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REVIEW

Transjugular Intrahepatic Portosystemic Shunt: An Update

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Abstract:
It is more than 50 years since the concept of transjugular intrahepatic portosystemic shunt (TIPS) was first introduced as a percutaneous procedure for patients with refractory variceal bleeding and ascites. TIPS has become widely accepted in the management of complications of portal hypertension because it is less invasive than surgery. In the early days of TIPS, complications included the poor long-term patency of the stent and a high incidence of hepatic encephalopathy. In addition, an excessive shunt diameter after TIPS often resulted in severe hepatic encephalopathy. Although recent covered stents have significantly reduced shunt dysfunction, the development of hepatic encephalopathy and early liver failure remain to be crucial post-TIPS complications. This study reviews the current literature on the status of TIPS in the treatment of cirrhosis.

Keywords:
portal hypertension, transjugular intrahepatic portosystemic shunt, TIPS, refractory ascites, variceal bleeding
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Introduction

In Japan, transjugular intrahepatic portosystemic shunt (TIPS) for hepatic ascites is not commonly performed. In the United States, ascites is one of the main indications for TIPS, with 80% to 90% of all TIPS being elective procedures [1, 2].

Recently, the effectiveness of early TIPS (TIPS performed within 72 h) has been reported for ruptured gastroesophageal varices associated with liver cirrhosis, and the expansion of indications for TIPS has been attracting greater attention [3-5]. Here, we discuss the current issues involving TIPS.

History

Rösch et al. introduced TIPS as a percutaneous procedure in 1969 using animal experiments [6]. Initially, however, the pathways created in the liver parenchyma could not be kept open for long periods due to the lack of a stent, and the technique could not be clinically applied.

Later, a balloon catheter for angioplasty was developed, and in 1982, Colapinto et al. used balloon dilatation of the TIPS tract clinically for the first time [7] performing TIPS in 15 patients with severe liver cirrhosis. They found that portal vein decompression and varices improved, but long-term benefits were difficult to attain. Only two patients survived more than 1 year without rebleeding, and long-term portal vein decompression could not be maintained by balloon dilation alone.

The expandable metallic stent developed in the mid-1980s made TIPS more practical. In animal experiments, Palmaz et al. demonstrated the development of neointimal proliferation on the luminal surface of the stent [8], and Rösch et al. showed that the stent maintained the patency of the shunt tract [9]. In 1989, Richter et al. performed TIPS using metallic stents similar to stents used in current techniques [10], and many cases were subsequently reported in Europe and the United States.

In Japan, TIPS was first employed in 1992 by Yamada et al. [11]. In 1995, Nishimine et al. reported employing a partly covered self-expanding stent [12]. Outside Japan, the VIATORR stent (Gore & Associates, Flagstaff, AZ, USA) became commercially available in 2003. This expanded the use of polytetrafluoroethylene (e-PTFE) covered stent grafts, which are now widely used in TIPS. Unfortunately, even as of 2022, there are no commercialized e-PTFE covered stents approved for TIPS in Japan.

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Basic Pathophysiological Principles

TIPS is one procedure that percutaneously reduces portal pressure effectively and rapidly. This method decreases portal resistance, increases portal inflow, immediately decompresses stasis in the mesenteric veins, and reduces portal pressure by approximately 50%. The reduction in portal pressure rapidly increases the hepatic arterial and total hepatic perfusion due to the extrahepatic hemodynamics during the first year [13]. Systemic activation of the vasoconstrictor system returns to normal within 6 months, and changes in intracellular signaling pathways, gene expression, and activation of vasoactive proteins in different vascular regions improve vasoconstriction [13-15].

Allegretti et al. observed changes in systemic and local vasoactive systems in patients 6 months after TIPS procedures. Improvements in renal function, bacterial migration, and reduction of systemic inflammation are seen as little as 2 weeks after the procedure [16]. Furthermore, TIPS stent placement induced an immediate increase in effective blood volume, leading to improvements in renal perfusion and sodium drainage and ascites management and a reversal of hepatorenal syndrome [16, 17].

Pre-therapeutic Imaging and Techniques

Pre-procedural images, particularly contrast-enhanced computed tomography, are reviewed to assess the portal vein patency, location of the portal vein bifurcation, the orientation of the portal veins to the hepatic veins, and the presence of gastroesophageal varices and other portosystemic shunts.

The procedure is performed with monoplane or preferably biplane digital subtraction angiography equipment from the left or right internal jugular vein. Approaching from the left internal jugular vein is useful when the anterior portal vein is at an acute angle to the right hepatic vein.

The TIPS set, usually a Rösch-Uchida TIPS set (Cook Medical; Bloomington, IN, USA), is introduced through the internal jugular vein and IVC into the right hepatic vein. The needle puncture of the liver, from the proximal portion of the right hepatic vein to the distal portion of the right main portal branch, is performed with the cannula rotated approximately 90° anteriorly. During the portal vein puncture, a right hepatic arterial guidewire insertion is useful for guidance.

Carbon dioxide wedged hepatic venography before the puncture and ultrasound guidance during the puncture help identify the portal vein. The needle tract is dilated with a balloon catheter, usually 8 mm, and an e-PTFE stent graft is inserted to maintain tract patency. Since bile leak is the most common cause of shunt obstruction, the risk of shunt obstruction can be greatly reduced by using an e-PTFE covered stent [18].

Additional balloon dilatation may be performed to finalize the shunt diameter. The shunt blood flow is proportional to the fourth power of the radius(a), as shown by the Hagen-Poiseuille law: $Q = (\pi a4/8\ \mu L)\ \delta p$. Therefore, the creation of an excessive shunt diameter increases the risk of subsequent hepatic encephalopathy. During TIPS, ruptured gastric varices are generally embolized simultaneously, but this is controversial in unruptured cases.

Combined therapy (TIPS and transvenous variceal obliteration) can improve the clinical outcome in patients with bleeding or high-risk gastric varices [19]. Evidence for anticoagulation is low, but intraoperative heparin plus dual antiplatelet therapy for 6 months after shunt creation has been used [20].

Table 1. The Main Outcomes for Esophageal Varices.

	Odds ratio [OR]	Confidence interval [CI]	P
Variceal rebleeding	0.32; 95%	0.24–0.43	<0.00001
Deaths from rebleeding	0.35; 95%	0.18–0.67	0.002
Post-treatment encephalopathy	2.21; 95%	1.61–3.03	<0.00001

Classical Indications and Contraindications for TIPS

The primary indicators for TIPS are variceal bleeding with secondary prophylaxis, refractory ascites, and refractory variceal bleeding. Clinical indications include hepatic hydrothorax and Budd-Chiari syndrome. Contraindications of TIPS include congestive heart failure, severe tricuspid regurgitation, and severe pulmonary hypertension (mean pulmonary pressure >45 mmHg). While many risk factors are associated with postprocedural death, patients with Model for End-stage Liver Disease (MELD) scores >15 are at a high risk of postprocedural death [21, 22]. Physicians commonly exclude patients with high MELD scores (≥15-18) [23, 24].

MELD score developed in 2000 assesses mortality in patients who are to undergo the creation of TIPS [25]. This standard was established using the data of patients undergoing elective TIPS and has since proven to be an accurate, robust metric for prognostic patient risk stratification and estimating the outcome of planned TIPS procedures.

Variceal Rebleeding

A meta-analysis [26] of the main outcomes after TIPS for esophageal varices (**Table 1**) showed a decreased incidence in variceal rebleeding and deaths from rebleeding and an increased rate of post-treatment encephalopathy, all positively correlating with TIPS.

Conversely, hospitalization days (weighted mean difference = -0.21; 95% CI, -3.50 to 3.08; P = 0.90) and deaths from all causes (OR = 1.17; 95% CI, 0.85-1.61; P = 0.33) negatively correlated in all patients with and without TIPS.

In 2010, early TIPS was compared with pharmacotherapy and endoscopic variceal ligation (EVL) (**Table 2**) in 63 randomly selected patients with Child-Pugh class B or C at a

Table 2. Early Tips Compared with Pharmacotherapy and Endoscopic Variceal Ligation (EVL) in Patients with Child–Pugh Class B or C at a High Risk of Treatment Failure [24].

	Early TIPS n = 32	Pharmacotherapy and EVL n = 31	P
Rebleeding/failure to control bleeding	1	14	0.001
1-year actuarial survival rate	86%	61%	< 0.001

high risk of treatment failure. Patients with early TIPS were less likely to have gastrointestinal bleeding, esophageal varices, and hepatic hydrothorax.

Free of Hepatic Encephalopathy

The main outcomes for refractory ascites and esophageal varices have also been reported (**Table 3**) in a meta-analysis [26]. Compared to paracentesis, TIPS significantly improved liver transplant-free survival. TIPS also significantly decreased liver disease-related death, recurrent ascites, and hepatorenal syndrome. However, TIPS increased the risk of hepatic encephalopathy (HE) and severe HE [26]. HE is refractory to these forms of treatment and develops in 3%-7% of patients [27].

Shunt Patency

Several studies have demonstrated in TIPS creation, patency rates of e-PTFE stents in the short-term prove to be superior to bare metal stents [28-30]. However, even when using standard techniques, e-PTFE-coated stents lose patency in approximately 10%-20% of patients at 2 years [31]. Furthermore, there is an agreement that the initial positioning of bare metal stents at deployment determines TIPS patency [32-34].

In particular, patency rates at 12 months are reported to be superior when the TIPS stent terminates at the hepato-caval junction, compared to stents terminating in the hepatic vein [32, 34]. As a result, to control the hepatic venous outflow, the distance to the hepato-caval junction becomes an essential technical consideration during TIPS deployment [35]. To reduce the hepatic venous outflow, TIPS are often extended according to the distance to the hepato-caval junction (**Fig. 1**).

New Topics for TIPS

Recent studies of the complications of cirrhosis and portal hypertension investigate the role of TIPS in their management, as a result significant increase in the indications for TIPS. Other conditions under investigation for TIPS include hepatic hydrothorax, portal hypertensive gastropathy, ectopic varices, hepatorenal syndrome, hepatopulmonary syndrome, non-tumoral portal vein thrombosis, and chylous ascites [36].

Table 3 TIPS Compared to Paracentesis.

	Hazard ratio [OR]	Confidence interval [CI]	P
Liver transplant-free (LTF) survival	0.61; 95%	0.46–0.82	< 0.001
Liver disease-related death	0.62; 95%	0.39–0.98	0.04
Recurrent ascites	0.15; 95%	0.09–0.24	< 0.001
Hepatorenal syndrome	0.32; 95%	0.12–0.86	0.02
Hepatic encephalopathy (HE)	2.95; 95%	1.87–4.66	0.02
Severe HE	2.18; 95%	1.27–3.76	0.005

Acute esophageal variceal hemorrhage

Esophageal varices are the dilation of the submucosal distal esophageal veins connecting the portal and systemic circulations resulting from portal hypertension and/or resistance to portal blood flow, with or without increased portal venous blood inflow. Treatment fails in approximately 10%-15% of patients, requiring repeated endoscopic intervention and resulting in a mortality rate of up to 80% [37, 38]. In addition, despite improvements in treatment, the overall mortality rate after 6 weeks in each episode of variceal hemorrhage remains high, ranging from about 15% to 25% [39, 40].

In recent years, several areas of research [4, 41-46] increasingly explore early TIPS (placed within 72 h after esophagogastroduodenoscopy or EVL) as an alternative to standard therapy (EVL plus nonselective beta-adrenergic blocker plus antibiotics) to become the primary therapy for acute variceal bleeding [5].

Another study reported a significantly lower rebleeding rate, with no change in mortality in patients who received TIPS, but TIPS patients experienced a higher incidence of HE [3, 42]. The Baveno VI consensus meets these findings and states that "after initial medical or endoscopic therapy, the risk of treatment failure is high." It recommends that "early TIPS should be considered within 72 h preferably." [44, 47].

The 2017 Practice Guidance issued by the American Association for the Study of Liver Diseases also recommends early TIPS be performed on patients with an elevated risk of treatment failure or rebleeding [48]. Furthermore, rescue TIPS is recommended in the event of persistent or recurring bleeding. Child B/C patients initially require antibiotic prophylaxis and a vasoactive drug, followed by endoscopy within 12 h together with EVL.

Child B patients presenting active bleeding or Child C patients scoring between 10 and 13 should undergo a TIPS procedure within 24 to 48 h. Child B patients without active bleeding continue vasoactive drug therapy and would only undergo a TIPS procedure if this treatment fails. A score of 14-15 in Child C patients is contraindicative for TIPS and listing for a transplant should be a priority [49]. The safety and efficacy of early TIPS has been evaluated in a series of

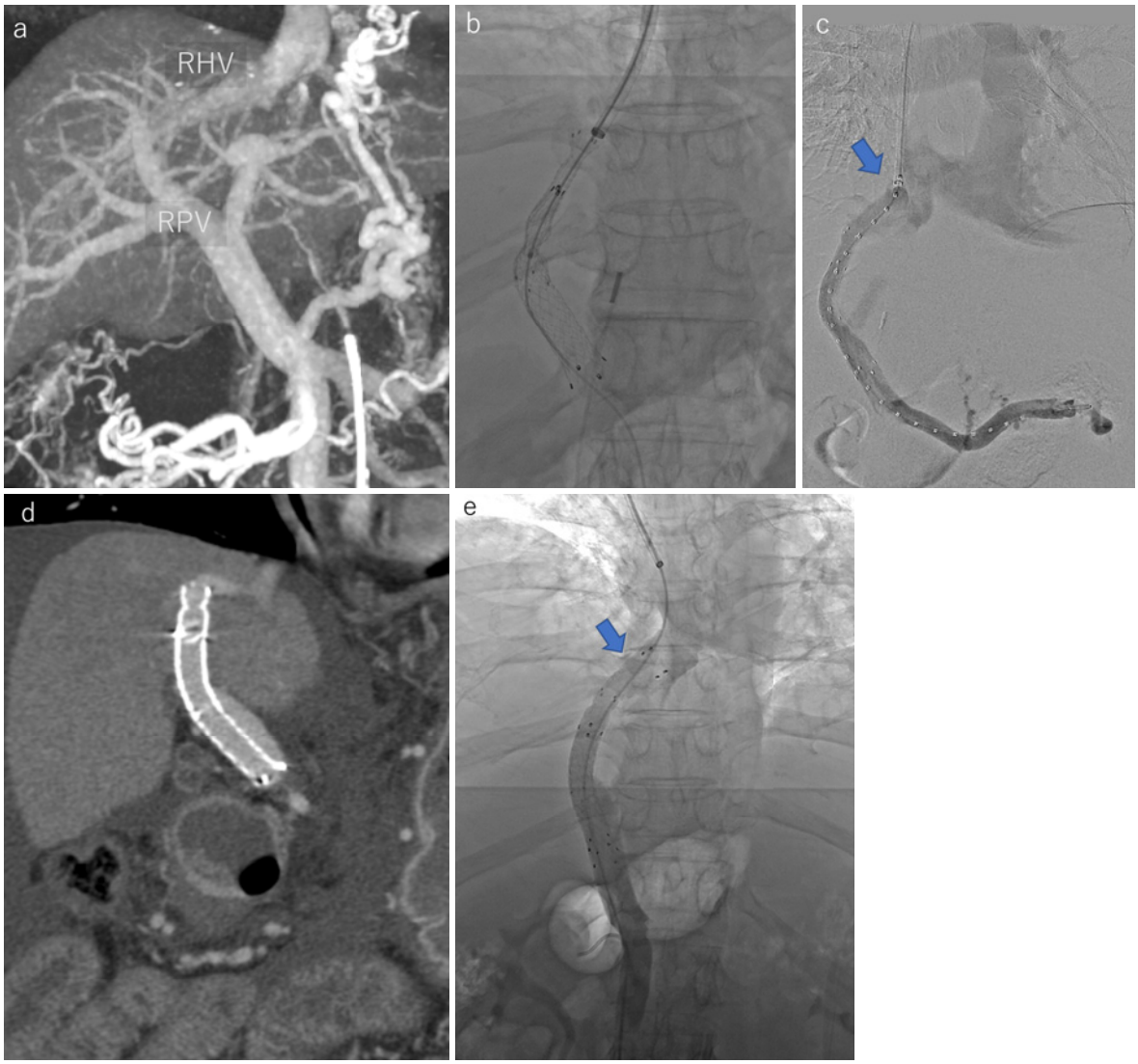

Figure 1. A 70-year-old male with a history of alcoholic cirrhosis, presenting with refractory ascites.
(a) Contrast-enhanced computed tomography MIP image shows the location of the right hepatic vein (RHV) and right portal vein (RPV).
(b) Viabahn (W.L. Gore & Associates, Phoenix, AZ, USA) (10 mm) within the liver parenchymal tract and Luminexx (BARD, Murray Hill, NJ) (10 mm) within the portal vein.
(c) Spleno-venogram reveals incomplete stent extension at the hepatic venous end, resulting in stenosis (arrow).
(d) Contrast-enhanced computed tomography coronal image shows that the covered stent is positioned toward the RHV.
(e) Resolution of stenosis is seen after shunt extension into the proximal part of the RHV with an additional bare metal stent.

randomized control trials.

A hepatic venous pressure gradient (HVPG) ≥20 mmHg is commonly associated with a substantial increase in the failure to control bleeding (e.g., more than fivefold). Considering the prognostic value of HVPG, HVPG ≥20 mmHg indicates patients at risk of in-hospital, bleeding-related, and 1-year mortality.

In their study, Monescillo et al. randomly selected 52 patients who presented with HVPG ≥20 mmHg (Child-Pugh B: 40%, C: 46%; active bleeding: 35%; and 22% with previous acute variceal bleeding) and who had undergone sclerotherapy to receive a bare metal TIPS or conventional therapy [41, 50]. In-hospital mortality (absolute risk reduction [ARR]: 20%) and 1-year mortality (ARR: 27%) decreased in patients receiving TIPS, while the decrease in bleeding-related mortality was not statistically significant despite an ARR of 19% [41].

TIPS for Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a severe complication of end-stage liver disease reducing patients' prognosis [51]. HRS is characterized by functional circulatory changes in the kidneys that overpower physiologic compensatory mechanisms and lead to a reduced glomerular filtration rate. The treatment of HRS comprises vasoconstrictors in combination with albumin infusion. The rationale for the TIPS procedure is mainly the shift of the splanchnic blood pool

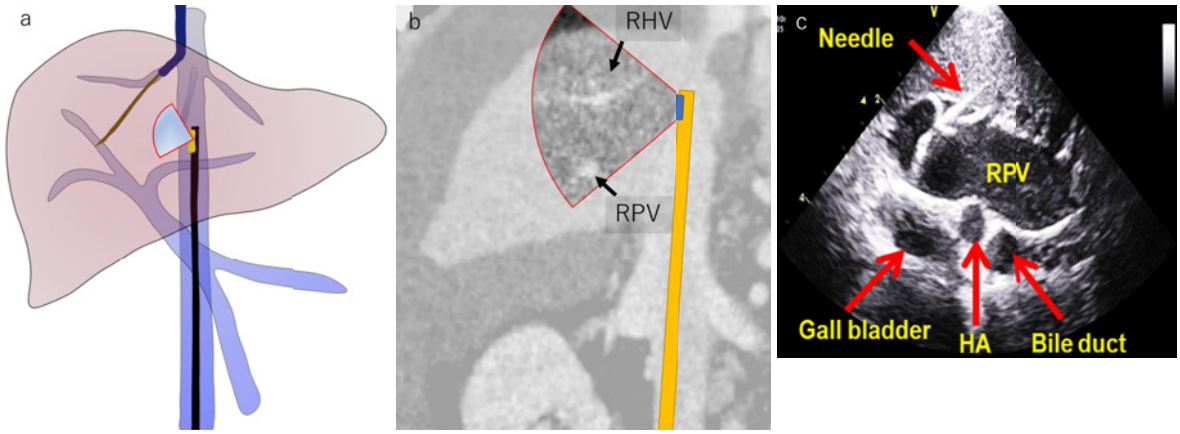

Figure 2.
a. Schematic of intracardiac echo (ICE) guidance during TIPS.
b. Schematic of intracardiac echo (ICE) guidance during TIPS. Right hepatic vein (RHV). Right portal vein (RPV).
c. Perpendicular-projecting intravascular ultrasound-guided access to RPV. Hepatic artery (HA).

into the central intrathoracic blood volume with de-escalation of vasoconstrictor formation that leads to a reduction of renal sodium reabsorption. Charilaou et al. used the National Inpatient Sample Database from 2005 to 2014 using ICD-9-CM codes for 4,840,843 cirrhotic patients and performed a retrospective study on 918 of 79,354 HRS patients in which TIPS was performed [52]. TIPS-only patients were 57% less likely to die as inpatient than non-TIPS patients [(OR) = 0.43, 95% CI 0.30-0.63; $p < 0.001$). It might be speculated that TIPS serves a role in improving the survival of HRS patients and potentially serving as a bridge to liver transplantation.

A New Type of Stent to Overcome Post-TIPS HE

After the demonstration of the usefulness of covered stents for TIPS, the Gore VIATORR (W.L. Gore & Associates, Phoenix, AZ, USA) was developed around 2000 as a stent explicitly designed for TIPS. This stent is covered in the hepatic parenchymal tract but bare in the portal vein. This stent can create a shunt tract without obstructing blood flow in the portal vein.

Similar TIPS procedures have been performed by combining covered stents, such as Viabahn (W.L. Gore & Associates, Phoenix, AZ, USA) or Fluency (Bard Incorporated, Karlsruhe, Germany), with bare stents. Trebicka et al. state that the optimal stent diameter for the short circuit pathway is "a smaller stent (nominal diameter of 8 mm) is associated with a prolonged survival rate compared with 10 mm stents, regardless of liver-specific prognostic criteria." [53].

While smaller 8-mm-diameter TIPS stents may be more effective than 10-mm-diameter TIPS stents, the conventional Viabahn and VIATORR stents are not designed to allow secondary dilation in the event of clinical ineffectiveness. Novel VIATORR, Controlled Expansion (VCX) stents (W.L. Gore & Associates, Phoenix, AZ, USA) were developed in about 2019 with a variable 8 mm-10 mm graft portion in the liver parenchyma. Using this stent may reduce the incidence of HE, stent malfunction, rehospitalization for sepsis, and ascites compared to more conventional stents [54].

Reducing Risk of Puncture Complications

TIPS is a two-dimensional puncture technique of the portal vein. The number of punctures varies with the operator's skill; therefore, the frequency of complications varies. Reducing the number of punctures is directly related to reducing the rate of complications. The most common methods for guiding needle passage are single of biplane fluoroscopy with a road map using wedged hepatic venous portography with CO_2. A guidewire placed in the right hepatic artery is often used for indirect real-time guidance for the right portal venous branch. Complications such as extrahepatic portal puncture, extracapsular puncture, thrombosis, and hemoptysis have been reported when needles are passed without real-time imaging [55].

Intracardiac echocardiography (ICE) is a recent advancement in imaging guidance that reduces fluoroscopy time, contrast agent use, and the overall TIPS procedure time with lower extracapsular puncture rates [56, 57]. The addition of real-time visualization using the Acunav ICE catheter (Biosense Webster Inc., CA, USA) has facilitated the TIPS procedure for challenging case such as cases with multiple liver cysts. Furthermore, anatomical differences (distance and angle between the hepatic and portal veins) that complicated TIPS procedures in the past can now be routinely performed under ICE guidance (**Fig. 2**) [58].

Conclusion

TIPS is a safe and effective treatment for the selected patients with complications of portal hypertension. TIPS is not limited to the treatment of hepatic ascites, and its application to the treatment of acute esophagogastric varices has also been discussed. TIPS procedure with a partly covered self-expanding stent and with a controllable diameter poten-

tially would be beneficial for further improvement in clinical outcomes after TIPS.

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