European Journal of Internal Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Portopulmonary hypertension and hepatorenal syndrome. Two faces of the same coin☆

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ARTICLE INFO

Article history:
Received 10 March 2017
Received in revised form 13 May 2017
Accepted 30 May 2017
Available online xxxx

Keywords:
Liver cirrhosis
Portal hypertension
Oesophageal varices

ABSTRACT

Portopulmonary hypertension and hepatorenal syndrome are both severe local hypertensive complications of liver cirrhosis and portal hypertension. Both are characterized by vasoconstrictive manifestations regarding pulmonary and renal vascular network, respectively.

This review addresses the mechanisms underlying the development of vasoconstriction that leads to local vascular hypertension in the lung and in the kidney with the result of organ dysfunction. Potential therapeutic options are available for the management of these two syndromes as a bridge for liver transplantation; clinical efficacy depends in part on the time and rapidity of intervention and in part on how serious the chain of events is that has triggered the entire vasoconstrictive process.

1. Introduction

Liver cirrhosis complicated by portal hypertension is at the origin of portopulmonary hypertension (PPH) and hepatorenal syndrome (HRS). Liver cirrhosis originates from a multifarious process in which hepatic fibrogenesis is no longer counterbalanced by fibrolysis, rather fibrosis prevails and there is a huge hepatic accumulation of extracellular matrix [1].

The development of portal hypertension is the direct consequence; the capillarization of hepatic sinusoids (with losing of fenestration), also contributes to favoring it [2]. The increase of inflammatory cytokines, of humoral factors and, especially, the imbalance between vasodilator and vasoconstrictor molecules toward a vasoconstrictive profile in liver microcircle, also plays a role [1,2]. Indeed, they favor the rise of hepatic vascular resistance, thus inducing and worsening the portal microcirculation resistance [1,2]. The parallel splanchnic vasodilation and the increase of splanchnic blood flow (hyperdynamic syndrome) contribute to establish and maintain the portal hypertension. Described in this review are the pathophysiological mechanisms that lead to the development of PPH and HRS. It is also given the clinical classification of these two serious complications, trying to shed light on how and why, in patients with liver cirrhosis and related portal hypertension, there is the development of vasoconstriction in the pulmonary and renal vascular bed and if is there any possibility to reduce or counter it.

1.1. Portal hypertension: pathophysiological mechanisms

Portal hypertension is defined as an increased portal vein pressure caused by prehepatic, intrahepatic or posthepatic high resistance, that is when the hepatic venous pressure gradient (HVPG) (the gradient between portal vein and intra-abdominal vena cava pressure) is above 5 mm Hg [3]. However, only an HVPG above 10-12 mm Hg is predictive of the development of several complications of cirrhosis such as ascites, collateral circulation, portal hypertensive gastropathy, gastric and esophageal varices, PPH and HRS [3]. These conditions are favored by an intrahepatic exaggerated production of vasoconstrictors (mainly endothelin) and, at the same time, a low production of vasodilators (mainly nitric oxide and prostacyclin). To counter portal hypertension, several solutions are attempted by the organism but they aggravate the pre-existent clinical condition. The hepatorenal reflex leads to renal vasoconstriction and to an increased tubular sodium reabsorption. The increased sympathetic activity, also consequent to hepatorenal reflex, through post-synaptic α_1-adrenoreceptors activation, tries to regulate the vascular tone of the mesenteric circulation; however, the increased splanchnic level of nitric oxide, prostacyclin and vascular

Abbreviations: HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; PPH, portopulmonary hypertension.

☆ Grant Support: none.Disclosures: the authors have nothing to disclose.

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http://dx.doi.org/10.1016/j.ejim.2017.05.028
0953-6205/

endothelial growth factor is opposed to this and greatly contributes to splanchnic arterial vasodilatation angiogenesis and opening existing vessels [4]. This causes a decreased effective arterial volume that, in turn, triggers the sympathetic nervous system and the renin-angiotensin-aldosterone system. Their stimulation leads to low urinary sodium excretion and renal sodium and water retention that enhances the intravascular volume and causes a hyperdynamic circulatory state; [4] the development of autonomic neuropathy also favors the hyporesponsiveness of the splanchnic bed to the elevated levels of circulating vasoconstrictors, aggravating splanchnic vasodilatation. The increase in blood flow (hyperdynamic circulation) further helps the opening up and formation of venovenous shunts and the development of splenomegaly thus worsening the clinical condition [4].

1.2. From portal hypertension to portopulmonary hypertension: pathophysiological mechanisms

PPH has a pulmonary vascular pathology similar but not equal to that seen in primary pulmonary hypertension (Fig. 1). The link of PPH with portal hypertension and liver cirrhosis is acclarated.

The deficiency in pulmonary endothelial prostacyclin production and other vasodilators, probably combined with lung endothelial smooth muscle hypertrophy, thrombosis and vasoconstriction due to the release of serotonin, interleukin 1, endothelin 1 and thromboxane, is recognized as a pivotal mechanism in the development of PPH [5]. PPH has been strictly associated with the presence of venovenous shunt and surgical portacaval shunt [6]. The function of these shunts is to divert a large quantity of portal blood flow away from the liver [7]. In this way, a number of vascular mediators, proinflammatory cytokines, proangiogenic factors and bacterial endotoxins may directly translocate from the gut to the lung, avoiding to be inactivated from the hepatic metabolism; thus, they may damage vascular pulmonary endothelium, promoting endothelial cell proliferation, smooth muscle hypertrophy and *in situ* thrombosis, and favor the development of PPH [6]. Furthermore, blood clots from portal vein can reach the pulmonary circulation through venovenous shunt contributing to increase the pulmonary hypertension [7].

Finally, the presence of high cardiac output, inducing, an increased shear stress in pulmonary vascular bed, consequently favors hypertrophy, proliferation and vasoconstriction of pulmonary endothelial cells.

The fact that only a small percentage of cirrhotics with portal hypertension (4 to 15%) undergoes PPH may depend on the lack of genetic predisposition. Indeed, inherited factors for PPH have been documented. Genetic variation in both the estrogen signaling and in several genes modulating angiogenesis, proliferation and migration of lung vascular smooth muscle cells, hypercoagulability and vasoconstriction, have been associated with PPH. The genetic polymorphism in estrogen and other pathways have a key role in increasing the risk to develop PPH in liver cirrhosis.

1.3. From portal hypertension to hepatorenal syndrome: pathophysiological mechanisms

The link of HRS with portal hypertension is well established as demonstrated by the outburst of hepatorenal reflex when portosinusoidal resistance increases and blood flow decreases into hepatic

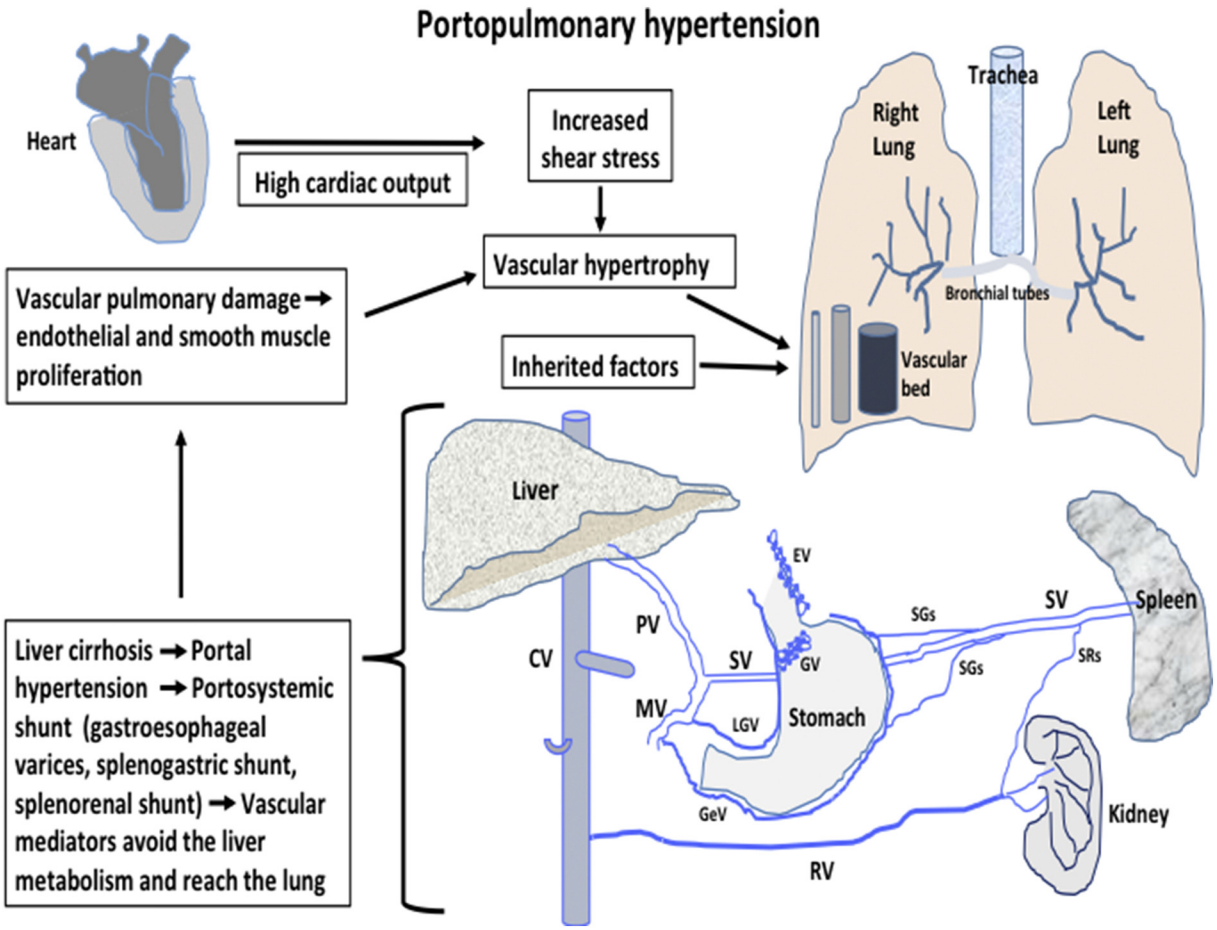

Fig. 1. The basic pathophysiology of portopulmonary hypertension starting from the liver cirrhosis.

Please cite this article as: Zardi EM, et al, Portopulmonary hypertension and hepatorenal syndrome. Two faces of the same coin, Eur J Intern Med (2017), http://dx.doi.org/10.1016/j.ejim.2017.05.028