EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

# Functional aspects on the pathophysiology of portal hypertension in cirrhosis

Juan-Carlos García-Pagán*, Jorge Gracia-Sancho, Jaume Bosch

*Hepatic Hemodynamic Laboratory, Liver Unit, IMDIM, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and CIBERehd, Spain*

Portal hypertension is a severe and frequent complication of chronic liver disease. Its consequences, bleeding from gastroesophageal varices and portal hypertensive gastropathy, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary/portopulmonary syndromes, and hepatic encephalopathy, represent the first cause of death and liver transplantation in patients with cirrhosis. The primary factor in the development of portal hypertension is a marked increase in hepatic vascular resistance (HVR) to portal blood flow, which was classically attributed to distortion of the liver architecture inherent to cirrhosis. However, over the past 20 years, a better understanding of the liver microcirculation has demonstrated that a dynamic component due to an increased hepatic vascular tone further contributes to augment HVR. Secondarily to the increased HVR, there is a progressive splanchnic vasodilatation that increments portal blood flow, which aggravates and perpetuates the portal hypertension syndrome [1] (Fig. 1).

## Intrahepatic vascular regulation

The analysis of the structural factors (fibrosis, vascular remodeling, vascular occlusion, nodule formation) contributing to increase HVR is out of the scope of this review that will focus on the dynamic component of the increased HVR.

During progression to cirrhosis, sinusoidal endothelial cells (SEC) become dysfunctional and among other features acquire a vasoconstrictor phenotype, characterized by elevated production of vasoconstrictors and reduced release of vasodilators. The resulting imbalance promotes the contraction of different cells of the cirrhotic liver, such as hepatic stellate cells (HSC), portal myofibroblasts and vascular smooth muscle cells that lead to increased hepatic vascular tone and portal pressure. HSC in turn also experience a profound phenotypical transformation, with morphologic and functional consequences: loss of vitamin A droplets, alpha-smooth muscle actin overexpression, hyperresponse to vasoconstrictors and enhanced proliferative and fibrogenic activity. Interestingly, in experimental models of cirrhosis, strategies aimed at improving the hepatic vascular tone by targeting SEC have also been shown to improve liver fibrosis. This may be due to the fact that cellular phenotype alterations share pathophysiological mechanisms, but also because SEC phenotype amelioration positively affects HSC phenotype [2].

### *Increase of vasoconstrictors in the liver*

Increased activity of several endogenous vasoconstrictors, such as endothelin, norepinephrine, angiotensin II, vasopressin, leukotrienes, and thromboxane $A_2$ has been demonstrated in the cirrhotic liver (Fig. 2). Additionally, there is an increased vasoconstrictive response of the hepatic vascular bed to these vasoconstrictors. Although all these systems are potential targets to decrease HVR in cirrhosis, the phospholipase $A_2$ – cycloxygenase-1 – thromboxane $A_2$ pathway has been one of the most extensively studied. This system has been shown to be upregulated in cirrhotic SEC and Kupffer cells [3,4], and its blockade significantly improves endothelial dysfunction and reduces HVR in the cirrhotic liver [5].

### *Reduced bioavailability of intrahepatic vasodilators*

Nitric oxide (NO) is probably the most important vasodilator involved in the regulation of hepatic vascular tone. Cirrhotic livers exhibit reduced NO availability, which is due both to decreased endothelial Nitric Oxide Synthase (eNOS) activity and to increased NO scavenging by elevated oxidative stress (Fig. 2).

Reduced eNOS activity is attributed to several alterations in its post-translational regulation, which have been described in detail in a recent review [1]. These alterations include reduced eNOS phosphorylation, low levels of its co-factor tetrahydrobiopterin ($BH_4$), increased caveolin expression and release of asymmetric-dimethyl-arginine [6]. Different studies have shown that interventions that increase eNOS activity improve liver endothelial dysfunction and reduce portal pressure in experimental models of cirrhosis. Statin administration probably represents the most promising therapeutic option; indeed, the beneficial effects of statin administration reducing portal pressure have been already confirmed in patients with cirrhosis in a recent double-blind study [7].

Keywords: Intrahepatic vascular resistance; Nitric oxide; Thromboxane $A_2$; Antioxidants; Angiogenesis.
*Received 8 February 2012; received in revised form 19 March 2012; accepted 26 March 2012*

* Corresponding author. Address: Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain. Tel.: +34 93 227 5400x2824; fax: +34 93 227 9856.
*E-mail address:* jcgarcia@clinic.ub.es (J.-C. García-Pagán).



Hepatology Snapshot

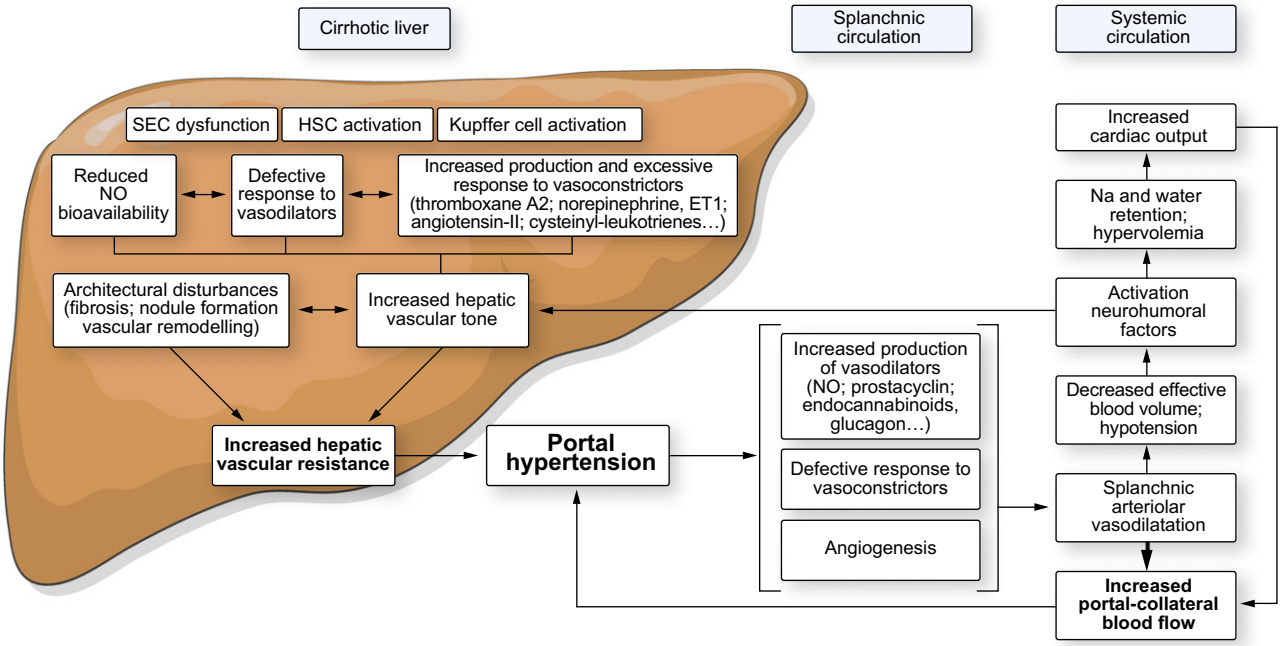


**Fig. 1. Pathophysiology of portal hypertension**. Intrahepatic vascular resistance increment due to architectural disturbances and to increased hepatic vascular tone leads to portal hypertension development. Splanchnic arteriolar vasodilation together with elevated cardiac output due to systemic hypotension aggravates and perpetuate this syndrome.

Increased superoxide levels in cirrhotic livers result from increased production and diminished elimination by superoxide dismutase (SOD) [8]. Superoxide reacts with NO leading to formation of peroxynitrite, a powerful pro-fibrogenic agent, and decreases NO availability. This is especially relevant in an infection situation, where increased inducible NOS (iNOS) overproduces NO that reacts with superoxide to form high levels of peroxynitrite [9]. In addition, superoxide can oxidize and therefore inactivate $BH_4$ further reducing NO bioavailability by decreasing eNOS activity. SOD supplementation reduces intrahepatic superoxide, increases NO, improves endothelial function and reduces portal pressure. In addition, peroxynitrite is also reduced, which may explain our recent finding of decreased liver fibrosis after SOD treatment (unpublished observation).

In addition to these mechanisms related to endothelial dysfunction, alterations in the contractile cells have also been described. HSC have been shown to hyperreact in response to vasoconstrictor stimuli. The RhoA/Rho-kinase pathway is essential for contraction of vascular smooth muscle cells and its upregulation in cirrhotic livers contributes to increase HVR by increasing the sensitivity of the hepatic vasculature to vasoconstrictors [10].

## Extrahepatic vascular regulation

Several vasodilators including NO, $PGI_2$, CO, glucagon, and endocannabinoids have been implicated in the splanchnic vasodilatation of liver cirrhosis (Fig. 1). In addition, and in opposition to what it is observed in the liver, a downregulation in the RhoA/Rho-kinase pathway has been found in the systemic circulation, suggesting that this may contribute to vascular hypocontractility and vasodilatation [11]. Recent data suggest that VEGF-driven splanchnic angiogenesis also plays a role in the development and maintenance of splanchnic hyperemia in portal hypertension [1]. The specific mechanisms responsible for this VEGF-dependent angiogenesis are largely conjectural, but several factors that increase VEGF expression, such as hypoxia or shear stress, take place in portal hypertension. Importantly, blockade of VEGF-derived signaling markedly decreases splanchnic vascularization and portal venous inflow in rodent models of portal hypertension [12]. The increased portal venous inflow can be corrected pharmacologically by means of splanchnic vasoconstrictors such as vasopressin and its derivatives, somatostatin and its analogs, and non-selective beta-adrenergic blockers.

On the other hand, splanchnic vasodilatation leads to decreased mean arterial pressure, which promotes the activation of endogenous neurohumoral systems, sodium retention and expansion of the plasma volume, followed by an increase in the cardiac output (the hyperkinetic syndrome) that in turn contributes to further increase splanchnic blood flow and portal pressure and to the development of ascites and circulatory dysfunction [13].

It is noteworthy that although the mesenteric and the hepatic vascular beds share alterations in the same vasoactive pathways they are working in an opposite manner. Increased vascular tone due to decreased vasodilators and increased local vasoconstrictors being the primary factors in the intrahepatic circulation while the mesenteric vascular bed shows an adaptive response characterized by overproduction of vasodilators, and a defective response to vasoconstrictors.

These inverse situations need to be considered when developing new strategies to treat portal hypertension. Indeed, administering vasodilators to reduce the increased intrahepatic

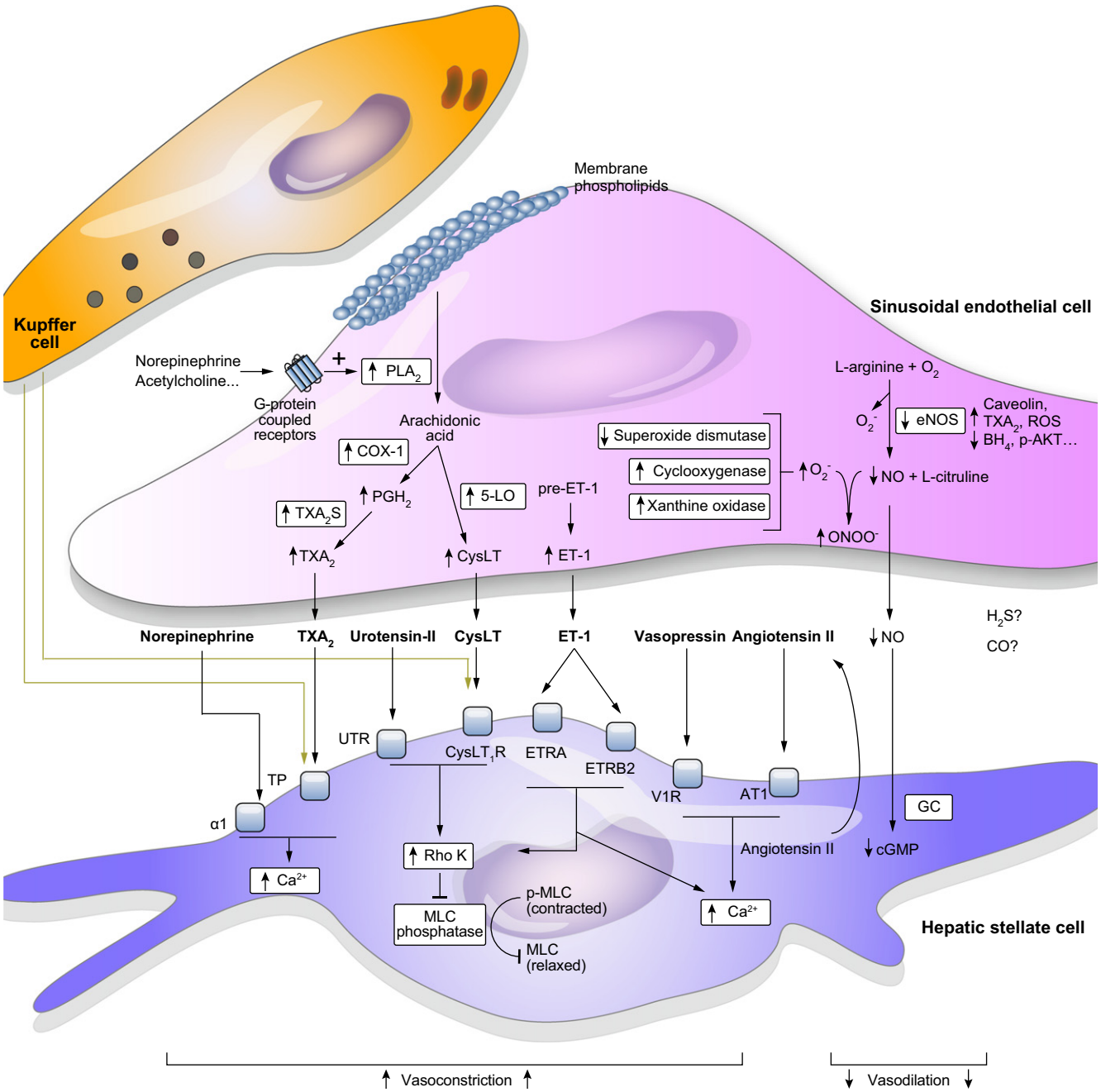


**Fig. 2. Intrahepatic vascular resistance modulation**. Hyperactive hepatic stellate cells overcontract in response to several vasoactive mediators from neighbor cells or from systemic circulation. Sinusoidal endothelial cells exhibit a marked dysfunctional phenotype defined by reduced vasodilators bioavailability, mainly nitric oxide (NO) but probably also carbon monoxide (CO) and hydrogen sulfide ($H_2S$), and exaggerated vasoconstrictors production. Kupffer cells further contribute to HSC vasoconstriction liberating, among others, thromboxane $A_2$ ($TXA_2$) and cysteinyl-leukotrienes (CysLT). ET-1, endothelin-1; ETR, endothelin receptor; UTR, urotensin-II receptor; $PLA_2$, phospholipase $A_2$; 5-LO, 5-lipooxygenase; COX-1, cyclooxygenase-1; $PGH_2$, prostaglandin $H_2$; $TXA_2S$, thromboxane $A_2$ synthase; TP, $TXA_2/PGH_2$ receptor; α1, α1 adrenergic receptor; $O_2^-$, superoxide; $ONOO^-$, peroxynitrite; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; $BH_4$, tetrahydrobiopterin; GC, guanylate cyclase; cGMP, cyclic guanosine monophosphate; Rho K, rho kinase; MLC, myosin light chain.

vascular tone could produce a deleterious further increase in splanchnic and systemic vasodilatation. Similarly, using vasoconstrictors to reduce splanchnic and systemic vasodilatation may aggravate the enhanced intrahepatic vascular tone [1].

**Financial support**

Supported by Ministerio de Economía y Competitividad (SAF 2010/17043) and Instituto de Salud Carlos III (FIS PS09/01261 and PI11/00235). J.G.-S. has a Ramón y Cajal contract from

Ministerio de Economía y Competitividad. Ciberehd is funded by the Instituto de Salud Carlos III.

### Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

### References

[1] Bosch J, Abraldes JG, Fernandez M, Garcia-Pagan JC. Hepatic endothelial dysfunction and abnormal angiogenesis: new targets in the treatment of portal hypertension. J Hepatol 2010;53:558–567.
[2] DeLeve LD, Wang X, Guo Y. Sinusoidal endothelial cells prevent rat stellate cell activation and promote reversion to quiescence. Hepatology 2008;48:920–930.
[3] Gracia-Sancho J, Lavina B, Rodriguez-Vilarrupla A, Garcia-Caldero H, Bosch J, Garcia-Pagan JC. Enhanced vasoconstrictor prostanoid production by sinusoidal endothelial cells increases portal perfusion pressure in cirrhotic rat livers. J Hepatol 2007;47:220–227.
[4] Steib CJ, Gerbes AL, Bystron M, Op dW, Hartl J, Roggel F, et al. Kupffer cell activation in normal and fibrotic livers increases portal pressure via thromboxane A(2). J Hepatol 2007;47:228–238.
[5] Graupera M, Garcia-Pagan JC, Pares M, Abraldes JG, Rosello J, Bosch J, et al. Cyclooxygenase-1 inhibition corrects endothelial dysfunction in cirrhotic rat livers. J Hepatol 2003;39:515–521.
[6] Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. Hepatology 2002;35:478–491.
[7] Abraldes JG, Albillos A, Banares R, Turnes J, Gonzalez R, Garcia-Pagan JC, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. Gastroenterology 2009;136:1651–1658.
[8] Gracia-Sancho J, Lavina B, Rodriguez-Vilarrupla A, Garcia-Caldero H, Fernandez M, Bosch J, et al. Increased oxidative stress in cirrhotic rat livers: a potential mechanism contributing to reduced nitric oxide bioavailability. Hepatology 2008;47:1248–1256.
[9] Thabut D, Tazi KA, Bonnefont-Rousselot D, Aller M, Farges O, Guimont MC, et al. High-density lipoprotein administration attenuates liver proinflammatory response, restores liver endothelial nitric oxide synthase activity, and lowers portal pressure in cirrhotic rats. Hepatology 2007;46:1893–1906.
[10] Zhou Q, Hennenberg M, Trebicka J, Jochem K, Leifeld L, Biecker E, et al. Intrahepatic upregulation of RhoA and Rho-kinase signalling contributes to increased hepatic vascular resistance in rats with secondary biliary cirrhosis. Gut 2006;55:1296–1305.
[11] Hennenberg M, Trebicka J, Sauerbruch T, Heller J. Mechanisms of extrahepatic vasodilation in portal hypertension. Gut 2008;57:1300–1314.
[12] Fernandez M, Mejias M, Angermayr B, Garcia-Pagan JC, Rodes J, Bosch J. Inhibition of VEGF receptor-2 decreases the development of hyperdynamic splanchnic circulation and portal-systemic collateral vessels in portal hypertensive rats. J Hepatol 2005;43:98–103.
[13] Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. Hepatology 2006;43:S121–S131.