-transplant predictor of mortality ($p = 0.002$).[11,68]

Unfortunately, it is difficult to determine the extent to which cirrhotic cardiomyopathy contributes to this post-transplant cardiac failure. Much of this problem lies with

the fact that most people with cirrhotic cardiomyopathy lack overt ventricular dysfunction; hence, the condition remains unseen and undiagnosed.[17]

MANAGEMENT

Until the expert working group comes up with consensus definitions of cirrhotic cardiomyopathy, diagnosis and management recommendations can only be made as general and somewhat empirical measures. The possibility that cardiac function may respond abnormally in stressful situations must be borne in mind. Moreover, clinical deterioration under conditions that challenge the cardiovascular system might be at least in part due to or aggravated by cirrhotic cardiomyopathy, and this should also be considered when searching for reasons for the deterioration. Conditions that are known to potentially precipitate more overt ventricular insufficiency in some cirrhotic patients include TIPSS insertion, infections (particularly spontaneous bacterial peritonitis), major surgery including liver transplantation, and volume depletion and haemorrhage. During these situations, the alert physician must carefully monitor cardiac function for evidence of deterioration.

Because of the marked peripheral vasodilatation characteristic of cirrhosis, the ventricular afterload is reduced. In other words, the cirrhotic patient is almost 'autoprotected' from developing severe or overt heart failure, at least in the absence of a major cardiovascular challenge. The problem of course potentially arises during the course of drugs or other stimuli that correct the peripheral vasodilatation or induce systemic vasoconstriction by whatever mechanism. This may explain the small incidence of overt ventricular failure in the early post-transplantation period when the systemic vascular resistance is restored to normal or near-normal values relatively rapidly.

If overt congestive heart failure supervenes, treatment measures are generally similar to those for non-cirrhotic ventricular insufficiency, with some important caveats. First, unlike the vasoconstricted peripheral circulation in non-cirrhotic patients with congestive failure, the peripheral vasodilatation of cirrhosis limits some primary therapeutic manoeuvres that depend on reducing afterload. Specifically, patients with cirrhosis frequently have very low arterial pressures (mean arterial pressures around 60 are not unusual) and poorly tolerate many drugs that reduce preload or afterload. In particular, vasodilators such as angiotensin converting enzyme inhibitors may induce a precipitous fall in blood pressure in some patients. Second, many cardiovascular drugs show relatively little effects due to desensitization. The vasodilator and positive-inotropic agent dobutamine shows blunted responses in patients with cirrhosis.[18] Nitrovasodilators such as sodium nitroprusside that act as nitric oxide donors are often ineffective due to high endogenous NO activity and consequent desensitization. Third, as noted previously, cardiac glycosides such as ouabain seem to be ineffective in improving contractility, although that has been tested in only one study dating back more than three decades.

The non-pharmacological therapeutic manoeuvres applicable to non-cirrhotic heart failure can be used: bed rest and oxygen supplementation. Although it may appear that pharmacological therapy is either ineffective or contraindicated, several promising avenues are currently being explored. In non-cirrhotic heart failure, the somewhat paradoxical use of β-adrenergic antagonists is based on the premise that protection from the cardiotoxic effects of high cardiac and circulating catecholamine levels outweighs the negative inotropic acute effect of β-blockade. A similar paradigm may apply to

cirrhotic cardiomyopathy. In an intriguing study in cirrhotic patients, Henriksen and colleagues administered a single dose of the β-blocker propranolol and noted transient shortening of the QT prolongation.[69] The effect of chronic dosing of β-blockers on contractility or electrophysiological abnormalities in cirrhotic cardiomyopathy requires further study.

Pozzi and colleagues administered the aldosterone antagonist potassium canrenoate for six months to cirrhotic patients without overt congestive heart failure.[70] They observed some decreases in the magnitude of left ventricular hypertrophy and wall thickness associated with a statistically non-significant trend towards improved diastolic function.[70] It is possible that a longer period of treatment may have produced significant effects on contractile function. Certainly, further study of drugs that block the fibrogenic angiotensin-aldosterone system are warranted.

Finally, although there may be a risk of cardiac failure and decompensation in the immediate and short term post-transplantation period, over the long term, heart function appears to gradually improve. In that respect, a recent study has shown improvement of cardiac function a mean of nine months after orthotopic liver transplantation. Torregrosa and colleagues demonstrated improvement in the E/A ratio, regression of ventricular hypertrophy and reversal of QT prolongation in 15 patients after transplantation.[71] These results contrast with an earlier Spanish study which reported a deterioration of diastolic function a mean of 21 months after liver transplantation.[72] However, the earlier study did not stress cardiac function but merely measured resting indices and thus may have been unable to detect improvement in ventricular responsiveness to stimuli. Therefore, although not yet incontrovertibly demonstrated, it does seem that like many of the extrahepatic complications of cirrhosis, cirrhotic cardiomyopathy is also 'curable' with liver transplantation. Future research in management and therapeutic options for cirrhotic cardiomyopathy, including pharmacological treatment is obviously required.

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Key clinical points

- Cirrhotic cardiomyopathy is found in all forms of cirrhosis, both alcoholic and non-alcoholic
- It is characterized by attenuated ventricular contractile response to stress challenge, and electrophysiological repolarization abnormalities
- Pathogenic mechanisms include impairment of β-adrenergic signalling pathways, cardiomyocyte plasma membrane function, and humoral factors such as nitric oxide and endocannabinoids
- It contributes to the pathogenesis of hepatorenal syndrome, and heart failure after liver transplantation and TIPS insertion
- Treatment strategies are mainly supportive

Research agenda

- How to define cirrhotic cardiomyopathy, in terms of these parameters:
  - Systolic dysfunction
  - Diastolic dysfunction
  - Electrophysiological abnormalities
- Serum markers, e.g. pro-BNP, troponin isoforms?
- Elucidation of how cirrhotic cardiomyopathy helps precipitate hepatorenal syndrome
- Further mechanistic insights at the cellular/molecular level
- Specific treatment regimens for those with overt heart failure

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