PO Box 2345, Beijing 100023, China
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EDITORIAL

Cardiac and vascular changes in cirrhosis: Pathogenic mechanisms

HongQun Liu, Seyed Ali Gaskari, Samuel S Lee

HongQun Liu, Seyed Ali Gaskari, Samuel S Lee, Liver Unit, University of Calgary, Calgary, Alberta, Canada
Co-first authors: HongQun Liu and Seyed Ali Gaskari
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Correspondence to: Samuel S Lee, MD, Professor of Medicine, Department of Medicine, University of Calgary. 3330 Hospital Drive NW, Calgary, AB, T2N 4N1, Canada. samlee@ucalgary.ca
Telephone: +1-403-220-8457 Fax: +1-403-270-0995
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Abstract

Cardiovascular abnormalities accompany both portal hypertension and cirrhosis. These consist of hyperdynamic circulation, defined as reduced mean arterial pressure and systemic vascular resistance, and increased cardiac output. Despite the baseline increased cardiac output, ventricular inotropic and chronotropic responses to stimuli are blunted, a condition known as cirrhotic cardiomyopathy. Both conditions may play an initiating or aggravating pathogenic role in many of the complications of liver failure or portal hypertension including ascites, variceal bleeding, hepatorenal syndrome and increased postoperative mortality after major surgery or liver transplantation. This review briefly examines the major mechanisms that may underlie these cardiovascular abnormalities, concentrating on nitric oxide, endogenous cannabinoids, central neural activation and adrenergic receptor changes. Future work should address the complex interrelationships between these systems.

Key words: Hyperdynamic circulation; Portal hypertension; Cirrhotic cardiomyopathy; Hemodynamics; Nitric oxide; Endocannabinoid; cGMP

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INTRODUCTION

The cardiovascular system in patients with cirrhosis or portal hypertension is abnormal. The circulation becomes hyperdynamic, characterized by increased cardiac output and decreased peripheral vascular resistance and arterial pressure. Moreover, despite the increased cardiac output at rest, with stressful stimuli such as hemorrhage, surgery or vasoactive drug administration, the ventricular response is blunted, a condition known as cirrhotic cardiomyopathy. These cardiovascular abnormalities have been suggested to induce or aggravate several complications of cirrhosis such as renal salt and water retention, variceal bleeding, hepatopulmonary syndrome, and increased cardiovascular fragility under stress. Recent reviews have detailed the clinical aspects of hyperdynamic circulation[1,2] and cirrhotic cardiomyopathy[3-5]. This review will summarize the recent work on pathogenic mechanisms underlying these two conditions.

HYPERDYNAMIC CIRCULATION

Peripheral vasodilatation is central to hyperdynamic circulation and portal hypertension in cirrhosis. However, the factors directly initiating vasodilatation remain obscure. A hypothesis that has received much attention over the past three decades is the "humoral factor" theory. In cirrhosis, increased intrahepatic resistance induces portosystemic collateral formation, allowing gut-derived humoral substances to directly enter the systemic circulation without detoxification by the liver. The following gut-derived or locally-produced humoral factors have been implicated as possible mediators of peripheral vasodilatation in cirrhosis or portal hypertension.

Endocannabinoids

Endocannabinoids are lipid-like substances that act on two inhibitory G protein-coupled receptors, CB1 and CB2. The vasodilatory effect of endogenous cannabinoids in cirrhosis was first reported in 2001[6]. Anandamide, an endogenous cannabinoid or endocannabinoid, is increased in monocytes of cirrhotic rats[6,7], and its receptor CB1 is also upregulated in the vascular endothelium of patients with cirrhosis[6]. Infusing monocytes isolated from cirrhotic rats into normal rats decreases the mean arterial pressure in the recipients. Furthermore, administering a CB1 receptor antagonist SR141716A to cirrhotic rats increases the total peripheral resistance[6,7], both studies demonstrated that SR141716A significantly increases the reduced arterial pressure in cirrhosis, and blocks the hypotension induced by the infusion of isolated cirrhotic monocytes into normal rats[6,7]. Batkai and colleagues also

found that SR141716A decreases mesenteric blood flow and portal venous pressure in cirrhotic rats[6]. All of these data indicate that the vascular tone in cirrhosis is regulated by CB1 receptors in both the splanchnic and systemic circulations.

Besides vasodilatation, anandamide rapidly and dose-dependently induces apoptosis in primary culture-activated and *in vivo*-activated hepatic stellate cells, with over 70% cell death after 4 h at 25 μmol/L[8]. This effect could alter the hepatic sinusoidal microcirculation and enhance the development of portal hypertension that leads to hyperdynamic circulation.

How does cirrhosis leads to increased endocannabinoids? Varga and co-workers found that bacterial endotoxin stimulates endocannabinoid production in cirrhosis[9]. The upregulation of CB1 receptors in cirrhotic vascular endothelium and thus increased end-organ sensitivity may also enhance endocannabinoid vasodilator tone[6].

Nitric oxide

NO has been extensively studied. It is now clear that in cirrhosis, changes in NO activity affect different vascular beds in variable ways. In the liver microcirculation, endothelial-constitutive NO synthase (eNOS or NOS3) expression is decreased in a cirrhotic rat model[10]. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis[11]. An NO donor[12] or NOS3 gene transfection[10], which compensates for the decreased hepatic NOS3 expression, significantly lowers the increased portal pressure in cirrhosis.

In contrast, systemic NO production is increased in cirrhotic patients and animal models[13-15]. Moreover, normalization of NO production in cirrhotic rats, by achieving normal concentrations of aortic cGMP with small doses of the NOS inhibitor L-NAME, normalizes the decreased peripheral vascular resistance and the increased cardiac output[16]. *In vitro,* an NO inhibitor reverses the hyporeactivity of blood vessels from cirrhotic rats to vasoconstrictors[17].

All these results strongly support the hypothesis that increased NO production is a major factor in the peripheral arterial vasodilation of cirrhosis. Agents promoting nitric oxide production include inflammatory cytokines and endotoxin. In that regard, selective intestinal decontamination with norfloxacin partially reverses the hyperdynamic circulatory state in cirrhotic patients, suggesting a role for the endotoxin-NO pathway[18]. Where does this endotoxin come from in cirrhosis? First, alcohol is a major cause of cirrhosis in Western countries, and alcoholic gastrointestinal mucosal damage[19], could potentially facilitate transfer of bacteria into the circulation. Second, portosystemic shunting allows gut-derived bacterial endotoxins passage to the systemic circulation. Third, cirrhotic patients with portal hypertension show intestinal structural abnormalities characterized by vascular congestion and edema, which leads to increased intestinal permeability to bacterial toxins[20]. Fourth, intestinal bacterial overgrowth and bacterial translocation are increased in cirrhosis[21]. Besides endotoxins, the other possible factors stimulating NO production include cytokines such as TNF-α, IL-1, IL-6, and IFN-γ[22-24] Among these, TNF-α has been studied the most. Lopez-Talavera *et al* found that anti-TNF-α antibody increases mean arterial pressure and systemic vascular resistance, and decreases cardiac index and portal pressure[25]. In our 4-week BDL rats, in parallel with increased serum TNF-α, aortic NOS3 expression and serum nitrate/nitrite concentrations were increased[26].

Although the evidence is strong that the increased NOS activity in cirrhosis plays an important role in hyperdynamic circulation in cirrhosis, it remains obscure which NOS isoform is involved. The majority of previous studies have used a nonspecific NOS inhibitor to diminish NO production. However, a recent study used aminoguanidine, a preferential inhibitor of NOS2 (inducible NOS), and showed that *in vivo,* the hyperdynamic circulation in portal hypertensive rats is reversed[27]. But in another study aminoguanidine had no *in vitro* effect on the hyporeactivity of aortic rings from cirrhotic rats[28]. We have recently evaluated the activity of the L-arginine-NO pathway at different levels[26]. Although NOS2 mRNA was detectable in the cirrhotic aorta, no NOS2 protein was observed in our Western blots. It is unclear why the mRNA was not expressed as a protein. It might have been degraded or not been transcribed. It is also possible that our method of Western blotting did not allow the detection of small amounts of NOS2 protein.

A consistent augmentation in the expression of NOS3 mRNA and protein levels is observed in cirrhotic rats. Because NOS3 can be upregulated by stimuli such as shear stress and mechanical deformation, some have suggested that hyperdynamic circulation is the cause rather than the consequence of the activation of the NO pathway[14,29,30]. In addition, there may be other reasons for the increased NOS3. Cirrhosis is associated with increased levels of estrogens[31,32], and these compounds have been shown to upregulate NOS3 activity[33]. Other factors which may stimulate NOS3 expression need further investigation.

What is the role of another isoform of NOS, neuronal NOS (nNOS or NOS1)? Xu and his colleagues have demonstrated that nNOS expression is significantly increased in rat cirrhotic aortae[34]. Furthermore, an nNOS-specific inhibitor, 7-nitroindazole (7-NI), significantly decreased the sodium and water retention and normalized the hyperdynamic indices such as cardiac index, mean arterial pressure, and systemic vascular resistance in these rats[34]. Biecker *et al* also showed that nNOS partially compensates for the absence of eNOS in producing hyperdynamic circulation in eNOS-gene knockout mice[35]. These data indicate that the nNOS isoform plays a major pathogenic role in hyperdynamic circulation, and perhaps even in renal salt and water retention in cirrhosis.

It seems that endocannabinoids and nitric oxide may both play an important role in hyperdynamic circulation, but what is the relationship between them? The literature remains inconclusive. In a kidney study, Deutsch *et al* found that the vasodilatation of anandamide is NO dependent, because the NOS inhibitor L-NAME completely blocked the vasodilatory effect of anandamide, similar to a CB1 antagonist[36]. However, another study showed no effect

of L-NAME infusion on the hypotensive effects of anandamide[7].

Some studies suggest the possible involvement of other humoral vasodilators, but a definitive pathogenic role for any of these substances remains elusive. This list includes: glucagons[37], prostaglandins[38], GABA[39], VIP[40], bile acids[41], endotoxin, histamine[42] and adenosine [43].

Central neural mechanisms

Although most research has focused on the humoral mediators, in recent years we and others have shown an important mechanistic role of central nervous system (CNS) activation. A decade ago, our laboratory demonstrated that primary afferent denervation by capsaicin reversed the hyperdynamic circulation in rats with cirrhosis or portal hypertension due to portal vein stenosis (PVS)[44]. What is the relationship between the CNS and hyperdynamic circulation in portal hypertension? Using *c-fos*, an immediate-early gene (whose protein product can be detected by immunohistochemistry as Fos), as a marker of central neuronal activation, we have showed that the brainstem and hypothalamic cardiovascular-regulatory nuclei are activated at the first day after PVS, whereas the hyperdynamic circulation does not start up until 3-5 days after PVS. This time sequence suggests that central neural activation is the initiating signal in the pathogenesis of hyperdynamic circulation.

Subsequently, in portal hypertensive rats, we microinjected *c-fos* antisense oligonucleotide into one of the major cardiovascular-regulatory brainstem nuclei, the nucleus tractus solitarius (NTS), to block local Fos expression. This treatment completely blocked the development of the hyperdynamic circulation, i.e., abnormalities in cardiac output, mean arterial pressure and systemic vascular resistance were completely eliminated[45]. In normal control rats, *c-fos* antisense oligonucleotides had no effect [45]. These results indicate that central neural activation is a *sine qua non* for the development of the hyperdynamic circulation in portal hypertension.

The CNS, as the controller of the circulation, presumably would not arbitrarily activate the cardiovascular system without reason. This raises the question of what the initiating signal is? Likely, it is somehow related to the portal hypertension *per se*. Moreover, the exact route of signaling from the periphery to the CNS remains unclear. The aforementioned capsaicin study suggests that primary afferent nerves may be the signaling pathway from the periphery to the CNS[44]. Our subsequent study showed that capsaicin-treated BDL rats improve the renal function and do not develop ascites[46]. Moreover, both BDL-cirrhotic and portal hypertensive rats show diminished Fos expression in NTS after capsaicin-induced denervation of the afferent nerves as neonates[46]. These observations indicate that intact primary afferent innervation is necessary for the central neuronal activation and development or maintenance of hyperdynamic circulation. Additionally, sodium retention and ascites formation is also dependent on either the presence of hyperdynamic circulation or intact afferent innervation, or both. The complex relationship between CNS activation, local or neurohormonal humoral factor stimulation, and cardiovascular disturbances in cirrhosis/portal hypertension continues to be studied in several labs.

CIRRHOTIC CARDIOMYOPATHY

This syndrome was first described in the late 1960s, although for many years, it was mistakenly attributed to latent or subclinical alcoholic cardiomyopathy[47-49]. However, studies in human and animal models with nonalcoholic cirrhosis, dating from the mid-1980s showed a similar pattern of increased baseline cardiac output with blunted response to stress[4]. The clinical features of cirrhotic cardiomyopathy include blunted systolic and diastolic contractile responses to stress, in conjunction with evidence of ventricular hypertrophy or chamber dilatation and electrophysiological abnormalities including prolonged QT interval. Recent studies suggest the presence of cirrhotic cardiomyopathy may contribute to the pathogenesis of hepatorenal syndrome precipitated by spontaneous bacterial peritonitis[50], acute heart failure after insertion of transjugular intrahepatic portosystemic shunts (TIPS)[51,52], and increased cardiovascular morbidity and mortality after liver transplantation[53]. Therefore this syndrome is more than an academic curiosity, but rather an important clinical entity. We herein review possible pathogenic mechanisms reported by our laboratory and others.

Endocannabinoids

Endocannabinoids are known to have a negative inotropic effect on cardiac contractility in both human[54] and rats[55]. The plasma level of an endogenous cannabinoid, anandamide, is known to be increased in cirrhosis[6]. We recently demonstrated a major role for increased local cardiac production of endocannabinoids in cirrhotic cardiomyopathy[56]. This conclusion is based on the restoration of blunted contractile response of isolated left ventricular papillary muscles from BDL-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. Other *in vitro* evidence suggest a main neuronal source for the increase in local production of endocannabinoids, as these effects were mostly abolished by pretreatment with the neurotoxin tetrodotoxin[56].

β*-adrenergic signaling*

Cardiac-adrenergic signaling is one of the main regulators of cardiac contractility. Adrenergic receptors increase adenylyl cyclase activity through stimulatory G proteins. Increased production of cAMP in turn results in an increase in calcium influx and contractile force mainly through activation of protein kinase A (PKA). We have previously shown that expression and responsiveness of β-adrenergic receptors[57] as well as its post receptor signaling pathway is blunted in cardiac tissue of cirrhotic rats. Post receptor impairment was found at different levels including content and function of stimulatory Gs-proteins[58], uncoupling of the β-adrenoceptor-ligand

complex from G protein[59], and responsiveness of adenylyl cyclase to stimuli[58,60].

Membrane fluidity

Biochemical and biophysical properties of the cell membrane determines the mobility of membrane-bound protein moieties. This mobility is known as membrane fluidity[61], which is shown to be an important factor in the function of a number of membrane-bound receptors including β-adrenergic receptors[62]. We have shown that membrane fluidity in cardiomyocytes from bile duct-ligated rats is decreased in association with an increase in membrane cholesterol content and cholesterol/phospholipid ratio[58]. Restoration of these abnormalities *in vitro* results in normalization of blunted response of β-adrenergic receptors[58]. Alterations in membrane fluidity may also play a role in abnormal function of other membrane-bound components in cirrhotic cardiomyocytes including ion channels. The significant decrease in K^+ currents through Ca^{2+}-independent transient outward K^+ channel and the delayed rectifier current reported by Ward *et al* is an example that requires further investigation[63].

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[64]. Balligand *et al* have reported that non-selective blockade of NOS augments the contractile response of rat ventricular myocytes to the β-agonist isoproterenol without affecting the baseline contractility[65]. Whether this effect is mediated by the inhibition of adenylyl cyclase activity by NO[66] or through the second messenger, cyclic guanosine monophosphate (cGMP), remains to be elucidated. Possible effects of NO on cardiac function in physiological and some pathophysiological states were extensively reviewed previously[67,68].

As noted previously, cirrhosis is known to be associated with NO overproduction[29]. Involvement of NO overproduction in the development of cirrhotic cardiomyopathy was first reported in 1996 by Van Obbergh *et al* in the BDL rat. They showed that a nonselective NOS inhibitor, L-NMMA, restored the blunted contractile function of isolated heart from cirrhotic rats while it had no significant effect in control animals[69]. We have reported a similar effect in isolated left ventricular papillary muscles of cirrhotic rats. Furthermore, we observed that iNOS and not eNOS mRNA and protein expression were significantly increased in the heart of a cirrhotic rat[22]. Increased levels of cGMP in cirrhotic ventricles and elevated serum and cardiac levels of cytokines like TNF-α suggest a cytokine/iNOS/cGMP pathway for this effect[22].

Carbon monoxide

Carbon monoxide (CO) is mainly produced in the body through the action of heme oxygenases. These enzymes are responsible for converting heme to biliverdin and CO. Like NO, CO activates soluble guanylate cyclase resulting in increased levels of cGMP[70,71]. Expression of inducible heme oxygenase (HO-1) mRNA was increased in the right ventricle in a canine model of congestive heart failure[72]. We previously reported an increase in mRNA and protein expression of HO-1 in left ventricle of bile duct-ligated rats, which was associated with an increase in left ventricular cGMP levels[73]. Furthermore, treatment of cirrhotic heart with an HO inhibitor, zinc protoporphyrin IX, restored the elevated cGMP levels[73]. These findings suggest the involvement of an HO-CO-cGMP pathway in the development of cirrhotic cardiomyopathy.

CONCLUSION

Cardiovascular abnormalities consisting of hyperdynamic circulation and cardiomyopathy are frequent complications in cirrhotic patients and may contribute to significant morbidity and mortality, especially under stressful conditions. Underlying mechanisms of cardiac dysfunction and vascular abnormalities in cirrhosis have been separately explored in recent years, but a number of vasoactive mediator systems may be common to the genesis of both conditions. We believe that central neural activation plays an important initiating role in the genesis of hyperdynamic circulation, eventually leading to an imbalance between the tonic vasodilator *vs* vasoconstrictor tone, with a predominance of the former. Predominant among these peripheral vasodilator pathways are NO and endocannabinoids. The mechanisms of cirrhotic cardiomyopathy include altered cardiomyocyte plasma membrane physicochemical properties, impairment of β-adrenergic receptor signaling pathways, and overactivity of NO, carbon monoxide and endocannabinoid systems. Considering the undeniable interrelation of these systems, further studies are required to elucidate the complex interactions between these mechanisms.

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