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REVIEW

The role of transjugular intrahepatic portosystemic shunt in patients with cirrhosis and ascites: Recent evolution and open questions

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Abstract

In selected patients with cirrhosis and ascites, transjugular intrahepatic portosystemic shunt (TIPS) placement improves control of ascites and may reduce mortality. In this review, we summarize the current knowledge concerning the use of TIPS for the treatment of ascites in patients with cirrhosis, from pathophysiology of ascites formation to hemodynamic consequences, patient selection, and technical issues of TIPS insertion. The combination of these factors is important to guide clinical decision-making and identify the best strategy for each individual patient. There is still a need to identify the best timing for TIPS placement in the natural history of ascites (recurrent vs. refractory) as well as which type and level of renal dysfunction is acceptable when TIPS is proposed for the treatment of ascites in cirrhosis. Future studies are needed to define the optimal stent diameter according to patient characteristics and individual risk of shunt-related side effects, particularly hepatic encephalopathy and insufficient cardiac response to hemodynamic consequences of TIPS insertion.

Abbreviations: AKI, acute kidney injury; BNP, brain natriuretic peptide; CCM, cirrhotic cardiomyopathy; CO, cardiac output; DIPS, direct intrahepatic portocaval shunt; FIPS, Freiburg index of post-TIPS survival; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; IVC, inferior vena cava; LVP, large volume paracentesis; MELD, Model for End-Stage Liver Disease; NAKI, non-AKI; NO, nitric oxide; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAMP, pathogen-associated molecular pattern; PCPG, porto-cava pressure gradient; PHT, portal hypertension; PTFE, polytetrafluoroethylene; PV, portal vein; PVT, portal vein thrombosis; RA, refractory ascites; RCT, randomized controlled trial; SVR, systemic vascular resistance; TIPS, transjugular intrahepatic portosystemic shunt.

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INTRODUCTION

Ascites is the most common cause of decompensation in compensated cirrhosis with an annual estimated incidence of 5%–10% of patients.[1] The occurrence of ascites significantly impairs prognosis with 1- and 5-year mortality rates around 30% and 70%, respectively.[1,2] Once ascites becomes refractory, median survival is reduced to 6 months.[1]

In patients with cirrhosis and ascites, the standard of care combining salt restriction, diuretics, and large volume paracentesis (LVP) is merely symptomatic and does not modify the natural course of the disease. Hence, therapeutic alternatives are required. The most promising approach is intrahepatic portosystemic shunting, usually using a transjugular approach. Transjugular intrahepatic portosystemic shunt (TIPS) has proven effective when placed in the setting of refractory ascites (RA) or even at earlier stages when ascites requires frequent paracenteses (i.e., recurrent ascites). In addition to improved control of ascites in a significant number of patients, current evidence suggests that, in selected patients, TIPS is also associated with improved survival.[3] However, the use of TIPS faces several challenges. First, TIPS can be harmful in patients with severe liver failure and should be considered with caution in those patients. Second, accurate predictive models that are able to precisely assess the prognosis of patients with ascites after TIPS insertion are lacking. Third, a number of nonhepatic factors, including heart and kidney function, have to be taken into consideration when TIPS is discussed for treating ascites. Fourth, several technical issues, such as the optimal stent diameter that should be used for portocaval shunting, are still unsettled. This review focuses on the pathophysiological consequences of TIPS placement, selection of candidates for TIPS, and technical considerations of intrahepatic portocaval shunting for the treatment of ascites in patients with cirrhosis.

BRIEF OVERVIEW OF THE PHYSIOPATHOLOGY OF ASCITES FORMATION IN CIRRHOSIS

Development of portal hypertension (PHT) and retention of sodium and water are the main factors involved in the pathogenesis of ascites formation. The starting point is the development of PHT due to increased resistance to portal outflow. Increases in resistance can be located at any point in the liver circulation, either before the sinusoids (presinusoidal PHT), at the sinusoidal level (sinusoidal PHT), or after the sinusoids (postsinusoidal PHT). In Western countries, 90% of PHT is related to cirrhosis that is responsible for a sinusoidal bloc. In this setting, ascites does not develop at a porto-cava pressure gradient (PCPG; i.e., the difference between portal and systemic vein pressure) below 10–12 mmHg.[4–6]

Architectural changes are the main mechanism underlying increased intrahepatic resistance to portal flow in the cirrhotic liver. Another mechanism is related to phenotypic changes of hepatic stellate cells that become activated and contractile due to a reduction in the bioavailability of nitric oxide (NO) and additional vasodilators within the hepatic lobule. This also makes hepatic stellate cells more susceptible to local and systemic vasoconstrictors, thereby leading to an additional functional increase in vascular resistance.[7,8] According to the classical vasodilation hypothesis of PHT, increased portal pressure induces shear stress that stimulates the endothelial production of vasodilators, including NO, in the splanchnic vascular bed. Furthermore, increased portal pressure leads to the synthesis of angiogenic factors, such as vascular endothelial growth factor, which promote opening of preexisting portosystemic shunts and formation of new shunts through which vasodilators enter the systemic circulation.[7,9,10] Together, these mechanisms induce a gradual reduction of effective arterial blood volume which, in turn, activates the sympathetic nervous system, the renin-angiotensin-aldosterone axis, and secretion of arginine-vasopressin. These mechanisms act to expand the total blood volume and promote a compensatory increase in cardiac output (CO).[11,12]

The development of cirrhotic cardiomyopathy (CCM)[13] impairs the ability of the heart to maintain adequate CO in response to the progressive decrease in effective arterial blood volume, which further induces kidney hypoperfusion and sodium and water retention. This ultimately results in ascites formation and hyponatremia. The progressive worsening of these mechanisms ultimately leads to RA, which is characterized by a sustained and severe reduction of effective arterial blood volume. In fact, patients with RA are at increased risk of developing complications due to reduced blood volume, such as hepatorenal syndrome (HRS).[14]

In addition to liver architectural/functional changes and hemodynamic derangement, systemic inflammation and immune system activation may contribute to PHT progression in cirrhosis.[12] Based on the observation that patients with decompensated cirrhosis show high levels of proinflammatory markers, the "inflammatory hypothesis" has been recently proposed[15] as an integration of the classical vasodilation hypothesis of PHT progression and development of decompensation.[12] According to this hypothesis, increased intestinal permeability driven by PHT may lead to translocation of bacteria or their products, such as bacterial DNA or lipopolysaccharides (pathogen-associated molecular patterns [PAMPs]), which leads to local and systemic inflammation.[16] Inflammation driven by bacteria and PAMPs is further aggravated by the release of damage-associated molecular patterns due to

ongoing chronic liver injury.[17] Taken together, these events contribute to the induction of NO synthase in artery muscle cells, resulting in additional NO production and further aggravation of splanchnic vasodilation. Proinflammatory molecules and reactive oxygen species can cause tissue hypoperfusion and organ damage. These factors all contribute to the perpetuation of the vicious cycle responsible for PHT and related complications (Figure 1).

PATHOPHYSIOLOGICAL CONSEQUENCES OF TIPS PLACEMENT IN PATIENTS WITH ASCITES

The hemodynamic consequences of TIPS placement can be classified as early (within hours after TIPS placement) or late (within months after TIPS placement).

Early hemodynamic consequences following TIPS placement

TIPS acts as a low resistance conduit that redirects the blood flow from portosystemic collaterals (at least those at higher resistance than TIPS) toward the portal vein (PV).[18,19] By directly connecting the PV to the inferior vena cava (IVC), TIPS is very effective for reducing the PCPG (approximately -60% in previous studies including patients with ascites).[20–26]

The return of shunted blood to the right atrium creates an increase in heart preload that, depending on diastolic and systolic cardiac reserve, raises CO.[13,27–29] Increased CO leads to a progressive expansion of the splanchnic arterial vascular bed due to endothelial shear stress,[30–32] which, in turn, increases the blood inflow toward the PV and right atrium.[9,33]

In parallel, the sudden decrease of portal pressure reduces the barrier to splenic vein outflow (i.e., resistance to the blood flow in the splenic vein), which increases PV blood inflow. Depending on the size of the spleen and, therefore, the amount of blood entering the splenic vein, this mechanism may further contribute to the return of blood from the splanchnic circulation to the right heart.[34,35]

In fact, direct measurements of PV blood flow after opening of TIPS show an immediate increase of 64% with a mean absolute increase from 691 to 1136 ml/min.[18] On the other hand, increased CO also leads to arterial vasodilation of nonsplanchnic vascular beds.[36] Therefore, the splanchnic and peripheral vasodilatory response to increased CO, which is measured by a decrease in systemic vascular resistance (SVR),[27,29,37] may cause a worsening of a pre-existing hyperdynamic circulation[38] or generate a new relative hyperdynamic state in patients without baseline features of hyperdynamic circulation (i.e., higher CO and lower SVR, respectively, than normal range in patients without PHT).[28,39,40]

In response to the increase in CO and to the decrease in SVR, cardiac and central vascular blood volume does not change immediately after TIPS deployment.[37,41] This explains why the mean arterial pressure remains unchanged[27,37,42] and renal blood flow does not substantially increase in the hours after TIPS creation.[37,43]

The final amount of blood shunted by the TIPS will depend on two additional factors: stent-graft diameter and cardiac reserve. A small increase in stent-graft diameter will have a quadratic effect on its area and thereby significantly reduce resistance to blood flow (Figure 2). In parallel, the sudden increase in venous return to the heart may unmask an underlying cardiomyopathy,[13] which would lead to an abrupt increase of right atrium and IVC pressure.[38,44]

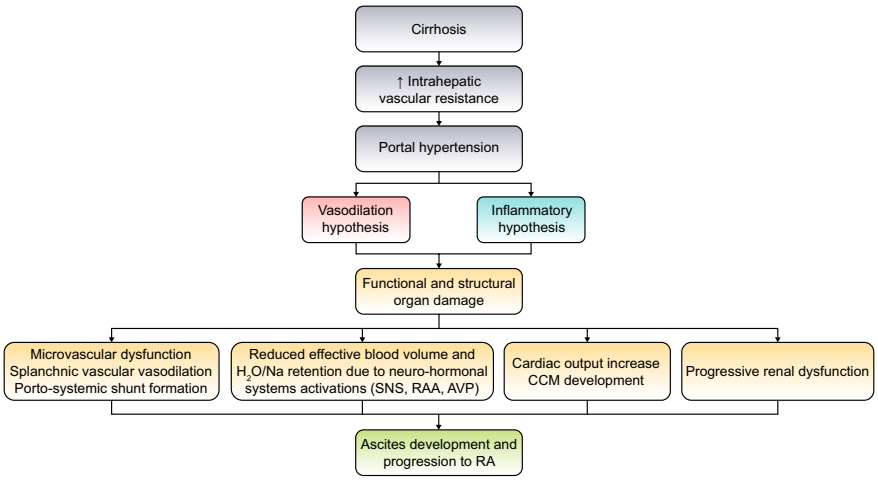

FIGURE 1 Pathophysiology of portal hypertension. AVP, arginine vasopressine; CCM, cirrhotic cardiomyopathy; RA, refractory ascites; RAA, Renin-Angiotensine-Aldosterone; SNS, Sympathetic Nervous System.

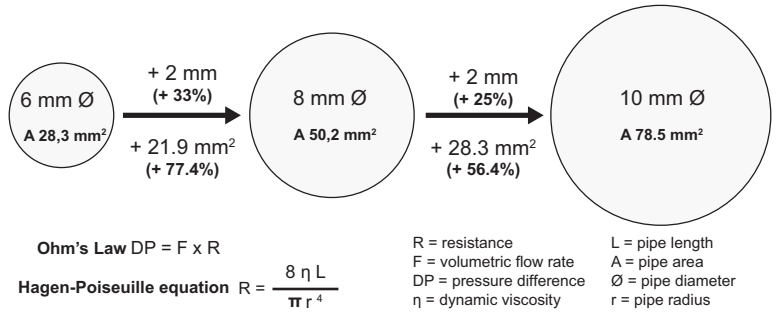

FIGURE 2 Effect of increased diameter on the caliber of transjugular intrahepatic portosystemic shunt (TIPS). PHT, portal hypertension.

The complex interplay between the aforementioned factors explains why, in clinical practice, the extent of PCPG decrease in patients undergoing TIPS is often unpredictable.[45] Similarly, in TIPS recipients, it is hard to estimate how much the PCPG will further decrease per each step of stent-graft dilation.

Late hemodynamic consequences following TIPS placement

The late hemodynamic effects of TIPS in patients with ascites are not yet completely understood. One issue is whether CO remains higher than pre-TIPS values and if this is associated with an increase in cardiac and central vascular volume. This issue was first addressed by Wong et al. in a seminal study including 10 patients with RA who were followed for a mean of 14 months after TIPS. By investigating hemodynamics through a radionuclide-based approach, they found that (a) cardiac index (i.e., CO normalized for body surface area) was only slightly increased compared to values before TIPS insertion (+26% at 6 months and +20% at 14 months); (b) cardiac and central vascular volume progressively and significantly increased from TIPS placement up to 14 months (+15.5% at 6 months and +21% at 14 months).[46] Importantly, all patients were maintained on a low-sodium diet and without diuretics for 7 days before each assessment in order to mitigate all potential confounding factors. To explain these findings, Rössle hypothesized that a redistribution of blood volume from the splanchnic area to the central circulation occurs after TIPS placement.[47] Surprisingly, despite the fact that this hypothesis is plausible from a pathophysiological point of view, it has not yet been validated by studies including patients with RA and specifically dedicated to investigating the hemodynamic effects of TIPS using gold-standard techniques.[37,38,43,44,48,49]

A second issue is whether increased cardiac and central vascular volume necessarily leads to an improved perfusion of nonsplanchnic organs such as the kidneys. In the aforementioned study, Wong et al. demonstrated that TIPS is associated with reduced renal vascular resistance, improvement of renal perfusion, and glomerular filtration rate (from 66 to 103 ml/min at 14 months; $p < 0.05$).[46] Levels of plasmatic renin activity and aldosterone both significantly increased at baseline and returned to within normal ranges at 6 and 14 months (renin: −417% and −500%; aldosterone: −279% and −367%, respectively; $p < 0.01$). This confirms the trend observed in another study from the same authors in which plasmatic renin activity and aldosterone levels started to drop 1–2 weeks after stent deployment.[29] In fact, renal sodium excretion also increased early after TIPS (within 2 weeks)[29] and continued to improve thereafter (7, 22, 51 mmol/day at baseline, 6, and 14 months, respectively; $p < 0.05$; $p < 0.01$).[46] Interestingly, mean arterial pressure remained stable throughout the study period from 78 mmHg at baseline to 82 and 84 mmHg at 6 and 14 months, respectively. This may be explained by the increase in effective arterial blood volume, which counteracts the decrease in neurohormonal systems.

These renal and neurohormonal effects of TIPS were confirmed in previous reviews combining results from 16 different studies, including 256 patients with cirrhosis who received TIPS (82% with RA).[47,50]

In another retrospective study evaluating the effects of polytetrafluoroethylene (PTFE)-covered TIPS in 140 patients with cirrhosis and RA, after a median follow-up of 94.6 months, only 5% achieved control of ascites with no need for diuretics and/or LVP. In the remaining patients, 49% of patients had ascites controlled using diuretics, 26% required sporadic paracentesis, and 20% still required frequent LVPs.[20] In one study including 12 patients with RA and followed 1 month after TIPS and in whom diuretics were discontinued, Wong et al. found that 17% of patients had a complete resolution of ascites within 1 month, 50% had incomplete resolution of ascites, and 33% had no further need of paracentesis but still experienced an increase in body weight due to recurrence of ascites.[29] In a further analysis extending the follow-up period to 14 months, the same authors found that all patients achieved resolution of ascites within 6 months after TIPS by adding diuretics.[46] The heterogeneity in the timing required to achieve clinical control of ascites may reflect a variable interaction

among the cardiocirculatory, neurohormonal, and renal responses to TIPS insertion. A better understanding of such effects in a given patient could be clinically relevant, as it may lead to more individualized management before and after TIPS insertion. This assertion is based on the hypothesis that the control of ascites could be more effectively achieved and the risk of side effects could be reduced using a strategy that takes into account the hemodynamic changes observed after TIPS deployment rather than focusing on achieving a predetermined PCPG reduction irrespective of individual patient characteristics.

Preliminary evidence indicates that TIPS is also associated with a decrease in inflammatory markers,[51] which potentially reflects a TIPS-driven improvement of systemic inflammation due to reduced translocation of bacteria and PAMPs from the leaky gut. The time to achieve this decrease may vary depending on the baseline severity of the liver disease and PHT, which may further explain the heterogeneity in the timing of response to TIPS between patients with recurrent and refractory ascites.[1,52]

It should be noted, however, that most studies investigating the early and late effects of TIPS in patients with ascites are relatively old, included few patients with relatively short follow-up, and did not assess hemodynamics, blood volume distribution, and renal response using gold-standard methods.[1,29,37,46,52–55] Of note, patients were only assessed in the supine position. Further comprehensive studies with a well-defined clinical setting are, therefore, still needed and, by clarifying the hemodynamic and nonhemodynamic consequences of TIPS, may help improve the clinical management of patients with ascites undergoing TIPS.

PORTOCAVAL SHUNTING FOR THE TREATMENT OF ASCITES IN CIRRHOSIS: SELECTION OF PATIENTS

Patients with difficult-to-treat ascites, particularly those with refractoriness to medical treatment, usually present with poor nutritional status and reduced quality of life.[1,56] TIPS has been proposed in selected patients with cirrhosis and ascites and may increase transplant-free survival.[3,57] However, the efficacy and the risk of side effects of TIPS depend on the interplay among multiple patient characteristics. TIPS can be harmful in patients with advanced chronic liver dysfunction and can be responsible for the onset of hepatic encephalopathy (HE) or for worsening preexisting HE.[58,59] In addition, the effectiveness of TIPS may differ between patients with recurrent ascites and those with RA. Finally, nonhepatic factors such as cardiac and kidney function may also affect clinical response after TIPS.[1,3,60]

Risk of HE and death after TIPS: two key issues that should be carefully evaluated before TIPS insertion

HE is the main complication of TIPS and is associated with reduced quality of life and increased mortality.[61] Furthermore, when placed in patients with advanced liver disease, TIPS may induce development of liver failure, which may precipitate the need for liver transplantation.[62,63]

The main risk factors for the development of post-TIPS overt HE include prior HE, advanced liver dysfunction (Child-Pugh class C, Model for End-Stage Liver Disease [MELD] score > 18),[21,57,64] older age,[65] increased creatinine level,[65] hyponatremia, and sarcopenia.[1,58,66–68]

Nardelli et al. proposed a prognostic model based on age, bilirubin levels, and the presence of pre-existing covert HE.[69] The final model (age/10 + Child-Pugh score + 4.88 if covert HE is present) had an area under the curve (AUC) of 0.75 for prediction of HE following TIPS. Using a cutoff of 17, the sensitivity of the model was 0.77, specificity was 0.75, positive predictive value was 0.64, and negative predictive value was 0.83, indicating that, in the population studied, a value <17 was able to accurately select patients at low risk of HE after TIPS. Of note, 77% of the patients included in this study had cirrhosis related to excessive alcohol intake or to chronic viral hepatitis. Whether the emerging etiology of NASH cirrhosis influences the risk of HE following TIPS insertion is currently unknown and should be evaluated in further studies.

Regarding survival, another study proposed the use of a simple predictive model based on bilirubin level and platelet count.[70] The 1-year survival rate was 73% in patients who had both a bilirubin level <50 μmol/L (or 3 mg/dl) and a platelet count >75,000/mm^3 compared to 31% in those with either a bilirubin level >50 μmol/L or a platelet count <75,000/mm^3. A recent study assessed the usefulness of 10 predictive models in 280 patients with recurrent or RA treated with TIPS.[71] The MELD score was combined with serum sodium and age (MELD score + [0.3 × (age, years)] - [0.7 × (Na, mmol/L)] + 100). The AUC values for the "integrated" MELD score for predicting survival at 6, 12, and 24 months were 0.75, 0.75, and 0.71, respectively. Remarkably, the "integrated" MELD score had the best performance in predicting survival compared to all other tested models, both in patients with recurrent ascites and in those with RA. Outcomes after TIPS significantly differed between patients with "integrated" MELD score <32, between 32 and 38, and >38, with 2-year transplant-free survival rates of 71%, 57%, and 26%, respectively.[71] In another recent study that included patients who received TIPS for RA (25% of the study population) and secondary prophylaxis for variceal bleeding (75% of

the study population), Bettinger et al. proposed the Freiburg index of post-TIPS survival (FIPS) score to identify high-risk patients with a poor prognosis after TIPS ([1.43 × (log10 bilirubin, mg/dl)] - [1.71 × (1/creatinine, mg/dl)] + [0.02 × (age, years)] - [0.02 × (albumin, g/L)] + 0.81).[72] Overall survival probability was equal to $S_0(t)^{\exp(FIPS+0.12)}$, where $S_0(1)$ is 0.96, $S_0(3)$ is 0.87, and $S_0(6)$ is 0.81 for 1, 3, and 6-month time points (t) after TIPS placement. The FIPS score had higher discriminative ability than all other prognostic models with a c-index of 0.741 and 0.716 for 3- and 6-month survival. In the subanalysis including only patients with RA, the c-index of the FIPS score was 0.961 and 0.705 for 3- and 6-month survival, respectively.

Although helpful, these studies have some biases, such as their retrospective nature, inclusion of a heterogeneous population of patients, and lack of strong validation, that limit their use in clinical practice at the individual patient level. However, it is clear that the risk of liver failure and/or HE increases with the degree of liver impairment and, therefore, TIPS indication should be considered on a case-by-case basis for the treatment of ascites in patients with severe hepatic dysfunction, a statement that differs from the situation when TIPS is discussed as a life-saving treatment for the management of PHT-related bleeding.[58,73–75]

The potential reversibility of PHT and liver dysfunction if the etiological factor of cirrhosis has been eliminated should also be taken into account when TIPS is considered for ascites. Cure/removal of etiological factor(s) responsible for chronic liver disease has a major positive impact on the natural history of cirrhosis.[76] In fact, etiological cure/removal may not only reduce disease progression but also reverse the disease from decompensation to recompensation.[77] Theoretically, by achieving recompensation without placing a TIPS, one would also prevent potential shunt-related complications. Unfortunately, at present there is no strong method to identify patients in whom cure/removal of etiological factors is associated with control of ascites.[77] This is particularly true for patients with alcohol-related liver disease who discontinue alcohol consumption and may also be relevant for those with hepatitis B or C virus infection-related cirrhosis who achieve viral suppression.[75,77–82] In patients with alcohol-related liver disease, improvement of liver function may take ≥3 months after alcohol withdrawal to be measurable, which may be a reasonable delay to reassess indication for TIPS.[83]

Overall, accurate selection of candidates who have minimal risk of liver function deterioration and/or HE after TIPS remains challenging, and the decision to place TIPS for ascites is often made on a case-by-case basis. In all cases, contraindications for TIPS need to be balanced against its potential benefit. Of note, available data summarized in this section only concern short- or medium-term consequences following TIPS insertion on patient outcomes. To the best of our knowledge, no data exist on long-term consequences following exposure of organs to blood that bypasses the liver and comes directly from the gut. This may be relevant for some organs, especially the brain in these patients already exposed to a risk of HE due to impaired liver function. Currently, experts advocate that TIPS is contraindicated in patients with a history of recurrent or persistent overt HE or in those with advanced liver dysfunction defined by a Child-Pugh score >13 or a MELD score >19.[74,84,85] However, there is insufficient evidence to recommend a cutoff value for bilirubin, MELD score, or Child-Pugh score above which TIPS should be contraindicated as a treatment for RA.[58]

Importance of ascites classification on outcome: recurrent vs. refractory ascites

RA refers to ascites that cannot be resolved or that recurs early after LVP and cannot be prevented by medication.[1,86] According to the original criteria of the International Club of Ascites, recurrent/recidivant ascites is defined as the requirement of ≥3 LVPs within 1 year despite dietary sodium restriction and adequate diuretic dosage.[1,77,87] However, in a recent randomized controlled trial (RCT) by Bureau et al. assessing the impact of TIPS on survival, recurrent ascites was defined as “ascites requiring at least 2 LVPs within a period of at least 3 weeks” in patients with well-preserved liver and renal function treated with intermediate dosage of diuretics.[21]

Most available data on the usefulness of TIPS in ascites concern patients with RA who received bare stents. Four RCTs have evaluated the usefulness of TIPS in patients with RA,[22,23,26,53] and two have evaluated mixed cohorts of patients with both recurrent and refractory ascites.[24,25] These results were synthesized in six meta-analyses that all came to the conclusion that TIPS was effective in preventing ascites recurrence in approximately 50% of patients without clearly worsening the risk of HE.[3,52,88–91] The effect of TIPS on patient survival is not as clear. The individual patient meta-analysis by Salerno et al., which included data from four of the five RCTs available in 2007, identified a transplant-free survival benefit in the TIPS group.[3] However, this meta-analysis did not include Lebrec et al.'s RCT, in which survival was significantly lower in patients receiving TIPS.[53] A more recent RCT by Narahara et al. also demonstrated a significant improvement in survival in patients receiving bare stent TIPS compared to patients receiving standard medical treatment (overall survival at 1 year: 80% vs. 49%, $p < 0.005$), a finding that may be related to inclusion of patients with well-preserved liver and kidney function (the mean MELD score was 9.6 in the TIPS group and 10 in the medical arm).[23]

In the era of PTFE-covered TIPS, only one RCT has assessed the usefulness of TIPS in patients with recurrent ascites.[21] Of note, 30% of the patients included in this study had previous variceal bleeding and 20% had a history of renal failure. The 1-year survival rate of patients in the TIPS group was significantly higher than that of control patients treated with standard of care (93% vs. 52%, $p = 0.003$). In addition, HE did not occur more frequently in the TIPS group. Interestingly, values for age, bilirubin, sodium, and MELD score of the patients included in the Bureau et al. study were very close to those of the patients included in the Narahara et al. study on RA,[23] suggesting that these variables are important determinants of post-TIPS outcome, a postulation that was originally proposed by Salerno et al. in a seminal meta-analysis published 10 years before.[3]

Although current guidelines allow the use of TIPS both in patients with recurrent and refractory ascites (Figure 3),[1] the robustness of the definition proposed by Bureau et al. for the identification of patients who would benefit from TIPS insertion needs confirmation in independent cohorts. Furthermore, it is still unsettled whether earlier placement of TIPS (i.e., in patients with recurrent ascites rather than with RA) may influence long-term outcomes (>1 year). Although promising, data on the efficacy of PTFE-covered stent-grafts in recurrent ascites require further confirmation.[58] Further studies should also focus on the identification of negative prognostic factors before TIPS according to the classification of ascites.

Finally, if the promising results of the ANSWER study[92] on the efficacy of long-term human albumin infusions in controlling ascites and improving survival are confirmed,[77] this approach deserves to be assessed in patients in whom PTFE-covered TIPS are used for "early ascites," either as an alternative treatment to TIPS or in combination with TIPS.[93]

Nonhepatic prognostic factors influencing outcomes after TIPS

Several nonhepatic factors may affect outcomes after TIPS insertion for ascites.

Cardiac decompensation

Recent data suggest that cardiac decompensation occurs in 10–20% of patients after TIPS insertion.[94–96] As discussed above, TIPS causes a sudden increase in cardiac preload. In patients with pre-existing alterations of cardiac reserve, such as CCM or a cardiopathy related to other causes, this cardiac hemodynamic stress may result in cardiac failure. Therefore, identification of patients with cardiomyopathy, regardless of its underlying nature, is of major importance in patients who are potential candidates for TIPS.[1] Previous studies found that diastolic dysfunction, either defined by a pre-TIPS E/A ratio (which corresponds to the ratio of peak velocity blood flow from left ventricular relaxation in early diastole [the E wave] to peak velocity flow in late diastole caused by atrial contraction [the A wave]) ≤1[95] or by an E/A ratio ≤1 one month after TIPS insertion,[97] was associated with mortality. However, E/A ratio alone is not enough to diagnose diastolic dysfunction.[98] Although recent guidelines recommend a detailed assessment of cardiac function in TIPS candidates, they also acknowledge that accurate markers of cardiac dysfunction are currently lacking.[1] A potential way to assess baseline cardiac function and its response to TIPS may be to perform right heart catheterization at baseline (before TIPS placement) and immediately after stent-graft opening. Indeed, these hemodynamic measurements provide information on the presence/severity and development of postcapillary pulmonary hypertension, a fair indicator of left heart diastolic function.[28,58]

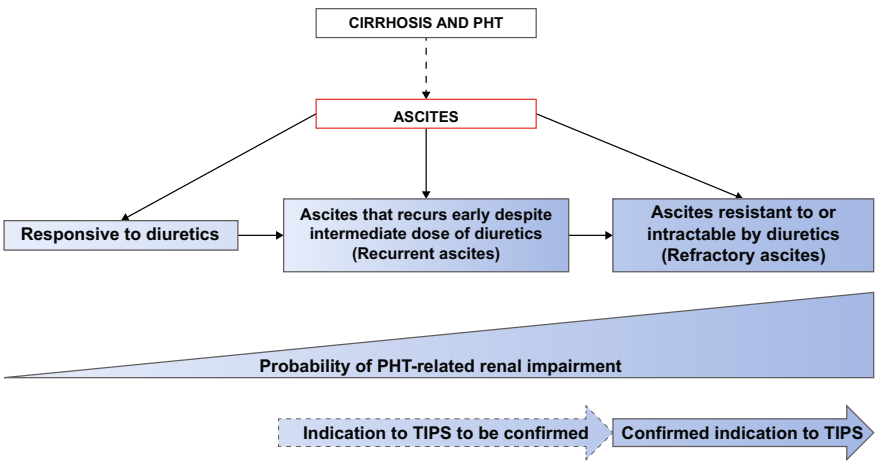

FIGURE 3 Classification of ascites in patients with cirrhosis and portal hypertension (PHT). TIPS, transjugular intrahepatic portosystemic shunt.

In a recent prospective study specifically dedicated to assessment of the risk of heart failure following TIPS insertion, several cardiac echocardiographic parameters reflecting diastolic dysfunction and pre-TIPS brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) were associated with the risk of post-TIPS liver failure.[94] More specifically, absence of diastolic dysfunction criteria at echocardiography, a level of BNP <40 pg/ml, and NT-proBNP <125 pg/ml allowed identification of patients with a negligible risk of cardiac decompensation. On the other hand, the presence of aortic stenosis was associated with cardiac decompensation. In this study, cardiac decompensation was the cause of death after TIPS in five out of the 18 deaths, and three of the five patients who died from cardiac complications within 1 year had aortic stenosis at the time of TIPS insertion. A main issue of this study, however, is that patients with potential risk factors for cardiac decompensation, such as aortic stenosis, were included. As these factors are generally considered to be contraindications for TIPS placement,[58] the findings by Billey et al.[94] need confirmation in independent cohort studies excluding patients without known cardiac contraindications for TIPS.

As discussed for HE, it is currently unknown whether the etiology of cirrhosis might influence the risk of cardiovascular events after TIPS insertion. Patients with NASH are at increased risk of cardiovascular events,[99] particularly those with advanced liver fibrosis.[100] Thus, these patients may be at higher risk of cardiac decompensation after TIPS and would need a particularly careful assessment of cardiovascular comorbidities prior to TIPS procedures. As NASH has now become a leading cause of chronic liver disease worldwide,[101] there is an urgent need for prospective studies investigating the impact of comorbidities and their treatment on the outcome of patients with NASH who undergo TIPS placement.

Older age

Few data are available regarding the impact of age on prognosis following TIPS insertion as patients older than 70–75 years were usually excluded from RCTs. However, age is a well-known independent predictor of HE[102] and survival[3,72] in patients undergoing TIPS. It could be hypothesized that increasing age above 60–65 years would compromise outcomes after TIPS. However, current evidence from retrospective cohorts is too limited to draw any conclusion regarding the impact of age on clinical control of ascites and survival in older patients.[103,104] Awaiting further data in patients who are not candidates for liver transplantation because they are considered too old, indication for TIPS may be considered on a case-by-case basis.[58,68]

Sarcopenia

Sarcopenia, defined as a generalized and progressive loss of skeletal muscle mass, is a risk factor for developing HE after TIPS. In a prospective study performed in 46 patients, undergoing TIPS, the 21 who developed HE after TIPS placement all had sarcopenia.[66] In a larger prospective cohort including 107 patients with RA, pre-TIPS sarcopenia independently predicted development of post-TIPS HE but not patient survival.[105] On the other hand, TIPS has been associated with skeletal muscle gain and reduced risk of HE,[106–108] which may translate into increased survival.[109] These apparently conflicting results may be related to patient selection and/or difference in definition of sarcopenia. Currently, the optimal way to assess the level of sarcopenia above which the risk of HE significantly increases remains to be defined and should be investigated in further prospective cohorts.

Kidney injury

The importance of kidney injury in the setting of ascites treated with TIPS is related to two issues: the impact of pre-TIPS renal failure on post-TIPS outcome and the impact of TIPS on kidney function in patients with pre-existing renal dysfunction.

Regarding the first issue, prospective studies investigating the role of TIPS in RA observed that the most common predictive factors of unfavorable response to TIPS were creatinine level or clearance.[110–113] This is not surprising because preserved kidney function is important to achieve elimination of ascites (see also pathophysiological consequences of TIPS) (Figures 1 and 3). Furthermore, pre-TIPS increased creatinine is predictive of post-TIPS overt HE.[65] Therefore, current international and national guidelines recommend assessment of kidney function, either by creatinine levels or glomerular filtration rate, in patients undergoing TIPS.[58,74] These considerations may be particularly important in patients with NASH cirrhosis in whom the risk of kidney dysfunction is potentially higher due to associated comorbidities (e.g., hypertension, diabetes) than in those with different etiologies of liver disease. While awaiting further data on the impact of renal comorbidities on the outcome of patients with NASH cirrhosis undergoing TIPS, a particularly careful assessment of renal function in these patients seems advisable.

Most RCTs that have investigated the efficacy and safety of TIPS in RA excluded patients with a baseline creatinine >3 mg/dl, and a baseline creatinine above this value has been considered a contraindication for TIPS.[74] However, this black-and-white approach seems unfeasible due to the multifactorial nature of kidney dysfunction in cirrhosis (organic vs. functional;

chronic and progressive vs. acute). Therefore, there is insufficient evidence to recommend an absolute value of serum creatinine or a certain degree of chronic kidney disease for which TIPS should be contraindicated.[58] Similarly, it is unclear whether TIPS is absolutely contraindicated in patients on renal replacement therapy.[58]

Regarding the second issue, TIPS improves kidney function in the majority of patients.[114,115] One study showed that improvements in serum creatinine were greater in patients with more severe baseline renal dysfunction.[116] However, it should be noted that patients included in this study had only moderate kidney dysfunction (mean creatinine level was between 1.2 and 1.9 mg/dl). Evaluation of kidney response to TIPS according to etiology of liver disease should also be further investigated. Few data are available in patients with type I or II HRS (HRS-acute kidney injury [AKI] and HRS-non-AKI [NAKI] following the new proposed classification[117]) awaiting liver transplantation. Renal improvement was observed in studies including a limited number of patients with HRS-AKI.[118,119] In a meta-analysis including nine studies, improvement of renal function was also observed in patients with RA further complicated by HRS-AKI or HRS-NAKI and treated with TIPS. One-year survival was 47% in those with HRS-AKI and 64% in patients with HRS-NAKI.[120] In this setting, TIPS may be considered as a bridge to liver transplantation in selected patients. However, evidence supporting the use of TIPS in patients with severely impaired kidney function is limited.[121] Therefore, the decision to place TIPS in patients with kidney dysfunction is usually made on a case-by-case basis and taking into account other predictors of outcome.

Conclusion and future perspectives

In conclusion, the efficacy and the risk of side effects of TIPS placed for treating ascites depends on a combination of patient characteristics including age, degree of liver dysfunction, history of HE, type of ascites (recurrent or RA), and nonhepatic factors such as cardiac and kidney function. The potential weight of etiological cure (i.e., treatment of chronic viral hepatitis, alcohol cessation) should also be considered. However, it is as yet unclear how to accurately identify patients with a high chance of hepatic improvement and resolution of clinically significant PHT after the etiological factor is cured/controlled. Overview graphics on the role of TIPS and identification of the "ideal" candidate for TIPS insertion in the setting of ascites occurring in cirrhosis are provided in Figures 3 and 4. Further studies are required to improve identification of patients in whom the benefit of TIPS for ascites can be maximized and, particularly, to define the best timing to implement TIPS in the natural history of ascites.

INTRAHEPATIC PORTOCAVAL SHUNTING: TECHNICAL CONSIDERATIONS

General considerations regarding patient preparation for TIPS (i.e., liver imaging, antibiotic prophylaxis, use of blood products) have been recently described elsewhere[58,74] and are not discussed in this review. One specific note for patients with tense ascites is to perform an LVP prior to TIPS to avoid medialization of the liver and its main venous branches and to facilitate extubation when general anesthesia is used.

«Ideal» criteria to define candidates for TIPS insertion in the setting of cirrhosis and ascites

Age-related	Liver-related			Heart-related
<65 years	No history of recurrent HE without known precipitants	Total bilirubin level <3 mg/dL (<50 umol/L)	Child-Pugh score ≤13	Normal value of BNP/NT-proBNP
	No persistent overt HE	Platelet count >75X10⁹/L	MELD score ≤19	No aortic stenosis and systolic/diastolic dysfunction

FIGURE 4 The "ideal" candidate for transjugular intrahepatic portosystemic shunt (TIPS) in the setting of cirrhosis and ascites. BNP, brain natriuretic peptide; HE, hepatic encephalopathy; MELD, Model for End-Stage Liver Disease; NT-proBNP, N-terminal pro-brain natriuretic peptide.

The key technical step of TIPS placement is the PV puncture,[122,123] which is facilitated by ultrasound guidance.[124] The stent-graft is released with creation of an artificial conduit between the PV (at high pressure) and the IVC (at low pressure).[122,123] Therefore, from a functional perspective, TIPS is similar to a side-to-side portosystemic shunt.[125]

Understanding the technical issues of the TIPS procedure, from deployment and dilation of the stent-graft (type, shape, diameter) to the assessment of early and late hemodynamic effects, is clinically important to achieving control of ascites without increasing the risk of shunt-related adverse events.[58,74,77]

Technical issues associated with the TIPS procedure

The most important advancement in TIPS has been the introduction of PTFE-covered stent-grafts. Covered stents have essentially abolished the risk of TIPS stenosis due to uncontrolled proliferation of a neointima inside the stent lumen.[4,126,127] This was a major drawback of bare stents that were responsible for reintervention in up to 60% of patients within 1 year.[57,128] Unlike patients with thrombophilic conditions, such as those with Budd-Chiari syndrome, TIPS thrombosis due to blood clotting in cirrhosis is rare[129] and should raise suspicion for TIPS mispositioning (further discussed below) or unrecognized thrombophilic conditions.

Three RCTs evaluating patency of TIPS for the treatment of various complications of PHT have demonstrated improved patency with PTFE-covered versus bare stents.[130–132] Two of these RCTs also demonstrated a reduced risk of clinical relapse in patients receiving PTFE-covered stent-grafts.[130,132] In the third RCT, rate of clinical relapse after TIPS was comparable between the groups (22% vs. 35%).[131] Regarding HE, one RCT indicated a reduced risk with covered versus bare stents,[130] whereas two others did not find any significant difference.[131,132]

In the most recent RCT using PTFE-covered stent-grafts in 29 patients with recurrent ascites,[21] only one patient experienced TIPS thrombosis (1-year primary patency rate 97%) compared with a significantly higher incidence of TIPS dysfunction in the most recent RCT using bare stents in RA (1-year primary patency rate 18%).[23] Furthermore, the 1-year survival after TIPS was higher in patients who had PTFE-covered TIPS than patients treated with bare stents despite similar liver and kidney dysfunction (93% vs. 80%, respectively).[21,23] Therefore, in addition to improvements in patient selection, it is likely that the use of PTFE-covered stent-grafts also improves survival.[21] As a result, current international guidelines recommend the use of PTFE-covered stent-grafts for the treatment of ascites in cirrhosis.[1,58,77,133]

As stent dysfunction is now relatively uncommon, further practical improvements in TIPS procedures should aim to reduce the risk of shunt-related adverse events such as HE and liver failure. Ideally, TIPS should effectively reduce the PCPG without shunting an excessive amount of blood from the PV toward the right atrium. In fact, an excessive diversion of portal inflow may lead to a detrimental cardiac response, which, together with an insufficient hepatic arterial buffer response, favors development of hepatic ischemia and liver failure.[18,134–136] This hypothesis needs to be evaluated in further studies investigating changes in hepatic perfusion and cardiac hemodynamics before and after TIPS insertion.

From a physiological point of view, resistance to blood flow (and therefore PCPG) is inversely related to the radius elevated to the fourth power (Poiseuille law, Figure 2). In line with this issue, the position and shape of the stent may affect PCPG. When technically doable, the stent-graft should be placed in a central position (i.e., between the right branch of the PV and the main right hepatic vein). Experts advocate that this type of “straight” TIPS may be more effective for decreasing the PCPG than a peripheral “C-shaped” TIPS (Figure 5). In fact, the cross-sectional area of a C-shaped TIPS tends to be elliptical and, therefore, would lead to increased resistance to blood flow and higher PCPG.[60] Furthermore, a higher resistance to blood flow may increase the risk of stent-graft thrombosis, a complication that may require TIPS revision and insertion of a new, “in-parallel” stent-graft (Figure 5).

Additional reasons for stent-graft dysfunction are related to mispositioning and/or incorrect release of the stent-graft.[137,138] It is important that the stent-graft is long enough to cover the whole segment from inside the PV (uncovered part of the TIPS) to the intrahepatic tract and the entire length of the hepatic vein (covered part of the TIPS), until the junction with the IVC. Otherwise, an endothelial hyperplasia will develop due to shear stress in correspondence to the nonstented tract of the hepatic vein, which causes stenosis, increased PCPG, and TIPS dysfunction (Figure 6).[137,138] Not surprisingly, a recent study demonstrated that a short “TIPS-distal end positioning,” as defined by a <6 mm distance between the distal end of the stent-graft and the hepato-cava junction, is highly predictive of recurrent complications of PHT after TIPS.[139] However, it is also important that TIPS does not compromise future liver transplantation. Therefore, the stent-graft should not extend toward the splenic/superior mesenteric vein confluence, as this may disrupt surgical PV anastomosis.[122,123] Similarly, a stent-graft placed near or into the right atrium may make surgical IVC anastomosis more challenging.[122,123]

PV thrombosis (PVT) is the most common thrombotic complication in decompensated cirrhosis.[140,141] The placement of TIPS in patients with cirrhosis with

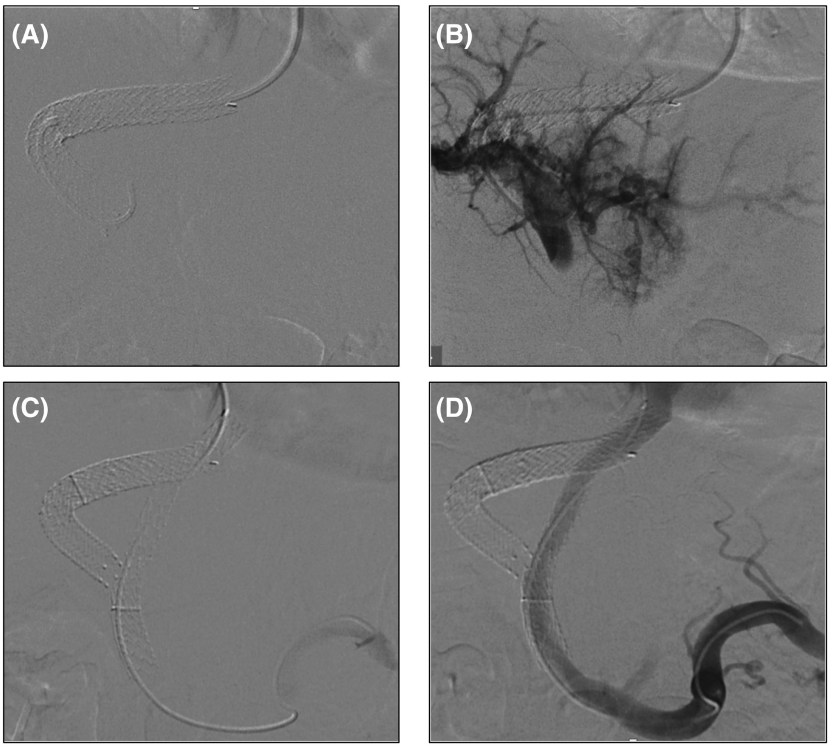

FIGURE 5 Example of C-shaped transjugular intrahepatic portosystemic shunt (TIPS) and in-parallel TIPS. (A) Revision of C-shaped TIPS in a patient who experienced recurrent ascites after TIPS; (B) evidence of complete thrombosis of the stent-graft; (C) in-parallel deployment of a new straight stent-graft; (D) demonstration of the patency of the new TIPS.

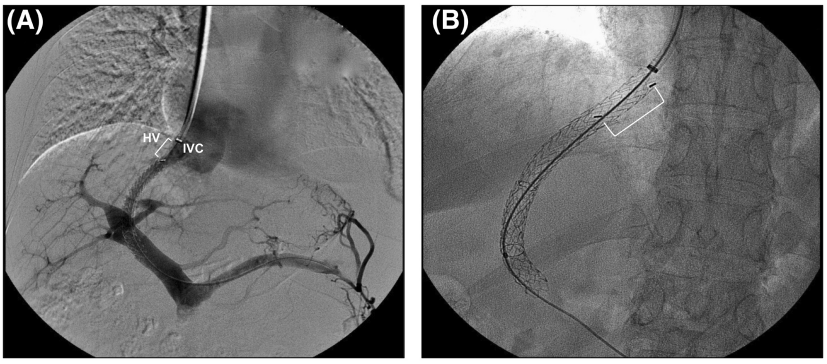

FIGURE 6 Example of transjugular intrahepatic portosystemic shunt (TIPS) dysfunction due to incomplete covering of hepatic vein. (A) Revision of TIPS in a patient who experienced recurrent ascites after TIPS demonstrated stent-graft malposition due to incomplete covering of hepatic vein; (B) A new coaxial stent-graft is placed inside the original stent-graft to cover the entire length of the HV past the junction with the IVC. The white bracket indicates the distance between distal markers of original and coaxial stent-grafts. HV, uncovered tract of hepatic vein; IVC, inferior vena cava at the junction with HV.

RA and PVT can be technically complex, especially if the PVT is chronic and extends to the intrahepatic branches and/or is associated with cavernomatous transformation.[122] However, in a recent series from a tertiary care center including 66 patients with cirrhosis and PVT—mostly complete and 48% with cavernomatous transformation—TIPS placement was successful in 98% of the cases.[142] A systematic review including patients with cirrhosis and PVT who underwent TIPS for various complications of PH showed that TIPS was feasible in 95% of patients.[143] Therefore, even in technically difficult cases, good results are achievable in highly specialized centers to which patients with cirrhosis with RA and PVT should be referred.

Effect of TIPS diameter on clinical outcome in patients undergoing TIPS for ascites

Following PV puncture and creation of an intraparenchymal channel between the portal and hepatic vein

using a balloon for angioplasty, the stent-graft is deployed and may be dilated with balloons of progressively increasing size (from that used to create the parenchymal channel to that equal to the nominal diameter of the stent-graft). Each dilation corresponds to increased reduction of blood flow resistance, lower PCPG, and increased shunting of splanchnic blood toward the right atrium (Figure 2). As discussed above, however, the final PCPG depends on multiple factors that are not entirely predictable or controllable, which explains the difficulty encountered when trying to predict the final PCPG decrease in a given patient.[45]

Previous studies have demonstrated that the achievement of a hepatic vein pressure gradient <12 mmHg (either by drugs or TIPS) or a decrease of PCPG of more than 50% from baseline value eliminated the risk of recurrent variceal hemorrhage.[77] Recurrent variceal hemorrhage and de novo ascites after TIPS were mostly observed in patients with a post-TIPS PCPG >12 mmHg.[4] Therefore, a post-TIPS PCPG <12 mmHg was initially proposed as a hemodynamic target of TIPS, independent of the indication.[144]

Several studies have investigated the correlation between post-TIPS PCPG and clinical response in patients with RA. In one study of 122 patients who underwent TIPS, Casado et al. correlated clinical events with hemodynamic findings, reporting that all 26 patients who developed ascites after TIPS had a PCPG >12 mmHg. However, not all patients with a post-TIPS PCPG >12 mmHg developed de novo ascites, indicating that additional factors were involved.[4] In a multicenter RCT of 109 patients with ascites randomized to medical therapy or medical therapy + TIPS, Sanyal et al. found no clear relationship between portal pressure reduction and recurrence of ascites (mean portosystemic pressure gradient after TIPS was 8.3 mmHg).[26] Similarly, in a smaller retrospective study including 28 patients (the mean final gradient between the PV and the free hepatic vein was 8.6 mmHg), the post-TIPS portohepatic gradient was not independently associated with clinical resolution of ascites.[145] Parvinian et al. recently reported results from a retrospective study in 80 patients with ascites treated with TIPS (mean final pressure gradient between the PV and the right atrium was 6.8 mmHg). Interestingly, there was no correlation between porto-atrial pressure gradient and clinical control of ascites (response rate for 8, 10, and 12 mmHg thresholds = 79%, 79%, 78%, respectively; $p = 0.9$).[146] Therefore, the optimal PCPG decrease needed to control ascites remains controversial. It should be further highlighted that most of these studies are relatively old, included patients who received bare stents directly dilated to nominal diameter (generally 10 mm), and had no clear definition/consensus on how and when to measure the PCPG after TIPS. Therefore, whether a post-TIPS PCPG target <12 mmHg is the best cutoff for patients receiving a covered stent for the treatment of ascites, independent of baseline PCPG, needs confirmation in well-designed RCTs. Furthermore, recent evidence suggests that reversal of additional, nonhemodynamic factors such as degree of systemic inflammation and cardiac or kidney structural impairment may influence control of ascites after TIPS, which further complicates accurate prediction of response in clinical practice.[12,13,51,117]

Stent diameter may also influence the risk of side effects after TIPS and survival. Older series advocated that a larger PFTE-covered TIPS (10 mm) was likely to be superior to a smaller stent-graft (8 mm) in the control of RA.[147,148] However, the probability of post-TIPS encephalopathy increases with the diameter of the shunt. In a recent RCT comparing 8 mm versus 10 mm covered TIPS for the prophylaxis of variceal rebleeding,[149] the risk of recurrent bleeding was comparable between patients who had a TIPS dilated to 8 mm or 10 mm, whereas 2-year incidence of encephalopathy post-TIPS was lower in patients who had a smaller TIPS (27% vs. 43%, $p = 0.03$). A propensity-matched analysis including patients who received TIPS for RA and variceal bleeding demonstrated increased survival in those who received PFTE-covered 8 mm versus 10 mm stent-grafts.[150] A secondary finding of this study was a comparable survival in patients receiving a 10 mm stent-graft underdilated to 8 mm versus those receiving 10 mm stents dilated to nominal diameter. This would suggest that underdilated self-expandable stents (VIATORR) may continue to spontaneously dilate over time until achieving their nominal diameter. Upon the introduction of controlled-expansion stent-grafts (VIATORR-CX), stents that cannot spontaneously dilate over the preset limit of 8 mm unless by balloon dilation,[151,152] a recent study from the same group retrospectively compared 10 mm nominal diameter VIATORR-CX (underdilated to 8 mm) versus 10 mm nominal diameter VIATORR (underdilated to 8 mm) versus 10 mm nominal diameter stent-graft (either VIATORR or VIATORR-CX) dilated to 10 mm.[153] Interestingly, 1-year survival was higher in patients who received underdilated VIATORR-CX, intermediate in underdilated VIATORR, and lowest in stent-grafts fully dilated to 10 mm. The superiority of VIATORR-CX, however, was not confirmed in a recent analysis by Mansour et al.,[154] which highlights the fact that post-TIPS outcomes are also determined by additional factors such as patient characteristics.[155]

Previous studies including small groups of patients suggested that 8 mm underdilated VIATORR stents may spontaneously dilate over time.[156–160] However, in a large prospective cohort including patients undergoing TIPS for RA and recurrent bleeding who received VIATORR stents dilated to 6–10 mm, Schepis et al. demonstrated that (a) none of these stent-grafts really reached the nominal diameter; (b) only a minor proportion of underdilated stent-grafts spontaneously dilated overtime in the range of 1 mm; (c) 1-year incidence of

HE was significantly lower in patients who received underdilated stent-graft to 6 mm versus those who had TIPS dilated to higher values (from 7 to 10 mm) (27% vs. 54%, respectively), without difference in the risk of recurrent bleeding or ascites and without any episode of stent-graft thrombosis.[102] Contrary to previous observations that either used nonoptimal methods, such as ultrasound[159] or digital angiography,[157,158] or assessed VIATORR stent diameter/area in the intraparenchymal tract,[156,160] Schepis et al. used gold-standard computed tomography scanning and found that stent-graft diameter remained stable in correspondence to fibrotic portal and hepatic vein walls, where an increased resistance to the radiation force of stent-graft is exerted.[102] If confirmed by further studies using the new generation of VIATORR-CX stents and investigating both ascites control and patient survival, these findings would, therefore, indicate that a stent-graft underdilated to <8 mm may be a pragmatic way to approach TIPS placement in patients with cirrhosis and ascites.

Direct intrahepatic portocaval shunt as a technical alternative for difficult to place TIPS

Direct intrahepatic portocaval shunt (DIPS) is an alternative radiological procedure in patients presenting with anatomical conditions that would make it infeasible to perform a traditional TIPS (Figure 7). Technically, DIPS consists of the direct placement of a stent-graft that connects the PV with the IVC. DIPS has been mostly used for patients with Budd-Chiari syndrome in whom hepatic vein remnants cannot be cannulated.[161,162]

In patients with cirrhosis, examples of anatomical conditions that may require DIPS include a particularly long intraparenchymal tract between the PV and the hepatic vein, presence of large obstacles between such as hepatic cysts or nodules, a distorted postsurgical anatomy,[163] a particularly severe stiffness of the liver parenchyma,[164] or a combination of these factors.

The frequency of patients with cirrhosis eligible for DIPS who present with these anatomical conditions is unknown. A recent study suggests that this population could represent up to 5–10% of patients with an indication for TIPS.[165] In our 12-year experience in positioning TIPS in patients with cirrhosis, however, we had to perform a DIPS only in one patient with a very large, central enlargement of the liver (Figure 7). With the exception of Budd-Chiari syndrome,[165] it seems unlikely that DIPS has a major role in the management of PHT in cirrhosis. On the other hand, it is worthwhile to ensure that hepatologists are aware of this technique that can be used in the very select cases where conventional TIPS is not feasible. Long-term data on the safety and efficacy of DIPS in patients with cirrhosis, including the risk of stent stenosis due to fibrotic reaction of IVC, are needed.

Conclusion and future perspectives

In conclusion, the significant improvement in TIPS technology, particularly the introduction of PTFE-covered stent-grafts, has helped improve clinical outcomes in patients undergoing TIPS for ascites, particularly with regard to reducing the risk of stent dysfunction. According to international guidelines, a “small” TIPS is currently recommended for the treatment of ascites (either recurrent or refractory) in patients with cirrhosis (EASL, AASLD, North American Practice Based Recommendations). However, significant heterogeneity exists regarding the definition of “small” TIPS. This has been defined as a diameter <10 mm in the AASLD guidelines[133] and a diameter of 8 mm in the North American Practice Based Recommendations[58] and has no clear definition in the European guidelines.[1]

Awaiting further evidence from well-designed RCTs and considering the additional factors that influence

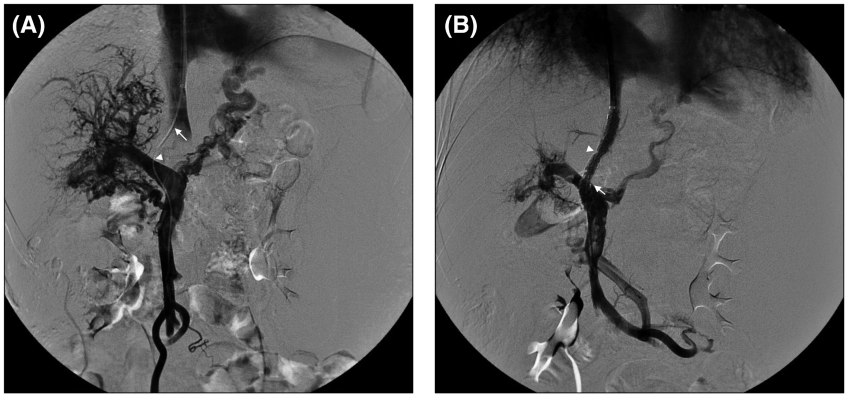

FIGURE 7 DIPS in a patient with cirrhosis. (A) Arrow: puncture site of the intrahepatic IVC; arrowhead: puncture site of the right branch of the PV; (B) arrow: distal marker of PTFE-covered stent-graft; arrowhead: stent-graft narrowing in correspondence of entry into the IVC. DIPS, direct intrahepatic portocaval shunt; IVC, inferior vena cava; PTFE, polytetrafluoroethylene; PV, portal vein.

PCPG decrease and patient response/tolerance to TIPS, a stepwise approach that does not target a given reduction of PCPG may be a good pragmatic approach to TIPS placement for ascites. Using this approach, one could start with a small TIPS (for instance underdilated to 6 mm)[60,102] and progressively dilate the stent-graft based on clinical response, cardiac tolerance, and development of shunt-related adverse events. A large RCT comparing the safety and efficacy of this type of approach versus PCPG-guided TIPS placement in patients with cirrhosis and ascites is eagerly awaited.

CONCLUSIONS

In selected patients with ascites requiring repeated LVPs, TIPS using PTFE-covered stent-graft improves control of ascites and survival. However, the hemodynamic effects of TIPS are not yet thoroughly understood, particularly with regard to how distribution of blood volume and CO change over time after TIPS. A better understanding of the hemodynamic consequences of TIPS insertion would help to identify the subgroup of patients with no reversal/progression of hyperdynamic circulation in whom to evaluate the potential benefit of add-on therapy with nonselective beta-blockers. Similarly, refinements in definition of baseline hemodynamic state (hyper- vs. normo- vs. relatively hypo-dynamic) together with evaluation of postcapillary pulmonary hypertension in patients undergoing TIPS may improve clinical decision-making regarding initial caliber of stent-graft.

Systemic inflammation is becoming increasingly recognized as prominent driver of decompensated cirrhosis progression. In patients undergoing TIPS, severity of inflammation and its evolution after TIPS may affect both clinical response and risk of shunt-related adverse events, particularly in patients with negative prognostic factors such as CCM, kidney impairment, or history of HE.

As resolution of inflammation-driven organ impairment and shutdown of hyperactivated neurohormonal systems may take time, a re-evaluation of hemodynamic changes after TIPS may help decide whether stent-graft dilation should be performed. Although stent-graft dilation can significantly reduce PCPG, thus potentially leading to improved control of ascites, this reduction is often unpredictable and uncontrollable. Furthermore, the cardiac response to the progressively increasing amount of shunted blood returned to the right atrium may be blunted due to an underlying CCM, thus favoring development of hepatic ischemia and acute liver function deterioration. Hence, in the individual patient, the positive effect of ascites resolution has to be carefully balanced against the potential risk of shunt-related complications.

To improve our understanding of TIPS in patients with cirrhosis decompensated by ascites, a clear definition of recurrent ascites needs to be established and evaluated in multicenter RCTs. Indeed, identification of appropriate timing for TIPS placement is essential to prevent further decompensation and increase survival. Of note, reversibility of liver dysfunction varies significantly across the spectrum of liver disease etiologies, and this should be considered in defining indications and timing for TIPS.

The optimal PCPG decrease after TIPS to control RA remains unclear. Based on available evidence, a one-size-fits-all strategy seems unrealistic and perhaps potentially inappropriate. By contrast, a stepwise approach of progressive stent-graft dilation with careful monitoring of TIPS-driven hemodynamic effects may be a pragmatic way to improve control of ascites and minimize the risk of shunt-related adverse events. Following the widespread adoption of controlled-expansion PTFE-covered stent-grafts, a multicenter RCT with clear standardization of patient evaluations, elements of TIPS procedure, and postprocedural follow-up is urgently needed to clarify the role of small stent-grafts in the management of patients with cirrhosis and ascites. Such a strategy could improve individual patient outcomes and extend the use of TIPS in the setting of ascites.

AUTHOR CONTRIBUTIONS

Review concept: Filippo Schepis and Christophe Moreno; drafting of the key points, pathophysiological consequences of TIPS, technical considerations, conclusion: Alberto Zanetto, Dario Saltini, and Filippo Schepis; drafting of the key points, abstract, overview of ascitic formation, patient selection: Pierre Deltenre and Christophe Moreno; revision: all authors; approval of final version: all authors.

CONFLICT OF INTEREST

Nothing to report.

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