Cardiovascular Abnormalities in Cirrhosis: the Possible Mechanisms

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Abstract

Cirrhosis is characterized by marked abnormalities in the cardiovascular system. A hyperdynamic splanchnic and systemic circulation is typical of cirrhotic patients and has been observed in all experimental forms of portal hypertension. The hyperdynamic circulation is most likely initiated by arterial vasodilatation, leading to central hypovolemia, sodium retention, and an increased intravascular volume. Despite the baseline increase in cardiac output, ventricular inotropic and chronotropic responses to stimuli are blunted, a condition known as cirrhotic cardiomyopathy. This review briefly examines the major mechanisms that may underlie these cardiovascular abnormalities, concentrating on nitric oxide, endocannabinoids, prostaglandins, carbon monoxide, endogenous opioids, and adrenergic receptor changes. Future work should address the complex interrelationships between these systems.

J Teh Univ Heart Ctr 4 (2007) 191-200

Keywords: Cirrhosis • Cardiomyopathy • Vasodilation

Introduction

The clinical picture of patients with cirrhosis is dominated by the classical complications to portal hypertension, such as ascites, bleeding from esophageal varices, and encephalopathy. In addition, a considerable number of patients show signs of peripheral vasodilatation with palmar erythema and reddish skin, raised and bounding pulse, and a low systemic blood pressure indicating a hyperdynamic circulation.¹ The hyperdynamic syndrome comprises an increased heart rate, cardiac output, and plasma volume, and a reduced systemic vascular resistance and arterial blood pressure.²,³ Despite the increased basal cardiac output, cardiac response to physiologic or pharmacologic stimuli is known to be subnormal⁴,⁵, a phenomenon called “cirrhotic cardiomyopathy”.⁶,⁷ Cirrhotic cardiomyopathy is variably associated with a baseline increase in cardiac output, defective myocardial contractility, and lowered systo-diastolic response to inotropic and chronotropic stimuli, down-regulated β-adrenergic function, slight histo-morphological changes, and impaired electric “recovery” ability of ventricular myocardium.⁸

In addition, patients with cirrhosis develop complications from a variety of organs including the lungs, kidneys, and other organ systems.⁹

This review will summarize the recent work on pathogenic mechanisms underlying two conditions of vascular and cardiac abnormalities in cirrhosis.

Vascular Changes in Cirrhosis

Vascular abnormalities are ubiquitous in cirrhosis. It has long been known that cirrhosis may be considered as a vascular disease of the liver, owing to the marked
anatomic changes that occur at the intrahepatic circulation. A hyperdynamic splanchnic and systemic circulation is typical of cirrhotic patients and has been observed in all experimental forms of portal hypertension. Its presence is associated with extensive portal-systemic shunting and/or hepatic failure, and contributes to the severity of portal hypertension and to other manifestations of chronic liver disease. The hyperdynamic circulation is most likely initiated by arterial vasodilatation, leading to central hypovolemia, sodium retention, and an increased intravascular volume. This combination of vasodilatation and an expanded intravascular volume is necessary for the full expression of the hyperdynamic circulatory state. In the vascular biologic aspect, this excessive arterial vasodilatation observed in the arterial splanchnic and systemic circulation is an extremely unique and interesting phenomenon because in the case of most diseases such as atherosclerosis and diabetes mellitus it is arterial vasoconstriction that is associated with the progressive development of symptoms. For several years, efforts have been made to understand the mechanism of arterial vasodilatation observed in the splanchnic and systemic circulation. This part of this review is to summarize our current knowledge about what molecules and factors are known to be involved in or potentially involved in the arterial vasodilatation in cirrhosis.

Nitric oxide (NO)

Nitric oxide was proposed as a putative mediator of splanchnic vasodilatation in portal hypertension in 1991. Since then; a strong body of evidence from human and experimental models of cirrhosis has supported the notion that changes in NO activity affect different vascular beds in variable ways.

Nitric oxide is synthesized in the vascular endothelium from L-arginine by NO synthase (NOS), of which three isoforms have been identified: inducible NOS (iNOS), constitutive endothelial NOS (eNOS), and neuronal NOS (nNOS). In portal hypertension, there seems to be a diminished release of NO from sinusoidal endothelial cells in the cirrhotic liver. In the liver microcirculation, eNOS expression is decreased in a cirrhotic rat model. Simvastatin enhances the hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis. An NO donor or eNOS gene transfection, which compensates for the decreased hepatic eNOS expression, significantly lowers the increased portal pressure in cirrhosis. On the other hand, in the systemic circulation, there is evidence of increased eNOS, iNOS, or nNOS upregulation. Exhaled air from cirrhotic patients contains higher NO levels than that of controls and correlates with the severity of disease and degree of hyperdynamic circulation; in animal models and cirrhotic patients, blockade of NO formation significantly increases arterial blood pressure and decreases plasma volume and sodium retention. Patients with cirrhosis have increased plasma levels of nitrates and nitrites, the NO degradation products. A study performed in cirrhotic patients undergoing liver transplantation showed a higher NOS activity in the hepatic artery of these patients than that in the controls, and this abnormality was more pronounced in patients with ascites. Inhibition of nitric oxide production reduces superior mesenteric artery flow, portal systemic shunting, and partially prevents the development of the characteristically hyperdynamic circulation of portal hypertension. Taken together, there is a growing body of evidence that the systemic NO production is increased and precedes the development of the hyperdynamic circulation in cirrhosis, thereby playing a major role in the arteriolar and splanchnic vasodilatation and vascular hyporeactivity.

Endocannabinoids

Cannabis has been used for psychoactive and recreational purposes as well as in traditional medicine, long before the advent of modern medicine and scientific research. The active component of cannabis, tetra-hydro-cannabinol (THC) was discovered in 1964. This finding led to the discovery of two specific receptors of cannabinoids. The cannabinoid receptor CB1 receptor was found initially in the brain and subsequently in the gut and vascular endothelium. The CB2 receptor was isolated primarily in the immune system. The first endogenous ligand for these receptors was found in 1992 and was designated as Anandamide. Following this breakthrough, several other ligands were reported, e.g. 2-arachidonyl-glycerol (2-AG), noladine, and oleamide. It has been shown that anandamide increased in cirrhotic monocytes and overactivation of CB1 receptors within the mesenteric vasculature may contribute to the development of splanchnic arterial vasodilatation and portal hypertension. The blockade of CB1 receptor by the antagonist SR141716A increases mean arterial pressure and peripheral resistance in rats with CCl4-induced cirrhosis. We also showed that AM251, a selective CB1 antagonist, increased blood pressure and systemic vascular resistance of bile duct ligated-cirrhotic rats, in agreement with previous studies. Batkai et al. (2001) demonstrated that SR141716A injection caused a decrease in mesenteric arterial blood flow and portal vein pressure in CCI4-induced cirrhotic animals. We also showed that AM251 administration induced the same effect in superior mesenteric artery blood flow in bile duct ligated rats. Yang et al. (2007) reported that following acute AM251 infusion, a simultaneous decrease in portal venous pressure and superior mesenteric artery blood flow and an increase in superior mesenteric artery resistance index were observed in bile duct ligated rats.
Using intravital microscopy shows that acute AM251 administration significantly constricts mesenteric arterioles (first order branch) of bile duct ligated rats, while it has no effect on bile duct ligated venules or arterioles and venules (first order branch) of control rats.44 On the other hand, chronic treatment for one week with AM251 significantly decreases portal venous pressure and superior mesenteric artery blood flow in bile duct ligated rats.45

Anandamide-induced relaxation is significantly potentiated in mesenteric vascular beds of cholestatic rats preconstricted with phenylephrine. Chronic treatment of bile duct-ligated animals with L-NAME (a non-selective iNOS inhibitor) and aminoguanidine (a selective iNOS inhibitor) blocks this hyperresponsiveness. Although acute L-NAME treatment of mesenteric beds completely blocks the anandamide-induced vasorelaxation in sham-operated rats, this vasorelaxation still is present in bile duct ligated animals. These effects indicate enhanced anandamide-induced vasorelaxation in 7-days’ bile duct ligated rats. Moreover, NO overproduction possibly through iNOS may be involved in cholestasis-induced vascular hyperresponsiveness.46

In another study by Domenicali et al. (2005), mesenteric vessels of CCl4 induced-cirrhotic animals displayed greater sensitivity to anandamide than those of the control vessels, which indicated that the endocannabinoid system might have greater local vasodilator activity in the splanchnic circulation.47 This vasodilator response was reverted by CB1 receptor blockade, but not after endothelium denudation or nitric oxide inhibition. This discrepancy for NO results between these two studies might be because of different models, as the first paper used 7-days’ bile duct ligated rats induced by cholestasis, whereas in the second experiment, rats were completely cirrhotic. Domenicali et al. (2005) also showed that anandamide had no effect on distal femoral arteries.48 These results emphasize the tissue selectivity of endocannabinoids and point to anandamide as an important local regulator of vascular tonicity in the mesenteric circulation in pathological conditions such as hepatic cirrhosis.

**Carbon monoxide (CO)**

Studies suggest a possible role of CO, an end product of the heme oxygenase (HO) pathway, in vasodilatation in cirrhosis.48,49 Heme oxygenase is an enzyme that catabolizes heme derived from heme-containing proteins, especially hemoglobin to biliverdin, which is then rapidly transformed to bilirubin and CO.50 Carbon monoxide has a number of important biological effects, including vasodilatation through activation of guanylyl cyclase of vascular smooth muscle cells, and seems to play an important role in the regulation of blood flow and resistance in several vascular beds.51

A constitutive isoform of HO, HO-2 is mainly expressed in the spleen, but can also be found in many other tissues, including blood vessels.52,53 Under pathologic conditions, HO activity may increase markedly due to the upregulation of an inducible isoform of the enzyme, HO-1, also known as heat shock protein 32.54 In portal hypertension, HO-1, not HO-2, is up-regulated in systemic and splanchnic arterial circulations. Carbon monoxide produced by HO-1, synergistically with NO, plays a role in arterial vasodilatation observed in cirrhosis with portal hypertension.48,49

**Prostaglandins**

Prostacyclin (PGI2), a major product of vascular cyclooxygenase, is formed primarily in endothelial cells and also in the media and adventitia in response to both physical and humoral stimuli that also release NO.55 Prostacyclin causes relaxation of vascular smooth muscle by activating adenyl cyclase and increasing the production of cyclic AMP.

An increased basal release of PGI2 is thought to have a major role in the pathogenesis of vasodilatation and vascular hypocontractility associated with portal hypertension. In agreement with this hypothesis, the whole-body production of PGI2 is increased in portal hypertensive animals.56,57 Moreover, portal venous PGI2 levels are substantially higher in portal hypertensive animals and cirrhotic patients, which suggests that portal venous release of PGI2 may play a role in the development of the splanchnic hyperemia, collateral circulation, and portal hypertensive gastropathy.57,58

Initial studies with indomethacin demonstrated a significant reduction in circulating PGI2 levels concomitant with a reduction in splanchnic blood flow in portal hypertensive animals.58,59

In addition to decreased hepatic metabolism due to pronounced portosystemic shunting (PSS), several studies have also implicated exaggerated cyclooxygenase expression and activity within the hyperemic vasculature as a possible reason for the enhanced circulating PGI2 levels.60

**Endogenous opioids**

It has been shown that cirrhosis is associated with increased plasma levels of the endogenous opioid peptides.61,62 They are also reputed to be possible mediators of some chronic liver disease complications such as ascites63 and bleeding esophageal varices.52 Furthermore, in our previous experiments, we demonstrated the endogenous opioid peptides’ role in the hyperresponsiveness of the cardiovascular system to exogenous stimulation in cholestatic rats.54-66 The precise reason for the increased opioid activity in cirrhosis is not yet completely understood, but it is likely that both the overproduction of the endogenous opioid peptides and protection of these peptides from degradation may contribute to the elevation of total opioid activity.61,62

Recently, we showed that biliary cirrhosis is accompanied with a decrease in baseline perfusion pressure in mesenteric vascular bed and that chronic opioid receptor blockade with
naltrexone significantly increases this pressure. The maximum mesenteric vascular bed pressure response to phenylephrine is decreased significantly in cirrhosis, and chronic naltrexone treatment completely improves it. Chronic opioid receptor blockade did not modulate the increased nitrite/nitrate levels following cholestasis. These results provided evidence on the contribution of the endogenous opioid system to vascular hyporesponsiveness in cirrhosis independent of NO production.

Cirrhotic Cardiomyopathy

The possibility of heart dysfunction in cirrhosis, first described in 1953, was regarded as just related to the eventual metabolic complications of alcohol intake or haemochromatosis. However, during the past 2 decades, it has become clear that blunted ventricular contractility with stress is also present in nonalcoholic patients and animal models of cirrhosis. In the 1990s, numerous studies in patients with nonalcoholic cirrhosis conclusively demonstrated that decreased ventricular contractile responses to stimuli are found in all forms of cirrhosis.

In the absence of consensus definitions, the term “cirrhotic cardiomyopathy” is defined at present as: 1) baseline increased cardiac output but blunted ventricular response to stimuli, 2) systolic and/or diastolic dysfunction, 3) absence of overt left ventricular failure at rest, and 4) electrophysiological abnormalities including prolonged QT interval on electrocardiography and chronotropic incompetence. Not all features are required for the diagnosis; for example, only 30–60% of patients show a prolonged QT interval.

Baik et al. (2007), believe that at least one feature of cirrhotic cardiomyopathy, such as electrophysiographic QT prolongation or diastolic dysfunction, is present in the majority of patients with cirrhosis who have reached Child-Pugh stage B or C (representing moderately or severely advanced liver failure). Moreover, diastolic dysfunction is probably present in virtually all patients with cirrhotic cardiomyopathy, and simple echocardiographic indices such as the E/A ratio may detect diastolic dysfunction even at rest. Indeed, once cirrhosis has advanced to a moderate stage, with the accumulation of peripheral edema or ascites, it appears that some element of diastolic dysfunction is universally present.

Cirrhotic cardiomyopathy is usually clinically latent or mild, likely because the peripheral vasodilatation significantly reduces the left ventricle after-load, thus actually “auto-treating” the patient and masking any severe manifestation of heart failure. In cirrhotic patients, the presence of cirrhotic cardiomyopathy may become unmasked and clinically evident by certain treatment interventions that increase the effective blood volume and cardiac pre-load, including surgical or transjugular intrahepatic porto-systemic shunts, peritoneo-venous shunts (LeVeen), and orthotopic liver transplantation. Under these circumstances, an often transient overt congestive heart failure may develop, with increased cardiac output as well as right atrial, pulmonary artery, and capillary wedge pressures. We herein review possible pathogenic mechanisms reported by our laboratory and others.

β-adrenergic signaling

In the subjects suffering from liver cirrhosis, a deep alteration of the autonomic adrenergic function has been reported, which correlates with the severity of the disease. In these patients, both inotropic and chronotropic responses to β-adrenergic agonist stimulation are actually diminished. In this way, the response to norepinephrine, angiotensin II, and dobutamine is decreased, and no significant heart rate increase occurs during the Valsalva maneuver, ice-cold skin stimulation, or mental stress. Moreover, the dose of isoproterenol required for heart rate to increase 25 beats/min is significantly higher in cirrhotic patients than that in controls. We also showed that the maximum effects of isoproterenol on chronotropic and inotropic responses were significantly reduced in isolated atria and papillary muscles of cirrhotic rats.

The response to posture variations is reduced too, due to a blunted baroreflex function, with a tendency to orthostatic hypotension, and no significant increase in heart rate during tilting test. A significant downregulation of the β-adrenergic receptors, which has been demonstrated in cirrhosis, may account for the above-mentioned clinical and experimental data.

It has been shown that the expression and responsiveness of β-adrenergic receptors as well as their post-receptor signaling pathway is blunted in the cardiac tissue of cirrhotic rats. Post-receptor impairment was found at different levels including content and function of stimulatory Gs proteins, uncoupling of the β-adrenergic receptor-ligand complex from G protein, and responsiveness of adenylyl cyclase to stimuli.

The cell membrane fluidity is critical in the correct function of several membrane-bound receptors, including β-adrenergic ones. In fact, a decreased membrane fluidity (due to an increased cholesterol content and cholesterol/phospholipid ratio) in the cardiomyocytes of bile duct ligated rats was reported to be associated with a blunted β-adrenergic receptor response, with an alteration of the signal transduction pathway and of the conductance of the gap–junction channels.

Nitric oxide

Nitric oxide is known to negatively regulate cardiac contractile function. It has been shown to be involved in
some types of cardiac dysfunction including ischemic heart disease. Balligand et al. (1993) found that the inhibition of NO synthesis by L-NMMA significantly increased the contractile response of rat ventricular myocytes to the β-agonist isoproterenol without affecting baseline contractility. In terms of a cirrhotic model, van Obbergh et al. (1996) reported on the role of NO in bile duct ligated cirrhotic rat. They showed that L-NMMA significantly increased contractile function in isolated working cirrhotic hearts but had no effect on controls. It has been also shown that in the cirrhotic rats, baseline isoproterenol-stimulated papillary muscle contractile force was lower than that 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. In addition, cirrhotic cardiomyocytes showed an increased iNOS mRNA and protein expression, whereas eNOS showed no significant difference in the expression between the bile duct ligated 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 the inhibition of adenyl cyclase activity or through cGMP remains to be further clarified. However, it has been reported that TNF-α and cGMP content in cardiac homogenates showed a significant increase in bile duct ligated rats, suggesting a possible cytokine-iNOS-cGMP mediated pathway of action for NO in the pathogenesis of cirrhotic cardiomyopathy.

In our recent paper, we showed that the basal abnormalities and the attenuated chronotropic and inotropic responses to isoproterenol were completely corrected by the administration of L-NAME and aminoguanidine in cirrhotic rats, implying the role of iNOS in these events. Previous experiments have shown that the endogenous cannabinoids anandamide increased 2.7-fold in the heart of the cirrhotic compared with control rats, without any change in 2-arachidonoylglycerol levels; whereas in the cirrhotic liver, both 2-arachidonoylglycerol (6-fold) and anandamide (3.5-fold) were markedly increased. CB1-receptor expression in the heart was unaffected by cirrhosis, as verified by Western blotting. Activation of cardiac CB1 receptors by endogenous anandamide contributes to the reduced cardiac contractility in liver cirrhosis, and CB1-receptor antagonists may be used to improve contractile function in cirrhotic cardiomyopathy and, possibly, in other forms of heart failure.

### Endocannabinoids

Hypotension and bradycardia are the most important features elicited by the systemic administration of cannabinoids, and endocannabinoids are known to have a negative inotropic effect on cardiac contractility in both humans and rats. The plasma level of anandamide is known to be increased in cirrhosis. Gaskari et al. (2005) demonstrated a negative inotropic effect of anandamide in the left ventricular papillary muscles of cirrhotic rats. This inhibitory effect on contractility was completely blocked by incubation with AM251, a known CB1 antagonist, thus confirming that the effect of anandamide is mediated by CB1 receptors. They also showed a major role for an increased local cardiac production of endocannabinoids in cirrhotic cardiomyopathy. That conclusion was based on the restoration of blunted contractile response of isolated left ventricular papillary muscles from bile duct ligated cirrhotic rats after preincubation with a CB1 antagonist, AM251. Additionally, endocannabinoid reuptake blockers (VDM11 and AM404) enhance the relaxant response of cirrhotic papillary muscle to higher frequencies of contraction in an AM251-sensitive fashion, suggesting an increase in the local production of endocannabinoids acting through CB1 receptors.

Bolus intravenous injection of the CB1 antagonist AM251 (3 mg/kg) acutely increased mean blood pressure, as well as both load-dependent and -independent indexes of systolic function, whereas no such changes were elicited by AM251 in the control rats. Furthermore, the tissue levels of the endocannabinoid anandamide increased 2.7-fold in the heart of the cirrhotic compared with control rats, without any change in 2-arachidonoylglycerol levels; whereas in the cirrhotic liver, both 2-arachidonoylglycerol (6-fold) and anandamide (3.5-fold) were markedly increased. CB1-receptor expression in the heart was unaffected by cirrhosis, as verified by Western blotting. Activation of cardiac CB1 receptors by endogenous anandamide contributes to the reduced cardiac contractility in liver cirrhosis, and CB1-receptor antagonists may be used to improve contractile function in cirrhotic cardiomyopathy and, possibly, in other forms of heart failure.

### Endogenous opioids

Previous experiments have shown that the endogenous opioid peptides are produced and secreted by the cardiac myocytes as well as the sympathetic nerves and adrenal glands. It is well known that the endogenous opioid peptides system have been reported in several pathophysiological conditions in both human and animal models of cardiovascular diseases such as acute or chronic heart ischemia and genetic hypertension. In our previous experiments, we demonstrated the endogenous opioid peptides’ role in bradycardia and hyposresponsiveness of cardiovascular system to exogenous stimulation in chelestatic rats. We also showed that the incubation of the cirrhotic papillary muscles with naltrexone restored the basal contractile impairment to the sham-control level, and also corrected the chronotropic and inotropic hyposresponsiveness of cirrhotic rats to isoproterenol stimulation. These findings provide the evidence for the endogenous opioid peptides regulatory role on the basal cardiac contractile impairment in cirrhosis.
Carbon monoxide

An increased expression of inducible HO and cGMP levels was demonstrated in the left ventricle of the bile duct ligated rats, whose isolated papillary muscles did exhibit a blunted contractility. The treatment with Zn-protoporphyrine IX (an HO inhibitor) reduced cGMP levels, thus normalizing the myocardial inotropic ability.104 These findings suggest that the 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 the stimulation of cGMP.105

Conclusion

Splanchnic vasodilatation in relation to portal hypertension is responsible for the hyperdynamic circulation and abnormal distribution of blood volume with a reduced “effective arterial blood volume” and activation of baroreceptor and volume-receptor reflexes as the outcome. The enhanced vasodilatation and counter regulatory overactivity of vasoconstrictor systems play major roles in the development of the multi-organ failure in cirrhosis with impaired function and perfusion of kidneys, lungs, brain, skin, and muscles. Underlying mechanisms of vascular abnormalities in cirrhosis have been extensively explored in recent years, and a number of vasoactive mediator systems including nitric oxide, endocannabinoids, carbon monoxide, prostaglandins, and endogenous opioids may be common to the genesis of these conditions.

Experimental and clinical studies of patients with cirrhosis strongly suggest the presence of latent heart failure with impaired reactions to standardized provocations. This has given rise to the introduction of the clinical entity cirrhotic cardiomyopathy. Cirrhotic cardiomyopathy is clinically and pathophysiologically different from alcoholic heart muscle disease. Cirrhotic cardiomyopathy comprises changes in impaired cardiac contractility during the preload and afterload, decreased β-adrenergic receptor function, post-receptor dysfunction, defective excitation contraction coupling, and in some patients conductance abnormalities. Cirrhotic cardiomyopathy may cover different pathophysiological mechanisms including β- adrenergic signaling, nitric oxide, endocannabinoids, endogenous opioids, and carbon monoxide abnormalities. Considering the undeniable interrelation of different systems in both hyperdynamic circulation and cardiomyopathy, further studies are required to elucidate the complex interactions between these mechanisms.

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