

Potential Therapeutic Targets in Cirrhotic Cardiomyopathy

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Abstract: Cirrhotic cardiomyopathy is a recently identified pathological condition defined as "a chronic cardiac dysfunction in patients with cirrhosis characterized by blunted contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease". Overall there seems to be a link between the progression of liver function impairment, the development of portal hypertension and the degree of hyperdynamic circulation, the hallmark of the deranged cardiovascular function in advanced liver diseases. Although mechanical factors contribute to much of the increased resistance within the liver in portal hypertension, there is clearly a vasculogenic component to the development, perpetuation and progression of this syndrome as well. The vascular component of portal hypertension includes an increase in splanchnic blood flow, as well as an increase in intrahepatic vascular resistance. Dysregulation of the nitric oxide system appears to play a key role in both these processes with a paradoxical reduction of intrahepatic availability despite increased disposal in the splanchnic and other vascular districts with adverse effects on cardiac function and structure. Nevertheless, other putative mediators of cardiac damage in cirrhosis have been proposed and their role in the pathogenesis of cirrhotic cardiomyopathy investigated.

This review involves a discussion of data achieved on pathogenesis and clinical features of cirrhotic cardiomyopathy but mainly focuses on considerations on potential therapeutic targets, in the light of the evidence that this mainly subclinical condition merges to clinical relevance when challenged with those therapeutic interventions and procedures currently employed to treat the major complications of cirrhosis that might produce a negative impact on the cardiovascular system.

Key Words: Cirrhotic cardiomyopathy, hyperdynamic circulation, diastolic dysfunction, portal hypertension, peripheral vasodilation, drug targets.

INTRODUCTION

Cirrhotic cardiomyopathy was recently defined in a recent workshop in conjunction with the World Congress of Gastroenterology in Montreal in September 2005 as "a chronic cardiac dysfunction in patients with cirrhosis characterized by blunted contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease". In the future this short statement will be known as the "Montreal definition for cirrhotic cardiomyopathy".

Cardiovascular dysfunction in patients with cirrhosis of the liver has been described extensively in the last decades. Kowalski and Abelmann [1] were the first to report that advanced liver disease is characterized by a hyperdynamic circulatory pattern, namely high cardiac output and stroke volume, low systolic blood pressure and increased heart rate along with arterial vasodilation, as suggested by decreased systemic vascular resistance. These abnormalities were ascribed for many years to ethanol toxicity. Studies performed in the late 1960s not only confirmed these findings but also showed that cardiac contractile function was adversely affected by chronic ethanol consumption: these findings contributed to corroborate the conviction that alcoholic cardiomyopathy was responsible not only of the derangement of

systemic circulation but also of the blunted ventricular contractile response to pharmacological and various physiological strains.

More recently many investigations performed in both human nonalcoholic cirrhosis and in animal models of non-alcoholic cirrhosis showed that the hemodynamic and functional cardiac derangements of cirrhotic patients are substantially independent of the etiology of liver disease, leading to the belief that the state of cirrhosis per se, irrespective of alcohol, could be associated with this syndrome. Accordingly, Lee and co-workers [2] termed this new entity "cirrhotic cardiomyopathy". Moreover, patterns of heart function abnormalities in non-alcoholic cirrhosis, quite distinct from alcoholic cardiac disease, were described, the ejection fraction of the left ventricle being substantially normal or even increased in the former and decreased in the latter.

Still the mechanisms involved in the hyperdynamic circulation in cirrhosis remain unclear, despite the many hypotheses and theories advanced. The initiation of the hyperdynamic circulatory syndrome has been classically attributed to arteriolar vasodilation [3] evoking an increase in cardiac output and heart rate as a homeostatic response. Noteworthy cardiac output is primarily determined by the interaction and balance between the venous return, the heart rate and myocardial contractility, all controlled by the autonomous nervous system. These physiological mechanisms are overall deranged to various extent in cirrhotic subjects: increased sympathetic nervous activity augments heart rate, stimulates contractility and cooperates to expand total blood volume. Nevertheless, cardiac output has been demonstrated to be

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increased before the occurrence of any reduction of peripheral vascular resistance: in preascitic cirrhotic patients with portal hypertension evidence of an enhanced cardiac pre-load due to expansion of total blood volume has been provided. Bernardi *et al.* [4] reported the occurrence of features of hyperdynamic circulation in cirrhotic subjects only after the assumption of the supine position: this is associated with the translocation of a portion of the blood volume towards the central area of circulation. The increase in cardiac output is the consequence of a greater than normal supine-induced cardiac pre-load which is followed by a compensatory reduction of peripheral vascular resistances.

Overall there seems to be a link between the progression of liver functional failure and the degree of hyperdynamic circulation.

Many circulating vasoactive substances have been investigated extensively and their role as cardiodepressants postulated. Glucagone, vasoactive intestinal peptide, endotoxins, tumor necrosis factor- α , prostacycline, bile salts, endothelins and nitric oxide are some of the proposed putative mediators involved in the pathophysiology of hyperdynamic circulation and cirrhotic cardiomyopathy [5]. According to literature data nitric oxide seems to be the most important factor involved [6].

According to the hypothesis of Vallance and Moncada [7], in liver cirrhosis the peripheral vasodilation can be ascribed mainly to the increased release of nitric oxide from the vascular endothelium in the splanchnic district, prompted by circulating cytokines and endotoxins in cirrhotic subjects, irrespective of etiology of disease. The endothelial release of nitric oxide seems to be mainly due to shear stress within a vascular compartment which physiologically expresses large amounts of constitutive oxide synthase. The more advanced the stage of disease the greater the decrease in peripheral vascular resistance and thereby the reduction in "effective" arterial blood volume and blood pressure due to splanchnic pooling of blood. The homeostatic release of neurohormones acting as vasoconstrictors and as water-sodium retaining substances, like norepinephrine, angiotensin, aldosterone, antidiuretic hormone and others, contribute on one side to maintain circulatory stability but on the other may adversely affect body fluid composition as well as structure and function of the heart.

A latent systolic dysfunction is notably unveiled by appropriate strains (such as infusion of vasoconstrictors, change of posture, expansion of the blood volume, physical exercise, etc) in advanced cirrhosis whereas it is normal or even increased at rest. Recent evidence [8-10] clearly indicates that diastolic function is impaired as well, even in the earliest phases of preascitic cirrhosis, as a consequence of circulatory overload and of direct negative effects of vasoactive and cardiodepressant substances [11].

Sodium retention is a cardinal feature of liver cirrhosis, starting in the pre-ascitic stage of the disease and initially occurring only in the erect posture. Natriuresis follows on assumption of the supine position, with development of hy-

perdynamic circulation. However sodium excretion in cirrhosis is lower as compared to normal subjects, leading to progressive plasma volume expansion. With the progression of liver disease sodium handling abnormalities in the kidney become more pronounced. Wong *et al.* [12] have demonstrated that cardiac dysfunction worsens with progression of cirrhosis, in parallel with the worsening of sodium retention, and with the clinical evidence of fluid retention up to the stage of diuretic resistant ascites. All this evidence suggests a possible link between cirrhotic cardiomyopathy and sodium retention of cirrhosis. Indeed, cirrhotic cardiomyopathy could contribute to sodium retention by reducing the "effective" circulatory volume, as a consequence of reduced contractile function (systolic incompetence), or altered elastic recoil properties of the cardiac parietal walls (diastolic dysfunction).

Despite the recognition of the condition of cirrhotic cardiomyopathy, its clinical significance has always been questioned, as frank cardiac failure is not a prominent feature of cirrhosis. However, there are several reports of decreased cardiac performance in cirrhosis, especially in response to stress like physical exercise [13-15] or infusion of vasoconstrictors [16-18] and after exposure to therapeutic procedures that may unmask a latent cardiac incompetence [19-24].

Thus, the entity of cirrhotic cardiomyopathy may not be simply a medical curiosity, but rather an entity that well deserves further investigations and therapeutic intervention.

POTENTIAL THERAPEUTIC APPROACH FOR THE CLINICAL MANAGEMENT OF CIRRHOTIC CARDIOMYOPATHY

Clinical management of cirrhotic cardiomyopathy remains uncertain since virtually no published data is available on specific treatment of this disorder [25]. Nevertheless, since portal hypertension, due to both increased resistance and blood flow within the portal venous system, is the main drive to the development of circulatory abnormalities in cirrhosis, efforts should be made to use agents that decrease the portal-collateral blood flow, the resistance that opposes that flow, or both. Pharmacological approach is warranted in patients in the decompensated ascitic stage of cirrhotic disease and this includes drugs with a direct or indirect beneficial effect on the cardiovascular system [26].

Loop Diuretics and Aldosterone Antagonists

Diuretic drugs have been shown to be highly effective in the stepped care management of fluid retention of cirrhosis: loop diuretics contribute to decrease reabsorption of sodium and water, decreasing the total blood volume, whereas aldosterone antagonists contribute to inhibit the renin-angiotensin-aldosterone axis, reduce total blood volume and portal hypertension thus finally potentially attenuating the hyperkinetic syndrome [27,28]. Indeed, besides their intrinsic diuretic activity, other effects, less clearly elucidated, could favorably impact cardiovascular function. Pozzi *et al.* have recently demonstrated [28] that aldosterone blockade reduces parietal wall thickness in cirrhotic patients and could thus

improve diastolic dysfunction in the long term. The antifibrotic properties of aldosterone antagonists are well known [29] and improved survival has been demonstrated in chronic heart failure patients treated with these drugs (RALES study). Reduction of circulatory overload, modulation of portal pressure and direct effects on heart remodeling could translate in beneficial effects on cardiac structural and functional abnormalities in cirrhosis as well: accordingly chronic aldosterone blockade could represent a novel therapeutic approach in the management of cirrhotic cardiomyopathy.

Beta Blockers and Nitrates

Since their introduction in the prevention of variceal bleeding in cirrhosis [30] the widespread use of β -blockers in cirrhotic patients with portal hypertension and medium-large size esophageal varices has been shown to have beneficial effect on β -adrenoceptor density, which is supposed to be down-regulated in cirrhosis [31]. This is the reason why patients with cirrhosis will probably not benefit significantly from inotropic β -agonists such as isoproterenol and dobutamine. Nitrates have been employed in combination with β -blockers to improve their effects on protection from bleeding [32]. Amrinone and milrinone, phosphodiesterase inhibitors that inhibit cAMP degradation, may be potentially effective given the various defects in β -adrenergic receptor signalling upstream of adenylate cyclase [33]. It has been shown that short-acting cardiac glycosides (as ouabain) are ineffective in ameliorating cardiac contractility in alcoholic cirrhosis and relatively severe cardiomyopathy but little is known if these findings might apply to the treatment of cirrhotic cardiomyopathy as well [16].

Intrahepatic Vasodilators and Systemic Vasoconstrictors

Pathophysiological data have provided evidence that the major drives to the development of circulatory disturbance of cirrhosis are the progression of intrahepatic vascular resistance on one side and vasodilation of the splanchnic district on the other. Accordingly, pharmacotherapy includes vasodilators and vasoconstrictors or a combination of both [34].

It has been partly clarified that in addition to morphostructural factors, actually supposed to be irreversible, there is a dynamic vasculogenic component of enhanced intrahepatic resistance in portal hypertension [35] which is clearly reversible and thus potentially a target for new therapeutic agents. In the last decades great progress has been made in the understanding of the specific vasoregulatory pathways responsible for increased intrahepatic vascular resistance: these pathways include the nitric oxide-soluble guanylate cyclase system, the paracrine endothelin-1 system, the sympathetic α -adrenergic pathway and the angiotensin-II system.

Studies of specific neuroendocrine antagonists and agonists show promising results and development of these agents are promising as future pharmacotherapy for the circulatory derangement of cirrhosis. Possible treatments of increased intrahepatic vascular resistance have focused on

boosting of vasodilatory signalling systems or counteracting the vasoconstrictive pathways.

Still, a major hurdle in the progress of experimental therapeutics is the difficulty in developing safe and effective compounds which are selective to the liver so as to curtail exacerbation of the systemic hyperdynamic circulatory state which accompanies portal hypertension [36]. Some treatment approaches are currently utilized whereas others are currently under investigation. Other potential therapeutic targets can be considered treatment approaches for the next generation.

The molecular and physiologic basis of the vasoregulatory signalling abnormalities which contribute to development of portal hypertension are a field of active research and experimental therapeutic strategies will continue to focus on the modulation of these systems.

The most well established approach to manage the increased intrahepatic vascular resistance is at present the use of organic nitrates, such as isosorbide-5-mononitrate, to augment the nitric oxide-cGMP system. This class of compounds degrade in the bloodstream, once orally administered, generating bioavailable nitric oxide. The newly generated nitric oxide diffuses directly to effector contractile cells inducing vasorelaxation by activating soluble guanylate cyclase and downstream kinases, thereby bypassing defects in the endothelial generation system within the liver. Such events translate in an attenuation in intrahepatic resistance. However, despite this ability, the systemic vasodilatory effects of oral nitrates may exacerbate the pre-existing hyperdynamic circulatory state, by an increase in venous capacitance and a reduction of systemic vascular resistance. This amplification of "underfilling" may, in the long-term, have deleterious consequences on hepatic and renal function. Still, this adverse effect is much attenuated when vasodilators are used in combination with a vasoconstrictor [34].

Another area under active investigation is the inhibition of sympathetic overactivity through α 1-adrenoceptor antagonism. Notably the hepatic vasculature is richly innervated with α 1-adrenergic nerve fibers. α 1-adrenergic antagonists such as prazosin [37] and clonidine [38] inhibit intrahepatic vasoconstriction in the perfused rat liver after norepinephrine infusion. In cirrhotic patients acute and chronic administration of prazosin is followed by a reduction in intrahepatic resistance and hence in portal pressure [39]. However, lack of intrahepatic selectivity of these agents causes detrimental systemic effects leading to hypotension subsequently generating a secondary sodium and water retention targeted to maintain circulatory homeostasis.

Antagonists of the Renin-Angiotensin System

The advanced stages of cirrhosis are clearly associated with an overactivity of the renin-angiotensin-aldosterone system. Attempts have been made to inhibit angiotensin II, which notably takes part in intrahepatic vasoconstriction: losartan, an angiotensin II receptor antagonist, has been shown to induce portal pressure reduction in cirrhotic pa-

tients both acutely as well as after chronic administration. Wong *et al.* [40] examined the effects of low-doses of losartan as a probe to assess the role of angiotensin II in the regulation of renal sodium handling in preascitic cirrhosis. A 7.5 mg dose of losartan had a maximum natriuretic effect without negatively affecting both renal and systemic hemodynamics, normalizing renal sodium handling even when patients were evaluated in the upright posture. However clinical results have been inconclusive because long term treatment at this dose was not followed by portal pressure reduction [41]. Higher doses of losartan or irbesartan [42] produce substantial decrease of portal pressure gradient but with evidence of negative systemic circulatory effects, mainly severe hypotension, in both preascitic [43] and ascitic patients [44] with cirrhosis associated with significant renal dysfunction.

Captopril, an angiotensin-converting enzyme inhibitor that antagonizes angiotensin II production, could suppress hyperaldosteronism without impairment of renal function and could thereby be a beneficial agent in the management of the circulatory abnormalities in ascitic cirrhotic patients. In a study by Lebrec *et al.* [45], after oral administration of captopril in ascitic subjects, cardiac output and renal blood flow did not change but mean arterial pressure, systemic and renal vascular resistances significantly decreased. They concluded that captopril mainly induces hypotension due to an increase in renal vasodilatation. Also low-doses of captopril, to avoid any change in arterial pressure, in cirrhotic subjects with and without ascites investigated by Gentilini *et al.* [46], induced reduction in glomerular filtration rate and urinary sodium excretion which follows local inhibition of angiotensin II, likely necessary in maintaining renal hemodynamics.

Intrahepatic Nitric Oxide Donors

Indeed, ability to selectively deliver drugs to the liver is a fascinating therapeutic field but encounters several practical difficulties. Research efforts are directed on modification of nitric oxide donor compounds to overcome this burden. A nitric oxide donor prodrug (V-PYRRO/NO) is metabolized selectively within hepatocytes by the cytochrome P-450 system into an active nitric oxide releasing compound.

Given the apparent defect of endothelial nitric oxide synthase function in sinusoidal endothelial cells Fiorucci *et al.* [47] recently postulated that a pharmacological approach to deliver nitric oxide directly to the liver should reduce intrahepatic resistance avoiding the systemic negative effects of nitrovasodilators. A new compound that releases nitric oxide in the liver (NCX-1000) was designed by adding a nitric oxide-releasing moiety to ursodeoxy-cholic acid, which is selectively metabolized by hepatocytes. NCX-1000 significantly reduced liver fibrosis and ameliorated portal hypertension in a rat model of fibrogenesis and portal hypertension. This compound also inhibited stellate cell contraction, thus acting on the reversible vasculogenic component of intrahepatic resistance: altogether these data emphasize that NCX-1000 may serve as a novel therapy for patients with portal hypertension.

Simvastatin is a putative intrahepatic nitric oxide donor compound and accordingly has been recently investigated in experimental models and in preliminary form in human cirrhosis [48]: this statine attenuated the postprandial increase in hepatic venous pressure gradient and nitric oxide product levels increased in hepatic venous blood but not in peripheral blood without affecting systemic hemodynamics. However, further investigations are required to assess the potential benefits.

Endothelin (ET) Antagonists

Also enhanced ET-1 signalling is involved in the development of increased intrahepatic vasoconstriction [49]. ET-1 blocking agents ameliorate this condition *via* their putative action on hepatic stellate cells. Bosentan (safely employed in human studies to treat heart failure, systemic and pulmonary hypertension) blocks either ET-A and ET-B receptors, reduces intrahepatic resistance but may worsen hepatic fibrosis with time. Moreover the most relevant problems reside on the systemic hypotensive effects of this compound [50,51]. Accordingly at present this drug cannot be considered a good candidate for future treatment of cirrhotic cardiomyopathy.

Significant technical and safety barriers limit the use of gene delivery approaches in humans despite potential utility in modulating intrahepatic resistance in animal studies.

Portal Hypotensive Drugs

The reduction of enhanced blood flow and vasodilation is another potential therapeutic target. Historically, most drugs used to treat portal hypertension are vasoconstrictors that act primarily by reducing blood flow. These include vasopressin, terlipressin, somatostatin, octreotide, vapreotide and many β -adrenergic blockers [52]. From a practical point of view, portal hypotensive agents can be divided according to their form of administration, oral versus parenteral, the former being adequate for long-term administration while the latter are appropriate for short term therapy.

The modern era of pharmacological therapy of portal hypertension started in 1981 with the milestone publication by Lebrec *et al.* [30] of the use of propranolol to prevent variceal hemorrhage in cirrhosis. Non selective β -blockers act both by decreasing cardiac output and by decreasing splanchnic arterial blood flow. In particular non selective β -adrenoceptor antagonists such as propranolol decrease enhanced splanchnic blood flow acting by different mechanisms. 1) the β_1 -antagonist effect of β -blockers reduces splanchnic blood flow by decreasing cardiac output (chronotropic and inotropic effect) which induces vasoconstriction in the splanchnic vascular bed by reflex activation of the α -receptors at this vascular level. 2) it has been shown that β_2 -adrenoceptor antagonism reduces splanchnic vasodilation without affecting the action of α -adrenoceptors (unopposed), thus contributing to a certain extent to splanchnic vasoconstriction [53]. 3) reduced blood flow by these two mechanisms decreases shear stress and thus decreases the splanchnic vasodilation promoted by local nitric oxide overproduc-

tion [34]. 4) bacterial translocation and cytokine production, responsible for nitric oxide synthase overactivation and thus of consequent vasodilation, can be reduced by β -blockers administration [53]. 5) Henriksen and colleagues have shown that acute administration of propranolol reduces the electrocardiographic QT interval [54], which is known to be prolonged in cirrhotic subjects. Whether this favorable effect is maintained during chronic treatment requires further investigation before this approach is warranted for patients with evidence of cirrhotic cardiomyopathy.

Combination Therapy

Finally, a mention on the role of combination therapy, which is based on the association of a vasoconstrictor and a vasodilator. This approach likely prevents most of the adverse effects of the vasodilator, while enhancing the fall in portal pressure prompted by the reduction in blood flow achieved by the vasoconstrictor [55]. A drug combination with proven efficacy for long-term treatment in the prevention of rebleeding is that of propranolol or nadolol plus isosorbide mononitrate according to findings of a recent meta-analysis by D'Amico *et al.* [56]. The use of propranolol plus prazosin has been recently investigated. Carvedilol is a new β -blocker that has a non-selective β -blocker effect and anti α -adrenergic effect, thus mimicking the effects of the association of propranolol plus prazosin, but may be better tolerated as proposed by Banares *et al.* [57]. Nevertheless, clinical applicability may be limited by its systemic hypotensive effects.

The circulatory effects of these drugs (when adverse systemic hemodynamic changes do not occur), despite mainly targeted to the prophylaxis of esophageal bleeding or rebleeding, modify loading conditions of the heart and might turn out to be useful in the treatment of the hemodynamic derangement of cirrhosis and ultimately of cirrhotic cardiomyopathy.

CONCLUSIONS

Cirrhotic cardiomyopathy is a novel disease entity. No definite treatment can be at present advised: nevertheless some drugs, currently employed for the clinical management of the complications of cirrhosis, seem to have the credentials to improve cardiac function and structure acting either on the heart and on the systemic circulation. Yet, beta blockers and aldosterone antagonists are widely employed in the setting of fluid retention and for the prophylaxis of variceal bleeding and their early use could delay these negative events. Future studies should be devoted to investigate whether these and other more recently developed drugs can exert overall favorable effects in the earlier stages of disease, thus counteracting the progression of cardiovascular derangement characterizing advanced cirrhosis.

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