

The cardiorenal link in advanced cirrhosis

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ABSTRACT

A considerable number of patients with advanced cirrhosis develop a hepatorenal syndrome. The pathogenesis involves liver dysfunction, splanchnic vasodilatation, and activation of vasoconstrictive systems. There are now several observations that indicate a relation between the renal failure and impaired cardiac function in patients with advanced cirrhosis. Cirrhotic cardiomyopathy has been described as a condition with impaired contractile responsiveness to stress and altered diastolic relaxation. We propose a cardiorenal interaction in patients with advanced cirrhosis and renal dysfunction that refers to a condition where cardiac dysfunction in cirrhosis is a major determinant of kidney function and survival. Thus, the relation between cardiac dysfunction and renal insufficiency should be target for future studies and development of new treatments should focus on ameliorating the cardiac dysfunction.

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Background

Approximately 20% of patients with cirrhosis and refractory ascites develop a hepatorenal syndrome (HRS), which is a functional renal failure in patients with cirrhosis [1]. The major elements in the development of HRS are the diseased liver, the circulatory dysfunction, and an abnormal systemic and renal neuro-humoral regulation but the pathophysiology of the HRS is far from clear. Two types of HRS have been defined depending on the speed of onset and extent of renal failure [1]. Type 1 HRS is an acute form with a rapid decrease in renal function, type 2 HRS is a chronic form with a less unstable renal dysfunction. The prognosis of HRS remains poor, with an average overall median survival time of approximately 3 months and for type 1 HRS about 1 month [1].

In cirrhosis, arterial splanchnic vasodilatation leads to several changes in the systemic circulation including a reduced systemic vascular resistance, arterial blood pressure, and effective or central blood volume. These changes activate potent vasoconstricting systems, like the sympathetic nervous system, the renin–angiotensin aldosterone system, and non-osmotic release of vasopressin [2]. The initial hemodynamic consequences are development of a hyperdynamic circulation with increased heart rate and cardiac output [2]. However, recent data indicate that a decrease in cardiac output at a much later stage of cirrhosis as part of the cirrhotic car-

diomyopathy may aggravate the underfilling of the arterial circulation [3–5]. This may constitute a major determinant in the genesis of HRS, see Fig. 1. The clinical entity called “cirrhotic cardiomyopathy” includes a chronic cardiac dysfunction, characterized by blunted contractile responsiveness to stress in the absence of any other cardiac disease [6]. In cirrhosis, there seems to be a complex and bi-directional relationship between the heart and the kidneys, which we believe, requires redefinition and we suggest refining the definition of HRS to recognize the symbiotic nature of these organs.

Ruiz-Del-Arbol et al. showed that patients with cirrhosis who developed renal failure during a course of spontaneous bacterial peritonitis had a lower cardiac output than those without renal failure (5.7 ± 0.9 vs. 7.4 ± 1.9 L/min) [4]. Moreover, after resolution of the infection those patients with renal failure had an even lower cardiac output (4.6 ± 0.7 vs. 6.8 ± 2.0 L/min). Cardiac output seems to be lower and decrease further in patients who develop renal failure, possibly due to a combination of sepsis and cirrhotic cardiomyopathy. Later on, the same group carried out a longitudinal study in 66 patients with cirrhosis and refractory ascites, in which 40% developed HRS [5]. Patients who developed HRS had a lower baseline cardiac output compared to those who did not (6.0 ± 1.2 vs. 7.2 ± 1.8 L/min), which further decreased during HRS (5.4 ± 1.5 L/min). In this study, the increased plasma renin activity and low cardiac output turned out to be strong prognostic determinants for the development of HRS [5]. Thus, deterioration in maintenance of cardiac contractility, as well as worsening of peripheral vasodilatation, seems to be of importance in the development of renal dysfunction and HRS.

Recently, we studied 24 patients with advanced cirrhosis. In patients with a low cardiac index, the glomerular filtration rate was

Abbreviation: HRS, hepatorenal syndrome.

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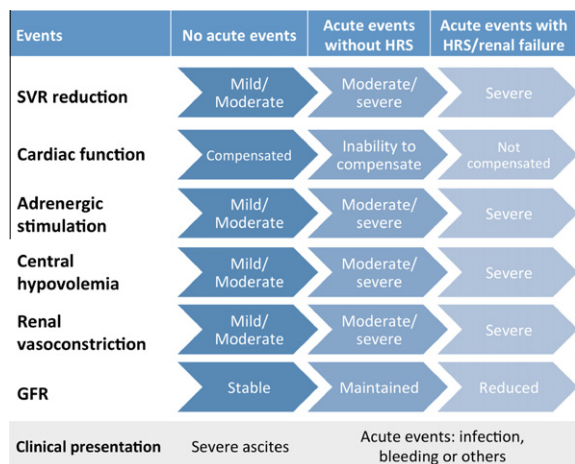


Fig. 1. Changes in systemic vascular resistance (SVR), cardiac function, adrenergic stimulation, central hypovolemia, renal vasoconstriction, and glomerular filtration rate (GFR) in relation to acute events with and without hepatorenal syndrome (HRS) and renal failure.

significantly lower than in those with a higher cardiac index [3]. The low cardiac index-group also demonstrated a lower renal blood flow and higher level of plasma creatinine. Moreover, the number of patients who developed HRS type 1 within 3 months was significantly higher in the group with suppressed cardiac function. This study further supports the association between cardiac dysfunction and renal failure and survival in cirrhosis [3,7,8]. In all three studies patients who developed HRS had signs of inotropic incompetence reflected by lower stroke volume or stroke work as well as chronotropic incompetence reflected by lower heart rate despite a decrease in blood pressure and an increase in norepinephrine [3–5].

Evaluation of the hypothesis

The development of bacterial infections is the most important precipitating risk factor for HRS [9]. Most patients have chronic elevation of proinflammatory cytokines such as IL-6 and TNF- α and endotoxins, which represent a chronic low-grade inflammatory state [10]. If infections or septicemia occur, a compensatory cardiac reserve is important to protect the perfusion of vital organs such as the kidneys during vasodilatation. The activation of cytokines, vasoactive hormones, and alteration in circulatory function in advanced cirrhosis and ascites without overt sepsis is similar to that seen in sepsis and septic shock without cirrhosis [10,11]. In septic shock it is estimated that approximately 40% of the patients develop myocardial dysfunction comprising systolic as well as diastolic dysfunction [11–14].

Beta-adrenergic signaling regulates both the heart rate and the contractility. In advanced cirrhosis with high levels of circulating noradrenalin, both beta 1- and 2-adrenoceptors are down-regulated whereas this is not the case regarding beta 3 adrenoceptors during intense adrenergic stimulation [15]. This could partly explain the chronotropic incompetence in cirrhosis as a consequence of maintained beta 3-adrenoceptor expression, leading to a decrease in cardiac output. Beta 3-adrenoceptors may serve to protect the myocardium against adverse effects of excessive catecholamine stimulation present in advanced cirrhosis. During non-selective beta 1- and 2-adrenoceptor-blockade, stimulation of beta 3 receptors with isoprenaline seems to produce a negative inotropic effect and similar results are obtained by the use of beta 3-adrenoceptor agonists [16]. This may explain why patients with cirrhosis and refractory ascites treated with non-selective beta-

blockers such as propranolol or nadolol may have a poorer survival as shown by Serste and colleagues, compared to those not treated with beta-blockers [17], although the validity of the association has been questioned [18] and further studies are needed. In these patients, endogenous noradrenaline may not stimulate beta 1- and 2-adrenoceptors resulting in chronotropic incompetence. Since beta-adrenergic-blockade decreases cardiac output, it is possible that the pronounced inhibitory effect of propranolol on cardiac function, particularly in high doses of 160 mg/day as documented in the study [17] may play a role for the increased mortality [19]. At the same time, the beta 3 adrenoceptors may still be susceptible to stimulation and impair myocardial contractility. In a different study 8 out of 10 patient on beta-blockers developed paracentesis induced circulatory dysfunction, which decreased to one in ten after discontinuation of beta-blockers [20].

Four decades ago it was shown that volume expansion with dextran in patients with decompensated cirrhosis, oliguria and low cardiac output, significantly increased cardiac output and renal blood flow [21]. Albumin infusion expands central blood volume and increases cardiac output and arterial blood pressure and thereby ameliorates arterial underfilling, prevents HRS, and reduces mortality in spontaneous bacterial peritonitis [22]. Infusion of albumin inhibits development of post-paracentesis-induced circulatory dysfunction [23] and in combination with terlipressin, albumin reverses HRS and improves survival [24]. High doses of albumin increase cardiac output by approximately 25% [25], a mechanism that may explain the beneficial therapeutic effects and highlights that impaired cardiac output is a key element in the development of renal failure in cirrhosis. Lastly, a further factor involved in the cardio depressant state may be adrenal insufficiency, particularly with acute stress that may result in critical illness related corticosteroid insufficiency [26,27].

The hypothesis

The evidence as outlined above strongly suggests that the combination of renal failure and decreased effective blood volume in cirrhosis, is not only a consequence of arterial vasodilatation but also of impaired cardiac contractility suggesting the existence of a cardiorenal syndrome in cirrhosis. We hypothesise that the cardiorenal relationship in decompensated cirrhosis is a result of an acute stress superimposed on an abnormal circulatory state. There may therefore be a link between the acute cardiac dysfunction and the development of a type 1 HRS.

Consequences of the hypothesis

Although the cardiac output is increased in patients with advanced cirrhosis, this increase is insufficient to maintain an adequate arterial blood pressure and renal perfusion and hence to prevent renal vasoconstriction and other counter-regulatory mechanisms. The recognition and understanding of a cardiac involvement would change the focus in prevention and treatment of renal dysfunction in cirrhosis and in the development of new treatments. The use of beta blockers, which is standard treatment in the prevention of variceal bleeding, would need careful review and further study, as the risk/benefit ratio in this particular sub group of patients may not be favourable [19]. The potential relationship with adrenal dysfunction should be explored [26,27].

Future studies should focus on repeated measurement of cardiac function in particular cardiac output in patients with refractory ascites and imminent HRS. Moreover, effects of supporting cardiac function in patients with low cardiac output should be studied especially the effects of increasing cardiac output and glomerular filtration rate, renal blood flow, and sodium and water

excretion and the effect of these interventions on survival in patients with types 1 and 2 HRS should be investigated.

Conflicts of interest

None declared.

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Authors' contributions

All authors contributed to concept and the writing and review of the paper.

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