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CLINICAL REVIEW

Vascular syndromes in liver cirrhosis

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Abstract
Liver cirrhosis is associated with multiple vascular syndromes affecting almost all body systems. Many of these syndromes are directly related to impaired liver function and sometimes reversible after liver transplantation while others arise secondary to portal hypertension and ascites. Altered expression of angiogenic and vasoactive compounds (most importantly nitric oxide), endothelial dysfunction, dysregulated neurohormonal control, and systemic inflammatory state play differential roles in mediating homeostatic instability and abnormal vasogenic response. Important vascular features encountered in liver disease include portal hypertension, splanchnic overflow, abnormal angiogenesis and shunts, portopulmonary syndrome, hepatopulmonary syndrome, and systemic hyperdynamic circulation. Redistribution of effective circulatory volume deviating from vital organs and pooling in splanchnic circulation is also encountered in liver patients which may lead to devastating outcomes as hepatorenal syndrome. Etiologically, vascular syndromes are not isolated phenomena and vascular dysfunction in one system may lead to the development of another in a different system. This review focuses on understanding the pathophysiological factors underlying vascular syndromes related to chronic liver disease and the potential links among them. Many of these syndromes are associated with high mortality, thus it is crucial to look for early biomarkers for these syndromes and develop novel preventive and therapeutic strategies.

Keywords Liver cirrhosis · Portal hypertension · Portopulmonary hypertension · Hepatopulmonary syndrome · Hepatorenal syndrome

Introduction

Patients with chronic liver disease, particularly liver cirrhosis, typically present with symptoms related to structural and functional liver damage and portal hypertension [1]. Portal hypertension leads to the formation and perpetuation of ascites [2]. Portal hypertension impairs the perfusion of the bowel and increases the enteral translocation of bacteria and associated endotoxins which stimulates the release of tumor necrosis factor-alpha (TNF-α), heme oxygenase (HO)-derived carbon monoxide (CO) and nitric oxide (NO) which is further complicated by impaired hepatic clearance of these vasoactive factors [3–6]. Over time a hyperdynamic, multi-organ failure syndrome develops with increased cardiac output (COP) and heart rate and decreased central blood volume [7–9]. Other organ systems also develop vascular syndromes related to liver cirrhosis such as the lungs: with development of the hepatopulmonary syndrome (HPS) [10] and portopulmonary hypertension (PPHTN) [11]; the heart with systemic cardiovascular dysfunction [12]; and the kidney with the development of hepatorenal syndrome (HRS) [13]. Despite that the affected organs are widely distributed anatomically they are still connected through a closed vascular circuit in which circulating vasoactive mediators are altered. This explains why vascular dysfunction in one system, e.g., splanchnic circulation may progress into other systems, e.g., renal circulation. This review will focus on the mechanisms behind the development of vascular dysfunction in different vascular compartments in chronic liver disease as well as the interplay among these compartments.

Portal hypertension

Portal hypertension represents a classic feature of cirrhotic patients. Dilatation of the portal vein and decrease in portal

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blood velocity are detected despite a net increase in portal, splenic, and mesenteric inflow [14]. Portal hypertension can arise secondary to intrahepatic and extrahepatic vascular events.

Intrahepatic vasculature dysfunction

The main mechanism responsible for the increase in portal pressure is the increase in intrahepatic resistance to portal blood outflow. Along with the cycles of liver-cell injury and regeneration encountered in chronic liver disease, the resistance to blood flow through the hepatic sinusoids increases gradually over time. The impedance of the intrahepatic vascular system to the portal flow might be caused by three main factors: mechanical compression over centrilobular venules, vasoconstriction, and endothelial dysfunction.

In the cirrhotic liver various anatomical and histological alterations are responsible for mechanical compression over hepatic sinusoids (Fig. 1). Collagen disposition in the hepatic acini progressively narrows the sinusoidal lumen. Regeneration nodules developing and growing over time compress centrilobular venules. The development of intrahepatic inflammation and granuloma may add to intrahepatic stiffness and reduced compliance to portal flow [15, 16].

Apart from the structural component, a vasogenic, potentially reversible component is also involved in the increase in hepatic vascular resistance. In cirrhosis, the contractile tone of smooth muscle cells and myofibroblasts, derived from activated stellate cells which serve as regulators of the sinusoidal blood flow [17, 18], around the sinusoids and hepatic venules is increased [19]. Activated stellate cells respond to various vasoactive compounds being derived and released in the liver, including norepinephrine [20], angiotensin II [21], and endothelin (ET) [22]. In addition, stellate cell-derived myofibroblasts are important in laying extracellular matrix, fibrosis and scar formation adding more structural abnormalities into a damaging liver [23]. Carrying high plasma level in cirrhosis [21], angiotensin II is considered as one of the potential mediators of intrahepatic portal hypertension. It enhances the adrenergic vasoconstrictor influence on the portal systems and has a direct contractile influence on stellate cells [24]. This can be further complicated by sodium and fluid retention induced by the stimulation of aldosterone secretion [25]. The role of angiotensin II has been further appreciated after the effectiveness of angiotensin receptors' blockers in reducing portal hypertension [26].

Intrahepatic liver sinusoidal endothelial cells, which may undergo complex structural dysfunction in liver disease [27, 28], are the main source of the dynamic increase in intrahepatic portal resistance [29, 30]. Besides, being an important source of growth factors pivotal for liver regeneration [31, 32], they are the source of various vasoactive substances that are essentially dysregulated in liver diseases. Decreased bioavailability of NO in the sinusoids [33] and increased production of cyclooxygenase [34, 35], and its derived prostanoids, such as prostaglandin H2 and thromboxane A2 [14, 36] seem to be the main factors related to endothelial dysfunction in cirrhosis. Like NO, CO is an activator of guanylyl cyclase and of large-conductance calcium-activated potassium channels. It has been hypothesized that NO and CO may act in a coordinated fashion to maintain the patency of the sinusoids as a reaction to the upregulation of sinusoidal constrictors such as ET. NO production in liver cirrhosis is reduced secondary to reduced eNOS activity [37]. It

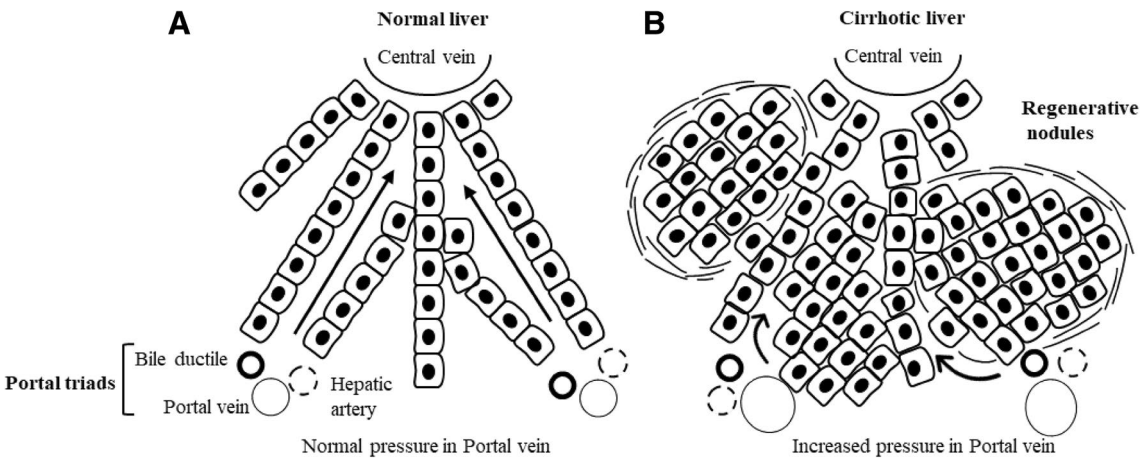

Fig. 1 Structural derangement in cirrhotic resulting in portal hypertension. **a** Normal liver: arrows represent smooth blood flow in hepatic sinusoids between organized liver cell sheets with low parenchymal resistance. **b** Resistance to the flow of the blood, originating mainly from the portal venous system in portal triads, because of the parenchymal stiffness, distorted hepatic sinusoidal structure, and regenerative nodules. Sinusoidal endothelial cells (not shown) lining hepatic sinusoids contribute to hepatic congestion by releasing vasoactive compounds

has been shown that enhanced expression and interaction of caveolin with eNOS contribute to impaired NO production, reduced NOS activity, and vasoconstriction in the intact cirrhotic liver [38]. In a cirrhotic liver, the downregulation of endothelial nitric oxide synthase (eNOS) activity may not be compensated by a sufficient upregulation of other dilators, such as CO, with an increase in sinusoidal resistance as a result [39].

Another remarkable intrahepatic vascular feature is the increased angiogenesis associated with endothelial dysfunction that was suggested to be due to growth factors released from activated stellate cells [40, 41]. Despite the increase in total vascular capacity provided by newly developed vessels, it seems that this might contribute to increased blood flow turbulence and irregular flow pattern [28]. Moreover, the lining endothelial cells seem to be functionally and structurally abnormal by carrying fewer fenestrations [28, 42].

Splanchnic circulation

Although the increase in resistance to portal flow is the main determinant of portal hypertension in cirrhosis [43] the increase in the inflow of blood onto the portal circulation may be partially implicated. An increase in total splanchnic inflow has been observed in patients with cirrhosis and demonstrated in experimental models of portal hypertension [44, 45].

One mechanism that might explain the maintenance of a high portal inflow in portal hypertension is the opening of portosystemic collaterals. Although these collaterals might be thought of as a source of the shunt to reduce portal pressure driving blood into systemic circulation, they may contribute the reverse. The opening of collateral circulation occurs through the dilatation of preexisting vessels and the generation of new vessels through the action of angiogenetic factors such as vascular endothelial growth factor (VEGF) [46].

Splanchnic vasodilation represents a major vascular phenomenon in liver patients. This is mediated through numerous compounds such as glucagon [47], prostacyclin (PGI2), intestinal vasoactive peptide, histamine, substance *P*, estrogens, cholecystokinin, ammonia, endotoxins, adenosine, biliary acids [8], NO [48], alpha-calcitonin gene-related peptide [49], adrenomedullin [50], VEGF [51], CO [52], endogenous cannabinoids [53], and angiotensin [54]. Many of these compounds are directly released from splanchnic endothelial cells [55].

Despite its relative deficiency in the intrahepatic circulation, NO seems to be excessively generated in splanchnic circulation. NOS activity is increased in the superior mesenteric artery of portal hypertension and decompensated cirrhosis [51, 56]. Upregulation of eNOS can be detected even in the early phases of the disease in portal hypertensive rats due to several factors. Inflammatory cytokines, VEGF, and mechanical forces such as shear stress induce signaling cascades to activate Akt and heat shock protein 90 (Hsp90) activate eNOS [57]. Bacterial translocation from the gut into mesenteric lymph nodes is another early mechanism responsible for increasing tumor necrosis factor-alpha, eNOS cofactor tetrahydrobiopterin and eNOS-derived NO [58].

In portal hypertension, the COX-1 enzyme was found to be overexpressed leading to the production of PGI2, an endogenous vasodilator produced by vascular endothelial cells, which in turn was found to be increased in patients with cirrhosis [59]. Inhibition of COX by indomethacin reduces portal pressure, improves hyperdynamic circulation [60] and reduces splanchnic blood flow [34]. Another suggested vasodilator that might work in parallel to NO and PGI2 is an endothelium-derived hyperpolarizing factor (EDHF) [61]; however, the exact role of EDHF in portal hypertension and regulation of splanchnic circulation is not fully elucidated [62, 63]. It has been shown that in contrast to the liver, the expression of HO-1 is increased in vessels in animal models of cirrhosis in the aorta [64] and in the mesenteric arteries [65] and while HO-1/CO-related vasodilation fails to provide adequate vasodilation in hepatic sinusoids, it adds to vasodilation in splanchnic vessels. More evidence is provided through pharmacological tools which showed that the inhibition of HO improves the hyperdynamic circulatory syndrome [64] and maintains adequate vascular response in cirrhotic animals [52].

Interestingly, experimental evidence suggests that endocannabinoids may also play a role in the development of splanchnic vasodilatation and portal hypertension by overactivating CB1 receptors within the mesenteric vasculature [66–68]; however, further exploration of the role of the endocannabinoid system in cirrhosis is demanded. In parallel with increased vasodilator substances, a variety of vasoconstrictor molecules are also decreased in splanchnic microvasculature and it has been shown that splanchnic vascular bed shows reduced responsivity for vasoconstrictors, e.g., neuropeptide Y [69] and urotensin II [70].

Systemic circulation

The main systemic vascular feature associated with liver cirrhosis is hyperdynamic circulation. Hyperdynamic circulation is a compensatory mechanism to the splanchnic arterial vasodilation correlating directly with the severity of cirrhosis [71]. In cirrhosis, the hyperdynamic circulation is characterized by increased plasma volume, COP, heart rate, and cardiac index, and decreased systemic vascular resistance and arterial blood pressure [72]. Unless PPHTN develops, the right atrial pressure and pulmonary pressures are normal or reduced [73] and the circulatory transit time from the right atria to the aorta is shortened [7]. The main cause of

the onset of the syndrome is the systemic and splanchnic vasodilatation. Although the total blood volume is increased, the central blood volume, that is the volume of blood contained in the heart, pulmonary circulation, and aorta before the renal arteries are reduced [72–74]. The reduction in central blood volume is sufficient to stimulate the volume receptors with reflex stimulation of the sympathetic nervous system and the renin–angiotensin system and vasopressin release [75, 76]. Plasma renin activity (PRA) and plasma aldosterone and norepinephrine concentration can be utilized as sensitive markers of circulatory dysfunction at different levels of decompensation [77].

In contrary to what is expected, systemic arterioles dilate despite the increase in mediators that are otherwise potently vasoconstrictive [75]. The explanation of this phenomenon is still not clear but at least partially explained by the increased availability of and arterial response to potent vasodilators as NO. NO is known to be upregulated in systemic arteries from cirrhotic rats. eNOS protein was also overexpressed and hyperactive which might be due to a mechanical over stretch secondary to increased intravascular volume [78] that would maintain continuous production of NO and positive feedback [77]. Another may be equally important, the mechanism of increased NO production is the cytokine-mediated mechanism. Patients or animals with cirrhosis and ascites have abnormal Gram-negative bacteria across the intestinal barrier [79, 80]. Most of the translocated bacteria are killed and this results in the systemic release of bacterial byproducts such as LPS, i.e., systemic endotoxemia [81] which may stimulate innate immune cells to produce cytokines including TNF-α and stimulate the increase of NO production by stimulating eNOS activity [58, 82–85] and iNOS induction [86]. Antibiotic therapy decreasing intestinal bacterial load and systemic escape of bacteria decreases vascular NO production [87]. In addition, anti-TNF-α therapy significantly attenuated the hyperdynamic circulation in experimental animals [88–91]. Chronic administration of a NOS inhibitor in ascitic cirrhotic rats completely normalized the parameters of hyperdynamic circulation [92]. Monocytes express iNOS and produce HO-1 that promotes CO production, augmenting vasodilation [4]. Together, these findings indicate that a systemic proinflammatory state existing in patients with cirrhosis that may be caused by leakage of intestinal bacteria to systemic circulation might be responsible at least partially for systemic hemodynamic abnormalities in cirrhosis. Refractory ascites, hyponatremia, and HRS are extreme complications of this process [77].

Due to the above-mentioned causes, it seems that in liver cirrhosis, the otherwise potent vasopressor mechanisms are less effective in increasing systemic blood pressure ending up with increased blood volume, COP, sodium retention with exacerbation of ascites, and at the same time systemic arteriolar dilation with less effective perfusion of vital organs. Even if overall peripheral and splanchnic vascular resistance is markedly reduced, a decrease in resistance is not present in all vascular beds [93]. The relentless splanchnic vasodilation leads to a progressive reduction in systemic vascular resistance that cannot be balanced by the increased cardiac output. Therefore, effective arterial hypovolemia due to the disparity between the intravascular blood volume and markedly enlarged arterial circulation develops. Moreover, evidence suggests that there is a decrease in cardiac output, probably related to cirrhotic cardiomyopathy [94] so-called cirrhotic cardiomyopathy is associated with impaired myocardial contractility with systolic and diastolic dysfunction in combination with electromechanical abnormalities [95]. A blood flow reduction has been most observed in the kidney [96], brain [97], and muscles [98]. The more the liver disease and the splanchnic vasodilatation worsen, the more the blood flow to other organs decreases. Renal vasoconstriction is a consequence of effective hypovolemia and the activation of neurohumoral systems, providing the rationale for improving renal blood flow not by renal vasodilators, but by albumin infusion and splanchnic vasoconstrictors such as terlipressin [99] or octreotide [13].

Portosystemic shunts

Collaterals develop to decompress the portal system (Fig. 2). Portal-systemic shunts are responsible for gastrointestinal hemorrhage (mostly due to the rupture of esophageal or gastric varices) and allow access to the systemic circulation of substances which are usually removed by the liver. These play a role in the pathogenesis of the hyperdynamic circulation, ascites, and hepatic encephalopathy [8].

The portosystemic collateral vascular bed is primarily triggered by an attempt to divert the stagnant portal blood flow to the systemic circulation. Complications include mainly hepatic encephalopathy caused by the noxious material draining into systemic circulation, and bleeding from the most prominent portosystemic shunts, gastroesophageal varices ensue. In addition, increased portal blood flow through the shunts leads to significant portosystemic shunting of bacterial products into the systemic circulation [17, 100] Portosystemic shunting thus contributes to severe sepsis associated with liver cirrhosis [101]. The pathophysiologic mechanisms involved in the development of the portal hypertensive syndrome include hemodynamic alterations, activation of inflammatory pathways, and induction of angiogenesis. Neoangiogenesis, the generation of new blood vessels from the preexisting vessels, is involved in the development of increased portal inflow and pressure as well as of portosystemic collaterals in portal hypertension. VEGF is pivotal in angiogenesis [102, 103]. However, the relative contribution of portosystemic collaterals to overall portal hypertension seems to be not significant [28, 104].

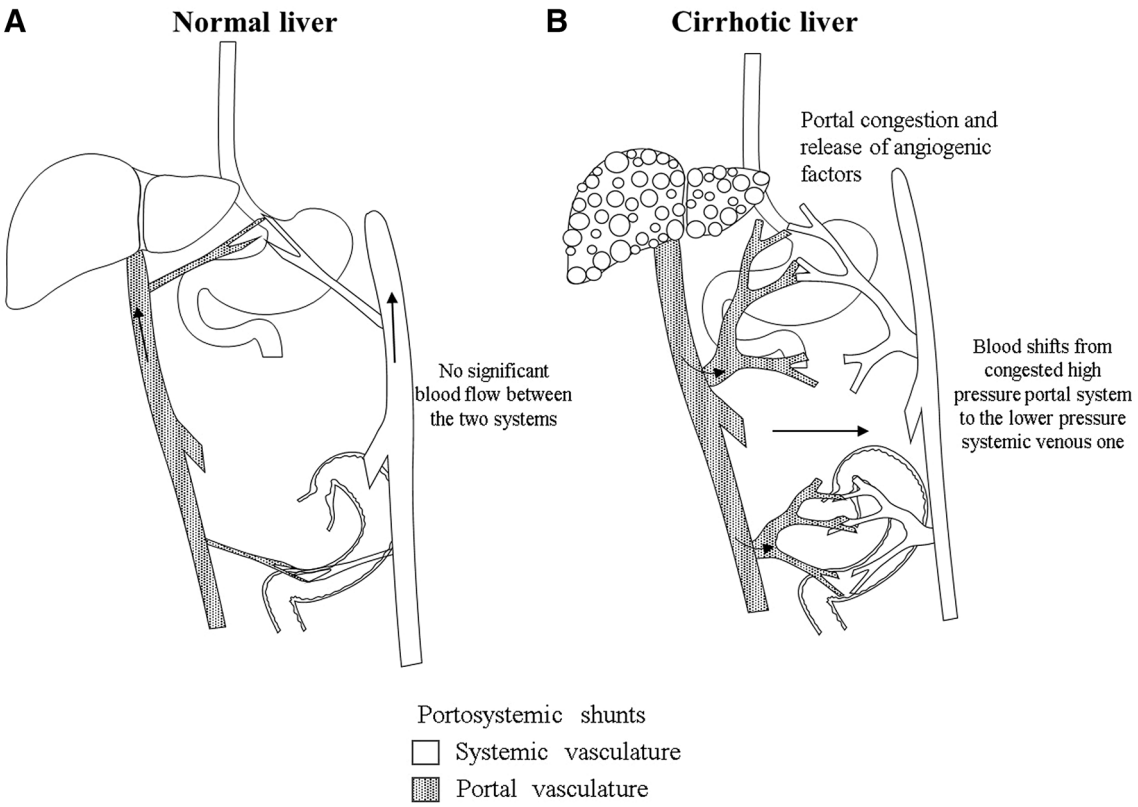

Fig. 2 Portosystemic shunts are not structurally nor functionally significant under normal circumstances (**a**). in patients with liver cirrhosis (**b**), collaterals develop with the formation of new vessels shunting blood from portal to systemic circulation. Collaterals are generated mainly because of congestion and pressure on the portal side as well as release of angiogenic factors as VEGF. Arrows represent direction of the blood flow

Hepatorenal syndrome

HRS is a functional renal failure due to systemic less-effective perfusion and intense renal vasoconstriction that frequently develops in patients with cirrhosis and ascites [105]. Two types of HRS have been identified [106]. Type 1 is characterized by rapidly progressive renal failure. It frequently follows a precipitating event—usually an infection—and is associated with extremely short survival. Type 2 is characterized by moderate and steady renal failure that develops insidiously [107]. It is usually detected in patients who respond poorly to diuretics and is associated with longer survival.

The exact pathophysiological mechanisms behind HRS are still not fully elucidated. However, HRS occurred in the setting of a complex vascular dysfunction in hepatic patients including a significant reduction in mean arterial pressure, cardiac output, and wedged pulmonary pressure and an increase in plasma renin activity, norepinephrine concentration, and hepatic venous pressure gradient. No clear association was observed in relation to peripheral vascular resistance [94]. Reduced GFR (< 40 mL/min) is elemental for HRS to happen which was referred to fall in renal perfusion secondary to renal vasoconstriction [108] and disruption in the renal autoregulatory process [109]. Many vasoactive compounds seem to be involved in HRS. Some studies showed that the plasma levels of ET are increased in patients with HRS [110] while other studies did not show any significant difference [111]. However, administration of an ET antagonist in patients with HRS did not improve kidney function [112], suggesting that the elevated levels of ET might directly contribute to HRS. Natriuretic hormones (atrial and brain natriuretic peptide) are present in elevated levels in patients with cirrhosis and ascites [113, 114]. However, the role of these peptides with vasodilator effects is not well known. Prostaglandins have protective effects in the kidney by compensating the vasoconstrictor effects of the RAAS, sympathetic nervous system, and AVP. The main renal prostaglandins, PGI2 and PGE2 have vasodilator effects in the kidney and are present at higher levels in patients with cirrhosis and ascites which might play an important role in maintaining adequate functional renal perfusion. Administration of nonsteroidal anti-inflammatory drugs, which inhibit prostaglandin synthesis, is frequently associated with the development of AKI in patients with cirrhosis and ascites [115]. Moreover, the increased activity of

the sympathetic nervous system likely plays a role in blood flow autoregulation [109].

Mechanisms other than vascular dysfunction have been proposed based on histological structural abnormality observed in HRS [116]. The increased systemic inflammatory state in advanced cirrhosis could be a triggering factor for the development of HRS not only by worsening the impaired circulatory function and leading to progressively decreased kidney perfusion [107] but through a direct effect on renal structural integrity.

Pulmonary circulation

Pulmonary complications related to chronic liver diseases are frequently observed. The two most significant complications among them are hepatopulmonary syndrome (HPS) and PPHTN [117]. Table 1.

Hepatopulmonary syndrome

HPS is a vascular syndrome characterized by diffuses or localized dilation of pulmonary microvasculature (pulmonary capillaries and, less commonly, pleural, and pulmonary arteriovenous communications) in the presence of cirrhosis and/or portal hypertension [118]. HPS is characterized by an increased alveolar–arterial oxygen gradient on room air, with or without hypoxemia, due to impaired oxygenation of venous blood as it passes through the pulmonary circulation [119]. HPS can produce dyspnea and hypoxemia which can be severe and often worsen in the upright position (platypnea) [120]. Two main pathological features are observed in HPS, vasodilatation, and angiogenesis.

The exact mechanism for the abnormal dilatation of pulmonary vasculature responsible for gas exchange is not clear, but NO seems to play a crucial role. Increased levels of exhaled NO derived from the lung are seen in cirrhosis patients with HPS, which normalize after liver transplantation [121]. Higher levels of monocyte chemoattractant protein-1 *(*MCP-1), an inflammation marker, in HPS suggest the role of inflammation in the development of pulmonary shunts. Patients overproducing MCP-1 are more susceptible for development of HPS [122, 123]. Moreover, macrophages produce HO-1, which leads to an increase in the production of CO and contributes to the vasodilatation [124, 125]. Although other mediators, such as somatostatin analog (octreotide), glucagon, prostacyclin, angiotensin-2, vasoactive intestinal peptide, calcitonin, substance *P*, atrial natriuretic factor and platelet-activating factor, may play a role in the pathogenesis of HPS, no clear relation was found between any of these mediators and vascular dilatation [126–130]. Accumulated monocytes have been observed to lead to the activation of VEGF-dependent signaling pathways [131]. Gene polymorphisms involved in the regulation of angiogenesis have also been associated with the risk of developing HPS [132].

Portopulmonary hypertension

PPHTN is defined as pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg) in the context of liver cirrhosis while other alternative causes are excluded [133]. PPHTN involves endothelial and smooth muscle proliferation, and have the same histological features of plexogenic arteriopathy of idiopathic pulmonary hypertension including concentric intimal fibrosis, and proliferation and muscularization of the pulmonary arterioles [134]. The pathophysiology of PPHTN is not fully understood, partly due to the absence of an animal model of PPHTN and the low prevalence of the condition [135]. There is not a clear link between portal hypertension and the development of PPHTN as only 5%–10% of patients with portal hypertension develop PPHTN. Moreover, the link between liver dysfunction and PPHTN is not obvious, because PPHTN may develop in cases of portal vein thrombosis or idiopathic hypertension, in absence of any liver dysfunction. A strong association between large portosystemic shunts, hepatofugal portal blood flow, and PPHTN has been shown. These data may support the hypothesis that vasoactive factors from the splanchnic circulation may

Table 1 Differences between hepatopulmonary syndrome and portopulmonary hypertension

Hepatopulmonary syndrome	Portopulmonary hypertension
Dilation of pulmonary microvasculature leading to pulmonary shunts	Vasoconstrictive process associated with pulmonary hypertension
Manifested by dyspnea and hypoxemia associated with platypnea in advanced cases	Dyspnea and hypoxemia with no associated platypnea
Mediators include NO and MCP-1	Associated with deficiency of PGI2 and elevated ET
The detection of an intrapulmonary right-to-left shunt by transthoracic contrast echocardiogram (bubble study) is an evidence for intrapulmonary dilation and hepatopulmonary syndrome in the setting of liver cirrhosis	Suspected in cirrhotic patients when right heart catheterization study demonstrates elevated mean pulmonary artery pressure (> 25 mmHg at rest) with normal pulmonary capillary wedge pressure (< 15 mmHg at rest), while other causes of pulmonary hypertension are excluded

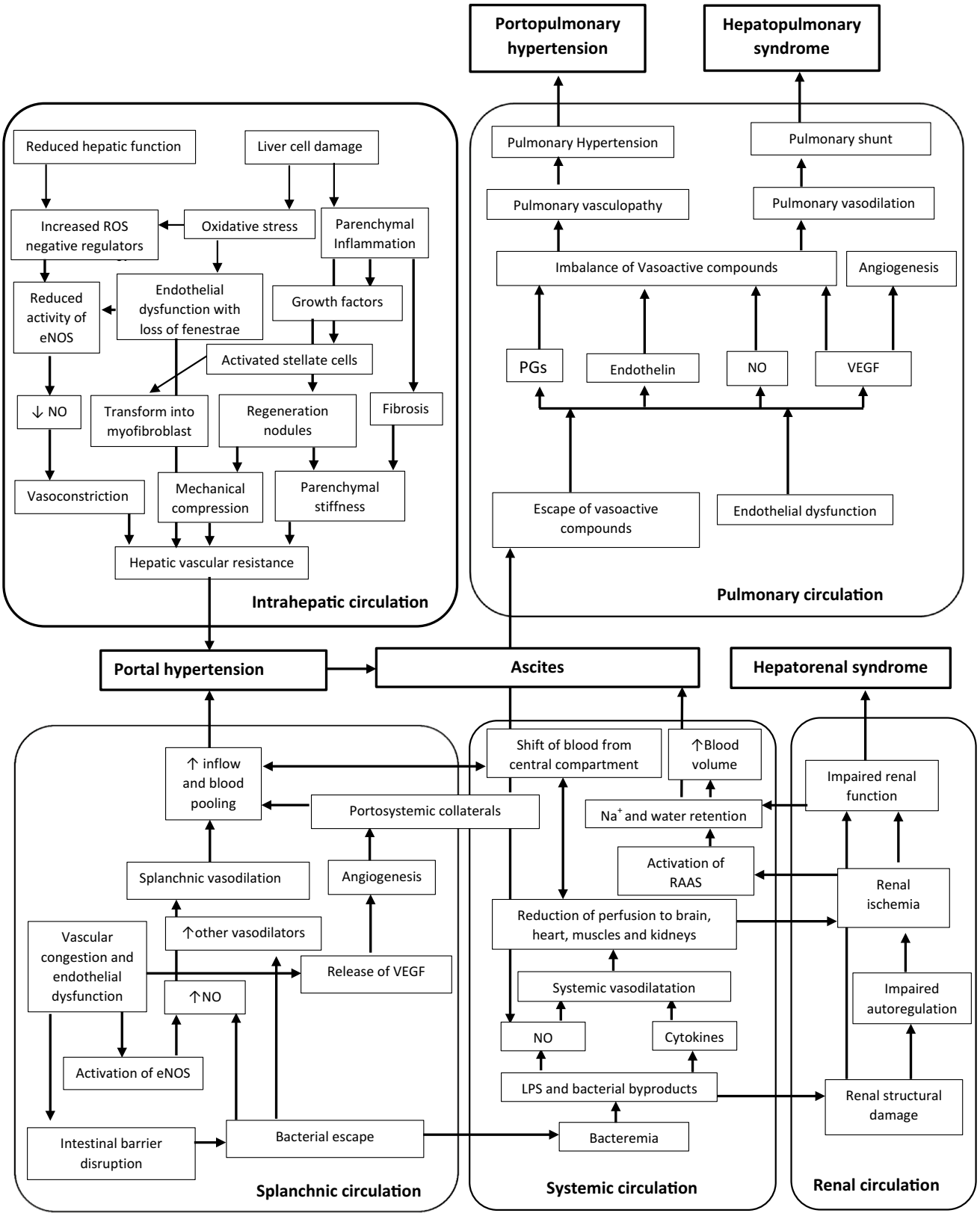

Fig. 3 Summary of vascular phenomena associated with and complicating liver cirrhosis. There are several points connecting pathological events in different vascular compartments propagating vascular dysfunctions

be pathogenic for PPHTN development. The fact that the most occurring shunt observed in this study was splenorenal might suggest that the blood flow coming from the spleen, which is involved in the destruction of platelets and prostaglandins delivery, might be of primary importance in the PPHTN pathogenesis. Moreover, the presence of large portosystemic shunts, such as those reported in this study, seems to be associated with lack of response to vasoactive treatment [136, 137].

PPHTN was associated with female sex, single-nucleotide polymorphisms in genes involved in estrogen metabolism (estrogen receptor-1, aromatase), and elevated circulating estrogen levels, supporting a potential role for sex hormones in PPHTN pathogenesis [11]. Other factors include deficiency of PGI_2 and elevated ET. Deficiency in endothelial prostacyclin synthase, causing platelet dysfunction and elevated ET-1 levels, has also been described in PPHTN [138]. ET-1 is produced in the pulmonary endothelium and binding to ET_A and ET_B receptors on the pulmonary smooth muscle cells leads to vasoconstriction [139, 140].

Summary and conclusion

Vascular syndromes in patients with chronic liver disease represent an important aspect of their illness. These syndromes do not arise in cirrhotic patients as primary diseases, but they are either directly or indirectly secondary to liver cirrhosis. In hepatic patients, impaired liver synthetic and catabolic functions together with portal hypertension trigger various vascular dysfunctions cascade, that affects splanchnic overflow with subsequent involvement of systemic circulation that will eventually affect renal blood flow. In parallel, the pulmonary vasculature is also affected by portal hypertension and shunts critically complicating liver disease. Vascular syndromes in multiple systems share some common pathophysiological features (Fig. 3). The development of shunts, e.g., portosystemic shunts allows the locally generated or accumulated vasoactive compounds to get access between different vascular compartments bypassing the liver. In addition, breakage of the intestinal barrier with the access of intestinal microbiome and their related bi-products carrying strong vasoactive, endothelial-targeting and cytotoxic properties can further complicate and disseminate vascular dysfunction. Diagnostic criteria have been set for these vascular disorders and mainly depend on happening in the context of liver cirrhosis. Understanding the pathophysiological factors involved in developing and connecting these vascular phenomena may pave the way for new strategies in the management of liver cirrhosis.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent For this type of study, informed consent is not required.

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