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Review Article

Effects of Transjugular Intrahepatic Portosystemic Shunt on Renal and Pulmonary Function in Hepatic Decompensation with and without Hepatorenal and Hepatopulmonary Syndromes: A Review

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Abstract

Cirrhosis is often characterized by decreased liver function, ranging from a compensated, typically asymptomatic phase to a decompensated phase characterized by the appearance of ascites or variceal bleeding, and ultimately hepatorenal syndrome (HRS) or hepatopulmonary syndrome (HPS). The latter two complications are associated with a poor prognosis and limited treatment efficacy. In cases of ascites or variceal bleeding resistant to medical therapy, transjugular intrahepatic portosystemic shunt (TIPS) is effective and safe. Shunting blood by TIPS diverts portal blood to the systemic circulation, potentially increasing systemic blood volume and benefiting renal function. However, TIPS could also divert nitric oxide to the systemic circulation, potentially worsening systemic hypotension and perfusion, which could be detrimental to renal function. Available evidence indicates that TIPS often improves renal function in patients with portal hypertension, with or without HRS. No studies have shown persistently decreased renal function after TIPS. However, these data are insufficient to support a recommendation for the use of TIPS specifically for HRS. In patients without pre-existing HPS, TIPS does not appear to significantly affect pulmonary gas exchange. Results of TIPS in HPS have been inconsistent; some studies have shown improvement, but effects were transient. No studies have shown a persistent decline in pulmonary function after TIPS. The evidence supports the need for large randomized controlled trials to investigate the beneficial effects of TIPS for HRS. Similar pulmonary function data are less clear regarding TIPS for HPS. The aim of the current report was to review the literature regarding the effects of TIPS on renal and pulmonary function in hepatic decompensation, with or without the development of HRS or HPS.

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Introduction

Cirrhosis is the fourth leading cause of mortality from non-communicable diseases worldwide. In the US, approximately 2.2 million adults have cirrhosis, with a mortality rate of 21.9 per 100,000 people.[1] The most common causes of cirrhosis are alcohol use, hepatitis C, and metabolic dysfunction-associated steatohepatitis.[2] Progressive loss of liver function can lead to a wide range of complications and hepatic decompensation, including variceal bleeding, ascites, hepatic encephalopathy, hepatorenal syndrome (HRS), and hepatopulmonary syndrome (HPS).[3] Most cases of variceal bleeding respond to endoscopic hemostasis followed by administration of beta-blockers to decrease splanchnic contribution to portal hypertension and decrease the risk of recurrent bleeding.[4] Ascites is managed by dietary salt restriction and diuretics,[5] while hepatic encephalopathy usually responds to lactulose or non-absorbable antibiotics such as rifaximin.[6] When these signs of hepatic decompensation fail to respond, transjugular intrahepatic portosystemic shunt (TIPS) can be helpful in alleviating symptoms in patients with adequate hepatic function. However, terminal complications of hepatic decompensation, HRS, and HPS are particularly serious and dreaded due to limited treatment options, efficacy, and high mortality.[7,8] Both HRS and HPS are thought to result from systemic vasodilation due to elevated levels of circulating vasodilators such as nitric oxide (NO) in hepatic decompensation.[9] As cirrhosis progresses, there is increased intrahepatic resistance and subsequent increase in intravascular tone due to decreased intrahepatic NO. This increased resistance triggers the release of NO, carbon monoxide, and endocannabinoids from endothelial cells of the splanchnic vascular bed.[10] This leads to progressive vasodilation of the splanchnic circulation and a subsequent decrease in systemic vascular resistance.[11] Additionally, bacterial overgrowth and alterations of tight junction proteins in cirrhosis can facilitate bacterial translocation from the gut to the mesenteric lymph nodes.[12] Bacterial translo-

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cation or active infection can increase levels of proinflammatory cytokines such as interleukin (IL)-6, IL-12), and tumor necrosis factor (TNF).[13] Other inflammatory mediators such as pathogen-associated molecular patterns and damage-associated molecular patterns can mediate an inflammatory response linked to further vasodilatory circulatory derangement.[14] This state of systemic vasodilation in decompensated cirrhosis leads to worsening renal and pulmonary function and the development of HRS and HPS. Another contributing mechanism to the deterioration of renal function is renal under-filling through activation of the renin-angiotensin-aldosterone system (RAAS). This activation compensates for the effects of splanchnic vasodilation on arterial circulation.[15] In addition, cardiac output increases to maintain normal arterial pressure. In end-stage cirrhosis, cardiac output is unable to completely compensate for decreased vascular resistance.[16] Ultimately, hypovolemic circulation and arterial hypotension develop, contributing to pre-renal azotemia that can lead to irreversible renal dysfunction and HRS.[17]

Similarly, in hepatic decompensation, there is increased blood flow in a dilated pulmonary bed, which can lead to the passage of mixed venous blood to the pulmonary veins.[18] Diffusion of oxygen becomes limited because increased diameters of the pulmonary vessels result in longer distances for oxygen to travel to bind to hemoglobin. In addition, arterial venous shunts can occur, leading to the direct mixing of venous and arterial blood, resulting in worsening pulmonary function and ultimately HPS.[19]

As mentioned above, for some forms of decompensation such as intractable ascites and persistent variceal bleeding, TIPS can be an effective treatment if liver function is adequate.[20] However, because large amounts of NO normally enter the portal circulation from the splanchnic system, the diversion of blood away from the liver into the systemic circulation could theoretically shunt NO to the systemic circulation and contribute to systemic vasodilation. On the other hand, increased blood flow from the portal circulation to the systemic circulation by TIPS could increase systemic perfusion, ameliorating some of the extrahepatic complications due to low intravascular volume.[21]

TIPS procedure

The TIPS procedure involves placing a portosystemic shunt within the liver parenchyma to connect the portal vein to a hepatic vein. This minimally invasive procedure is performed percutaneously by inserting a catheter into a jugular vein and a stent into an intrahepatic branch of the portal vein. The newly created channel increases the flow of portal blood to the inferior vena cava, bypassing the liver and lowering portal pressure. TIPS is mainly indicated for the treatment of refractory conditions including variceal bleeding, ascites, hepatic hydrothorax, and gastropathy[22,23]

Safety and adverse effects of TIPS

Despite its efficacy in these patients, an important consequence is a decrease in hepatic ammonia metabolism. The creation of a channel between the portal and systemic circulation shunts ammonia directly into the systemic circulation, which results in hepatic encephalopathy in around 30% of patients.[23,24] Masson *et al*. studied 197 patients who underwent TIPS for refractory ascites or secondary prophylaxis for variceal bleeding. In 136 patients available for post-procedural analysis, hepatic encephalopathy occurred in 38.2% of patients, with an actual incidence of 34.5% attributed to TIPS placement after excluding other causes. The authors demonstrated that pre-existing HE was the only significant predictive factor for subsequent HE occurrence after the procedure. A strength of the study was its ability to screen patients for ongoing alcohol consumption, which could falsely increase the incidence of HE attributed to TIPS. However, the sample size was small, recruited from a single institution, and 26% of post-TIPS patients were not available for analysis due to early mortality.[25]

Busk *et al*. assessed the effects of TIPS on blood volume distribution in patients with cirrhosis. Authors demonstrated increased central blood volume, preload, and subsequently inotropy in 25 cirrhotic patients after TIPS insertion. The authors assessed hemodynamic variations using initial right heart catheterization and subsequent echocardiography, which strengthened the study. However, the sample size was very small. Additionally, patients with cardiovascular impairment were not referred for the procedure, potentially introducing selection bias. Therefore, the impact of TIPS on worsening cardiovascular outcomes was not adequately assessed.[26] Another risk of TIPS is that the hepatic artery may theoretically assume an increased proportion of liver sinusoidal perfusion, posing a risk of worsening liver function if the arterial flow becomes compromised. Acute hepatic failure after TIPS can occur due to decreased portal perfusion pressure and/or reversal of portal vein flow, resulting in hepatic ischemia in some cases. Depending on the configuration, TIPS carries the risk of occluding hepatic artery or portal vein branches, causing infarction in their distribution. TIPS can also occlude one or more hepatic veins, leading to hepatic failure resembling Budd-Chiari syndrome.[27]

Several pre-existing clinical conditions, such as heart failure, can worsen outcomes after TIPS. Absolute contraindications include active sepsis, severe pulmonary hypertension, decompensated congestive heart failure, and severe tricuspid regurgitation. Relative contraindications include well-compensated heart failure, moderate pulmonary hypertension, severe obstructive arteriopathy, hepatic artery stenosis, and celiac artery stenosis that may prevent adequate sinusoidal perfusion. Previous episodes of hepatic encephalopathy must be considered when selecting TIPS candidates but should not be considered absolute contraindications.[27,28]

There have been no large randomized trials on the safety of TIPS specifically in patients with HRS and HPS. However, patients who develop these terminal syndromes usually have severe hepatic decompensation and typically high scores of model of end-stage liver disease (MELD).[29,30] A recent study by Krishnan *et al*. showed that the MELD score might offer a better prognostic tool for mortality in cirrhotic patients after TIPS compared to the newer MELD-Na score, although the study was retrospective.[31] Earlier studies indicated that three-month survival after TIPS was significantly lower in patients with MELD scores >18 compared to those with lower MELD scores.[32,33] Another study by Pan *et al*. showed that a MELD score greater than 15 was significantly associated with poor survival at 30 days, 90 days, and one year after TIPS placement.[34] These differences in cutoffs could be attributed to variations in patient populations. Despite this consensus, a cohort study analyzing the association between TIPS outcomes and MELD in 106 TIPS patients and 79 patients with intractable ascites without TIPS revealed that high MELD scores and TIPS were independent risk factors for post-TIPS mortality. However, mortality increased considerably less than expected after TIPS placement in patients with MELD scores >18. The authors suggested that TIPS did not independently increase the risk of death in patients with higher MELD scores, although the study sample was small.[35] A meta-analysis comparing TIPS versus large-volume paracentesis in refractory ascites demonstrated improved prog-

nosis and mortality across all MELD categories.[36] Another cohort study by Lv *et al*. included patients with acute variceal bleeding and found that early TIPS was associated with improved one-year survival in patients with MELD >19, but not in those with lower MELD scores, compared to patients receiving standard-of-care vasoactive drugs and endoscopic ligation.[37] These results are significant as they indicate that despite theoretical risks, TIPS may benefit selected patients with high MELD scores and can still be offered in clinical practice with acceptable safety.[38] More randomized controlled studies are needed to evaluate the safety of TIPS specifically in patients with HRS or HPS.

Effects of TIPS on renal function in hepatic decompensation in the absence of HRS

A retrospective study by Allegretti *et al*. assessed the effects of TIPS on renal function in patients with refractory ascites without HRS. They compared 138 patients who underwent TIPS with 138 patients who underwent a series of large volume paracentesis. After 90 days, patients with estimated glomerular filtration rate (eGFR) less than 60 mL/m before TIPS showed a significant increase in their eGFR compared to those who only had paracentesis. There was no difference in patients with pretreatment glomerular filtration rate (GFR) greater than 60 mL/m between the two groups. The mortality rates between the groups were similar. However, routine documentation of parameters such as urine sodium, serum renin, and serum aldosterone was not performed.[39]

Lang *et al*. conducted a retrospective analysis of 593 patients with cirrhosis who underwent TIPS. Among the enrolled patients, 21.4% had serum creatinine >1.5 mg/dL, while the rest had normal kidney function. The authors demonstrated that patients with elevated baseline creatinine experienced significant decreases in post-TIPS serum creatinine (difference, −0.60 mg/dL). Furthermore, those with sustained elevation in creatinine 15 days after the procedure had a higher risk of one-year mortality. Although patients with baseline renal dysfunction showed significant improvement after TIPS, data on intravenous hydration before and after TIPS placement were unavailable and could have influenced outcomes.[40]

In a randomized controlled trial, Rossle *et al*. investigated the mortality benefit of TIPS compared to large-volume paracentesis in patients with advanced cirrhosis. Out of 60 patients with refractory or recurrent ascites, 29 were assigned to TIPS treatment and 31 to large-volume paracentesis. Survival rates without liver transplantation in the shunt group were 69% and 58% at one year and two years, respectively, compared to 52% and 32% in the paracentesis group. However, these results were not statistically significant. The study also showed that monthly follow-up of urinary variables revealed increased creatinine clearance from 41 ± 27 mL per minute to 61 ± 36 mL per minute in the shunt group, along with a significant increase in urinary sodium excretion, whereas these variables remained unchanged in the paracentesis group. The strengths of this study included randomization and intention-to-treat analysis. A limitation was the exclusion of patients with creatinine levels >3 mg/dL, and patients who died within three months were not included in the response analysis.[41]

Anderson *et al*. examined the effects of TIPS on renal function in 129 patients. Patients with a mean baseline creatinine of 1.5 mg/dL improved to 1.1 mg/dL, while those with a mean baseline >2 mg/dL improved from 2.8 to 1.5 mg/dL. The study demonstrated a direct correlation between the severity of renal dysfunction before TIPS and the degree of improvement after the procedure. However, 58 patients were lost to follow-up.[42] No studies have shown persistently decreased renal function after TIPS.

HRS

Definition and epidemiology

HRS has a reported incidence of 20% during the first year after the diagnosis of decompensated cirrhosis, and up to 40% within five years thereafter.[29–43] The terms HRS-acute kidney injury (HRS-AKI) and HRS-chronic kidney injury (HRS-CKD) have replaced the older definitions of HRS Type 1 and Type 2, respectively. HRS-AKI is defined as an absolute increase in serum creatinine >0.3 mg/dL within 48 h, or urinary output <0.5 mL/kg/body weight in 6 h or more, or a 50% or greater increase in serum creatinine compared to the last available value within the past three months. HRS-CKD is defined as a GFR of less than 60 mL/m per 1.73 m^2 for more than three months in the absence of renal structural causes.[44] Some patients do not meet all the criteria for HRS-AKI but instead develop a slowly progressive decline in renal function over time. Patients who do not fully recover after the initial episode of AKI may also fall into this category. If kidney function impairment lasts for less than 90 days, it is termed hepatorenal syndrome-acute kidney disease (HRS-AKD). The definition of the terminology is renal function characterized by an eGFR less than 60 mL/m/1.73 m^2 for less than 90 days without renal structural causes or less than a 50% increase in serum creatinine compared to the last outpatient value within three months. If kidney impairment persists for more than 90 days, it is called HRS-CKD.[45,46] It is important to rule out other causes of renal diseases, including shock, withdrawal of diuretics, and the use of nephrotoxic medications.[47]

Common risk factors associated with HRS include systemic inflammation and infection, such as spontaneous bacterial peritonitis, which has a reported incidence rate of 30% in HRS patients. Additionally, acute hemodynamic changes, such as those occurring in large-volume paracentesis without albumin infusion, and massive variceal bleeding, can also precipitate HRS.[48] In a retrospective study by Alessandria *et al*. involving 41 patients with HRS Type 1 and 64 patients with HRS Type 2, the authors demonstrated that patients with HRS Type 1 had more severe hepatic and renal derangements and subsequent hemodynamic instability with lower arterial pressure. They had markedly higher serum levels of norepinephrine and vasopressin compared to the HRS Type 2 group. The prognosis in the HRS Type 1 group was very poor and independent of the MELD score. In HRS Type 2, there was a significant increase in three-month mortality associated with increased MELD scores. For patients with MELD scores less than 20, the median survival duration was 11 months, whereas for MELD scores greater than 20, the median survival duration was less than three months. However, these data were obtained before current advances in disease understanding and standard of care with albumin and vasoconstrictors.[49]

Pathophysiology of HRS

The pathophysiology of HRS is thought to be mainly related to alterations in arterial circulation secondary to increases in portal pressure and hyperdynamic circulation (Fig. 1).[50] Additionally, more recent studies have suggested that increases in inflammatory mediators play a role in the circulatory and renal dysfunction that occurs in HRS.[51]

The role of systemic inflammation and cytokines: Sole *et al*. recruited 161 hospitalized patients with decompensated cirrhosis, among whom 58 were diagnosed with

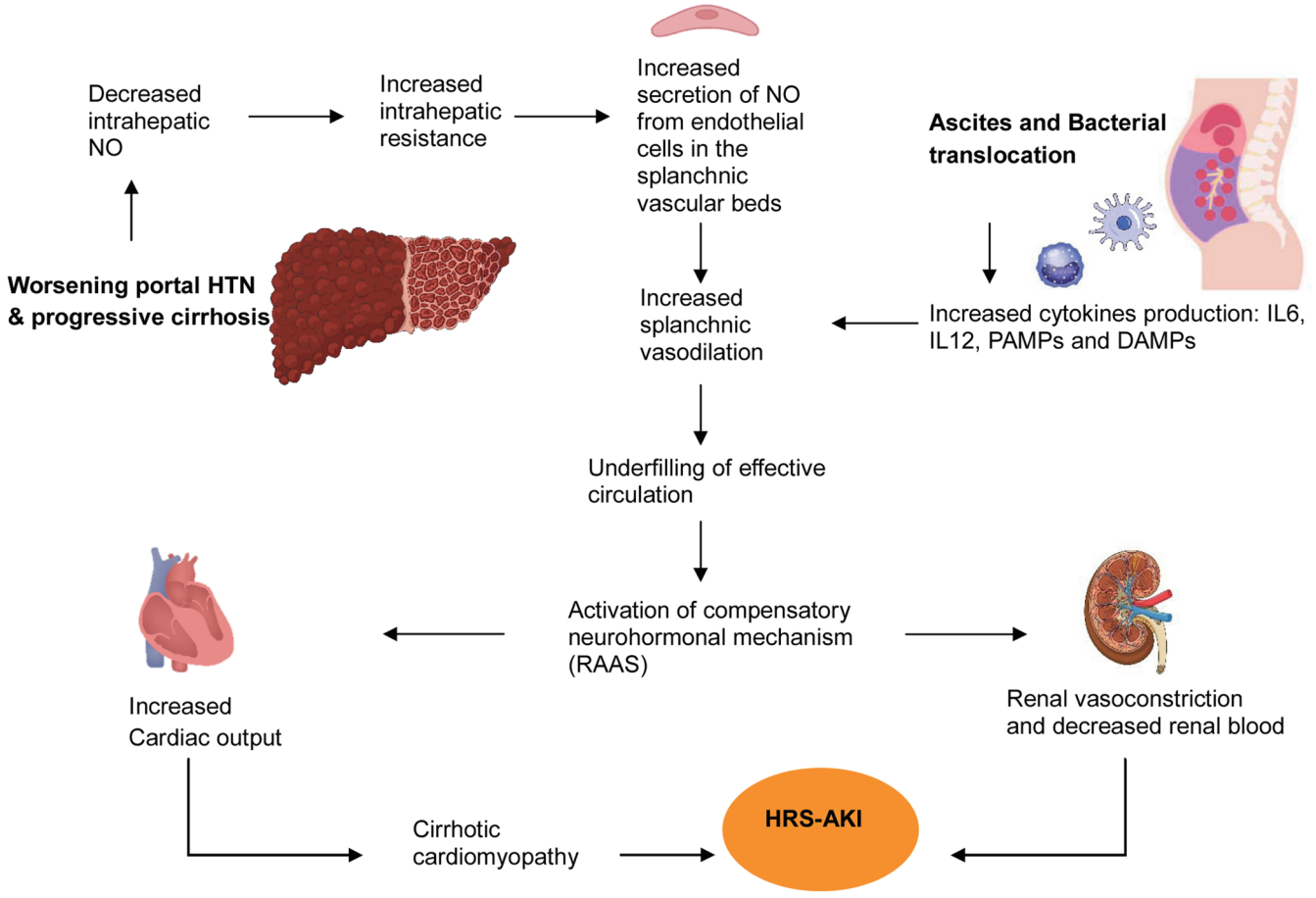

Fig. 1. Pathophysiology of the hepatorenal syndrome acute kidney injury (HRS-AKI). The progressive worsening of liver cirrhosis and portal hypertension (HTN) decreases intra-hepatic nitric oxide (NO), which is counterbalanced by increased NO secretion from adjacent endothelial cells. Bacterial translocation from ascites and gut barrier disruption lead to increased production of inflammatory cytokines and mediators into the systemic circulation, including interleukin (IL) 6 and 12, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs). Both processes lead to splanchnic vasodilation, decreased systemic vascular resistance, and underfilling of the effective circulation. A compensatory mechanism occurs, and the renin-angiotensin-aldosterone system (RAAS) is activated, causing increased water retention, heart rate, and cardiac output. This increases renal vasoconstriction and decreases renal blood flow (RBF). Persistent vasodilation ultimately leads to renal hypoperfusion, sustained renal vasoconstriction, and may also contribute to cirrhotic cardiomyopathy, all contributing to the development of HRS-AKI. DAMPs, damage-associated molecular patterns; HRS-AKI, hepatorenal syndrome acute kidney injury; IL, interleukin; NO, nitric oxide; PAMPs, pathogen-associated molecular patterns; Portal HTN, portal hypertension; RAAS, renin-angiotensin aldosterone system; RBF, renal blood flow.

HRS-AKI, 63 had hypovolemia-induced AKI, and 44 had no kidney injury. The authors used a multiplex cytokine assay to detect 18 cytokines and vascular adhesion molecules, including interferon gamma, IL-6, IL-8, IL-10, vascular endothelial growth factor (VEGF), and vascular cell adhesion molecule-1. Levels of systemic inflammatory mediators, leukocytes, and serum CRP were higher in the HRS group compared to controls. Patients with HRS-AKI had significantly elevated levels of cytokines such as monocyte chemoattractant protein-1, IL-6, IL-8, and vascular cell adhesion molecule-1, indicating increased systemic inflammation and altered cytokine production compared to patients with decompensated cirrhosis without kidney injury or those with AKI due solely to volume depletion. Additionally, the inflammatory response was not associated with active infection or acute-on-chronic liver failure (ACLF). Increased inflammation was most commonly correlated with HRS rather than ACLF. Patients with HRS-AKI without ACLF showed similar cytokine levels to those with HRS-AKI and ACLF. Furthermore, cytokine levels were not correlated with ACLF severity. However, IL-10 levels beyond the detection range were not assessed in this study, and the sample size was small.[52]

Systemic hypotension and compensatory response: Systemic arterial hypotension, low peripheral vascular resistance, and increased cardiac output can trigger a compensatory homeostatic response that leads to systemic vasoconstriction and volume expansion through activation of the RAAS, sympathetic nervous system, and release of arginine vasopressin to maintain normal arterial pressure. However, adverse consequences can result, including sodium and water retention and decreased free water excretion, which causes dilutional hyponatremia. In late stages, marked vasoconstriction leads to decreased GFR and HRS.[53] This compensatory mechanism can ultimately result in circulatory dysfunction and cirrhotic cardiomyopathy, which can contribute to the development of HRS due to decreased effective circulatory volume.[54] Nazar *et al*. demonstrated that diastolic dysfunction was found in 50–60% of patients with cirrhosis. However, the authors did not explain the correlation between cirrhotic cardiomyopathy and the severity of HRS.[55]

Ruiz-del-Arbol *et al*. investigated circulatory function in patients with cirrhosis before and after the development of

HRS. They followed 66 patients who had cirrhosis and tense ascites but normal kidney function, 27 of whom developed HRS. The HRS group had significantly higher hepatic venous pressure gradients, plasma renin activity, and serum norepinephrine levels. Mean arterial pressure and cardiac output were lower compared to their baselines in patients who developed HRS. The authors demonstrated that plasma renin activity and cardiac output were the only independent predictors of HRS. The study had a small number of patients.[11]

Prostaglandins and vasoconstriction: Another consequence of unopposed vasoconstriction is decreased production of endogenous prostaglandins. Rimola *et al*. investigated the excretion of prostaglandin I2, E2, and thromboxane A2 in 18 normal subjects, 49 patients with cirrhosis without renal dysfunction, and 20 patients with renal failure. Excretion of these prostaglandins in patients with cirrhosis and renal dysfunction was significantly lower compared to patients with renal failure without cirrhosis. Additionally, cirrhotic patients had significantly higher levels of plasma renin activity, plasma antidiuretic hormone, and norepinephrine. However, this study was conducted before the formulation of the current definition of hepatorenal syndrome and its diagnostic criteria.[56]

Gines *et al*. investigated whether the administration of prostaglandins could improve renal function in 16 cirrhotic patients with renal failure. After the administration of oral misoprostol or intravenous prostaglandin E2, there were no significant changes in glomerular filtration rate, sodium excretion, or free water clearance. Additionally, patients did not exhibit an improved natriuretic response to diuretics. Supplemental prostaglandin E2 did not improve renal function in patients with cirrhosis. A weakness of this study was the very small patient sample.[57]

Preclinical studies

Preclinical studies have shown that hyperammonemia in a bile duct ligation (BDL) biliary cirrhosis model leads to up-regulation of renal arginase-2 and down-regulation of argininosuccinate synthase, causing intracellular arginine deficiency. Because arginine is an important substrate for NO synthesis, its deficiency decreases endothelial nitric oxide synthase (eNOS) levels, resulting in tubular dilation, tubulointerstitial nephritis, and impaired microvascular flow. Furthermore, in human cultured proximal tubular cells, hyperammonemia upregulated arginase-2 and increased markers of tubular cell injury. Genetic deletion of arginase-2 reduced kidney injury and protected renal microcirculation. However, these findings may not apply to other cirrhosis etiologies and HRS.[58]

Management of HRS

Vasoconstrictors plus albumin infusion: Treatment of HRS remains very challenging. Several randomized trials have demonstrated the benefit of albumin infusion to increase effective circulation volume when combined with vasoconstrictors, especially terlipressin, to counteract splanchnic vasodilatation. This management is often considered a stabilization bridge to liver transplant.[59,60] In a multicenter double-blinded study, Wong *et al*. assigned 300 patients with HRS in a 2:1 ratio to either receive terlipressin and albumin or placebo for 14 days. In the terlipressin group, 32% of patients experienced reversal of HRS compared to only 17% in the placebo arm. However, serious complications including cardiac ischemia, intestinal ischemia, and respiratory failure were more frequent in the treatment arm. The 90-day mortality rate due to respiratory failure was higher in the terlipressin group (11% vs. 2% in the placebo group). The authors used a composite primary endpoint for HRS, defined as two consecutive serum creatinine measurements ≤ 1.5 mg/dL by day 14, absence of renal replacement therapy for 10 days, and survival for at least 10 days, which strengthened the clinical significance of kidney function improvement. Limitations included a lack of follow-up beyond the 90-day study period and therefore, a lack of assessment of long-term outcomes. Additionally, the trial was not powered to assess between-group differences in survival.[61]

Another study demonstrated the benefit of midodrine and octreotide combined with albumin infusion in restoring renal function in 40% of patients. However, the sample size was very small with only 13 patients enrolled.[62] A randomized controlled trial by Cavallin *et al*. showed that renal recovery was more likely in patients who received terlipressin plus albumin compared to those who received albumin, octreotide, and midodrine (70.4% vs. 28.6%). However, randomization in the study was not optimal for ethical reasons, as some non-responders received rescue treatment, including crossover from one study regimen to another.[63] A small randomized controlled trial indicated that norepinephrine might have efficacy similar to terlipressin in improving renal function in HRS. Norepinephrine is inexpensive but must be administered in an intensive care unit under close hemodynamic surveillance.[64] Unfortunately, treatment with vasoconstrictors plus albumin has questionable long-term mortality benefits.[62,63]

Molecular adsorbent recirculation system: The molecular adsorbent recirculating system (MARS) is a modified dialysis technique that can remove albumin-bound toxins, serum bilirubin, and ammonia. Although earlier studies showed improvements in biochemical derangements in patients with cirrhosis, the actual benefit of MARS on survival is unproven.[65] Banares *et al*. reported on a large randomized controlled trial using MARS in patients with ACLF. The study randomized 189 patients, of whom 58 had HRS, to receive either standard medical therapy alone or in addition to MARS. The primary endpoint was liver transplantation-free survival within 28 days. Patients treated with MARS showed significant decreases in bilirubin levels. However, there were no statistically significant decreases in serum creatinine levels and no improvement in short- or mid-term survival between the two groups. The study had a small sample size.[66] In 10 patients with HRS who received MARS treatment, there was a significant decrease in bilirubin and creatinine levels without changes in hemodynamic parameters. The study's value was limited by the very small number of patients, but the results were consistent with findings from previous studies.[67]

Effects of TIPS on renal function in patients with HRS

A prospective study by Testino *et al*. assessed the effects of TIPS in 18 patients with refractory ascites and HRS Type 2. The authors compared serum creatinine, creatinine clearance, sodium excretion, and urine volume before intervention and 12 weeks after TIPS. Complete resolution of ascites was achieved in 10 patients, while a partial response was seen in the remaining eight patients. Significant improvement in renal parameters was observed in all patients. The authors suggested that TIPS could be an option in the treatment of HRS as a bridge to orthotopic liver transplantation. However, the study did not assess long-term mortality outcomes, and the sample size was small.[68]

Guevara *et al*. evaluated the effects of TIPS on renal function and vasoactive systems in seven patients with HRS Type 1. Parameters such as GFR, renal plasma flow, plasma renin activity, norepinephrine, aldosterone, and endothelin levels were compared before, and 7 and 30 days after the procedure. There was a marked decrease in portal pressure gradi-

ents in all patients. The authors demonstrated very slow but significant improvement in renal function after one month, with GFR and renal plasma flow increasing two- or three-fold. Activity of RAAS and the sympathetic nervous system was significantly suppressed after TIPS, with decreased plasma renin activity, aldosterone, and norepinephrine levels. Six patients showed significant increases in free water clearance and urine sodium. Despite the improvement in kidney function, five patients died within nine, 22, 35, 45, and 102 days after insertion. The results were based on a small number of patients, and there was no control group included, limiting the validity of the study.[69]

Brensing *et al*. studied TIPS in 41 patients diagnosed with HRS. Fourteen had HRS Type 1, and 17 had HRS Type 2, receiving TIPS. Ten patients were excluded due to advanced liver failure and decreased liver residual capacity. TIPS significantly reduced portal pressure gradient and increased creatinine clearance and sodium excretion. The three-, six-, and 12-month survival rates in the TIPS group were 81%, 71%, and 48%, respectively, while only one patient in the non-TIPS group survived beyond three months. Hemodialysis was withdrawn in four out of seven patients, who survived at least 10 months. However, there was one procedure-related death (3.2%). The study had a small number of patients, and 25% of high-risk patients were not included, which might have affected the outcomes.[70]

Wong *et al*. assessed the effects of combined vasoconstrictor therapy, albumin, and TIPS in 14 patients with HRS Type 1 treated with a combination of midodrine, octreotide, and albumin for 14 days. Medical therapy improved renal function and sodium excretion in 10 of the 14 patients. Five patients who received TIPS showed improved renal function and sodium excretion to a normal range within 12 months. Furthermore, the authors demonstrated a decrease in renin and aldosterone levels and elimination of ascites. Despite the small sample size, the study showed a potential effect of TIPS on maintaining kidney function in patients with HRS after medical optimization rather than solely being an alternative to medical optimization.[71]

A meta-analysis by Song *et al*. included nine publications and 128 patients with HRS who received TIPS. The study demonstrated that after TIPS, patients had significant improvements in serum creatinine, blood urea nitrogen, serum sodium, and urine excretion. Renal function improved in 93% of HRS Type 1 and 83% of HRS Type 2 patients. The pooled survival rates after one year were 47% in HRS Type 1 and 64% in HRS Type 2 patients. No procedure-related mortality was observed.[72]

In nine patients with acute alcoholic hepatitis and HRS Type 1, Testino *et al*. investigated the effects of TIPS on renal function and mortality. There was a significant improvement in serum creatinine, BUN, and urine volume. Changes in serum or urine sodium were not significant.[73]

Ponzo *et al*. retrospectively studied the effects of TIPS in 212 patients, of whom 41 met the criteria for HRS-CKD. Patients with previous liver transplantation or unresolved AKI at the time of TIPS placement were excluded. All patients had resistant or intractable ascites and were followed for a year after TIPS placement. Serum creatinine decreased significantly one week after the procedure (from 1.94 ± 0.54 mg/dL to 1.37 ± 0.23 mg/dL). Improvement in renal function was significant in all CKD stages and remained stable in subsequent assessments, although none returned to baseline. In the 12-month follow-up, 17 patients were alive, 11 had liver transplants, and 12 died (29%). One patient was lost to follow-up. This was the first study to examine the effects of HRS-CKD with new criteria. The authors excluded patients who had AKI before TIPS placement. Limitations included a single-center study and a retrospective design. The study demonstrated the potential use of TIPS in HRS-CKD.[74]

As of this writing, Ripoll *et al*. are conducting a randomized controlled trial comparing the effectiveness and safety of TIPS placement in patients with HRS-AKI with standard treatment of vasopressin and albumin. The main endpoint is 12-month liver transplant-free survival. In the TIPS group, the procedure will be performed within 72 h of diagnosis, and patients will be weaned off terlipressin and albumin after placement. This study is important as it will clarify whether TIPS could potentially be incorporated into routine clinical practice for managing patients with HRS-AKI.[75]

HPS

Definition and epidemiology

HPS is defined as hypoxemia secondary to pulmonary vascular dilatation in patients with liver disease and portal hypertension or congenital portosystemic shunts. The prevalence of HPS in patients with end-stage liver disease reportedly ranges between 5% and 32%. HPS is characterized by the clinical triad of liver disease, arterial hypoxia, and intrapulmonary vasodilation.[76] Other less common causes of HPS include non-cirrhotic portal hypertension, extrahepatic pulmonary fibrosis, and acute hepatitis.[77] Non-Hispanic white patients have been reported to be more likely to develop HPS compared to other groups.[78] There are data supporting the association of the development of HPS with variations in genes encoding Von Willebrand factor and endoglin, a transmembrane auxiliary receptor for transforming growth factor-β, which are involved in vascular growth and development.[79]

Pathophysiology of HPS

Chronic liver disease and cirrhosis may lead to hypoxemia through various mechanisms. HPS is primarily caused by intrapulmonary vasodilation, whereas porto-pulmonary hypertension results from pulmonary vasoconstriction. It is crucial to differentiate between these conditions despite their potential to cause similar clinical presentations.[80] Hypoxemia in HPS is mainly due to ventilation-perfusion mismatch, diffusion defects in dilated pulmonary beds, and the presence of arterial-venous communications.[81,82] The underlying pathophysiology of this microvascular alteration is thought to involve vasodilation attributed to increased levels of circulating endothelin-1, nitric oxide, and carbon monoxide. Bacterial translocation and endotoxemia may exacerbate vasodilation. Pulmonary angiogenesis is another significant contributor to impairment of the diffusion process (Fig. 2).[81–83]

HPS occurs more commonly in patients with advanced cirrhosis compared to those with early-stage cirrhosis.[84] Elevated plasma levels of endothelin-1 increase the production of eNOS by acting on endothelin B-receptors on endothelial cells.[85] Additionally, bacterial translocation in the lungs increases iNOS by accumulating macrophages in the lungs.[76] These processes result in significant vasodilation, creating intrapulmonary shunts and hyperdynamic circulation.[79–81] Another critical mechanism in the development of HPS involves the activation of angiogenic growth factors such as VEGF, which promotes angiogenesis and exacerbates hyperdynamic circulation, leading to alveolar dysfunction.[80] VEGF-A and placental growth factor belong to the VEGF family and are produced by monocytes, triggering a cellular cascade by binding to tyrosine kinase receptors on the cell surface. VEGF-A binds to VEGF receptor 2, responsible for pro-angiogenic

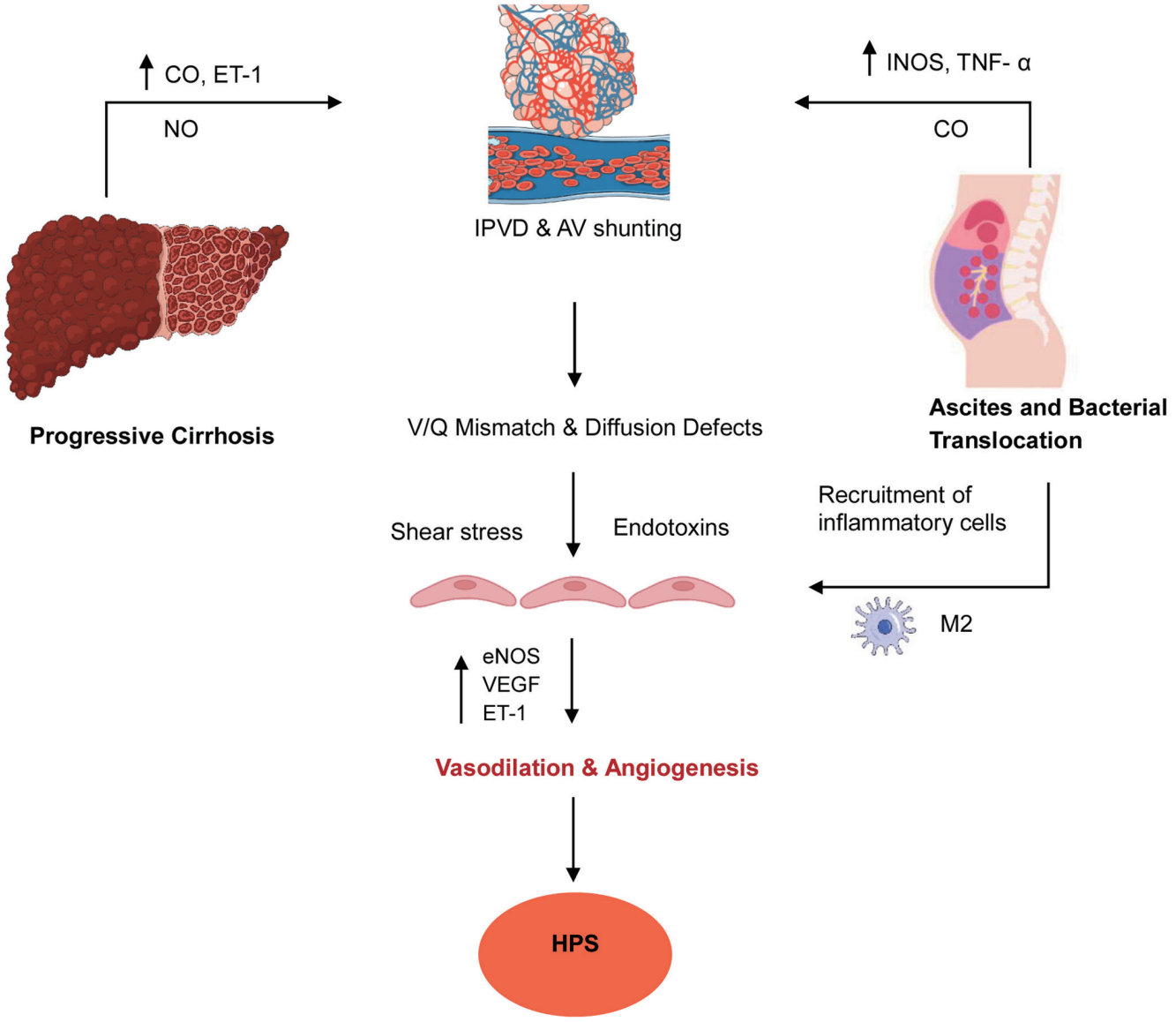

Fig. 2. Pathophysiology of Hepatopulmonary syndrome (HPS). Elevated plasma levels of endothelin-1 (ET-1) in combination with HPS increase endothelial nitric oxide synthase (eNOS) production by acting on endothelin B-receptors on endothelial cells. Additionally, bacterial translocation in the lungs increases inducible nitric oxide synthase (iNOS) through macrophage accumulation, resulting in significant nitric oxide (NO)-mediated vasodilation, intrapulmonary shunts, and hyperdynamic circulation. Another important mechanism in HPS involves activation of vascular endothelial growth factor A (VEGF-A), which promotes angiogenesis, worsens hyperdynamic circulation, and contributes to alveolar dysfunction. Progressive liver cirrhosis and subsequent gut barrier disruption increase production of vasodilators such as carbon monoxide (CO), endothelin 1 (ET-1), tumor necrosis factor (TNF) α, iNOS, and NO, leading to potent vasodilation causing intrapulmonary vasodilation (IPVD) and arterial venous (AV) shunting. This process can result in ventilation-perfusion (V/Q) mismatch and diffusion defects. Furthermore, the shear stress from hyperdynamic circulation and recruitment of inflammatory cells as macrophages type-2 (M2) affect endothelial cells, increasing their production of eNOS, VEGF, and ET-1 that exerts its action on ET-B receptors, further promoting vasodilation and angiogenesis, all contributing to HPS development. AV, arterial venous; CO, carbon monoxide; eNOS, endothelial nitric oxide synthase; ET-1, endothelin 1; ET-B, endothelin B; HPS, hepatopulmonary syndrome; iNOS, induced nitric oxide synthase; IPVD, intrapulmonary vasodilation; M2, macrophages type-2; NO, nitric oxide; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; V/Q mismatch, ventilation-perfusion mismatch.

signaling.[86] Although experimental studies have shown an increase in angiogenic growth factor levels, the exact mechanism of their activation and the role of angiogenic pathways in gas exchange abnormalities in HPS remain unclear.[83] In a randomized double-blinded controlled trial, Kawut *et al*. evaluated the effects of sorafenib, a tyrosine kinase inhibitor, in patients with HPS. They included 30 patients with HPS who received 400 mg of sorafenib daily and 30 patients without HPS who received placebo treatment. The primary endpoint was a reduction in the alveolar-arterial oxygen gradient after 12 weeks in patients with HPS. Secondary endpoints included the degree of intrapulmonary shunting and exercise capacity. The authors found no effects of sorafenib on the alveolar-arterial oxygen gradient or the degree of intrapulmonary shunting, despite reducing circulating levels of VEGFR-1 and 2. Patients did not experience improvements in exercise capacity or dyspnea symptoms. The study had several limitations, including a small number of HPS patients.

Additionally, many patients underwent liver transplantation, necessitating their withdrawal from the study. Nevertheless, the observation that targeting an important component of the angiogenesis pathway in HPS did not improve outcomes supports the conclusion that other pathways may play more significant roles.[87]

Animal models of HPS

Experimental rat models showed that cholestatic cirrhosis secondary to BDL led to HPS with intrapulmonary vascular dilatation (IPVD).[88] There was an association between increased activity and production of eNOS and NO in BDL rats and the development of IPVD and subsequent shunting.[89] Ling *et al*. demonstrated an increase in hepatic and plasma endothelin-1 (ET-1) within one week of BDL, which persisted for three weeks. ET-1, elevated in humans with decompensated cirrhosis,[90] acts on the endothelin B receptor (ET-B) of endothelial cells, leading to up-regulation of eNOS and increased NO production. The authors showed that eNOS and ET-B receptor levels increased in the pulmonary vasculature, corresponding with the development of HPS.[91] However, whether the mechanisms of increased ET-1 in experimental HPS with BDL are the same in humans with cirrhosis and HPS has not been proven.[92] Both shear stress and targeted overexpression of ET-B in pulmonary microvascular endothelial cells resulted in enhanced eNOS activation through calcium-mediated pathways.[93]

Stzyrmf *et al*. demonstrated that rat models with bacterial translocation and increased plasma TNF-α had higher recruitment of macrophages in lung tissues. This recruitment was associated with a higher incidence and severity of HPS than in rats without bacterial translocation.[94] However, increased production of TNF alone in thioacetamide cirrhosis model studies did not promote the development of molecular or pathological evidence of HPS.[95] In a BDL model, prevention of gram-negative bacterial translocation decreased the severity of HPS in rats. The percentage of macrophages in pulmonary vasculature, iNOS levels, and IPVD were significantly decreased in antibiotic-treated rats compared to those that were not treated.[96]

Chen *et al*. demonstrated that M2 macrophages accumulated after administration of granulocyte-macrophage colony-stimulating factor and monocyte chemoattractant protein-1. This led to increased pulmonary fibrosis, progressive vascular dilation, hypoxemia, and subsequent development of HPS in BDL mice. This highlighted the role of M2 macrophages in pulmonary angiogenesis and fibrosis leading to HPS.[97]

A study by Chang *et al*. assessed the effects of sorafenib, a multi-kinase inhibitor, in BDL rats compared to a control group that received placebos. The study showed that animals treated with anti-angiogenesis therapy had decreased alveolar-arterial oxygen gradients, reduced VEGF levels, and significantly decreased intrapulmonary shunting.[98]

Diagnosis of HPS

The criteria proposed for the diagnosis of HPS include the presence of liver disease, arterial hypoxemia defined as an arterial oxygen pressure (PaO_2) level below 80 mmHg, and an elevated alveolar-arterial oxygen gradient exceeding 15 mmHg or more than 20 mmHg detected by arterial blood gas analysis in a seated position in patients over 64 years old. A hallmark finding in HPS is IPVD, which can typically be assessed using contrast-enhanced echocardiography. Under physiological conditions, injected contrast creates bubbles that are trapped in the pulmonary vascular bed. In contrast, in patients with HPS, the bubbles bypass the pulmonary circulation and are seen on the left side of the circulation. The presence of IPVD can also be diagnosed using the macroaggregated albumin lung perfusion scan and pulmonary arteriography. However, contrast-enhanced echocardiography remains the gold standard for screening for HPS.[99]

Management of HPS

Liver transplantation remains the only known and approved effective therapy for HPS. Gupta *et al*. assessed the outcomes of 21 HPS patients who underwent liver transplantation, among whom 11 had severe HPS defined as arterial oxygen less than 50 mmHg on room air. The overall mortality rate was 4.7% (1/21), with a mortality rate of 9% (1/11) in severe HPS cases. Peri-transplant hypoxic respiratory failure occurred in 24% of the patients. Post-transplantation, oxygenation improved in all 19 patients with recorded results. Their PaO_2 increased from 52.2 ± 13.2 to 90.3 ± 11.5 mmHg on room air. The study had a small sample size and was retrospective.[100]

Iyer *et al*. evaluated 106 patients with HPS, of whom 49 underwent liver transplantation (LT). Post-transplant survival at 1, 3, 5, and 10 years did not differ between groups based on the severity of HPS or the degree of hypoxemia at baseline. The 10-year survival rate in HPS patients who underwent liver transplantation was 64%. The study had a larger number of patients compared to prior studies in the literature but was a retrospective single-center study. The subsequent management of these patients was not controlled in the study and may have affected the long-term outcomes and non-LT outcomes.[101]

In a prospective analysis, Pacasio *et al*. evaluated 316 cirrhotic patients for LT, among whom 177 underwent LT. Among these patients, 25.6% had HPS, with the majority (92.6%) having mild to moderate HPS. In patients with or without HPS, the mortality rates were not significantly different between those on the LT waiting list and those post-LT. Importantly, HPS was reversed in all cases after LT. The study demonstrated the absence of increased overall mortality in patients with HPS, suggesting that systemic prioritization policies should be avoided in these patients. The study was a single-center study and lacked cases of severe HPS.[102]

Methylene blue, pentoxifylline, aspirin, somatostatin, garlic, indomethacin, and mycophenolate mofetil have been studied without demonstrating benefit in HPS.[99]

Effects of TIPS on pulmonary function in hepatic decompensation in the absence of HPS

Theoretically, TIPS could increase vasodilatory effects by diverting NO-rich blood from the splanchnic circulation to the pulmonary vessels, resulting in alveolar vascular dilation and increased blood flow, and worsening ventilation-perfusion mismatch.[25–27] No studies have specifically focused on pulmonary function after TIPS in cases of hepatic decompensation in the absence of HPS. However, several series have studied such patients as controls for those with HPS. A case series assessed the impact of TIPS on pulmonary gas exchange in seven patients with hepatic decompensation, of whom three had severe HPS, and four controls did not have HPS. Pulmonary function was assessed before and after TIPS. All patients underwent measurements of forced spirometry, plethysmography, and single carbon monoxide diffusion capacity. Patients with hepatic decompensation but without HPS had stable pulmonary function tests and gas exchange data after TIPS placement. The study suggested that TIPS did not alter pulmonary function in patients with decompensated cirrhosis in the absence of HPS. However,

the sample size was very small.[103]

A study by Denié *et al*. evaluated the effects of TIPS on tissue oxygenation in patients with cirrhosis without HPS. Sixteen patients with cirrhosis and refractory ascites were included, of whom eight received TIPS and the other group underwent paracentesis. Arterial and venous blood samples were obtained for all patients before the assigned procedure, and 12 days and four months afterward. Two patients died after TIPS placement, and one was lost to follow-up and excluded from the study. Before treatment, there was no significant difference between both groups in pulmonary function or oxygenation. The values of PaO_2 remained unchanged in patients with TIPS placement throughout the study. Additionally, patients in the TIPS group had higher PCO_2 and improved respiratory alkalosis. In patients who received paracentesis, PaO_2 decreased significantly after four months. The study had a very small sample size, and the age group of patients who received paracentesis was significantly higher.[104]

A retrospective study evaluated changes in arterial oxygenation after portal decompression in Budd-Chiari syndrome patients. Eleven patients with HPS and 14 patients without HPS were included in this study. Participants had arterial blood gases performed with patients upright and breathing room air at two to three days, one month, and three months after TIPS placement. The alveolar-arterial oxygen gradient in those patients without HPS remained comparable to baseline at all three points after the procedure. Pulmonary function tests were not performed after the procedure.[105]

In patients without pre-existing HPS, the limited available data indicate that TIPS does not appear to affect pulmonary gas exchange. However, there have been reports of increasing pulmonary pressures and worsening pulmonary hypertension.[106,107]

The effects of TIPS on pulmonary function in HPS

A case series assessed the impact of TIPS on pulmonary function in three patients with severe HPS. Pulmonary function tests were conducted before and after TIPS placement. Only one patient with HPS showed transient improvement in gas exchange, which was not sustained after a four-month period. The authors suggested that the change in patients with HPS was minimal, if any, and not persistent.[103]

Zhao *et al*. conducted a retrospective study on 81 TIPS patients with HPS and gastrointestinal bleeding. Among these patients, 30 had TIPS performed through the main portal vein (Group A), 24 through the left branch of the portal vein (Group B), and 27 through the right branch (Group C). The authors assessed PaO_2, oxygen saturation, outcomes, and adverse effects. In Group A, there was higher oxygen saturation postoperatively at 15 days and at the three-month follow-up. However, there was no significant difference observed between the 12-month postoperative follow-up and preoperative values. In Group C, there was no significant difference in PaO_2 and O_2 saturation at any point postoperatively. In Group B, all indicators at each follow-up time after TIPS demonstrated improvements in hypoxemia. A strength of this study was the relatively large number of cases. Additionally, the effects of TIPS were evaluated using three different approaches. However, it was a single-center retrospective study. The one-year survival rates were equivalent among the three groups, which underscores the transient nature of beneficial effects. Furthermore, patients were not stratified according to the severity of HPS. All patients included in the study had a PaO_2 of more than 60 mmHg in an upright position, indicating the absence of severe HPS before TIPS.[108]

Tsauo *et al*. conducted a retrospective study to evaluate the effects of TIPS on pulmonary gas exchange in 24 patients with Budd-Chiari syndrome, of whom 11 had HPS. HPS was diagnosed using contrast-enhanced echocardiography to identify intrapulmonary vascular dilation and arterial blood gas analysis showing arterial oxygenation defects. In patients with HPS, arterial blood gas analysis was performed at one- and three-month intervals. Symptomatically, 80% of patients with dyspnea reported improvement, but this effect was transient, disappearing after three months. The mean change in alveolar-arterial oxygen gradient was statistically significant after one month but not at three months. A lack of follow-up contrast-enhanced echocardiography or lung perfusion scan was a weakness.[105]

Tsauo *et al*. also conducted a systematic literature review including 10 studies and 12 patients with HPS who received TIPS, of whom eight had very severe HPS, two had severe, and two had moderate HPS. All patients received TIPS without complications. The portosystemic pressure gradient decreased in all patients. Oxygenation improved in nine patients, but this improvement was not sustained after four months in two patients. In three other cases, oxygenation did not change. One-third of the cases underwent LTs, and 3 patients died. The mean follow-up for the patients was nine months, which was insufficient to provide long-term mortality or morbidity estimates.[109]

For patients with HPS, the effects of TIPS on pulmonary gas exchange were inconsistent, and beneficial effects were transient. However, no studies have shown a persistent decline in pulmonary function.

Conclusions

Few studies have specifically compared the renal effects of TIPS in patients with hepatic decompensation with and without HRS. The available evidence indicates that TIPS often improves renal function in patients with portal hypertension, with or without HRS, and no studies have shown persistent decreased renal function after TIPS. However, these data are insufficient to support a recommendation for the use of TIPS specifically for HRS. Due to the extent of liver damage, patients with HRS often have liver function too compromised to tolerate TIPS. In patients without pre-existing HPS, TIPS does not appear to significantly affect pulmonary gas exchange. Studies of TIPS in HPS have been inconsistent; while some studies showed improvement, the effects were transient. No studies have shown a persistent decline in pulmonary function after TIPS.

Current management consists of supportive medical care, with liver transplantation being the only current definitive long-term treatment for HRS and HPS. In terms of future research directions, the evidence supports the advisability of large randomized controlled trials on the beneficial effects of TIPS for HRS. Similar supportive data are less clear for HPS.

Novel aspects of this review include: 1) laboratory evidence on the effects of TIPS on renal and pulmonary function in patients with hepatic decompensation with and without HRS or HPS, respectively, 2) evidence that TIPS does not impair renal or pulmonary function in cases of hepatic decompensation, 3) evidence that supports large randomized controlled trials on the beneficial effects of TIPS for HRS. However, for HPS, evidence of benefit is less clear, and 4) discussion of possible mechanisms that may explain the apparent differences in the benefit of TIPS in HRS versus HPS.

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Conflict of interest

GYW has been an Editor-in-Chief of the *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflicts of interest related to this publication.

Author contributions

Proposing concept for review and revising manuscript critically (GYW), collecting relevant information, drafting the article, and revising the manuscript with critical revisions (AHA, MA). All authors have approved the final version and the publication of the manuscript.

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