Review Article
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Hepatorenal syndrome-current concepts in pathophysiology

Abstract

Hepatorenal syndrome (HRS) is a functional renal impairment that occurs in advanced liver cirrhosis or fulminant hepatic failure due to diminished renal blood flow in histological normal kidneys. The pathophysiologic hallmark of HRS is splanchnic vasodilation and renal vasoconstriction leading to renal hypoperfusion and decline in glomerular filtration rate. Two subtypes of HRS i.e. Type 1 and type 2 have been identified with type 1 carrying poor prognosis.

Keywords: hepatorenal syndrome, splanchnic vasodilation, renal vasoconstriction, glomerular filtration rate

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Introduction

Hepatorenal syndrome (HRS) is a functional renal impairment that occurs in advanced liver cirrhosis or fulminant hepatic failure due to diminished renal blood flow in histological normal kidneys. This pathophysiologic correlation was first described by Hecker and Sherlock in 1958.[1] The functional nature of HRS was confirmed further by the ability to transplant kidneys from patients with HRS and the normalization of renal function after liver transplantation.[2,3] The pathophysiologic hallmark of HRS is splanchnic vasodilation and renal vasoconstriction which has been established in multiple studies.[4-8] Here we present brief overview of current concepts in pathophysiology of HRS.

Definition

The hepatorenal syndrome is defined as potentially reversible functional impairment of renal function in a patient who has established or clinically evident acute or chronic liver disease. It is characterized clinically by progressive rise in serum creatinine with or without oliguria and urine sediment is often bland. Two subtypes of HRS have been identified:

Type 1 HRS: It is defined as at least a twofold increase in serum creatinine to a level greater than 2.5mg/dL or by 50% reduction in creatinine clearance to a level <20ml/min during a period of less than two weeks. It is usually precipitated by infection and has a worse prognosis with median survival of less than 10% at 3 months.[9-11]

Type 2 HRS: It is defined as renal impairment that is less severe than that observed with type 1 disease and is characterized by refractory ascites.

Pathophysiology-current concepts

The pathophysiologic process of HRS begins early and progresses with worsening liver function and involves multiple interrelated pathways ultimately leading to splanchnic vasodilation and renal vasoconstriction which are the hallmark of HRS. In liver disease, portal hypertension leads to splanchnic vasodilation, which progressively increases with advancing disease causing altered cardiovascular function and hyperdynamic circulation leading to decrease in effective arterial volume with activation of endogenous vasoactive systems. These hemodynamic changes ultimately lead to renal hypoperfusion and decline in glomerular filtration rate (GFR). Figure 1 shows pathophysiology of HRS.

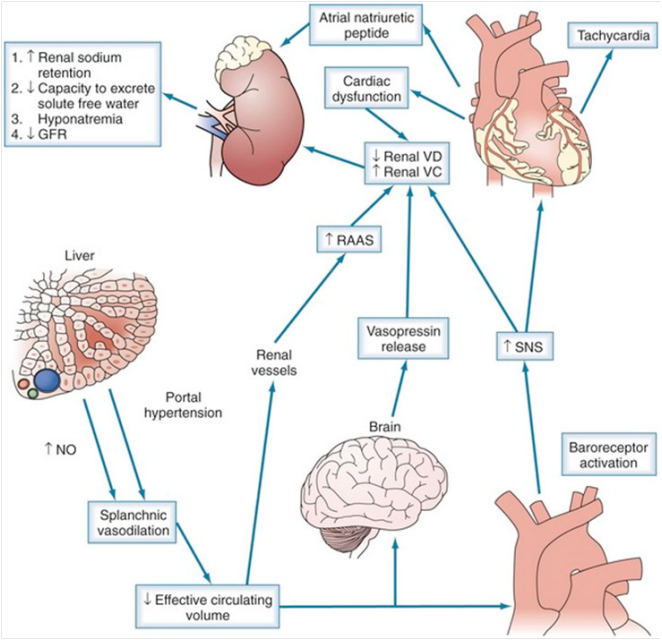

Figure 1 Pathophysiology of HRS: GFR, glomerular filtration rate; NO, nitric oxide; RAAS, rennin angiotensin aldosterone system; SNS, sympathetic nervous system;VC, vasoconstriction;VD, vasodilation

Portal hypertension and splanchnic vasodilation

In the setting of advanced liver disease, rise in resistance and the enhanced portal inflow play an important role in the development of portal hypertension (PHT). PHT is a hyperdynamic state characterized by increased cardiac output, increased blood volume and decreased splanchnic vascular resistance. Two major factors play important role in splanchnic vasodilation:

a. Increased production of local and systemic vasodilators

b. Decreased responsiveness to vasoconstrictors.

Recently another mechanism of mesenteric angioneogenesis has also been proposed for splanchnic vasodilation.[12-15] Elevation of venous pressure in liver disease leads to redistribution of blood flow in intestinal circulation which causes mucosal hypoxia resulting in stimulation of vascular endothelial growth factor (VEGF) production[16,17] and expression of endothelial nitric oxide synthetase (eNOS).[18] Shear stress in vascular bed further leads to increased production of nitric oxide (NO).[19] Three different isoforms of NO are known: endothelial (eNOS), neuronal (nNOS) and inducible (iNOS). Production of NO by activation of eNOS plays a major role in splanchnic and systemic vasodilation, however increased inducible NOS activity and neuronal NOS production has also been demonstrated.[20-22] Together with NO, prostacyclin (PGI2),[23-25] carbon monoxide (CO),[26,27] various other vasodilators like endocannabinoids,[28] hydrogen sulfide[29] etc also play a role in splanchnic and systemic vasodilation. As a consequence of splanchnic and systemic vasodilation, effective arterial volume decreases and to compensate arterial hypovolemia, cardiac output increases setting in a hyperdynamic state. This hyperdynamic circulation maintains blood volume sufficient to perfuse various organs including kidneys but as disease advances, arterial vasodilation further increases and increased cardiac output now is insufficient to correct arterial hypovolemia. To compensate for effective arterial hypovolemia, vasoconstrictor systems such as rennin angiotensin aldosterone (RAAS) and sympathetic nervous system (SNS) are activated, leading to renal vasoconstriction and hypoperfusion. Recent evidence shows that angiogenesis modulates the formation of portal-systemic collaterals and the increased splanchnic blood flow which are involved in pathogenesis of HRS.[30,31] Study by Fernandez et al.,[32] showed that vascular endothelial growth factor (VEGF)/ platelet-derived growth factor (PDGF) driven angiogenesis is of paramount importance in the formation of portal-systemic collaterals and of the hyperdynamic circulation which are responsible for the main complications of cirrhosis. VEGF-dependent angiogenesis in portal hypertension is most likely to be multifactorial with several factors such as tissue hypoxia, cytokines, and mechanical stress, have been shown to promote VEGF expression in various cell types and tissues.[33]

Excess vasoconstrictors versus insufficient renal vasodilators

In advanced cirrhosis, decreased effective circulating volume unloads the high pressure baroreceptors in the carotid body and aortic arch with subsequent compensatory activation of the SNS, RAAS and non-osmotic release of arginine vasopressin (AVP).[34,35] Activation of all these systems tries to maintain blood volume and pressure by causing salt and water retention, ascites formation. Stimulation of AVP release leads to solute free water retention causing dilutional hyponatremia. All these changes further stimulate RAAS and SNS leading to very high circulating levels of angiotensin II, noradrenaline, and vasopressin. These agents causes intense vasoconstriction in extrasplancnic beds like kidneys, muscles and brain but splanchnic circulation is unresponsive to these vasoconstrictors due to local release of NO and other vasodilators.

Intense renal vasoconstriction decreases renal flow and resulting renal ischemia increases production of intra renal vasoconstrictors such as angiotensin II, adenosine, and endothelin which further compromises renal hemodynamics and function. In the kidney, the renal vasoconstriction is counterbalanced by increased intrarenal production of vasodilating prostaglandins[36,37] nitric oxide, and kallikreins.[38] However, as cirrhosis advances and with any precipitating factor such as gastrointestinal bleed or bacterial infection, intra renal vasodilators are unable to counterbalance vasoconstrictors causing vasoconstrictor-vasodilator imbalance, thereby intensifying renal vasoconstriction and subsequent decline in GFR.

Besides vasoconstrictor-vasodilator mismatch, loss of renal autoregulation[39] also plays an important role in renal dysfunction. Renal autoregulation is ability of the kidney to maintain a constant renal blood flow (RBF) and glomerular filtration rate (GFR) as renal perfusion pressure is altered. This autoregulation is achieved by proportionate changes in the preglomerular resistance and is believed to be mediated by two mechanisms, tubuloglomerular feedback (TGF) and the renal myogenic response.[40] These two mechanisms act in concert and that their primary role is to stabilize renal function by preventing pressure-induced fluctuations in RBF, GFR. However, in cirrhosis, this autoregulatory function of kidney is lost and for every given level of renal perfusion pressure, the renal blood flow progressively falls shifting autoregulation curve to the right.[41] Therefore, in end stage cirrhosis, despite of maintenance of renal perfusion pressure, renal blood flow is severely compromised.

Cardiac dysfunction in HRS

The hyperdynamic circulation in cirrhosis is characterized by increased heart rate and cardiac output (CO) in response to decreased systemic vascular resistance (SVR) to maintain hemodynamic stability. However, in recent studies, cardiac output was found to be reduced.[42,43] Ruiz-del-Arbol et al.,[42] demonstrated reduction in CO at time of diagnosis of spontaneous bacterial peritonitis (SBP) without a change in systemic vascular resistance in patients who had cirrhosis and subsequently developed HRS. CO further decreased after resolution of infection in the HRS group but not in those without renal failure. In their subsequent longitudinal study Ruiz et al.,[43] concluded that hepatorenal syndrome is the result of a decrease in cardiac output in the setting of a severe arterial vasodilation. Plasma renin activity and cardiac output were the only independent predictors of hepatorenal syndrome in this study. Another study by Kraq et al.,[44] also showed that development of renal failure and poor outcome in patients with advanced cirrhosis and ascites seem to be related to a cardiac systolic dysfunction. This is the state of systolic incompetence where low cardiac output, low mean arterial pressure and reduced renal blood flow leads to development of renal dysfunction in cirrhosis. Various studies have demonstrated impaired myocardial contractility,[45] diastolic dysfunction in cirrhotic patients.[46] The term "cirrhotic cardiomyopathy" is characterized by impaired contractile responsiveness to stress, diastolic dysfunction and electrophysiological abnormalities in patients with cirrhosis without known cardiac disease and is reversible after liver transplant.[46] The pathogenic mechanisms of cirrhotic cardiomyopathy include impairment of the b-adrenergic receptor signaling,[47,48] abnormal cardiomyocyte membrane lipid composition and biophysical properties,[49] ion channel defects[50] and overactivity of humoral cardiodepressant factors.[51]

Precipitating factors for HRS

Reduction in effective arterial volume secondary to systemic vasodilation is the key pathogenetic mechanism for development of HRS, so anything which reduces circulatory volume further, or increases systemic vasodilation, will likely to precipitate renal injury. Therefore hypovolemia due to any reason like gastrointestinal bleed, vomiting, diarrhea, large volume paracentesis without albumin

infusion or overzealous use of diuretics can all put cirrhotic patient at risk for development of acute kidney injury (AKI).

However, bacterial infections are by far the most common cause of AKI in cirrhosis. Many inflammatory mediators like tumor necrosis factor (TNF), interlukin 6 (IL6) and other cytokines are released in response to bacterial infection.[52] These inflammatory cytokines initiates complex and interrelated pathogentic mechanisms which leads to endothelial dysfunction, development of microthrombi, NO overproduction, increased capillary permeability resulting in cellular injury and organ dysfunction. Since the renal circulation is already hypoperfused, further compromise in circulation with bacterial infection can precipitate renal injury.

Drugs like NSAIDs and angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACE-I) can also precipitate AKI in cirrhotic. NSAIDs inhibit prostaglandin synthesis which shifts balance towards vasoconstrictors as prostaglandins are important to maintain intrarenal vasodilation. Use of angiotensin II antagonists abolishes RAAS mediated systemic vasoconstriction responsible for maintenance of blood pressure causing arterial hypotension and renal dysfunction.

In conclusion, HRS results from interrelated pathophysiologic mechanisms including splanchnic vasodilation mediated by local and systemic vasodilators, cirrhotic cardiomyopathy, intense renal vasoconstriction resulting from imbalance between vasodilators and vasoconstrictors.[53]

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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