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IM - REVIEW

Transjugular intrahepatic portosystemic shunt (TIPS): current indications and strategies to improve the outcomes

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Abstract

Transjugular intrahepatic portosystemic shunt (TIPS) represents a very effective treatment of complications of portal hypertension. Established indications to TIPS in cirrhotic patients include portal hypertensive bleeding and refractory ascites. Over the years additional indications have been proposed, such as the treatment of vascular disease of the liver, hepatic hydrothorax, hepatorenal syndrome and bleeding from ectopic varices. Indications under evaluation include treatment of portal hypertension prior to major abdominal surgery and treatment of portal vein thrombosis. In spite of these advances, there are still uncertainties regarding the appropriate workup for patients to be scheduled for TIPS. Moreover, prevention and management of post-TIPS complications including hepatic encephalopathy and heart failure are still suboptimal. These issues are particularly relevant considering aging in TIPS candidates in Western countries. Correct selection of patients is mandatory to prevent complications which may eventually frustrate the good hemodynamic results and worsen the patient's quality of life or even life expectancy. The possible role of small diameter TIPS to prevent post-procedural complications is discussed.

Keywords Hepatic encephalopathy · Heart failure · Variceal bleeding · Ascites

Abbreviations

PH	Portal hypertension
HVPG	Hepatic venous pressure gradient
TIPS	Trans-jugular intrahepatic portosystemic shunt
PCG	Portal caval gradient
HE	Hepatic encephalopathy
IGV	Isolated gastric varices
GOV	Gastroesophageal varices
GAVE	Gastric antral vascular ectasia
HRS	Hepatorenal syndrome
PVT	Portal vein thrombosis
BCS	Budd–Chiari syndrome
SOS	Sinusoidal obstruction syndrome
MELD	Model for end-stage liver disease
PV	Portal vein
PTFE	Polytetrafluoroethylene
CHE	Cover hepatic encephalopathy
MHE	Minimal hepatic encephalopathy
LVEF	Left ventricular ejection fraction
sPAP	Systolic pulmonary arterial pressure
mPAP	Mean pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PFO	Patent foramen ovale

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Introduction

Portal hypertension (PH) is the major mechanism leading to complications responsible for morbidity and mortality of cirrhotic patients. PH is defined by a pressure gradient (hepatic

venous pressure gradient, HVPG) above 5 mmHg. However, the main complications of PH usually develop above the threshold of 10–12 mmHg [1, 2]. Prevention and treatment of PH-related complications in cirrhotic patients is based on endoscopic procedures, non-selective beta-blockers, nitrates, vasoactive drugs such as somatostatin and vasopressin analogues, in case of bleeding complications, and diuretics, albumin and paracentesis in case of ascites.

The introduction of transjugular intrahepatic portosystemic shunt (TIPS) in clinical practice has been one of the most relevant improvements in the management of complications of PH [3]. TIPS acts as a side-to-side portosystemic shunt obtained by percutaneously connecting an intra-parenchymal branch of the portal vein and a hepatic vein, with much lower morbidity and mortality compared to surgical shunting [3].

The hemodynamic effect of TIPS is the reduction of portal caval pressure gradient (PCG) obtained by connecting the portal hypertensive district with the systemic circulation (Figs. 1 and 2a), through a low-resistance conduit stabilized by a self-expandable metal stent deployed across the shunt and counteracting the parenchymal recoil (Fig. 2b). It is important to emphasize that currently TIPS is no longer viewed as a salvage therapy or a bridge to liver transplantation, but is indicated for a number of conditions related to portal hypertension where remarkable results on patients' prognosis have been obtained [3–5]. In the present paper, we review TIPS indications, contraindications and potential intra- and peri-procedural complications. In particular, we focus on strategies aimed to limit the occurrence of post-derivative hepatic encephalopathy (HE) and propose a cardiologic workup to identify subjects with a higher likelihood to develop post-TIPS cardiac failure, together with strategies to limit its occurrence.

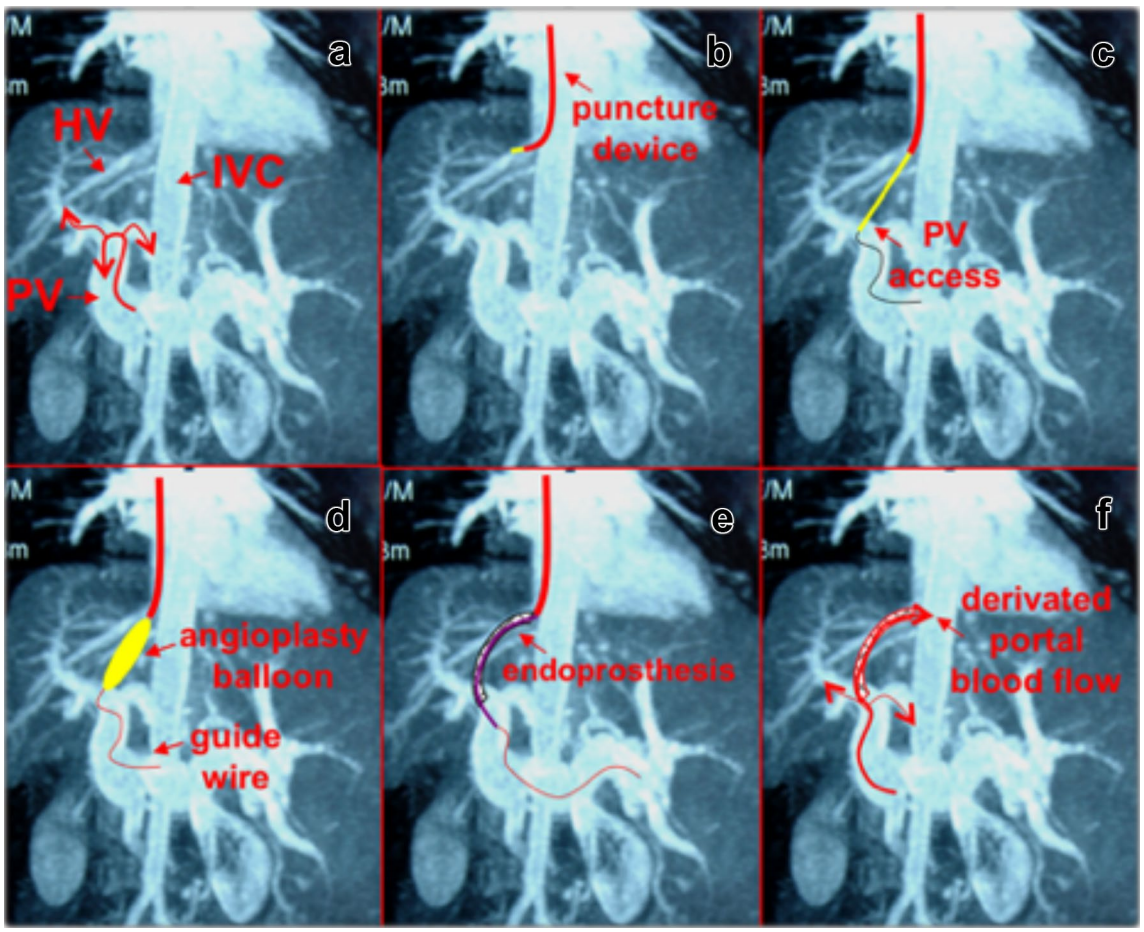

Fig. 1 TIPS technique. **a** representation of vascular districts of interest for TIPS procedure; **b** trans-hepatic puncture device advanced within one of the main HVs after a vascular access is obtained (generally right internal jugular vein); **c** trans-parenchymal puncture of one of the main intra-hepatic branches of PV (real-time ultrasound guidance is advised); *d* balloon dilatation of the parenchyma interposed between the HE and PV branch; **e** deployment of a stent/endoprosthesis within the parenchymal tract to avoid parenchymal recoil; **f** systemic derivation of portal blood flow and consequent drop in PCG. *HV* hepatic vein, *IVC* inferior vena cava, *PV* portal vein, *PCG* portal caval gradient

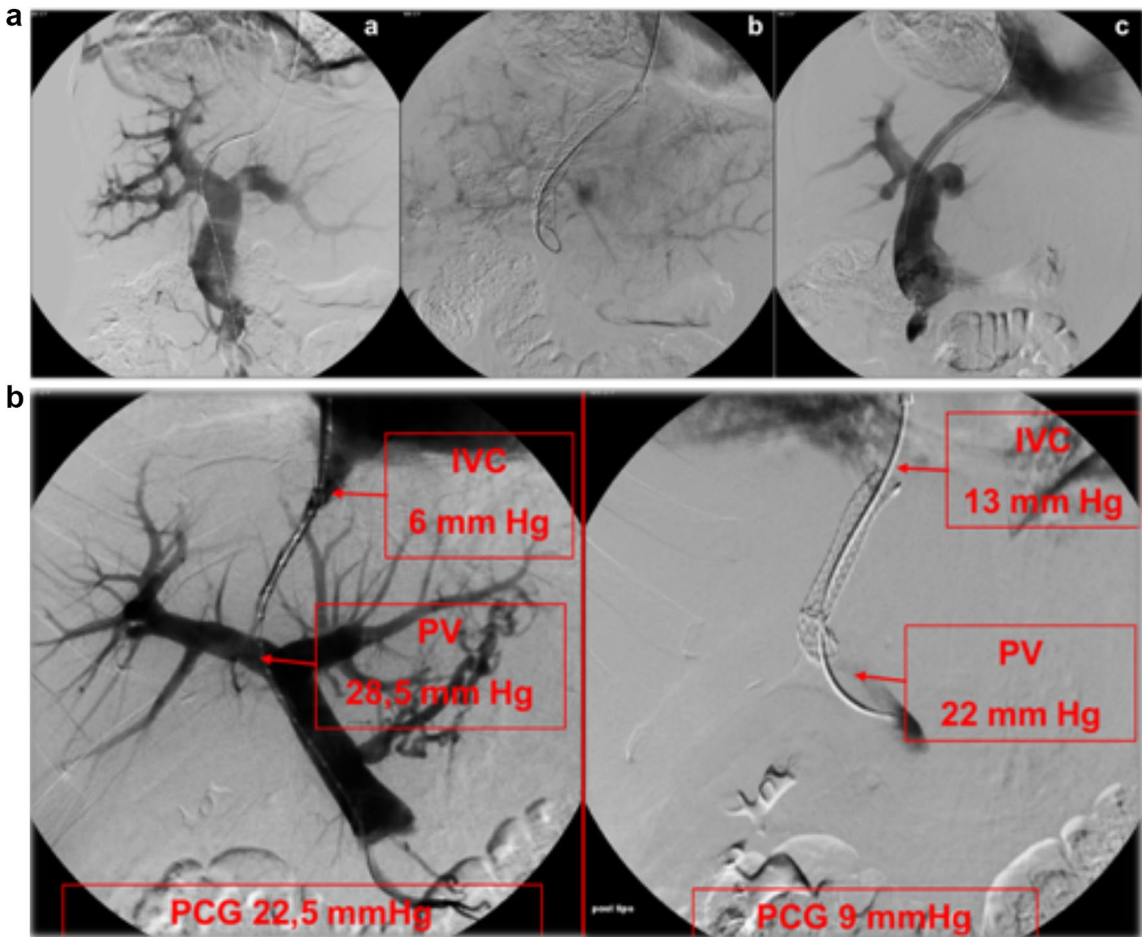

Fig. 2 TIPS procedure (**A**) including hemodynamic determinations (**B**). **A**—a PV access; b endoprosthesis released across the hepatic vein and punctured portal vein branch, within the intra-parenchymal tract; c angiography showing systemic derivation of contrast medium injected into the PV trunk. **B** On the left, basal hemodynamic determinations. On the right, PCG reduction obtained after endoprosthesis deployment. *IVC* inferior vena cava, *PV* portal vein, PCG porta caval gradient i.e. PV pressure—IVC pressure.

TIPS indications

TIPS is directed to the treatment of patients with PH-related complications, mainly bleeding and ascites (Table 1).

Acute variceal bleeding and secondary prophylaxis

In acutely bleeding cirrhotic patients, TIPS placement is indicated at an early time point, within 72 h (ideally ≤ 24 h) in patients at high risk of treatment failure (i.e., Child–Pugh class B with active bleeding at index endoscopy or in Child–Pugh class C score lower than 14 points) [4, 6]. In particular, early TIPS determines a relevant advantage in terms of survival in patients with MELD ≥ 19 or Child–Pugh C cirrhosis, but not in patients with MELD ≤ 11 or Child–Pugh A cirrhosis. For intermediate cases (MELD 12–18 or Child–Pugh B patients), data are uncertain [7].

TIPS should also be indicated in patients with persistent bleeding despite combined pharmacological and endoscopic treatment, as well as in those with severe rebleeding episodes taking place within 5 days from index bleeding [8, 9]. In patients who fail secondary pharmacologic and endoscopic prophylaxis of variceal bleeding, TIPS represents the preferred option [2, 10, 11]. Rapid referral to a center where TIPS is available is necessary for patients suitable for early TIPS or with uncontrolled bleeding and/or early rebleeding.

In addition, TIPS may be employed in cases of bleeding from isolated gastric varices (IGV) or gastroesophageal varices (GOV). However, more data are required in this latter setting to define the timing of the derivative approach, especially for subjects at higher bleeding risk and with a worse prognosis, such as those bleeding from IGV and GOV2. Indeed, the use of TIPS as a first-line prophylactic treatment of bleeding from IGV and GOV2 vs. repeated cyanoacrylate injections or non-selective beta-blockers needs further investigation [11].

Hemodynamic non-responders to secondary pharmacologic prophylaxis of PH-related bleeding (evaluated

Table 1 Indications for TIPS

Portal hypertension-related bleeding due to esophageal or gastric varices
High-risk acutely bleeding patients
Rescue treatment for persistent bleeding or early rebleeding (occurring within 5 days from index bleed)
Failure of pharmacological/endoscopic secondary prophylaxis of variceal bleeding
Other types of portal hypertension-related bleeding
Recurrent bleeding from ectopic varices or stomas, for which non-selective beta-blockers and/or endoscopic treatment fails
Severe transfusion-dependent portal hypertensive gastropathy, in which non-selective beta-blockers and/or endoscopic treatment fails
Vascular diseases of the liver
Portal vein thrombosis
Budd–Chiari syndrome
Sinusoidal obstruction syndrome related to solid organ transplantation
Nodular regenerative hyperplasia
Portal hypertension complications related to hepatic myeloid metaplasia
Ascites
Refractory ascites
Refractory hydrothorax
Hepatorenal syndrome
Miscellanea
Treatment of portal hypertension prior to gastrointestinal/abdominal surgery
Portal hypertension-related complications in malignancies (palliation)

Marginal indications not supported by sufficient and/or concordant data are reported in italic font. In the hepatopulmonary syndrome (not reported in the table) TIPS was shown to substantially ameliorate hypoxemia in some patients. Moreover, TIPS can be safely performed for the treatment of other complications of portal hypertension in the presence of hepatopulmonary syndrome and reasonably used as a bridge toward liver transplantation

by HVPG assessment) represent an additional group which could be investigated for TIPS placement [10, 12]. Indeed, adding endoscopic treatment in these patients does not reduce the high rebleeding risk [12]. Earlier TIPS placement should be evaluated in case of comorbidities that worsen the prognosis of bleeding episodes, or when the presence of gastroesophageal varices limits the therapeutic approach to other diseases (i.e., coronary artery disease). Along these lines, patients with intolerance/contraindication to non-selective beta-blockers should also be considered for earlier TIPS in secondary prophylaxis.

In case of uncommon bleeding sites such as ectopic varices, portal hypertensive gastropathy, and stomas, local endoscopic treatment is often impossible or ineffective. In these cases, TIPS may be employed not only to reduce portal pressure, but also to embolize the feeding vessels. Moreover, TIPS facilitates further re-intervention in case of rebleeding [11, 13, 14]. In contrast, persistent or recurrent bleeding from gastric antral vascular ectasia (GAVE), which may be associated with cirrhosis but is not pathogenetically related to PH, may not be effectively managed by TIPS [11].

Refractory ascites, hepatorenal syndrome and hepatic hydrothorax

Current definitions for these conditions are reported in Supplementary Tables 1, 2 and 3. The treatment of refractory ascites is another common indication for TIPS in cirrhotic patients. Large volume paracentesis (LVP) with concomitant infusion of albumin is a well-established treatment of this condition, but is associated with negative effects on systemic hemodynamics, renal function and, with time, on nutritional status [15–18]. Thus, the use of paracentesis as a long-term therapeutic approach may be suboptimal. Although TIPS is effective for the treatment of refractory ascites, the major concern for this indication was related to the uncertain effect on patient's survival, reported in different studies. However, two meta-analyses, which eliminated literature heterogeneity [19] and analyzed individual patients' data [5], confirmed the efficacy of TIPS in this group of cirrhotic patients, resolving ascites and/or facilitating its pharmacological treatment. More important, these studies showed that patients with TIPS have better survival compared to patients chronically submitted to large volume paracentesis. Remarkably, the prognosis of these patients appears to be improved if TIPS is placed earlier in the course of the disease, before a compromised nutritional status develops [5, 20]. These data

suggest the opportunity to investigate the effects of TIPS placement at an earlier stage of dysfunction, i.e., with recurrent, but not yet refractory, ascites.

The use of TIPS in hepatorenal syndrome (HRS) is limited by the fact that these patients suffer from a more advanced hepatic dysfunction as regrettably often observed in patients affected by refractory ascites belatedly referred for TIPS. Additionally, the availability of effective pharmacological treatments for HRS [21] further limits TIPS application to this condition. Nevertheless, TIPS may have a role in preserving renal function in patients listed for liver transplantation who respond to pharmacological treatment of HRS [22, 23].

Patients with advanced liver disease may present with hepatic hydrothorax. It is assumed that diaphragmatic defects allow direct passage of peritoneal fluid in the pleural cavity, a process that is facilitated by the negative pressure during inspiration, coupled with a persistently positive pressure in the abdominal cavity. Compared to other treatment options, TIPS is highly effective in controlling pleural effusion when it is recurrent or refractory to medical treatment. Moreover, these patients could have a reasonably good long-term prognosis controlling the underlying refractory ascites [24].

Portal vein thrombosis

Vascular diseases of the liver represent an emerging and relevant indication to TIPS. Portal vein thrombosis (PVT) is a frequent complication of cirrhosis and associated particularly with moderate–severe liver failure, hepatocellular carcinoma, previous gastrointestinal bleeding and older age. PVT in cirrhosis is often an underestimated and undertreated condition [25].

Cirrhotic and non-cirrhotic PVT is an area of active investigation in TIPS practice.

Excellent rates of improvement and recanalization of PVT with TIPS have been reported [26]. However, anticoagulation is also associated with similar results [11, 27]. The simultaneous presence of complications of portal hypertension that could potentially limit or delay the use of anticoagulants and the progression of thrombosis (after a maximum of 6 months treatment) are the main determinants that could argue in favor of TIPS. Derivative treatment must be considered in patients listed or suitable for liver transplantation [11]. Interestingly, because portal perfusion is already compromised by PVT, some of the deleterious effects of the shunt (detailed below) are expected to be limited. Notably, TIPS may also be proposed to control PH-related complications in patients with cirrhotic or non-cirrhotic portal vein thrombosis with cavernomatous transformation if a relevant communication exists between a patent intrahepatic portal vein branch and an extra-hepatic collateral vessel to be used as a valid "landing zone" or if recanalization of the native portal vein could be obtained [11, 28, 29]. In a recently published systematic review and meta-analysis including 18 studies, the technical success rate was 86.7%, with whole recanalization in 73.7% and portal patency in 86.9% of cases [30]. On the other hand, HE was found in about one-quarter of patients.

In conclusion, the use of TIPS in the management of PVT is feasible and effective in achieving a significant and sustainable reduction in clot burden with a low risk of major complications. TIPS should be considered as a viable treatment option in patients with PVT. Given the limited amount of randomized comparative studies reported, additional trials are warranted to assess the safety and efficacy of TIPS as a treatment modality in PVT, in comparison to other treatment options, such as anticoagulation.

'Neoadiuvant' TIPS

Whether TIPS should be proposed to cirrhotic patients scheduled for elective major surgery, with previous episodes of decompensation or at high risk of decompensation for a barely compensated disease, remains debatable [31]. Decompensation may be severe and even irreversible, and may benefit from derivative treatment prior to surgery. These latter indications clearly warrant future, specifically designed studies, before entering clinical practice.

TIPS contraindications

The overall prognosis of the patients should be carefully evaluated prior to TIPS placement, and the procedure-related risks cautiously weighed against the expected benefit(s). In the presence of relative contraindications (Table 2) [11], an extensive discussion with the patient is mandatory, and multidisciplinary interaction with other specialists may support the physician in the decision-making process. History of episodes of HE before TIPS, particularly if not precipitated by modifiable factors, advanced age, severe renal failure, and plasma bilirubin above 3 mg/dL are considered main predictors of poor TIPS outcome and therefore represent relative contraindications. Moreover, severe heart failure and/or severe pulmonary hypertension exposes patients to an unacceptable risk of life-threatening pulmonary congestion (see the specific section below). Several scoring systems have been proposed to predict TIPS outcome [32]. Child–Pugh score appears inadequate to discriminate among patients with more compromised liver function due to its "ceiling effect" and its dependence on subjective evaluation. Model for end-stage liver disease (MELD) score was specifically designed and was found to be the most reliable. A significant

Table 2 Absolute and relative contraindication to TIPS placement

Absolute
Heart failure
Severe pulmonary hypertension (mPAP > 45 mmHg at RHC)
Unrelieved biliary obstruction or Caroli's disease
Uncontrolled systemic infection/sepsis
Multiple hepatic cysts
CPS ≥ 14 points (> 11 points for RA as indication), bilirubin > 5 mg/dL, MELD > 18
Absence of vascular access
Relative
Severe organic renal failure (serum creatinine > 3 mg/dL)
HCC, especially central and large if interjected in the expected TIPS route
Moderate pulmonary hypertension (mPAP within 35–45 mm Hg)
Serum total bilirubin > 3 mg/dl
Persistent or recurrent HE (especially if not precipitated by modifiable factors) grade ≥ 2 (West-Heaven scale) despite adequate treatment
INR prolongation (INR ≥ 5) or thrombocytopenia (< 20,000/cm^3)
Presence of portal vein thrombosis resulting in a portal cavernoma

Relative contraindications mainly comprise anatomic alterations and patients' features that can complicate TIPS procedure in terms of technical success and or potential higher incidence of complication. Those must be balanced with the clinical scenario that indicate TIPS procedure

PH portal hypertension, *mPAP* mean pulmonary artery pressure, *RHC* right heart catheterization, *CPS* Child–Pugh score, *RA* refractory ascites, *HCC* hepatocellular carcinoma, *PVT* portal vein thrombosis, *HE* hepatic encephalopathy, *INR* international normalized ratio

survival benefit was recently shown in patients with a pre-TIPS MELD score not higher than 12 [20].

Intra-procedural complications

Unfortunately, prospective studies investigating intra-procedural complications are lacking, and for a comprehensive review of this subject the reader should refer to Ripamonti et al. [33] (Table 3). Complications related to the attempt to puncture the portal vein (PV) include perforation of the liver capsule with or without intra-peritoneal bleeding described in as many as 33% and 1–2% of the procedures, respectively. Further life-threatening complications are extra-hepatic PV perforation, and injury to the bile duct or the hepatic artery, eventually leading to formation of fistulas. The extensive use of ultrasonographic assistance for portal vein puncture and a clear knowledge of liver vascular anatomy are expected to significantly decrease the incidence of these complications and is therefore strongly recommended [11, 34].

Post-TIPS major complications

Shunt dysfunction

Occurrence of shunt dysfunction and HE have been reported in 30–70% [3, 35] and 30–55% [36] of cirrhotic patients within the first year, respectively. The availability of polytetrafluoroethylene (PTFE)-covered endoprotheses has dramatically reduced shunt dysfunction related to intimal proliferation and the occurrence of shunt thrombosis that results in recurrence of portal hypertension-related complications [3, 37–40]. Dedicated covered stents have been preferentially used in the Western countries since they determine a meaningful drop in the 2-year dysfunction compared to bare ones [41].

On the other hand, the occurrence of HE may still have a deep impact on the patient's quality of life, especially in subjects affected by refractory ascites. In these patients, where the survival benefit of TIPS placement is more debated, a negative impact of the procedure on the quality of life could be detrimental. The possible occurrence of heart failure, even in the absence of pre-exiting overt underlying heart disease represents another emerging drawback of TIPS that potentially affects both the patient's quality of life and life expectancy.

Post-derivative HE

HE is a neuropsychiatric syndrome caused by liver failure and/or portal-systemic shunt. It presents with a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alteration to coma [42]. Post-TIPS HE generally belongs to types B and/or C, i.e., results predominantly from portosystemic shunting and from hepatocellular failure, respectively [43]. Factors recognized to confer an

Table 3 Complications related to TIPS procedure

Intra- and post-procedural complications
Carotid artery puncture with hematoma
Heart arrhythmias
Pneumothorax
Laceration of IVC during trans-caval puncture (during DIPS)
Hepatic capsule perforation or laceration
Non-target organ puncture/injury/fistula (mainly bile tract, gallbladder, hepatic artery, kidney)
PV wall injury
Extra-hepatic PV laceration (intra-peritoneal bleeding)
Stent misplacement/migration/recoil (wall stents)
Contrast dye induced allergic reaction
CIN
Sepsis/endotipsitis
Heart failure
Stent related haemolysis
Acute liver failure/partial Budd–Chiari syndrome
Shunt occlusion or stenosis and thrombosis
HE (new or worse/chronic)
Radiation injury

The availability of self-expandable polytetrafluoroethylene-covered endoprostheses (PTCE) dramatically reduces the incidence of shunt dysfunction, hence improving its long-term patency. Therefore, the main drawback of TIPS is the occurrence of hepatic encephalopathy (30–55% of patients within the first year of TIPS placement). Among potentially severe intra-procedural complications, hepatic capsule perforation is the most frequent while the others are infrequent especially if ultrasonography guidance is employed. Partial Budd–Chiari syndrome (generally followed by complete recovery) due to occlusion of the hepatic vein employed for TIPS deployment and probably concomitant protrusion of the covered portion of the endoprosthesis in the portal vein branch is an emerging issue of PTCE

IVC inferior vena cava, *DIPS* direct intrahepatic portosystemic shunt, *PV* portal vein, *CIN* contrast dye induced nephropathy, *HE* hepatic encephalopathy

increased risk of post-TIPS HE include advanced age, a low post-TIPS PCG (particularly if lower than 10 mmHg), a large diameter of the shunt, poor hepatocellular function, previous episodes of HE or covert HE (CHE), high serum creatinine, hyponatremia, low baseline albumin levels, arterial hypotension, bare vs. covered stents (expected to be lower with covered devices) and sarcopenia [11]. Currently, prevention of post-TIPS HE is mainly based on a careful selection of the patient, to identify known risk factors or to "uncover" CHE [43, 44] that includes patients affected by minimal (MHE) and grade I HE. MHE and grade I HE are defined as the presence of test-dependent or clinical signs of brain dysfunction in patients with chronic liver disease, respectively. Clearly, these patients are not disoriented temporally and spatially and do not show asterixis. Identification of subjects affected by CHE could be particularly relevant when the indication to TIPS placement is marginal and for those patients in whom the possible occurrence of HE is not counterbalanced by a clear effect on survival.

Montagnese et al. [44] reported that CHE is a heterogeneous entity that should be screened for by a combination of clinical, neurophysiological and neuropsychological indexes. However, their agreement is poor and conflicting results among different tools have been obtained. Nevertheless, in grade I HE, electroencephalography and paper-and-pencil psychometry predicted HE-related hospitalization [44] and suggested that the association of these two tests may represent a pragmatic way to screen for CHE. A further promising and easily obtainable screening test for HE is the adjusted animal naming test that showed excellent correlation with psychometric score and electroencephalography findings [45]. Nonetheless, the significance of a diagnosis of CHE in candidates to TIPS placement remains uncertain, due to confounding factors related to concomitant medications and/or episodes of decompensation that potentially have an independent negative effect on brain function, facilitating episodic HE. For example, in bleeding subjects, psychometric tests are barely applicable since bleeding may affect neurological performance per se. On the contrary, in patients affected by refractory ascites, TIPS could improve factors such as systemic hemodynamics (low mean arterial pressure), serum sodium levels (hyponatremia), renal function, and nutritional status and sarcopenia, which potentially worsen brain function and affect clinical and neuropsychological indexes [46].

The above considerations underscore the need for identification of more sensitive prognostic scores [47]. Indeed, national and international registries on TIPS practice are being designed to collect data from large patients' cohorts. The results of these studies will be instrumental to develop newer prognostic models. Technical refinements in TIPS procedure aimed at limiting the occurrence of HE are also emerging. Indeed, a large diameter of the shunt and the consequent post-derivative low PCG are critical factors for the appearance of HE [48]. TIPS affect hepatic hemodynamics by reducing portal blood inflow to hepatocytes, which makes the hepatic perfusion strongly dependent on hepatic artery inflow [49]. Cirrhotic patients with a poor hepatic artery buffer response could therefore experience a hepatocellular ischemic injury that affects the residual hepatic function [49]. Along these lines, Mullen et al. [50] hypothesized that in patients with an insufficient hepatic artery buffer response, TIPS could provoke an insufficient second-passage hepatic clearance (through the hepatic artery) of circulating neurotoxins responsible for HE [42]. In fact, cirrhotic patients with a hepatofugal portal flow or PVT have a lower likelihood to experience post-TIPS HE due to a pre-existing increased arterial inflow [51].

A number of clinical observations and the measurement of the portal pressure gradient support the relationship

between post-TIPS HE and the amount of portal blood shunted into the systemic circulation. In fact, post-TIPS HE may be improved by reduction of the shunt diameter [52]. A PCG lower than 10 mmHg is clearly associated with a higher likelihood to develop HE, and the optimal end-procedural PCG that warrants protection from PH-related complications, with a lower burden of HE, is between 12 and 10 mmHg [5, 48]. However, this interval appears difficult to be reached in clinical practice.

Interesting data suggest that a multi-step dilatation approach for TIPS deployment in patients affected by refractory ascites could be rational to reduce post-TIPS HE [53, 54]. It is conceivable that positioning a TIPS of smaller diameter (i.e., endoprostheses sub-dilated with respect to their maximal, nominal, diameter) would have a lower effect on hepatic perfusion, allowing the hepatic artery buffer response to gradually develop with time. Remarkable results have been recently obtained in a multicenter Italian study evaluating the effects of under-dimensioned endoprostheses on the control of complications of portal hypertension, and on the eventual occurrence of HE [55]. It was showed that the diameter of PTFE-covered endoprostheses could be successfully modulated and maintained over time. More important, TIPS deployment to a diameter of ≤ 6 mm vs. > 6 mm (from 7 to 10 mm) afforded similar control of PH-related complications, but with a significantly lower burden of HE (27% vs. 54% at 1 year). These promising data could be explained by a lower likelihood to develop a post-derivative PCG lower than 10 mmHg, which is associated with a lower risk of HE [48]. Accordingly, the percentage of patients with post-TIPS PCG below 10 mm Hg was significantly lower in underdilated subjects. Bleeding patients with partial hemodynamic response (final PCG higher than 12 mmHg) could be immediately subjected to further endoprostheses dilatation, while in patients affected by refractory ascites further dilatation can be reasonably delayed and reserved to those with absent or insufficient clinical response during follow-up [11]. Notably, it cannot be excluded that, similarly to patients in secondary pharmacological prophylaxis of variceal bleeding [1], a partial but substantial hemodynamic response after placement of an under-dimensioned TIPS (at least 20% PCG reduction) may adequately prevent rebleeding. Nevertheless, in approximately half of the underdilated patients a complete hemodynamic effect was observed. Notably, no differences in the incidence of TIPS dysfunction was observed comparing underdilated patients with the control group. Specifically designed randomized controlled studies to further validate the above strategies are warranted.

Cardiopulmonary complications

Vasodilatation of the splanchnic arterial bed is considered the primary pathophysiologic mechanism that maintains the portal hypertensive state [56] and leads to ascites formation in cirrhotic patients [57]. The peripheral vasodilatation hypothesis proposes that an early reduction in effective volume induced by vasodilatation is partially compensated by the activation of sodium-retaining systems aimed to increase total blood volume, to maintain arterial pressure and renal perfusion [58]. However, activation of these mechanisms would be insufficient without a parallel increase in cardiac output (i.e., hyperdynamic circulation). Indeed, in advanced stage of the disease, blunted contractile responsiveness and/or altered diastolic relaxation of the heart, a syndrome known as "cirrhotic cardiomyopathy" [59] (Table 4) has been suggested as a key factor for the development of refractory ascites, hyponatremia and the hepatorenal syndrome [60]. Although the exact prevalence of cirrhotic cardiomyopathy is not clearly defined, as many as 50% of end-stage patients undergoing liver transplantation show signs of cardiac dysfunction [58] and about 7–21% of patients die from heart failure in the post-transplantation period [61]. Several cardiac complications have been described following TIPS insertion [62], including appearance of clinically evident heart failure (i.e., pulmonary edema) in patients treated for refractory ascites, reported to be around 10% [63].

TIPS insertion leads to significant hemodynamic changes with a sudden increase in cardiac preload [64, 65] and output that rapidly worsen the hyperdynamic circulatory state [66, 67]. This phase is without consequences and transitory only in patients with a good heart competence (i.e., systolic, diastolic, and electric) [62, 68, 69]. In addition, the effects of cirrhotic cardiomyopathy after TIPS positioning may reflect on the liver rather than the cardiopulmonary system. As previously discussed, TIPS creation makes liver perfusion dependent on arterial buffer response that is preserved in cirrhotic liver. However, local blood flow can become insufficient to cover the metabolic needs of the liver as a consequence of a blunted heart response to the increased pre-load. This worsens liver function and patient survival. Moreover, a high-output heart failure may also explain the lack of efficacy of TIPS in some cases of refractory ascites, with the transition from hepatic to cardiac ascites.

Based on the above concepts, identification of determinants and predictors of cardiac complications following TIPS is mandatory. However, it remains difficult to stratify the risk of cardiac failure in cirrhotic patients, candidate to TIPS, because scientific evidence is still limited and reliable predictors are not currently available [11, 70]. The left ventricular ejection fraction (LVEF), which reflects systolic function, is normal in patients with cirrhosis at rest [71] and it should not rule out the diagnosis of cardiomyopathy [72]. Conversely, an attenuated LVEF has been shown after several stimuli such as exercise, sodium load or orthostatism [71, 72]. There is evidence suggesting that patients with diastolic dysfunction defined by a

Table 4 Cirrhotic cardiomyopathy definition and diagnostic criteria

Definition: A cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease
Main diagnostic criteria
Systolic dysfunction
Blunted increase in cardiac output with exercise, volume challenge or pharmacological stimuli
Resting EF < 55%
Diastolic dysfunction
E/A ratio < 1.0 (age-corrected)
E/e' ratio ≥ 10
Prolonged deceleration time (> 200 ms)
Prolonged isovolumetric relaxation time (> 80 ms)
Additional criteria
Prolonged *Q–T* interval
Abnormal chronotropic response
Increased myocardial mass
Increased BNP and pro-BNP
Increased troponin I

EF ejection fraction, *BNP* brain natriuretic peptide, *E/A* ratio of peak velocity flow in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave), *E/e'* ratio of peak velocity flow in early diastole (the E wave) to peak mitral annular velocity during early filling (the e' wave)

E/A ratio ≤ 1, a common feature in decompensated cirrhotics [62, 67], have a less effective clearance of ascites after TIPS, and their probability of survival is lower than the one of patients with an E/A ratio > 1 [73]. However, E/A is highly determined by preload, and age-related [74]. Therefore, additional non-invasive parameters including the E/e' ratio are being currently tested as more sensitive measures of diastolic dysfunction [74]. With this in mind, a multi-specialist group has recently proposed a pre-TIPS cardiologic workup [11] including right heart catheterization in all patients at the time of TIPS positioning. In particular, this procedure is justified to confirm pulmonary hypertension in case of systolic pulmonary arterial pressure (sPAP) values on Doppler echocardiography higher than 50 mmHg. TIPS should be avoided in all patients in whom severe portopulmunary hypertension (mean pulmonary arterial pressure, mPAP ≥ 45 and pulmonary capillary wedged pressure, PCWP ≤ 15 mmHg) or severe post-capillary pulmonary hypertension (mPAP ≥ 45 and PCWP > 15 mmHg) are diagnosed. Moreover, in case of moderate pulmonary hypertension (mPAP between 35–45 mmHg), TIPS should be positioned only in patients at high risk of death (i.e., variceal bleeding refractory to combined endoscopic/pharmacologic treatment) or creating small caliber TIPS and with post-TIPS intensive monitoring of cardiac and kidney function. Mild pulmonary hypertension (mPAP between 25 and 34 mmHg) does not represent a contraindication to TIPS positioning. Nevertheless, TIPS occlusion is indicated in cases of cardiac failure unresponsive to both pharmacological therapy and reduction of stent diameter.

The cardiologic workup may also include contrast echocardiography aimed to demonstrate a patent foramen ovale, particularly in patients with portal vein thrombosis. Foramen ovale may serve as a conduit for paradoxical embolization, the occurrence of which has been reported following TIPS [75–78]. Patients submitted to TIPS may present some peculiarities that could increase the likelihood of paradoxical embolization, if a PFO is present [76, 79]. Therefore, contrast-enhanced echocardiography should be performed at least in high-risk patients as expressed by pre-existing PVT and/or in the presence of a hypercoagulable state, increased pulmonary pressures, or history of cerebral ischemic events of undetermined etiology. Moreover, as we reported [76], percutaneous closure of PFO should be considered in patients with concomitant risk factors for paradoxical embolization.

An interesting scenario is represented by patients affected by chronic organic renal failure, even with end-stage renal disease requiring renal replacement therapy. In these latter subjects, even in the absence of cirrhotic cardiomyopathy, a prompt post-procedural dialysis and strict fluid management are warranted, especially in patients already on renal replacement therapy, to prevent pulmonary edema and ischemic hepatitis. Moreover, right atrial pressure is a determinant of the afterload to TIPS and could therefore affect its efficacy if too high. The risk of marked encephalopathy appears much higher than in patients with normal renal function or mild renal insufficiency. This could be explained at

least in part by the important role played by the kidney in ammonia generation. Therefore, in this setting TIPS should be reserved to patients eligible for transplantation [80] or to individually selected cases with life-threatening portal hypertension-related bleeding complications or requiring frequent large volume paracentesis that causes incipient detrimental effects on the nutritional status or substantially worsens the patient's quality of life.

Conclusions

TIPS availability has been one of the most relevant improvements in the management of PH complications. However, potentially relevant drawbacks could limit the benefits of this procedure. TIPS dysfunction represented a major concern due to recurrence of PH complications. However, the availability of covered stents substantially overcame this limitation. The possible occurrence of HE and post-derivative heart failure still represent a relevant aspect to be addressed. Available data support the development of technical refinements, such as TIPS undersizing, aimed at preserving hepatic perfusion while maintaining hemodynamic effect of TIPS and preventing PH complication recurrence. A careful selection of patients to be derived, employing available tests and developing more sensitive prognostic indexes, represents a parallel strategy to avoid post-derivative HE. Selection of patients should include a careful cardiopulmonary workup, including invasive procedures such as right heart catheterization when indicated. Anyhow, intensive monitoring of cardiac and kidney function should be constantly implemented to limit the effects of post-TIPS cardiac dysfunction. In conclusion, TIPS represents the most powerful approach to control potentially lethal PH complications. However, the above complications could frustrate these relevant results by worsening the patient's quality of life or even life expectancy.

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Compliance with ethical standards

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Informed consent Written informed consent was obtained from each patient.

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