Review

Hepatorenal Syndrome or Hepatocardiorenal Syndrome: Revisiting Basic Concepts in View of Emerging Data

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Hepatorenal syndrome · Cardiorenal syndrome · Cirrhosis · Cirrhotic cardiomyopathy

Abstract

Background: Accumulating evidence on the pathophysiology of hepatorenal syndrome has challenged the conventional model of liver-kidney connection. While liver cirrhosis is traditionally considered the origin of a cascade of pathophysiologic mechanisms directly affecting other organs such as the kidney, emerging data point to the heart as the potential mediator of the untoward renal effects. **Summary:** Herein, we briefly review the often-overlooked contribution of the heart to circulatory dysfunction in hepatorenal syndrome and put forward evidence arguing for the involvement of systemic inflammation and endothelial dysfunction in this setting. The temporality of cardiorenal interactions in hepatorenal syndrome and the observed beneficial effects of portosystemic shunting on these pathways lend further support to the notion that cardiac involvement plays a key role in the development of renal dysfunction in severe cirrhosis. **Key Messages:** The disturbances traditionally bundled within hepatorenal syndrome could represent a hepatic form of cardiorenal syndrome whereby the liver affects the kidney in part through cardiorenal pathways. This new model has practical implications and calls for a shift in the focus of diagnostic and therapeutic approaches to renal dysfunction in advanced cirrhosis.

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Background

Hepatorenal syndrome (HRS) denotes a form of volume-unresponsive kidney dysfunction that develops in the setting of advanced cirrhosis in the absence of shock, structural kidney disease, and use of nephrotoxic agents. In the conventional Ptolemaic model of HRS, the liver is stationed at the center of a multitude of pathologic features representing a state of complex multisystem failure. In this model, the liver-kidney connection is explained by portal hypertension and splanchnic arterial vasodilation, which then triggers a cascade of pathophysiologic events, including maladaptive neurohormonal activation. The hyperactive neurohormonal axis will then adversely affect renal hemodynamics (e.g., profound cortical vasoconstriction) as well as urinary sodium excretion, resulting in worsening renal function and progressive fluid overload.

The Heart in Cirrhosis

Although the untoward impact of liver dysfunction on the heart and circulatory system has long been recognized, the advent of newer technology and biomarkers has recently allowed for a more precise evaluation and monitoring of cardiocirculatory function. As such, our understanding of the previously undetected changes taking place in the setting of severe liver disease has dramatically improved. Cirrhotic cardiomyopathy defines a specific form of cardiac dysfunction characterized by blunted contractile responsiveness to stress stimuli and altered diastolic relaxation with electrophysiological abnormalities, in the absence of a known cardiac disease [1].

Traditional teaching of HRS views the kidney and the heart as 2 separate complications of worsening liver disease with distinct pathophysiologic pathways. However, emerging data points to these 2 organs as being mechanistically entangled; cardiac dysfunction could mediate impairment in renal function (i.e., cardiorenal syndrome [CRS]) in a subset of these patients [2]. Herein, the arguments in favor of a frequently underappreciated CRS in the setting of HRS are put forward, and the clinical and therapeutic implications of this notion are briefly mentioned.

Cardiac Contribution to Circulatory Dysfunction in HRS

In the earlier stages of cirrhosis, circulatory homeostasis is maintained by the development of hyperdynamic circulation characterized by increased cardiac output, heart rate, and plasma volume. Due to normal or increased cardiac output, it was previously assumed that the heart remains largely intact during the disease process; low systemic vascular resistance and arterial underfilling (i.e., central hypovolemia) were thought to be the sole mechanisms of circulatory dysfunction in cirrhosis. However, it is now recognized that in the later stages, the progressive decline in the afterload is no longer followed by an increase in cardiac output, hence contributing to the hemodynamic derangement. The lack of appropriate cardiac response to hemodynamic and neurohormonal stress was reported by Nazar et al. [3] who observed no difference in the left ventricular function and heart rate among patients with compensated cirrhosis, patients with ascites, and those with HRS despite marked differences in mean arterial pressure and plasma norepinephrine concentration. In a longitudinal study on cirrhotic patients with refractory ascites, baseline markers of cardiac function (e.g., cardiac output and stroke volume) were found to be significantly lower in those patients who subsequently developed HRS and further decreased at the time of HRS [4]. Interestingly, systemic vascular resistance remained unchanged between baseline and follow-up in these patients. The neurohormonal activity was also higher in those patients whose cirrhosis progressed to

HRS, which, in the face of unchanged systemic vascular resistance but disturbed cardiac output, points to the heart as the main driving factor. In another study, patients with cirrhosis who developed renal failure in the course of spontaneous bacterial peritonitis had a lower cardiac output than those without renal dysfunction [5]. After resolution of the infection, patients with renal failure had an even lower cardiac output. Overall, current evidence suggests that cardiac inotropic and chronotropic dysfunction is a key component of the circulatory dysfunction observed in HRS. Maladaptive neurohormonal activation represents the key pathophysiologic mechanism linking cardiac dysfunction to HRS. It is also the cornerstone of the pathways involved in the development of CRS [6]. In patients with cardiac dysfunction, a number of factors, such as low cardiac output and use of diuretics, can lead to elevated levels of neurohormones and their downstream renal adverse consequences, such as reduction in glomerular filtration rate and impaired sodium and water excretion (low forward flow) [7]. Moreover, increased cardiac right-sided pressures could result in renal venous congestion and further deterioration in renal hemodynamics and function (high backward pressure) [8, 9]. As such, cardiac dysfunction could contribute to further deterioration of renal function in HRS, whereby there is already a tendency for activation of the neurohormonal axis.

Inflammation and Cardiorenal Interactions in HRS

Hemodynamic and neurohormonal mechanisms have long dominated the literature on the pathophysiology of HRS. However, emerging data points to systemic inflammation and endothelial dysfunction, not only as a trigger for hepatorenal pathways (e.g., splanchnic arterial vasodilation), but also as a direct contributor to derangements of the extrahepatic organs, particularly the heart. Cirrhosis is associated with features of inflammation, including increased markers of macrophage activation, proinflammatory cytokines, systemic oxidative stress, and activated circulating monocytes and neutrophils [10]. The degree of inflammation and endothelial dysfunction, stemming from translocation of bacteria and pathogen-associated molecular patterns from the intestine, parallels the severity of liver, circulatory, and renal dysfunction [11]. Besides, HRS is often precipitated by bacterial infections, especially if a profound inflammatory response develops [12]. In animal models of decompensated cirrhosis, oxidative stress and tumor necrosis factor α have been shown to induce alterations of β -receptor signaling and impaired systolic dysfunction [13]. Serum levels of lipopolysaccharide-binding protein, a marker of exposure to bacterial endotoxin, are also independently associated with left ventricular diastolic dysfunction [14]. These observations, coupled with the strong evidence on the central role of endothelial dysfunction in CRS, make it conceivable that inflammation would represent a less well studied link in the liver-heart-kidney connection [15, 16].

Accordingly, in addition to being a potent plasma expander, albumin is known to possess significant anti-inflammatory properties [17]. In cirrhotic rats, albumin increases cardiac contractility by counteracting myocardial oxidative stress and inflammation [13]. In spontaneous bacterial peritonitis, albumin, but not hydroxyethyl starch, increased systemic vascular resistance and left ventricular stroke work index, illustrating the presence of a mechanism beyond volume expansion [18]. In support of this notion, the rate of HRS and mortality decreases by more than half in cirrhotic patients with spontaneous bacterial peritonitis if albumin is added to antibiotics [19]. As such, the beneficial impact of albumin on the treatment of HRS could conceivably be through improvement in inflammatory state and endothelial dysfunction, a common mechanism within cardiorenal interactions. The proposed pathways linking liver, heart, and kidney in the setting of HRS are depicted in Figure 1.

Fig. 1. Pathophysiologic pathways linking the liver, heart, and kidney in patients with advanced cirrhosis. The orange circle depicts the conventional concept of hepatorenal syndrome where renal dysfunction is mediated through splanchnic vasodilation and consequent neurohormonal activation. The green circle highlights the hepatocardi pathways through which cirrhosis leads to cardiac dysfunction (i.e., cirrhotic cardiomyopathy). The yellow circle summarizes the bidirectional mechanisms linking cardiac dysfunction to aberrant renal function (i.e., cardiorenal syndrome). SNS, sympathetic nervous system; AVP, arginine vasopressin; GFR, glomerular filtration rate; LVEDP, left ventricular end-diastolic pressure.

Temporality of Cardiorenal Interactions in HRS

If we hypothesize that cardiac dysfunction has a contributory role in the subsequent development of renal impairment in the setting of advanced cirrhosis, then it is expected to precede HRS. In the study by Ruiz-del-Arbol [4], those cirrhotic patients who subsequently developed HRS already had stigmata of cardiac dysfunction (e.g., lower stroke volume) prior to the decline in renal function. Moreover, low cardiac output at baseline, along with increased plasma renin activity, were found to be the only independent predictors for the development of HRS. Similarly, in another study, more patients developed HRS in the group with baseline low cardiac index (i.e., $<1.5 \text{ L/min/m}^2$) as measured by gated myocardial perfusion imaging [20]. These observations on the temporal pattern of cardiac and renal dysfunction make it plausible that involvement of the heart contributes to the pathogenesis of HRS rather than being a mere consequence of it [21].

Cardiorenal Interactions after Portosystemic Shunting

A subset of patients with cirrhosis receive a transjugular intrahepatic portosystemic shunt (TIPS) to alleviate portal hypertension. Immediately after the procedure, blood from the splanchnic bed and portal system is unloaded into the systemic circulation. As renal veins

drain directly into the systemic circulation, intrarenal hemodynamics are not expected to be directly affected unless there is a change in renal perfusion. There is avid evidence on the salutary impact of TIPS on renal function, including improved urinary sodium excretion (indicative of ameliorated renal perfusion) as well as an increase in clearance of creatinine [22]. Based on recent data, cardiorenal interplay is the key mediator of the beneficial renal effects of TIPS, as it significantly enhances cardiac inotropy, leading to increased central blood volume and renal perfusion [23]. Furthermore, the benefits of TIPS could partly be explained by improvement in endothelial function that follows mitigation of systemic inflammation through lowering pressures and shear stress in the portal system and hindering of the intestinal translocation of bacteria. Since the effect of venous congestion with end-stage liver cirrhosis and addition of TIPS may indeed reflect entirely different physiologic mechanisms, future studies are needed to investigate the 2 distinct profiles of renal dysfunction in the setting of simultaneous liver and cardiac dysfunction.

Pragmatic Implications of Cardiorenal Interactions in HRS

In view of the evidence on the contribution of the heart to a host of pathophysiologic features in HRS, systematic evaluation and monitoring of cardiac function should be recommended to these patients, even to those without apparent cardiac impairment. While diastolic dysfunction is observed in as high as 58% of cirrhotics, left ventricular systolic function is commonly latent and is typically diagnosed in the face of blunted responsiveness to hemodynamic or pharmacologic stress [3]. If disturbed, it could have a significant prognostic value by identifying the subgroup at higher risk for subsequent development of HRS. Newer imaging techniques may identify patients with subclinical cardiac dysfunction more accurately than conventional methods. Two-dimensional speckle-tracking echocardiography allows assessment of left ventricular regional myocardium and global strain by tracking natural acoustic markers (i.e., speckles) and is less likely to be dependent on preload or afterload compared to standard echocardiography. Using this technique has revealed that reduced longitudinal systolic function is common in cirrhosis patients despite having a normal ejection fraction [24].

The conventional treatments of HRS (i.e., albumin and vasoconstrictors) have important cardiac benefits and, therefore, might portend their salutary impact on the kidney in part through cardiorenal mechanisms. Since there is downregulation of β -adrenergic receptors in cirrhosis, β -agonists have commonly been considered unhelpful. However, there are reports of the successful use of cardiac inotropes to reverse renal dysfunction in refractory HRS, further emphasizing the significant contribution of cardiorenal pathways [25]. It remains to be clarified whether emerging treatments with potential benefit in heart failure (e.g., empagliflozin, urodilatin, and urocortin) would also find applications in HRS. In a phase II randomized controlled trial, serelaxin, the recombinant human relaxin-2 with cardioprotective effects in acute heart failure, significantly improved renal blood flow in patients with cirrhosis and ascites [26].

Summary and Conclusion

Accumulating evidence on the pathophysiology of HRS has challenged the conventional model of liver-kidney connection. There are several facts to consider: (1) The heart is commonly involved in the course of cirrhosis and HRS, albeit with variable degrees of severity and presentations. (2) The circulatory dysfunction in HRS is in part due to cardiac impairment.

(3) Cardiac dysfunction in cirrhotic patients who subsequently develop HRS frequently exists prior to the decline in renal function. (4) HRS and CRS share a number of cardinal pathophysiologic pathways, namely neurohormonal activation and endothelial dysfunction. (5) The treatments known to improve renal dysfunction in HRS also have direct beneficial effects on cardiorenal mechanisms. As such, the disturbances traditionally bundled within the HRS definition could represent a hepatic form of CRS (i.e., hepatocardiorenal syndrome) where the liver affects the kidney in part through cardiorenal pathways. This new model has practical implications and calls for a shift in the focus of prevention, treatment, and prognostication of renal dysfunction in advanced cirrhosis and HRS. It is noteworthy that the interactions between the heart and the kidney in the setting of CRS, as well as those between the liver and the kidney in HRS, are multifactorial, complex, and not entirely understood. Therefore, due to the sparsity of the data, the aforementioned arguments in support of the involvement of the heart in these interactions are to be considered a hypothesis that would need to be evaluated in future studies.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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