



Review Article

The Role of Nitric Oxide in Chronic Liver Disease: A Review



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Received: March 09, 2026 | Revised: April 22, 2026 | Accepted: May 12, 2026 | Published online: July 02, 2026

Abstract

Nitric oxide (NO) is a crucial regulator of hepatic and systemic vascular tone. Abnormal distribution of NO in various anatomical locations is a pathogenetic characteristic of portal hypertension. Under normal portal pressure conditions, liver sinusoidal endothelial cells produce NO, which promotes both vasodilation and hepatic stellate cell relaxation. In portal hypertension, endothelial dysfunction, imbalance of asymmetric dimethylarginine levels, and production of superoxide result in impaired intrahepatic NO availability, leading to activation and contraction of hepatic stellate cells and worsening portal hypertension. Excess extrahepatic NO levels in the splanchnic vasculature result in systemic vasodilation, hyperdynamic circulation, and collateral vascular formation, worsening portal pressure. Abnormal clearance and production of NO can lead to extrahepatic complications, including hepatorenal syndrome and hepatopulmonary syndrome. Therapies including statins, phosphodiesterase-5 inhibitors, and midodrine have been developed to restore NO homeostasis but have achieved only partial success in modulating NO production, bioavailability, and distribution. The aim of this review is to update the understanding of the mechanisms and effects of NO dysregulation in cirrhosis as they relate to current and future therapeutic options.

Citation of this article: Zhao D, Wu GY. The Role of Nitric Oxide in Chronic Liver Disease: A Review. *J Clin Transl Hepatol* 2026;14(7):729–735. doi: 10.14218/JCTH.2026.00173.

Introduction

Nitric oxide (NO) plays an important role as a signaling molecule and vasodilator in the liver and many other organ systems.^{1–3} It is generated both enzymatically through nitric oxide synthases (NOS), which include neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS), and non-enzymatically by nitrite and nitrate.² In the hepatic circulation, eNOS is expressed in liver sinusoidal endothelial cells (LSECs) and the endothelium of the hepatic vasculature.⁴ eNOS-derived NO is generally protective and maintains

normal hepatic vascular tone and blood flow, whereas iNOS-derived NO is produced under pathological conditions and can contribute to nitrosative stress through the formation of reactive nitrogen species such as peroxynitrite (ONOO[−]), generated by the reaction of NO with superoxide. iNOS is produced in Kupffer cells, hepatic stellate cells, and LSECs, among other cell types.⁵

In cirrhosis, excessive extracellular matrix deposition due to hepatic stellate cell activation results in increased resistance within the portal system. In response, increased NO production in the splanchnic circulation leads to vasodilation, as well as translocation of gut bacteria and disruption of tight junctions, further worsening vasodilation.⁶ The resulting decrease in effective arterial blood volume leads to activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system.⁷ Cardiac output increases to compensate for the effectively low circulatory blood volume, contributing to a hyperdynamic state and perpetuating the cycle by further increasing portal inflow and portal hypertension.⁸ Splanchnic vasodilation and portosystemic collateral pathways develop due to increased portal pressures.⁹ As a result, several organs, including the lungs and kidneys, can develop complications of decompensated cirrhosis.¹⁰ While our knowledge of the complexities of NO derangements in portal hypertension is incomplete, it is clear that a better understanding of NO dysregulation is important for the evaluation and design of new and more effective agents to restore NO homeostasis. The aim of this review is to update the mechanisms and sites of NO production and clearance in cirrhosis and to discuss current targeted therapeutic approaches to address abnormal NO distribution.

Normal NO homeostasis

Intrahepatic sinusoidal production of NO

LSECs are a major source of hepatic NO.^{11–13} As a response to shear stress on LSECs, Kruppel-like factor 2 (KLF2) transcription is upregulated, which activates eNOS, producing NO from L-arginine.¹⁴ NO activates soluble guanylate cyclase, leading to the production of cyclic guanosine monophosphate (cGMP), resulting in sinusoidal vasodilation. In a negative feedback mechanism, cGMP activates phosphodiesterase-5 (PDE-5), which then degrades cGMP, thereby inhibiting and self-regulating the vasodilatory effect of NO (Figs. 1A and 2A).^{14–17}

Normal NO elimination

NO is normally rapidly oxidized to nitrate and nitrite in hepatic sinusoids and eliminated by the kidneys.^{18,19} About 65% of

Keywords: Nitric oxide; Splanchnic vasodilation; Hepatopulmonary syndrome; Portopulmonary hypertension; Hyperdynamic circulation; Hepatorenal syndrome.

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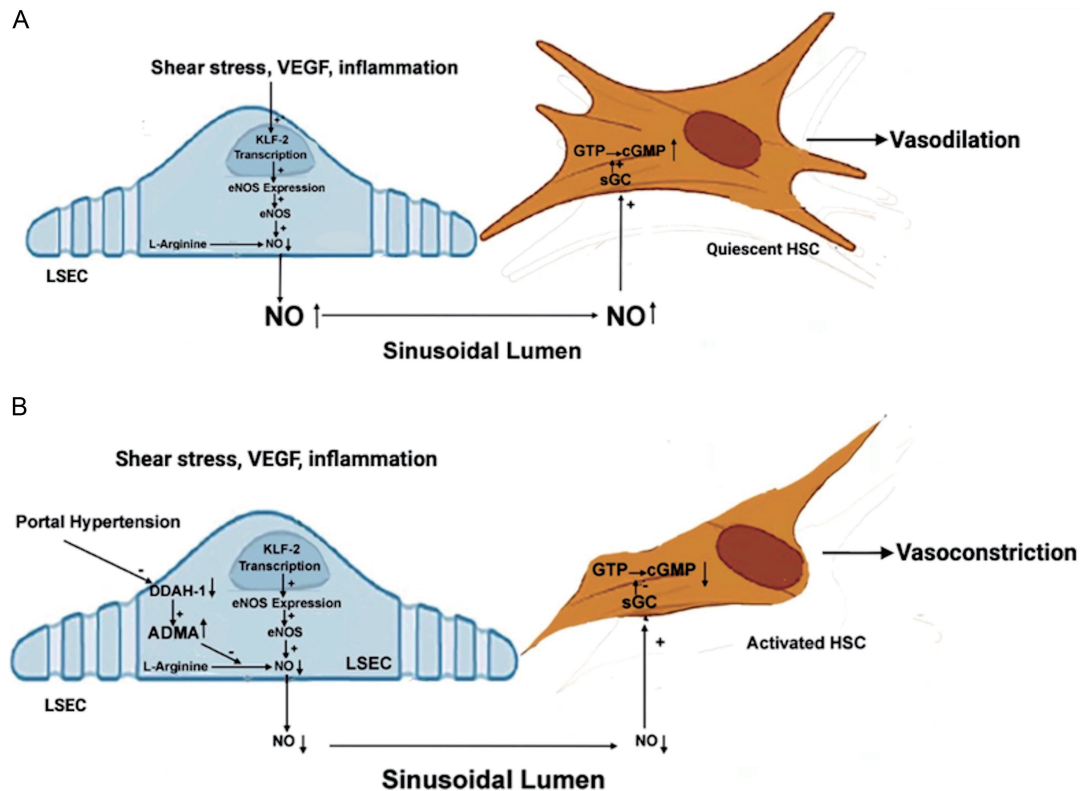


Fig. 1. LSECs and HSC interactions in regulating NO levels. (A) Normal portal pressure. As a response to shear stress and other factors such as VEGF and inflammation on LSECs, KLF2 and eNOS are activated and convert L-arginine to NO. NO diffuses to nearby HSCs, which activates sGC,¹⁴ generating cGMP and resulting in hepatic stellate cell and sinusoidal vasodilation.¹⁷ (B) Portal hypertension. In portal hypertension, DDAH1 expression is decreased, leading to impaired degradation and accumulation of ADMA and, therefore, decreased NO production by acting as an endogenous competitive inhibitor of L-arginine.¹⁶ HSCs become activated, transforming into myofibroblasts with contractile properties. Decreased NO levels trigger their contraction, which further leads to sinusoidal constriction and increased portal pressure. Image created by BioRender. VEGF, vascular endothelial growth factor; KLF2, Kruppel-like factor 2; LSECs, liver sinusoidal endothelial cells; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; HSC, hepatic stellate cell; ADMA, asymmetric dimethylarginine; DDAH1, dimethylarginine dimethylaminohydrolase 1. Arrows with (+) indicate stimulation, arrows with (–) indicate suppression, plain arrows indicate movement. ↓, decreased expression/production; ↑, increased expression/production.

orally administered ¹⁵N-nitrate was eliminated in the urine, while 0.1% was found in the feces.²⁰ Williams *et al.* observed a strong positive correlation between estimated glomerular filtration rate (eGFR) and urinary nitrate ($R = 0.7665$, $P < 0.0001$), supporting urinary excretion as the major mechanism of NO elimination.²¹

Hemoglobin also plays a role in scavenging and eliminating NO. When oxygen binds to hemoglobin to form oxyhemoglobin, the iron heme can rapidly sequester and eliminate NO, forming methemoglobin and nitrate.^{4,22}

Derangements of NO homeostasis

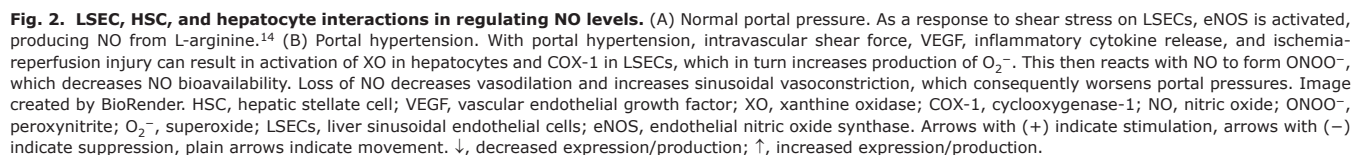
Abnormal NO production in the hepatic sinusoid in portal hypertension

Portal hypertension has been shown to induce hemodynamic stress in the form of intravascular shear force, inflammatory cytokine release, and ischemia-reperfusion injury. These result in activation of xanthine oxidase and cyclooxygenase-1, which in turn increase production of superoxide^{23–25} Superoxide rapidly reacts with available NO, forming peroxynitrite (ONOO[–]), which is highly reactive and decreases NO bioavailability in the hepatic circulation.²⁴ Loss of NO decreases soluble guanylate cyclase activity and, in turn, cGMP-mediated vasodilation, resulting in increased sinusoidal vasocon-

striction and worsening portal pressure (Fig. 2B).^{24,26} Studies have shown that hepatic stellate cells located in the Space of Disse contract in the hepatic sinusoid once activated into myofibroblasts, a process triggered by liver injury and reduced NO production (Fig. 1B).^{27,28}

In portal hypertension, asymmetric dimethylarginine (ADMA) is also a prominent regulator of NO production, acting as an endogenous inhibitor of eNOS^{29–31} by competing with L-arginine for the binding site of NOS,¹⁶ consequently reducing NO biosynthesis (Fig. 1B).³² Dimethylarginine dimethylaminohydrolase 1 (DDAH1) in the liver degrades ADMA and typically regulates NO bioavailability. In cirrhosis, DDAH1 expression is reduced, leading to impaired degradation of ADMA.³³ ADMA levels were found to be approximately 10 times higher in patients with end-stage liver disease prior to liver transplantation compared to healthy volunteers, although the study was limited by a small sample size (12 patients).³⁴ Lluch *et al.* paradoxically observed both elevated peripheral plasma ADMA (two-fold) and NO levels in decompensated alcoholic cirrhosis (Pugh class B and C) compared with compensated cirrhosis (Pugh class A) and healthy patients ($P < 0.05$).³⁵ This suggests that elevated ADMA concentrations result from impaired hepatic removal of ADMA. However, its inhibitory effect occurs primarily within the cirrhotic liver, causing increased intrahepatic vascular resistance (worsened portal hypertension), while systemic NO is

Vizzutti *et al.* found a significant positive correlation between hepatic venous pressure gradient (HVPG) and ADMA levels in hepatic veins of patients with hepatitis C virus-related chronic liver disease ($r = 0.77$, $P < 0.0001$), and a



negative correlation between HVPG and NO concentrations ($r = -0.50$, $P = 0.005$).³⁶ This suggests that high ADMA levels may directly increase portal pressures and reduce intrahepatic NO levels, contributing to increased intrahepatic vascular resistance and portal hypertension. This study used direct sampling of hepatic venous ADMA and NO levels, allowing accurate measurements; however, it was limited by small sample size and cross-sectional design.

Shunting of NO away from intrahepatic sinusoids

Varices and portosystemic collaterals develop as a result of high portal pressures (greater than 8–10 mmHg)^{37,38} in watershed regions where portal and systemic circulation communicate. Elevated portal pressures exceeding this threshold dilate collateral channels and activate angiogenesis, forming new portosystemic pathways.³⁹ Shunts divert blood away from the portal system into the systemic venous circulation, bypassing the liver.³⁷ In this way, elevated NO levels from the splanchnic circulation enter the systemic circulation²⁹ decreasing intrahepatic NO bioavailability and exacerbating intrahepatic vascular resistance.²⁵

Abnormal NO production in the splanchnic circulation

In cirrhosis, shear stress from increased portal pressure also results in eNOS activation and NO production, leading to splanchnic vasodilation.³⁹ Shear stress, oxidative stress, and inflammation drive intestinal vascular endothelial growth factor (VEGF) expression, which triggers eNOS activation and initiation of portosystemic collateralization.^{25,40,41} Horowitz *et al.* found evidence that VEGF stimulates eNOS-derived NO production.⁴² Abrales *et al.* also found that VEGF up-regulates eNOS in the intestinal microcirculation in mild portal hypertensive rats.⁴³ Muti *et al.* assessed nitro-oxidative stress and VEGF levels in portal hypertensive patients and found significant increases in serum nitrite, nitrate, and VEGF levels in both cirrhotic and non-cirrhotic portal hypertensive patients.⁴⁴ These studies suggest that eNOS activation and NO production driven by VEGF expression contribute to compensatory portosystemic shunt formation.

Effects on renal microcirculation

Kayali *et al.* observed significant rises in plasma NO metabolites with worsening renal function in patients with decompensated cirrhosis, with the highest levels observed in patients with hepatorenal syndrome (HRS) ($P < 0.001$).⁴⁵ Türkay *et al.* similarly studied NO levels and GFR in 11 patients with preascitic cirrhosis and 13 with ascitic cirrhosis and found a significant negative correlation between NO and GFR ($R = -0.49$, $P = 0.002$), suggesting that NO elimination decreases with worsening renal function.⁴⁶ These studies suggest that patients who develop renal insufficiency have decreased renal NO elimination, increasing systemic NO levels and compounding renal hypoperfusion, ultimately contributing to HRS.⁴⁷ The decreased production of other renal vasodilators, including prostaglandins, and increased production of vasoconstrictors such as vasopressin and endothelin, also contribute to HRS.⁷

Effects on pulmonary circulation

Hepatopulmonary syndrome (HPS) results from intrapulmonary vasodilation linked to increased NO. About 30% of patients with cirrhosis or portal hypertension develop HPS.⁴⁸ Portal hypertension can also lead to changes in the pulmonary microcirculation, resulting in NO-induced vasodilation of pulmonary vessels at the alveolar capillaries. This increases

pulmonary blood flow but decreases oxygen diffusion, causing hypoxemia.⁴⁹ Inefficient oxygen exchange at the alveoli causes gas exchange dysfunction,⁵⁰ and arteriovenous shunting occurs, resulting in HPS.⁵¹

Increased pulmonary endothelin production from shear stress stimulates pulmonary eNOS expression, resulting in vasodilation of the pulmonary vasculature.⁵² Rolla *et al.* observed significantly higher levels of exhaled NO in patients with HPS compared with those without HPS (331 ± 73.2 vs. 223 ± 118.4 nL/min/m², $P < 0.05$).⁵³

Therapeutic approaches and their effects on NO

Because of the significant effects of NO on intrahepatic resistance and systemic vasodilation in cirrhosis, several therapies have been studied to selectively target NO pathways and downstream effects.

PDE-5 inhibitors

PDE-5 inhibitors block the conversion of cGMP to its inactive form, prolonging the vasodilatory effect of NO in the NO-cGMP system. This increases intrahepatic blood flow by decreasing intrahepatic vascular resistance.

Udenafil is a substrate of cytochrome P450-3A and is metabolized primarily in the liver. Kreisel *et al.* found that hepatic venous pressure gradient decreased by 15.7% ($P = 0.040$) with udenafil (75–100 mg/d).⁵⁴ Lee *et al.* demonstrated that hepatic venous NO levels significantly increased after sildenafil administration compared with placebo in cirrhotic patients (12.3 ± 43.5 to 325.3 ± 117.5 nM, $P = 0.018$).⁵⁵ There were no significant complications such as encephalopathy, esophageal bleeding, or spontaneous bacterial peritonitis after 1 week of therapy, suggesting a favorable safety profile, although long-term effects were not studied.

Statins

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) induce NO production through stimulation of eNOS in the intrahepatic vasculature mediated by KLF2.⁴ This primarily results in increased intrahepatic blood flow due to increased NO production and decreased intrahepatic resistance. Simvastatin appears to be the most well-studied statin in clinical studies. Its effects on localized hepatic eNOS expression, NO production, and hemodynamics effectively lower portal pressure in cirrhosis without significantly affecting systemic vasculature.⁵⁶

In a randomized controlled trial, Abrales *et al.* observed a significant decrease in HVPG in patients receiving simvastatin (-5.9% , $P = 0.013$), while mean arterial pressure and cardiac index did not significantly change. This suggests efficacy of simvastatin in reducing portal pressure without systemic hemodynamic effects, although NO levels were not specifically measured.⁵⁷

Zafra *et al.* measured systemic hemodynamics, HVPG, and NO products after simvastatin administration in 30 patients with cirrhosis, and NO product levels were significantly increased in hepatic venous blood (31.4 ± 12.3 nmol/mL to 35.8 ± 10.7 nmol/mL; $P = 0.04$), while systemic hemodynamics did not change, suggesting reduced portal pressure without systemic involvement.⁵⁷

Midodrine

Midodrine is an alpha-adrenergic vasoconstrictor that significantly reduces cardiac output and increases systemic vascular resistance.⁵⁸ Angeli *et al.* found that midodrine decreased serum nitrite and nitrate levels from 49.3 ± 7.3 to 33.4 ± 5.0

$\mu\text{mol/L}$ ($P < 0.05$) in cirrhotic patients with ascites within the first 3 h of administration. This demonstrated the potential therapeutic effect of midodrine on NO levels in cirrhotic patients.⁵⁹ There was also a significant increase in mean arterial pressure (89.6 ± 1.7 vs. 81.8 ± 1.3 mmHg; $P < 0.0001$), while heart rate significantly decreased (69 ± 2 vs. 77 ± 3 bpm; $P < 0.005$).⁵⁹

Solà *et al.* performed a multicenter, double-blinded randomized controlled trial of patients with cirrhosis and ascites awaiting liver transplantation. Patients either received midodrine and albumin or placebo for one year, until liver transplantation or until no longer meeting inclusion criteria. No significant difference between either group was found in terms of complications of cirrhosis or rate of one-year mortality. MELD scores also did not significantly change between the two groups.⁶⁰ Plasma renin and aldosterone levels were slightly but significantly decreased compared to placebo (renin -4.3 vs. 0.1 ng/mL/h, $P < 0.001$; aldosterone -38 vs. 6 ng/dL, $P = 0.02$), suggesting a slight decrease in vasoconstrictor activity, but this did not prevent complications of cirrhosis or improve survival.⁶⁰

Effects of transjugular intrahepatic portosystemic shunt (TIPS) on NO levels

TIPS diverts portal blood to the systemic vasculature, increasing systemic blood flow.⁶¹ TIPS placement reduces portal pressures by diverting portal blood flow away from the high-resistance intrahepatic circulation to the systemic vasculature. The resulting decreased shear stress reduces NO production.³⁹ However, Jalan *et al.* studied 12 patients with cirrhosis who had undergone TIPS and observed significant increases in systemic NO production compared to prior to TIPS insertion (40.6 to 71.2 nmol/kg body weight per minute, $P < 0.05$), likely due to exacerbation of endotoxemia.⁶² Mean arterial pressure was significantly decreased, correlating with increased NO synthesis ($r = -0.89$, $P < 0.001$). Endpoints such as mortality, effect on model for end-stage liver disease (MELD) score, and other complications of cirrhosis were not studied.

With TIPS placement, shunting of blood to the systemic circulation and reduction of degradation by hepatic dimethylarginine dimethylaminohydrolase resulted in increased ADMA levels and improved renal function.⁶³ Siroen *et al.* studied the effect of TIPS on ADMA and NO plasma levels, as well as renal and hepatic function in patients with cirrhosis three months after TIPS placement. They observed increased ADMA and overall improved renal function in patients with renal dysfunction prior to receiving TIPS, but hepatic function and Child-Pugh score did not significantly change after TIPS placement.⁶⁴ MELD scores and survival rates were not studied. NO plasma levels decreased after TIPS placement, and there was a significant positive correlation between ADMA and NO levels ($r = 0.67$; $P = 0.009$), likely explained by the reduction of portal pressures post-TIPS, reducing the stimuli for splanchnic NO production.⁶⁴

Halabi *et al.* performed a meta-analysis of over 600 patients with cirrhosis and observed a significant decrease in 1-year mortality (RR 0.68; 95% CI 0.49–0.96; $P = 0.03$) and 1-year rebleeding rate (RR 0.28; 95% CI 0.20–0.40; $P < 0.001$) with TIPS placement.^{65,66} Overall 1-year mortality was significantly decreased with TIPS. MELD scores were not studied. Despite concern for increased risk of hepatic encephalopathy (HE) with TIPS placement, Halabi *et al.* did not find a significant difference in HE incidence at 1 year. Long-term outcomes were not studied, and confounding factors, despite being minimized by sensitivity analysis for liver disease severity, cannot be completely excluded. Bai *et al.* also performed a meta-analysis on patients with refractory as-

cites and average MELD scores of 13.6–20.9 who underwent TIPS. They noted decreased liver disease-related mortality in those who received TIPS compared to those who did not (odds ratio [OR] = 0.62, 95% CI 0.39–0.98, $P = 0.04$), but found a significantly increased risk of HE (OR = 2.95, 95% CI 1.87–4.66, $P = 0.02$).⁶⁷

Ascha *et al.* studied patients with cirrhosis and MELD score ≥ 15 and found increased mortality or need for liver transplantation in patients who received TIPS in the first 2 months compared to those who did not. However, the result was not statistically significant (30% higher hazard ratio, $P < 0.07$). After 2 months, they observed a 56% lower mortality risk or need for liver transplantation compared to those who did not receive TIPS ($P < 0.01$).⁶⁸ TIPS overall appears to have a mortality benefit in patients with cirrhosis and may reduce the need for transplantation.

Larrue *et al.* performed a systematic review of over 2,000 patients comparing survival in patients with cirrhosis and portal hypertension who received TIPS compared to those who received standard of care (large-volume paracenteses, albumin, endoscopic band ligation, etc.) and observed a 2-year cumulative survival of 0.71 compared to 0.63 ($P = 0.0001$), respectively.⁶⁹ This study suggests improved long-term survival in patients with cirrhosis who received TIPS compared to standard of care.

Conclusions

NO dysregulation has a significant impact on the development of pathologic conditions in the liver. Furthermore, NO derived from various cell types plays differing roles in liver pathology. eNOS-derived NO supports liver homeostasis and is protective against pathologic changes in the liver.⁴ In contrast, iNOS-derived NO produces reactive nitrogen species, resulting in damage at the nucleic acid and cellular levels. Pathologic conditions that predispose the liver to a pro-inflammatory state and bacterial endotoxin release upregulate iNOS while decreasing eNOS activity.⁴ Endotoxemia from gut bacterial translocation of lipopolysaccharide stimulates endothelin and NO production.⁷⁰ Lipopolysaccharide can also activate transcription factors such as nuclear factor κB ²⁹ and cytokines such as tumor necrosis factor- α that promote iNOS production. iNOS upregulation results in overproduction of NO in the superior mesenteric artery, contributing to the hyperdynamic state in cirrhosis.²⁹

Based on the current understanding of altered NO homeostasis in portal hypertension, treatment strategies should decrease portal pressure by increasing intrahepatic NO levels, improving hepatocyte perfusion and function. At the same time, systemic vasodilation should be decreased by reducing systemic NO levels to restore intravascular volume and thereby increase systemic blood pressure and perfusion.

Clinical studies on NO levels related to the effects of PDE-5 inhibitors, statins, and midodrine are limited. Simvastatin has been shown to significantly increase intrahepatic NO production, although its potential for liver and muscle injury and increased risk of mortality in cirrhosis are disadvantages.⁷¹

Midodrine has been shown to improve hepatic NO bioavailability and systemic mean arterial pressure, as well as preventing progression of portal hypertension.⁵⁹ Although significant decreases in heart rate can limit certain patient populations, particularly those with hemodynamic instability, PDE-5 inhibitors generally appear to have favorable safety profiles.⁵⁵ Their efficacy as well as long-term adverse effects compared to other therapies such as statins and midodrine have not been studied.

The effects of TIPS placement often include initiation or

worsening of HE. However, diversion of splanchnic NO to the systemic circulation does not appear to worsen systemic vasodilation and hypotension. Rather, TIPS has been shown to improve systemic blood pressure, presumably due to increased effective intravascular volume by returning pooled splanchnic blood to the systemic circulation.^{39,61} Of course, intrahepatic portal blood flow is decreased, compromising hepatic function and regeneration. However, for patients with good liver function, i.e., low MELD scores, TIPS has been shown to be beneficial in decreasing the hyperdynamic state caused by NO excess.⁶⁴ Although mortality within the first 2 months after TIPS may be increased in patients with MELD scores >15, long-term transplant-free survival after 2 months was significantly increased compared to standard medical therapy.^{65,66,69}

Although modulation of NO bioavailability and production represents a promising therapeutic approach, large randomized controlled studies are needed to clarify its effects on NO homeostasis, clinical benefit, and potential long-term risks in head-to-head comparative studies.

Acknowledgments

We gratefully acknowledge support from the Herman Lopata Chair in Hepatitis Research, which made this work possible.

Funding

None to declare.

Conflict of interest

GYW has been Editor-in-Chief of the *Journal of Clinical and Translational Hepatology* since 2013. He has no role in the publisher's decisions regarding this manuscript. DZ has no conflicts of interest related to this publication.

Author contributions

Review concept (GYW), information collection, drafting of the manuscript (DZ), and revision of the manuscript (GYW, DZ). All authors have approved the final version and publication of the manuscript.

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