

REVIEW ARTICLE

Transjugular Intrahepatic Portosystemic Shunt (TIPS): Current Status and Future Possibilities

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Abstract

Since the insertion of the first TIPS in 1989 much has been learned about this therapeutic procedure. It has an established role for the treatment of some complications of portal hypertension: prevention of recurrent variceal bleeding and rescue of patients with acute uncontrollable variceal bleeding. In addition TIPS is useful for Budd-Chiari syndrome, refractory ascites and hepatorenal syndrome, although its specific role in these indications remains to be definitively established. However, the decrease in sinusoidal blood flow induced by TIPS can lead to the patient developing hepatic encephalopathy and liver failure in some cases. Therefore, TIPS should be used with caution in patients with very poor liver function. From a technical point of view, successful placement of TIPS is achieved in more than 98% of cases by experienced groups. At present, evaluation of TIPS dysfunction based on morphology probably leads to an overdiagnosis of this complication since most of these cases are not associated with clinical manifestations (recurrent bleeding or refractory ascites). The major disadvantage of TIPS remains its poor long-term patency requiring a mandatory surveillance program. The indicator for shunt function/malfunction should be the portosystemic pressure gradient, which is best assessed by intravascular measurements. Shunt obstructions may be prevented or reduced by the use of stent-grafts in the future.

Key words: Portal hypertension—Portal interventions—Endovascular prostheses—Portosystemic shunts—TIPS

Introduction: History, Indications and Technique

Liver cirrhosis is the final pathologic and clinical expression of a wide variety of chronic liver diseases. The commonest

causes of cirrhosis are alcohol abuse and chronic hepatitis C virus infection (nearly 90% of the total cases of cirrhosis). Chronic hepatitis B infection, chronic cholestatic diseases such as primary biliary cirrhosis and primary sclerosing cholangitis, metabolic diseases such as hereditary hemochromatosis, Wilson's disease and alpha-1-antitrypsin deficiency, autoimmune chronic hepatitis and a variety of less frequent conditions account for the remaining cases of adulthood cirrhosis [1]. In the United States, the prevalence of cirrhosis is estimated at 3,600 cases per million population and accounts for 30,000–40,000 deaths per year [2].

Pathologically, cirrhosis is characterized by the loss of the normal architecture of the liver with the presence of liver cell necrosis, widespread fibrosis and the formation of regenerative nodules. Pathophysiologically, the clinical manifestations of liver cirrhosis arise from the occurrence of two major events: hepatocellular insufficiency and portal hypertension.

In a vascular system pressure results from the product flow \times resistance. In liver cirrhosis, portal hypertension develops, initially, as a result of an increased sinusoidal and, in some cases, also post-sinusoidal portal resistance to blood flow, due to the loss of the normal hepatic architecture and the collagenization of the space of Disse. In addition, patients with cirrhosis show a hyperkinetic systemic circulation with high cardiac output and decreased total peripheral vascular resistances which is mainly due to a marked vasodilation of the splanchnic vascular bed. As a result, arterial inflow to the splanchnic area is increased and therefore portal inflow increases as well. Hence, a second mechanism, that is, an increased blood flow to the portal system, contributes to portal hypertension in cirrhotic patients [1].

The major pathophysiologic consequences of portal hypertension include the opening of portal-systemic collaterals, the increased production of hepatic lymph and the retrograde transmission of increased pressure to the spleen leading to splenomegaly. Portal-systemic collateralization produces anatomic and functional disturbances. The ingurgitation of the

portal collaterals draining in submucosal gastric and esophageal veins produces gastric and esophageal varices which constitute the major cause of life-threatening digestive bleeding in cirrhosis. Portal hypertensive gastropathy is another potentially bleeding lesion secondary to portal hypertension. The opening of portal-systemic collaterals is responsible for the shunting of large amounts of blood coming from the splanchnic vascular bed to the systemic circulation, thus avoiding detoxification of this blood in the liver. Hepatic encephalopathy, endotoxemia and altered drug pharmacokinetics are, among others, the major consequences of this shunt. The increased production of hepatic lymph leads to the accumulation of ascites in the abdominal cavity when the capacity of the thoracic duct is overwhelmed. Finally, the increased retrograde pressure transmitted to the spleen induces spleen enlargement which, in addition to the overstimulation of the splenic mononuclear-phagocytic system because of the presence in blood of an excess of antigens of intestinal origin, leads to hypersplenism [1].

At present, beta-blockers constitute the first-line treatment for the prevention of variceal bleeding since these drugs lower portal pressure. Mechanical decompression of the portal system was the basis for the introduction of surgical portosystemic shunts as a therapy for portal hypertension. The rationale is the same in the case of TIPS.

History of TIPS Creation

The idea of establishing percutaneously an intrahepatic connection between the hepatic veins and the portal vein dates back to 1969. In that year, Rösch and Hanafée [3] described the technique in laboratory animals. The intrahepatic tract between the portal vein and the hepatic vein was dilated using Teflon dilators and the connection was kept patent with a plastic tube. The introduction of the angioplasty balloon catheter allowed the dilatation to be performed in a less traumatic fashion. Colapinto, in 1983 [4], presented a group of patients in whom the procedure had been carried out without inserting an intervening device as a means of stabilizing the venous connection; the patency rate, as expected, was poor. The animal studies carried out by Palmaz [5], with the prosthesis designed by him, finally allowed TIPS to be performed in a safe and efficient manner. The first human cases were presented by Richter in 1989 [6], and since then many series with variable numbers of patients, case reports and clinical notes have been published.

Indications

Since the first procedures performed by Richter on patients with poor liver function and active hemorrhage caused by gastroesophageal varices, the indications for performing TIPS have increased. After a consensus meeting between the main groups which perform the procedure, definitions were agreed of the unanimously accepted indications, indications accepted by only some groups, and a series of contraindications [7].

Various subsequent articles [8], and a series of recommendations made by particular societies [9] and large-scale case reviews [10], have led to the present situation in which five groups of indications and/or contraindications have been established. The first of these are the indications accepted by all groups, in which TIPS has proven to be of great efficacy (+++); the second are those accepted by a broad majority but in which the large reviews of cases have not demonstrated sufficient evidence of proven efficacy (++); the third are those groups of patients in which TIPS has been shown to be effective in individual cases but in which there are only a few experiences to justify its use (+). Among the contraindications, there are those which are relative (-), which may include case reports in the literature which claim that TIPS proved useful, and finally a series of absolute contraindications (--) in which TIPS should not be performed, or cases in which a patient had severe complications or died after TIPS was performed.

1. Accepted Indications (+++)

Active Variceal Hemorrhage Not Controlled by Endoscopic and Pharmacologic Treatment. In cirrhotic patients with portal hypertension presenting active bleeding from gastroesophageal varices, endoscopic techniques (sclerotherapy or banding) are highly effective (80–90%) either alone or in combination with drugs. The group of patients who do not respond to this treatment (10–20%) and therefore require a different therapeutic measure must be identified at an early stage, as both continuing hemorrhage and the increased morbidity due to the techniques being used may have a fatal outcome. In cases in which TIPS is to be performed, the possible candidates need to be identified as swiftly as possible. It is also useful to distinguish the patients with bleeding from esophageal varices or varices in the lesser gastric curvature (area of the left gastric vein) from those with bleeding from the greater gastric curvature (area of spleno-renal shunts) or varices classified as ectopic (intestinal, stomach, etc.). In the former, hemorrhage occurs where gradients exceed 12 mmHg. In the latter, the flow often competes with the TIPS, and there may be bleeding with gradients below 12 mmHg. In these cases it may be useful to embolize these connections. In the management of patients who are not awaiting liver transplant, who have good liver function (Child A) and a good clinical condition, derivative surgery, be it portosystemic or spleno-renal, may prove as useful as TIPS or even more so.

Recurrent Variceal Hemorrhage Despite (or Intolerant to) Endoscopic and Pharmacologic Treatment. First, it is important to define what is meant by “recurrent hemorrhage”. According to various authors, this means “recurrence of variceal hemorrhage despite at least two sessions of endoscopic treatment performed no more than 2 weeks apart”. When drug-associated sclerotherapy or banding has proved

ineffective, TIPS is often proposed and, as we shall see below, various studies have demonstrated its efficacy. Some authors consider that surgery is the more appropriate treatment for Child A patients who are not candidates for a liver transplant, as the long-term patency would seem to be greater.

2. Potential Indications with Proven Efficacy (+ +)

Refractory Ascites. This widely accepted indication is still a subject of controversy, as the published series include dissimilar patients, and the results therefore differ widely from group to group. For this reason, it is important to define what is understood by refractory ascites: “serious tense ascites that does not respond to standard therapy within 4 weeks or where the patient develops secondary effects making treatment impossible”. The same could be said of patients with hepatic hydrothorax, in whom the selection of patients is similar to that with refractory ascites. In this group of patients, in whom the liver is usually small and its functional reserve is poor, the procedure is more difficult and the index of complications is higher, and so great care must be taken when choosing the patient of whom good results can be expected.

Budd-Chiari and Veno-occlusive Syndrome. In patients with chronic Budd-Chiari syndrome the indications are the same as those in patients with other causes of portal hypertension. The management of its complications—active or recurrent hemorrhage and refractory ascites—is facilitated by the use of TIPS. A different problem is that of acute Budd-Chiari syndrome. In such cases it was initially established that TIPS was of use in patients awaiting liver transplant who required effective palliation of the symptoms, particularly ascites. It was later realized that TIPS is not only a measure of temporary support but an effective alternative to transplant while the etiologic problem underlying Budd-Chiari syndrome or veno-occlusive disease is being treated.

3. Experimental Indications with Efficacy Not Proven by Large-Scale Series (+)

- Some series have shown that TIPS is a highly effective means of obtaining long-term patency in both cirrhotic and non-cirrhotic patients with portal thrombosis who require a means of ensuring the outflow of the portal system after it has been repermeated percutaneously. Only a few case reports have managed to show that it is technically possible to perform TIPS in patients with portal cavernomatosis, and it has yet to be demonstrated that this measure is lasting and beneficial for the patient.
- Also unproven to date is the notion that the surgical technique may be facilitated or greater stabilization achieved in patients who are going to be treated by liver

transplant and are waiting for an organ to become available.

- Bleeding portal gastropathy.
- Preoperative portal decompression in abdominal tumors that require surgical resection. This is indicated in cirrhotic patients with portal hypertension and varices around the tumoral area.

4. Indications Not Accepted (Case Reports Only) (–)

- Caroli’s disease and obstructive dilatation of the bile duct. The possibility of allowing bile to enter the bloodstream (bilhema) is raised, and the septic consequences may be severe.
- Correction of hypersplenism.
- Hepatopulmonary syndrome.
- In some series, TIPS has been used as primary prophylaxis for variceal hemorrhage. However, this is not an accepted indication.
- Polycystic disease [11]. One clinical case reports that TIPS was useful for two particular patients; however, this technique cannot be recommended in general for these patients.

5. Absolute Contraindications (– –)

- Hepatic insufficiency and chronic encephalopathy. In these cases, the patient’s clinical situation deteriorates significantly after TIPS, and there is a strong possibility of death occurring within a short time.
- Severe right cardiac insufficiency. After the portosystemic derivation and the sudden increase in pressure in these chambers of the heart, patients undergo a considerable deterioration in heart function.
- Diffuse or multinodular liver cancer, or tumors in the proposed route of the TIPS. This would result in hematogenous dissemination of the disease.
- Spontaneous bacterial peritonitis.

Technique

Since the first cases presented by Richter, the technique has been modified. The basic technical points are described below.

Portal Vein Puncture. TIPS consists of a percutaneous connection between a portal vein and the hepatic vein. Over the years, new variations have been added in which, using the percutaneous approach, the portal system is connected to the systemic circulation either via the hepatic vein or directly through the cava. In any case, the most complex step in the procedure is to identify the anatomic structures. The hepatic veins and the intrahepatic branches of the vena porta are subject to a great number of morphologic variations. In up to



Fig. 1. Indirect portography performed after the wedged injection of CO₂ in the right hepatic vein. Portal morphology is clearly depicted.

about 60% of patients there are anatomic variations in the hepatic venous drainage. Of these, 30% may present two or three right veins with variable caliber and morphology; the size may even be smaller than 1 cm in diameter. In these cases the dorsal hepatic vein may be larger than the right hepatic vein. Therefore careful selection of the vein is recommended. Equally, 25% of patients may have a large area if not the whole of the portal bifurcation not covered by liver. The right portal vein may show a large variety of anatomic variants, to such an extent that there is no common anatomic disposition described for the majority of patients [12]. In addition, cirrhosis produces a severe distortion of the venous anatomy. It is therefore difficult to establish technical recommendations for venous catheterization and portal puncture using a blind technique.

One of the main areas of technical interest has been (and still is) the identification of the portal vein. Initially direct portography was performed through a transhepatic approach. This also facilitated the subsequent manipulation of catheters introduced via a transjugular approach. The high rate of haemorrhagic complications made it advisable to discontinue this method. Indirect portography using different approaches has been described, among which the most commonly performed is the wedged hepatic injection of CO₂ [13] (Fig. 1). The images obtained are comparable in quality to the direct injection of contrast [14]. CO₂ has also been employed injected transhepatically through fine needles (21G) [15]. The best method, in the opinion of many, for selecting the hepatic vein with the added benefit of real-time guidance during portal vein puncture is ultrasound [16] (Fig. 2). In the majority of cases access to the portal vein is gained at the first attempt, there is virtually no risk of performing an extrahepatic puncture and the use of iodinated contrast diminishes considerably. It is always advisable to study care-

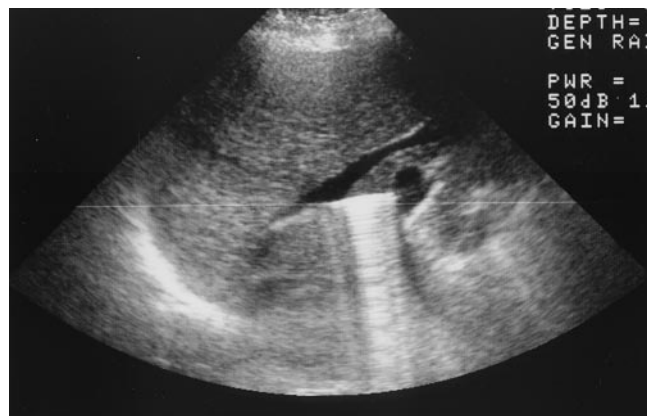


Fig. 2. Portal vein puncture under ultrasound guidance using a hyperechogenic needle.

fully the hepatic and vascular anatomy with cross-sectional imaging techniques such as CT and MRI. Once the tract between the two venous structures has been established, it is necessary to detect possible complications at an early stage. These include extrahepatic portal puncture, dissection of the portal vein, or portal thrombosis caused by manipulation. The tract is dilated with balloons, preferably short ones, which are placed in separate positions in the portal area and in the connection with the hepatic vein.

Prosthesis. The first TIPS were performed with Palmaz balloon-expandable steel prostheses [6]. Their use was recommended because they allowed a “tailored” shunt to be performed that could be dilated as required to obtain a portosystemic pressure gradient below 12–15 mmHg. The disadvantage of this prosthesis is its rigidity, which makes it difficult to place in curved paths, and there was the risk of it becoming dislocated when several were placed in tandem. Research was carried out with devices made of different materials and with different characteristics. Possibly the most widely used self-expandable metallic prosthesis is the Wallstent [17]. Because of its flexibility it allows TIPS to be performed in patients with diverse morphologies. Nevertheless, its shortening, which is often unpredictable, has made others use new devices such as the Memotherm stent.

Although the Wallstent is possibly the most widely used prosthesis it has been shown to have several disadvantages. Apart from the shortening, its radial force is less than that of other stents and it is not possible to overdilate it. A recent comparative study also indicates that its thrombogenicity is greater than that of the “long-medium Palmaz-stent”, with a higher rate of postprocedural thrombosis [18]. Both have the disadvantage of not being able to isolate the hepatic parenchyma from the blood flow within the TIPS. This contact with the free hepatic surface could be the cause of the high rate of restenosis during follow-up (biliary contamination) [19].

Table 1. Results of treatment of refractory acute variceal bleeding with TIPS

First author	No. of patients	Child-Pugh class (A/B/C)	Immediate control	1-month rebleeding	1-month mortality
McCormick [21]	20	1/7/12	20/20 (100%)	6/20 (30%)	10/20 (50%)
Jalan [22]	19	3/3/13	19/19 (100%)	3/19 (16%)	8/20 (40%)
Sanyal [23]	30	1/7/22	29/30 (97%)	2/30 (7%)	37%
Tyburski [24]	33	0/5/28	33/33 (100%)	5/33 (15%)	9/33 (27%)
Chau [25]	112	5/27/80	110/112 (98%)	24–30%	34–42%
Patch [26]	54	5/20/29	49/54 (91%)	11/54 (20%) ^a	26/54 (48%) ^a
Bañares [27]	56	11/22/23	53/56 (95%)	8/56 (22%)	28%
Barange [28]	32	3/14/15	18/20 (90%)	14%	25%

^aDuring 6 weeks.

Results of the use of TIPS

Emergency Treatment of Gastroesophageal Variceal Bleeding

In the first report of patients treated with TIPS, two of three patients with uncontrolled variceal bleeding achieved hemostasis after TIPS [20]. Since then, several papers have reported the efficacy of TIPS as a rescue therapy in patients with uncontrolled hemorrhage [21–28]. These are outlined in Table 1. As may be seen, the efficacy of TIPS in this situation is greater than 90% in all the reports, but the rebleeding rate in the first month after TIPS placement averages 15%.

These series have a 1-month mortality rate ranging from 25% to 30%. This is significantly higher than mortality after elective TIPS. Three papers analyze which factors are related to early mortality. Bañares et al. [27] found that hepatic encephalopathy before TIPS, ascites before TIPS and serum albumin lower than 2.7 g/l were independently related to 1-month mortality. In their series, Sanyal et al. [23] found only aspiration and grade IV encephalopathy to be independent predictors of death. Finally, Patch et al. [26] obtained a prognostic index score combining the six variables with independent prognostic value: moderate or severe ascites, requirement for ventilation, white blood cell count, platelet count, partial thromboplastin time with kaolin and creatinine. This prognostic index was prospectively validated in an independent series of patients, giving a 100% predictive value for the prediction of death in 6 weeks. In their series, Jalan et al. [22] compared emergency treatment of uncontrolled variceal hemorrhage with TIPS or with esophageal transection. In this retrospective and nonrandomized study, 30-day mortality was found to be greater with surgical management (79% vs 42%; $p < 0.05$). In contrast, when Rosemurgy et al. [29] performed a randomized prospective trial comparing TIPS with small-diameter prosthetic H-graft portocaval surgical shunt they found that shunt failure (defined as the inability to accomplish shunting, major variceal rebleeding, shunt occlusion, death or transplantation) was 57% after TIPS and 26% after surgery ($p < 0.02$).

Prophylaxis of Gastroesophageal Variceal Rebleeding

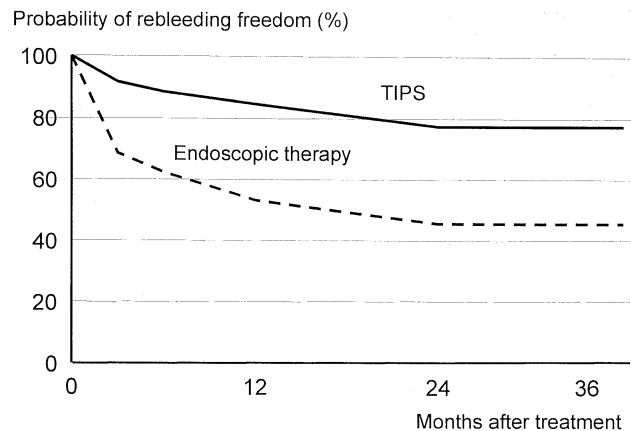
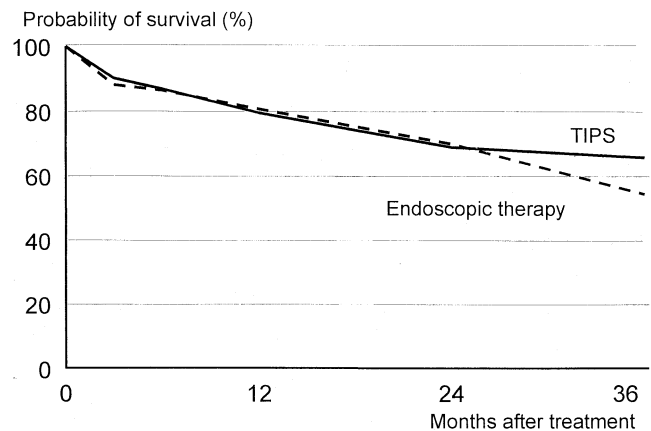
Initial data from uncontrolled studies showed that TIPS was effective in the prevention of variceal rebleeding [30], but this enthusiasm was tempered by evidence of the frequency of its malfunction or thrombosis and the risk of encephalopathy. Furthermore, to establish whether TIPS may be considered the treatment of choice in the prevention of variceal rebleeding, its use must show a reduction in mortality or an improvement in the quality of life.

To date, nine randomized trials comparing the efficacy of TIPS and endoscopic treatment (\pm pharmacologic treatment) have been published as full articles [30–39] in peer-reviewed journals and two trials have been published as abstracts [40, 41]. Furthermore, two meta-analyses have evaluated these 11 trials [42, 43]. In this section, the methodology and results of the nine full papers are reviewed (Table 2).

Five of these studies compared TIPS with endoscopic sclerotherapy [31, 33, 34, 37, 38], two with endoscopic variceal ligation [36, 39], one with sclerotherapy/ligation plus propranolol [31] and one with sclerotherapy plus propranolol [35]. All the papers but one [33] found TIPS to be more effective than endoscopic therapy (\pm propranolol) in avoiding variceal rebleeding. The 1-year rebleeding rate ranged between 10% and 27% for TIPS and between 21% and 57% for endoscopic treatment. Fig. 3 illustrates the average values of rebleeding in patients treated with sclerotherapy or TIPS. The incidence of encephalopathy was significantly higher in patients treated with TIPS in four of these nine trials [31, 32, 35, 37]. Seven of the trials found no significant difference between the survival of patients treated with TIPS and patients treated with endoscopic therapy [31, 32, 34–37, 39]. In one trial, the survival of patients treated with sclerotherapy was significantly higher than that of TIPS patients [33], and in another trial patients treated with TIPS had better survival than patients treated with sclerotherapy [38]. A striking difference between this study and the others is the proportion of patients rescued with TIPS after failure of endoscopic therapy. While Garcia-Villareal et al. [38] rescued only one of 24 (4%) patients with TIPS, the rest of

Table 2. Randomized clinical trials comparing TIPS and endoscopic (\pm pharmacologic) treatment in the prophylaxis of variceal rebleeding in patients with liver cirrhosis

First author	No. of patients	Child-Pugh class (A/B/C)	Follow-up (months)	Bleeding at 1 year (%)	Encephalopathy at 1 year (%)	Death at 1 year (%)	Cross of treatment
Cabrera [31]	Sclerotherapy	32	14/16/2	15	52*	11*	18
	TIPS	31	14/13/4	15	27	39	7
Rössle [32]	Scler/ligation+propranolol	65	22/31/12	13	41*	18*	11
	TIPS	61	17/33/11	14	15	36	10
Sanyal [33]	Sclerotherapy	39	6/15/18	33	21	13	10*
	TIPS	41	7/13/21	32	23	29	28
Cello [34]	Sclerotherapy	25		19	48* ^a	44* ^a	32* ^a
	TIPS	24		19	13	50	33
Sauer [35]	Scler+propranolol	41	12/18/11	17	57* ^a	13*	15
	TIPS	42	15/18/9	19	23	26	23
Jalan [36]	Ligation	27	5/9/13	17	52* ^a	33* ^a	37* ^a
	TIPS	31	2/14/15	16	10	35	42
Merli [37]	Sclerotherapy	43	13/25/5	18	52*	26* ^a	14
	TIPS	39	13/20/5	17	21	55	16
García-Villarreal [38]	Sclerotherapy	24	3/14/7	17	54*	25* ^a	28*
	TIPS	22	5/10/7	25	10	23	0
Pomier-Layrargues [39]	Ligation	39	0/17/22	19	57*	40	38
	TIPS	41	0/20/21	22	11	32	25

* $p < 0.05$.^aDuring follow-up.**Fig. 3.** Average estimate of rebleeding in cirrhotic patients treated with TIPS (continuous line) or with endoscopic therapy (dotted line) for prevention of variceal rebleeding.**Fig. 4.** Average survival in cirrhotic patients treated with TIPS (continuous line) or with endoscopic therapy (dotted line) for prevention of variceal rebleeding.

the trials rescued an average of 18.6% (range 14–28%) of patients after failure of endoscopic treatment. Average values of patient survival after treatment with sclerotherapy or TIPS are represented in Fig. 4.

The potential effect of TIPS on other aspects has been less studied. Jalan et al. found a significant reduction in the days spent in the hospital in patients treated with TIPS [36], but other authors have not found such a difference [31–34, 38, 39]. With respect to analysis of costs, there is also no concordance. Jalan et al. [36] found that the care of patients treated with TIPS was cheaper than the care of patients treated with variceal band ligation, Sauer et al. [35] did not find any difference between TIPS and conventional treat-

ment and Meddi et al. [44] found TIPS to be more expensive than sclerotherapy.

In conclusion, prophylaxis of variceal rebleeding with TIPS is more effective than endoscopic (\pm pharmacologic) treatment but increases the risk of encephalopathy. Survival of patients treated with TIPS is not higher than survival of patients treated with endoscopic therapy (and TIPS rescue).

To date, TIPS and surgical treatment of portal hypertension have not been compared in any randomized controlled trial. The two treatments have been compared only in a decision analysis model where the outcomes of Child class A cirrhotic patients undergoing TIPS or distal splenorenal shunt were compared. In this paper, TIPS was shown to be

Table 3. TIPS in refractory ascites: data from some non-controlled studies

Author [reference]	No. of patients	Child C (%)	Technical success (%)	Ascites response (%)	Early mortality (%)	1-year survival (%)
Ochs [61]	50	59	100	92	4 (30 days)	53
Somberg [62]	24	46	100	79	0 (30 days)	–
Quiroga [63]	17	47	100	80	23 (90 days)	63
Crenshaw [65]	54	56	93	78	18 (30 days)	48
Martinet [66]	30	36	100	86	–	41
Nazarian [67]	50	42	100	63	14 (30 days)	33
Rees [68]	25	54	100	68	48 (90 days)	37
Deschenes [72]	53	64	100	90	22 (90 days)	48
Peron [75]	48	34	97	73	12 (90 days)	52

Modified from Rössle et al. [10].

more effective than surgery, but at a high price (\$150,000 per life-year saved) [45].

Management of Other Locations of Bleeding

TIPS has been successfully used in the management of non-gastroesophageal bleeding varices, such as small bowel [46], intra-abdominal [47], stomal [48] and rectal varices [48]. In these cases, portography may also be used to embolize the bleeding varix.

The usefulness of TIPS in the management of bleeding from angiodysplasia-like colonic lesions in a patient with cirrhosis has been reported [49], but in a series of seven patients treated with TIPS for bleeding gastric antral vascular ectasia the reduction in portal hypertension was not followed by control of bleeding [50].

Treatment of Budd-Chiari Syndrome and Venocclusive Disease

The resolution of hepatic congestion in hepatic outflow block syndromes may improve liver function. In cases of Budd-Chiari syndrome with fulminant presentation or with significant fibrosis/cirrhosis liver transplantation may be the treatment of choice, but shunting may be followed by an improvement in liver function and better control of ascites, even in patients with chronic Budd-Chiari syndrome [51]. TIPS may have a role also in patients with fulminant Budd-Chiari syndrome [52, 53], and liver transplantation may be performed in case of failure to improve.

The experience with TIPS in Budd-Chiari syndrome has been published as case reports. The largest series published to date included 12 patients [54]; two of them (with a fulminant form) died and 10 (5 subacute and 5 chronic cases) improved. Another series of four patients showed worse results: three patients required portocaval shunt or liver transplantation and only one did well with TIPS [55].

The experience with the use of TIPS in veno-occlusive disease is also limited to case reports, with the exception of a series of six patients [56]. In this series, three of the patients died without showing any improvement, one died of veno-occlusive disease after a transient improvement and

one died of recurrent malignancy. Thus, only one of six patients had a prolonged survival.

Refractory Ascites

Refractory ascites is a late complication in the evolution of liver cirrhosis which develops in about 10% of cirrhotics with ascites and is associated with a 2-year survival of less than 50%. Refractory ascites is defined as tense ascites that does not respond to standard therapy within 4 weeks (sodium intake less than 60 mmol/day, 300–400 mg/day of spironolactone and 120 mg/day of furosemide) or if the patient develops secondary effects of diuretics making the treatment impossible (hyponatremia <125 mmol/l, renal failure or hepatic encephalopathy) [57]. Recurrent ascites is defined as tense ascites recurring at least three times within a year despite the correct standard treatment.

For ascites to develop in cirrhosis there are two necessary and interrelated events: sinusoidal portal hypertension and renal sodium retention. Therefore, pathophysiologic treatments of ascites should be directed to reduce portal hypertension, to enhance renal sodium excretion or both. This gives a rationale for the use of TIPS in the treatment of refractory ascites since it directly lowers portal pressure. TIPS offers, therefore, an alternative to surgical shunts [58], peritoneovenous shunts [59] and paracentesis plus albumin infusion [59] for the treatment of patients with cirrhosis and refractory ascites. It should be noted, however, that the only definitive treatment for refractory ascites in the long term is liver transplantation.

Efficacy of TIPS in Refractory Ascites. Several non-controlled studies [60–75] and two controlled studies published as full papers [76, 77] have evaluated the effect of TIPS on refractory ascites. Table 3 shows a summary of the major findings in some non-controlled studies. Portal pressure reductions were about 50% and in most cases the portal systemic venous pressure gradient was below 12 mmHg. The efficacy of TIPS in solving refractory ascites ranged from 50% to 92%. In the largest controlled study, full resolution of ascites was achieved in 61% and 79% of patients at 3 and 6 months after the procedure, whereas the corresponding

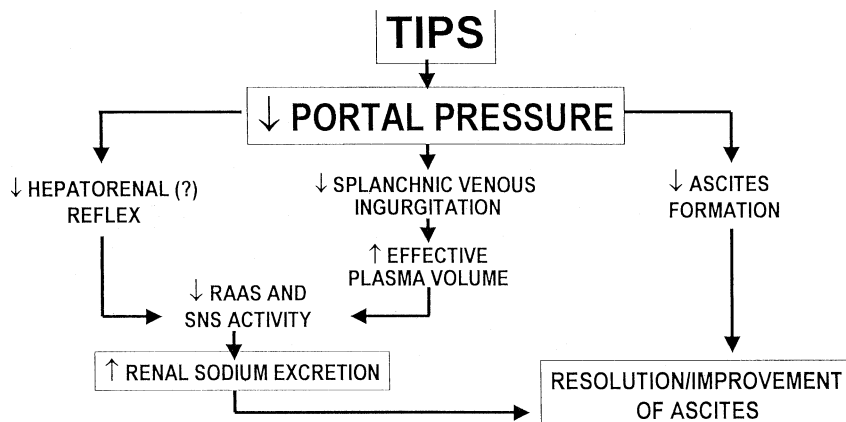


Fig. 5. Summary of the major mechanisms acting in the resolution of refractory ascites after TIPS. RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

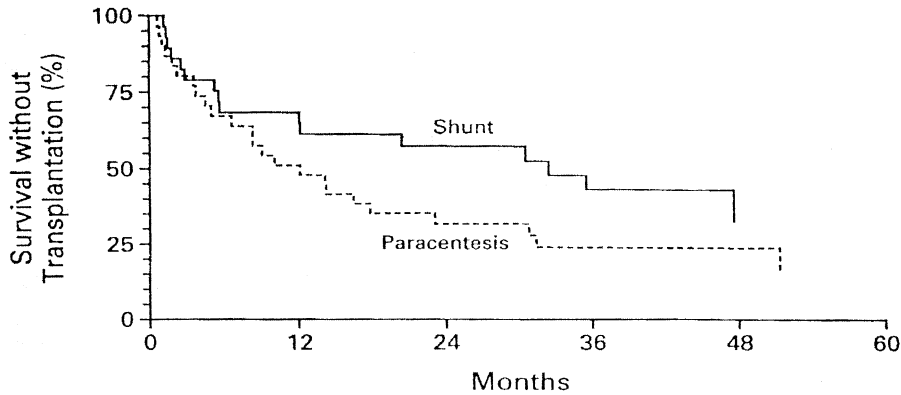
figures for patients treated with paracentesis plus albumin infusion were 18% and 24%, respectively [77]. Creatinine clearance >36 ml/min [72] and colloid osmotic pressure <20 mmHg [73] before TIPS have been identified as predictors of ascites response to TIPS. In addition, a reduction in body weight and an increase in lean body mass have been reported in patients with refractory ascites treated with TIPS [71]. The effectiveness of TIPS is limited by the frequent dysfunction of the prosthesis, which requires close surveillance and dilatation in most cases (see the section on TIPS failure below). If not corrected, the stenosis of the prosthesis led to an increase in portal pressure and reaccumulation of ascites.

Effects of TIPS on Renal Sodium Handling, Renal Function and Systemic Hemodynamics. All patients with refractory ascites show avid renal sodium retention. TIPS placement increases renal sodium excretion, slightly in the first few days [64, 69] and markedly thereafter [63, 64, 66, 70]. Although TIPS may increase glomerular filtration rate [62, 63], its major effect on sodium handling is a reduction in the pre-existing abnormal sodium renal tubular reabsorption [63, 64, 66, 70]. A significant number of these patients will maintain a negative sodium balance after TIPS in spite of an increase in sodium intake and a reduction in diuretic doses [62, 63]. This effect of TIPS is due to marked decreases in the activity of the renin-angiotensin-aldosterone axis and, in some cases, of the sympathetic nervous system [62–64], secondary to an increase in effective plasma volume following TIPS and, perhaps, an attenuation of the so-called hepatorenal reflex induced by portal hypertension (Fig. 5). Related to this deactivation of pressor systems there is an exacerbation of the hyperkinetic systemic circulation following TIPS which tends to attenuate in the long term [63, 64, 78]. As a rule, no marked changes in renal hemodynamics have been observed after TIPS [64, 69] in patients with normal or near-normal renal function. However, an increase in glomerular filtration rate was observed in patients with type I and type II hepatorenal syndrome [74, 79, 80] or renal failure associated with parenchymal renal disease [74], sug-

gesting that TIPS may be useful in this subgroup of patients as a bridge for allowing liver transplantation.

Effects of TIPS on Patients Survival and Prognostic Factors. Non-randomized trials have shown 1-year survival rates ranging from 33%–63% [61–63, 65–68, 72, 75], with early mortality after the procedure between 12% and 48% at 90 days [61–63, 65–68, 72, 75]. The major cause of death in these patients is progressive liver failure due to the decrease in sinusoidal portal blood flow induced by TIPS. The first randomized trial comparing TIPS and paracentesis plus albumin infusion included a small number of patients and showed a significantly better 2-year survival in patients treated with paracentesis [76]. Rössle et al. [77] have recently published a second randomized trial including 29 patients treated with TIPS and 31 treated with paracentesis. The probability of survival without liver transplantation at 1 and 2 years was 69% and 58% in the TIPS group and 52% and 32%, respectively, in the paracentesis group (Fig. 6). Although this difference was not significant, multivariate analysis showed that treatment with TIPS was independently and significantly associated with survival [77]. However, a recent report published in abstract form did not confirm this benefit [80]. Therefore, TIPS seems to offer no clear benefit in terms of survival in comparison with paracentesis. However, trials including large number of patients are needed for identifying a possible subgroup of patients with refractory ascites with good prognosis after TIPS. Some prognostic models have been developed recently (see below).

Indication for TIPS in Refractory Ascites. This is an unsolved question. Taking into account the state of present knowledge, patients with refractory ascites undergoing TIPS should be included in prospective trials. For an individual patient a possible schema for decision-making is presented in Fig. 7. This schema considers whether or not the patient is a candidate for liver transplantation, the expected time on the waiting list and an estimation of the risk of death after TIPS (calculated according to recent published models: see the section on survival below). The major alternative to TIPS is



No. AT RISK	0	12	24	36	48	60
Shunt	29	20	15	9	3	0
Paracentesis	31	16	9	6	5	1

Fig. 6. Patient survival after treatment of refractory ascites with TIPS or paracentesis. (From Rössle et al. [77] with permission.)

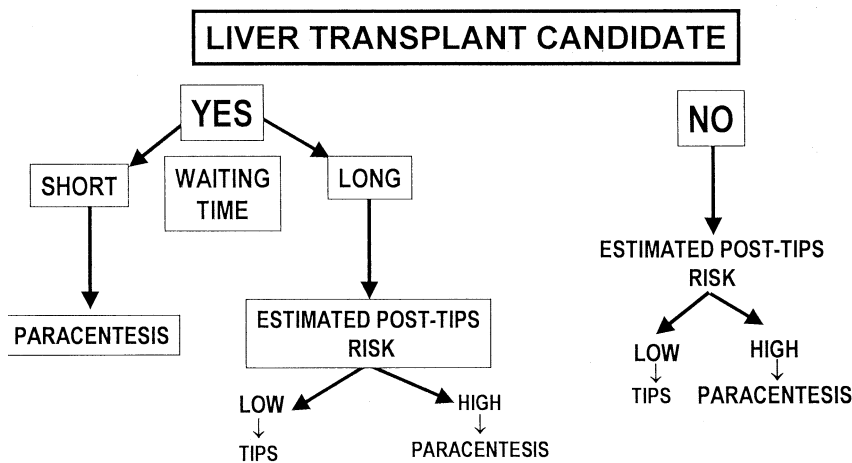


Fig. 7. A possible schema of decision-making for the indication of TIPS in patients with refractory ascites.

repeated paracentesis, although in some patients the use of peritoneovenous shunts might be considered.

Several reports have shown that TIPS may also be useful in patients with refractory hepatic hydrothorax [81, 82].

Other Indications

Portal vein thrombosis was initially considered a contraindication for TIPS, but some series of cirrhotic patients with portal occlusion treated with TIPS have been reported [83, 84]. Furthermore, TIPS have been successfully placed in patients with partially thrombosed portal veins, with the progressive disappearance of portal thrombi [85]. It may be very useful to avoid the progression of portal thrombosis that may preclude liver transplantation. TIPS has also been used in the treatment of portal thrombosis in patients without liver disease [86].

Although the mechanism of improvement is not clear, three cases of improvement of hepatopulmonary syndrome have been reported [87–89].

TIPS Failure

TIPS has been demonstrated, since its introduction in 1989, as an effective therapy for complications of portal hypertension; however, shunt failure may occur that limits long-term shunt patency and therefore shunt function [7, 20, 29, 90–93]. Although there is still not a consensus regarding the definition of TIPS failure (also known as insufficiency, malfunction or dysfunction) [94], failure includes occlusion, shunt tract stenosis or hepatic draining vein stenosis, and angiographic findings that may coexist and usually produce elevation of the portosystemic gradient (Figs. 8–10) [91, 94–100].

It is also accepted that both a reduction of at least 50% in luminal shunt diameter and/or elevation of the portosystemic gradient above 12–15 mmHg are the morphologic-hemodynamic criteria for diagnosing shunt insufficiency, although it has been demonstrated that negative complications of portal hypertension can be controlled effectively when the portosystemic gradient is below 12 mmHg [96, 99, 101–103].

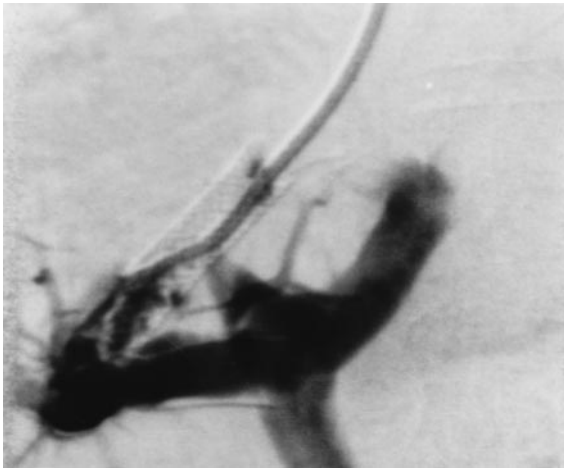


Fig. 8. Portography during the recanalization of an occluded TIPS.



Fig. 9. Significant shunt tract stenosis 18 months after TIPS placement with elevation of the portosystemic gradient.

Incidence and Classification

It has been very difficult to determine or to compare TIPS dysfunction among series, because of differences in failure definition, diagnostic methods to assess function, size of the series, and follow-up [29, 91, 94, 96, 99–104]. Reported cumulative rates of TIPS dysfunction vary between 17–73% (6 months), 23–87% (12 months), and 80–83% (24 months) [29, 91, 93, 95, 96, 99, 101, 105, 106].

Stenoses are the most frequent shunt problem and can appear between 4 and 6 months after TIPS placement [29, 95, 96, 99, 101, 107, 108]. In most series the main location of these stenoses is the draining hepatic vein, but it is not clear because series with longer follow-up have shown a higher shunt tract stenosis rate [29, 95, 96, 102, 106].

Shunt occlusion usually occurs in the early period (first month) after TIPS placement and is the least frequent shunt

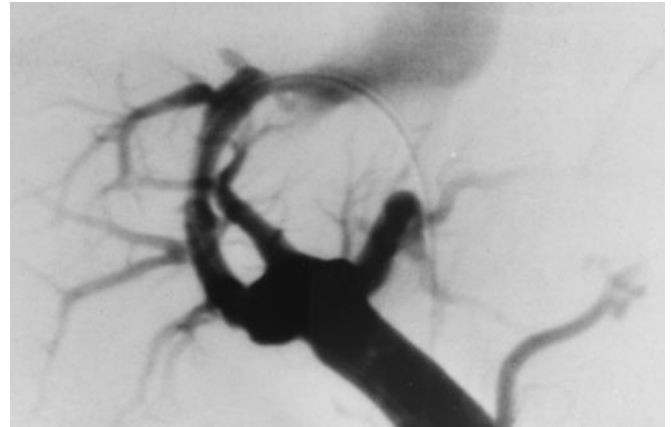


Fig. 10. Portography performed 6 months after TIPS placement shows an important hepatic vein stenosis.

problem (0–23% of cases) [10, 29, 34, 91, 96, 102, 109, 110].

Histopathology

Shunt tract stenoses are the result of intimal thickening secondary to pseudointimal hyperplasia (proliferation of dense collagen and myofibroblasts). Biliary-TIPS fistulae have been implicated in the etiology of shunt tract stenosis (Fig. 11) [19, 111, 112], but recently others have demonstrated marked shunt stenoses (dense collagen and smooth muscle cell proliferation) without bile staining or bile duct proliferation [113].

In stenosis of the draining hepatic vein intimal vein hyperplasia is demonstrable, which may be due to traumatic stress during shunt procedure, high flow after TIPS or activation of smooth muscle cells by growth factors. In occlusion thrombosis can be observed [19, 111–113].

Follow-up: TIPS Failure Diagnosis and Treatment

Although less than a third of patients with TIPS insufficiency show clinical symptoms, occlusion or stenosis may be present in nearly all patients when variceal hemorrhage or ascites recur [7, 96, 107].

Since the occurrence of failure, timing of shunt insufficiency, and recurrence (43–86% of cases) cannot be predicted, routine surveillance programs and percutaneous intervention are needed [29, 95, 96, 101, 103].

The best method for TIPS surveillance is unknown. Strategies vary among institutions and investigators and may include portal venography, Doppler sonography, and endoscopy (only in patients treated for variceal bleeding) used alone or in combination at different intervals. Common surveillance tactics consist of baseline examinations performed within the first few days after shunt placement and

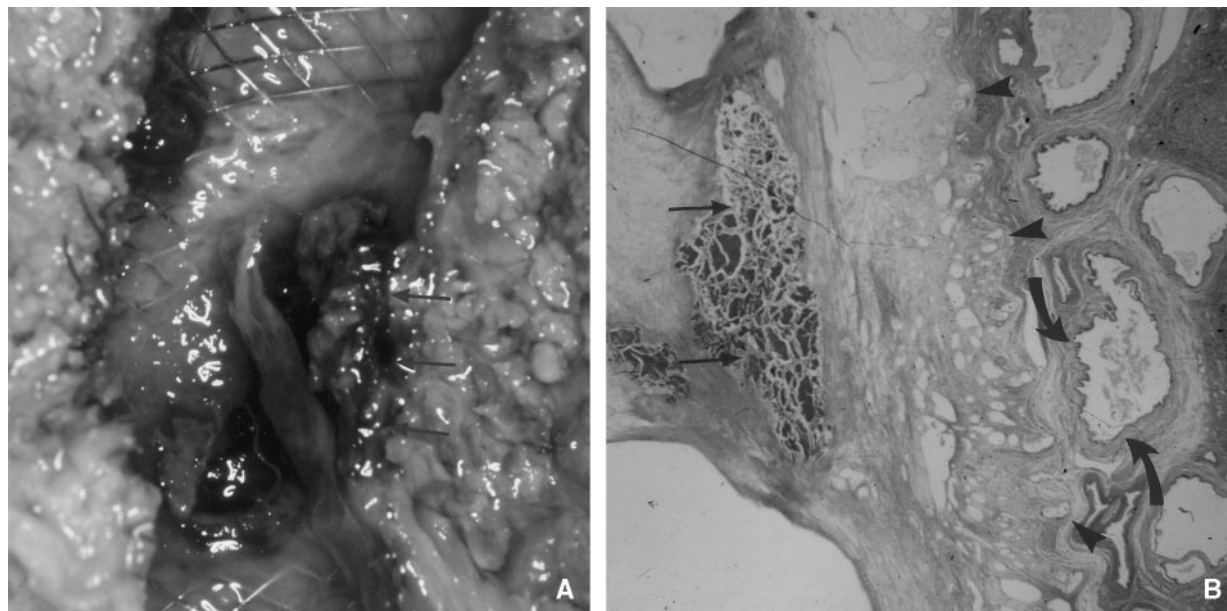


Fig. 11. **A** Histologic specimen obtained after liver transplantation. TIPS was created 6 months earlier and several episodes of restenosis occurred that required several balloon dilatations. An irregular bile-pigmented thrombus is clearly depicted in the middle third of the shunt (arrows). **B** Microscopic specimen. A bile-pigmented thrombus within the TIPS lumen is observed (arrows). Holes made by the wires of the Wallstent prosthesis can be seen (arrowheads). Note that a bile duct is in close contact with the shunt lumen (curved arrows).

further evaluations at 1, 3, 6 or 12 months, and every 6 or 12 months thereafter.

Portal venography is the gold standard in TIPS evaluation because it allows anatomic demonstration of stenosis, variceal filling and direct portosystemic gradient measurement during a single procedure. However, due to its cost and its invasive nature (outpatient procedure in some institutions), other noninvasive examinations (such as Doppler sonography) have been proposed as an alternative.

Doppler ultrasonography has been considered the main noninvasive method in shunt follow-up, but its accuracy in detecting dysfunction is not well established [96, 114–124]. The role of Doppler in detecting shunt occlusion is clearly defined (85–100% sensitivity, 96–100% of specificity), but stenoses and/or elevation of the portosystemic gradient are not so easy to see (Figs. 12–14) [112, 115, 118, 120, 121, 125, 126]. Some authors have established lower velocity thresholds of normality for suspected stenosis (50–60 cm/sec for intra-shunt maximum velocity), showing respective sensitivities and specificities of 6–100% and 62–100% [112, 115, 118–121, 123, 126, 127]. The highest accuracy has been reported using several Doppler criteria (combination of decreased intra-shunt velocities, portal velocities, intra-hepatic portal flow, draining hepatic vein flow) [121, 127]. However, recent published articles show poor correlation between portal venography and sonography [122, 123], results confirmed in our series of 105 patients with 422 venographic-sonographic correlations, where we obtained a maximum sensitivity of 82% but a specificity of 55% (unpublished data). It is therefore not clear established that



Fig. 12. TIPS occlusion is clearly depicted by color Doppler ultrasonography. There is no color Doppler signal in the shunt.

Doppler sonography should replace portal venography in TIPS follow-up.

The major problem of TIPS is the low primary patency rate, which requires a mandatory surveillance program following shunt creation. In the treatment of TIPS dysfunction

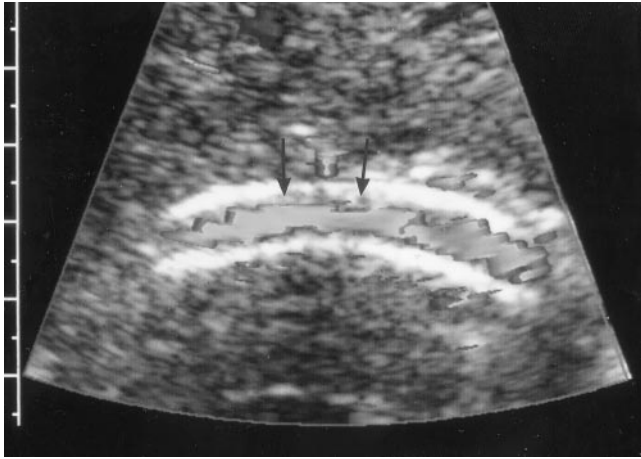


Fig. 13. Incomplete color filling of the shunt tract column due to pseudointimal hyperplasia (arrows).

classic percutaneous techniques (balloon dilatation or additional prostheses) have been used effectively (at least initially), raising the primary assisted patency to approximately 90% [95, 96, 99, 101, 102, 109, 128]. Repeated interventions are needed periodically, though it has been observed that fewer and fewer reinterventions are required if patients survive longer than 2 years (also seen in our institution) [129].

Because of the need of reintervention multiple studies have been carried out with prostheses covered with more or less impermeable material, i.e., stent-grafts (a metallic stent covered internally by a biocompatible graft material). A variety of grafts and coatings to avoid direct bile-lumen contact or pseudointimal proliferation have been investigated [130–137]. Although the research is still preliminary it seems that the Dacron-covered stent-grafts are excessively porous and therefore do not prevent restenosis [131] (Fig. 15). Several studies in either animals or humans have shown the successful use of polytetrafluoroethylene (PTFE)-covered stent-graft prostheses for both shunt revisions or de novo shunt creation; however, careful anatomic assessment is required to place the graft so that neither the portal nor hepatic vein branches are compromised because of partial or total coverage by the graft [131, 133, 135, 138] (Fig. 16).

Systemic Complications of TIPS

Encephalopathy

Not surprisingly, the increase in portosystemic shunting caused by TIPS has been associated with the development of hepatic encephalopathy [139, 140]. In fact, it may be considered the price to pay for a functioning shunt. As Casado et al. [141] have shown, recurrent bleeding or ascites after TIPS may occur if the portocaval pressure gradient is higher than 12 mmHg, and nearly all the patients with hepatic encephalopathy in their series had a portocaval pressure gradient below this threshold.

The 1-year incidence of encephalopathy ranges between 20% and 40% [30–32, 140, 142]. It is most frequent in the first few months after TIPS placement and is usually easily managed [140]. When it is recurrent or chronic despite medical therapy and dietary advice, partial or total occlusion of the shunt may be needed. Sicker patients are more prone to develop encephalopathy after TIPS. Jalan et al. [142] found that the only factor independently predicting hepatic encephalopathy after TIPS was the presence of encephalopathy prior to TIPS. In their series, Somberg et al. [140] found that non-alcoholic liver cirrhosis, female sex and hypoalbuminemia were independent predictors of encephalopathy.

Hemolysis

As in patients with artificial heart valves, TIPS may be associated with the development of hemolysis. In a series studying the hematologic consequences of TIPS, seven of 60 patients were found to have hemolysis, but only five of them developed anemia and only two had severe hemolysis as defined by a hemoglobin concentration decrease greater than 4 g/dl [143]. Hemolysis improved in most cases within 12 weeks after TIPS placement, probably because the formation of neointima may decrease turbulence within the stent.

Cardiovascular Complications

Immediately after opening of the TIPS, the increased cardiac preload coming from the portal vein may enhance the characteristic hyperdynamic circulation of patients with liver cirrhosis [144], even leading to cardiac failure [145]. Immediately after TIPS a sharp increase in right atrial pressure, mean pulmonary artery pressure, total pulmonary resistance and cardiac output, and a decrease in systemic vascular resistance are found [146]. Most of these changes gradually return to baseline values, but the elevation of cardiac output persists. Pulmonary hypertension has also been described after TIPS, but it seems to be very infrequent (3/900 cases in the series of Rössle et al. [10]). In patients with pulmonary hypertension, TIPS is contraindicated since a further increase in pulmonary arterial pressure may lead to acute fatal right cardiac failure.

Progressive Liver Failure

The increase in portal-systemic shunting caused by TIPS may reduce sinusoidal blood flow, thus enhancing liver failure. Its incidence has been estimated to be 1–5% [7] and it is one of the leading causes of death after TIPS placement, mainly in the long term [147]. Liver failure is much more frequent in patients with poor liver function prior to TIPS (i.e., Child-Pugh class C). Therefore in many centers TIPS is not considered in patients with advanced liver dysfunction.

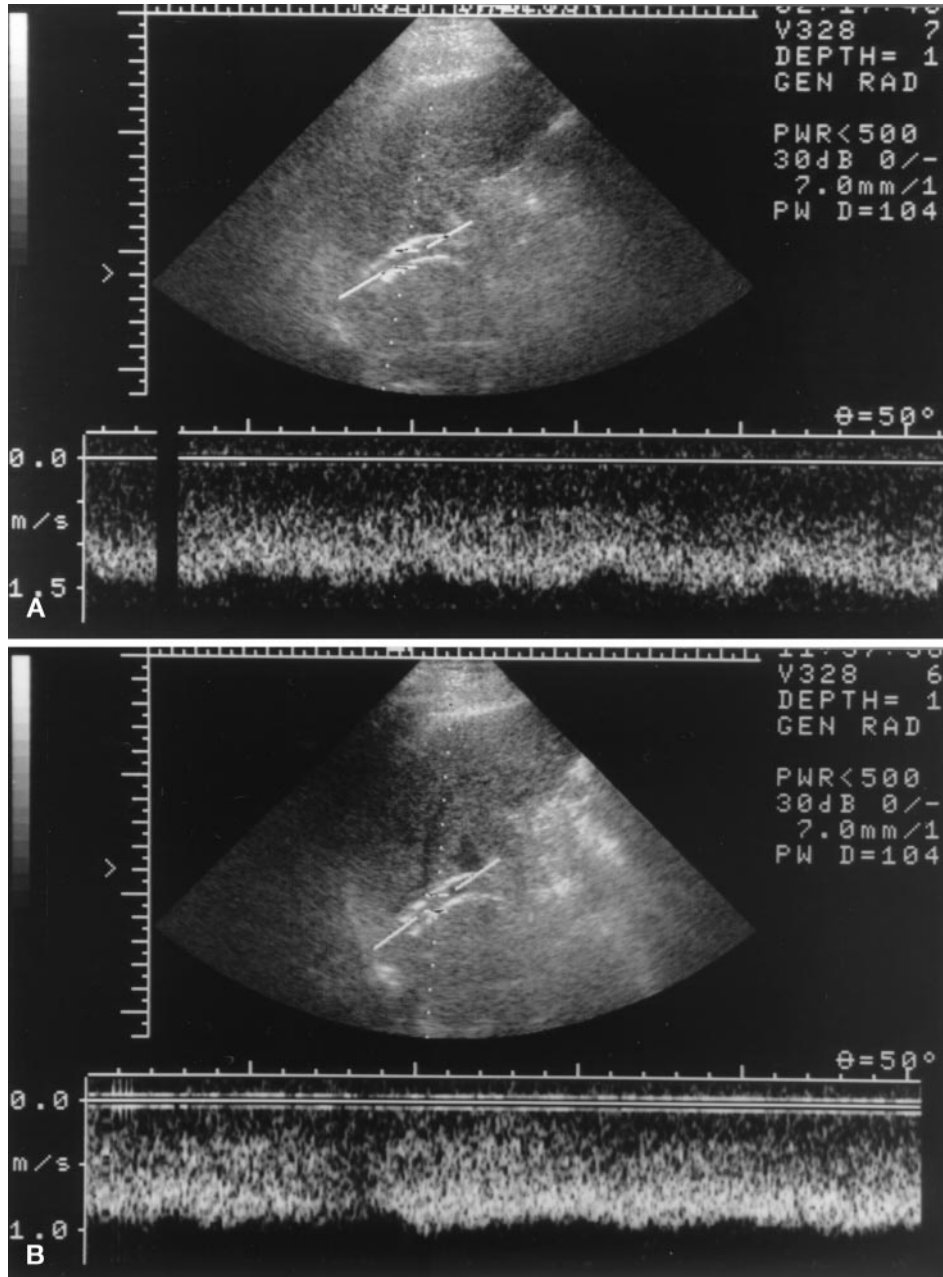


Fig. 14. **A** Doppler spectrum of a normal shunt. Maximal intra-shunt velocity immediately after TIPS placement is approximately 150 cm/sec. **B** Eighteen months later intra-shunt velocity has decreased to 90 cm/sec. A significant shunt stenosis was detected on portal venography.

Infection of TIPS

Infection of TIPS has been infrequently reported [148].

Survival

Several studies have tried to establish which factors are related to mortality after TIPS in order to avoid this treatment in patients with extremely high risk. Jalan et al. [142] found the 30-day mortality to be related to Child-Pugh class and hyponatremia before TIPS placement. Patients with hyponatremia and Child-Pugh class C had a 30-day mortality

of about 80%. Rubin et al. [149] found a relation between the 30-day mortality and Child-Pugh class and APACHE II score. In this series, only one of 17 patients with an APACHE II score higher than 18 and Child-Pugh C class survived more than 30 days.

Two recent studies have investigated which factors are related to post-TIPS survival, validating the models obtained in different series. Chalasani et al. [147] found that emergency TIPS placement, bilirubin concentration above 3 mg/dl, alanine aminotransferase above 100 IU/L and pre-TIPS encephalopathy unrelated to bleeding independently predicted death during the follow-up period. Combining these

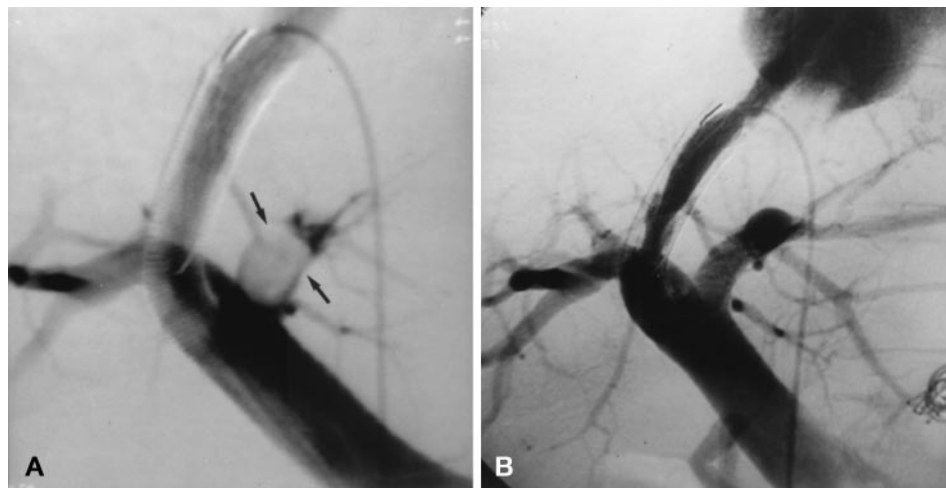


Fig. 15. **A** Portography performed during the placement of a Dacron-covered prosthesis. TIPS was created 16 months earlier and the patient presented several episodes of restenosis that required balloon dilatations. A fresh thrombus in the left portal vein is also observed (arrows). **B** Portography performed 6 months later. A new stenosis has appeared.

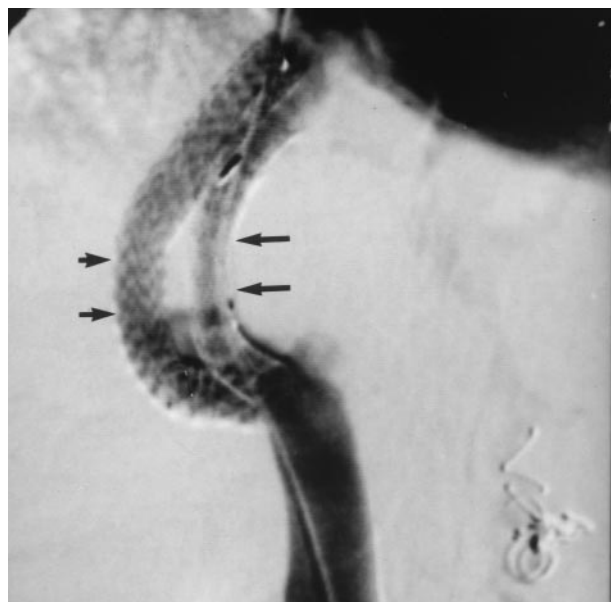


Fig. 16. A 40-year-old woman in whom TIPS was performed due to acute variceal gastroesophageal bleeding. After several episodes of restenosis a Dacron-covered prosthesis was placed (long arrows). Unfortunately new episodes of restenosis were observed within the TIPS. A new parallel TIPS was then created with a PTFE-covered prosthesis. Portography performed 6 months later shows excellent flow through the new TIPS (short arrows).

variables, they developed a model that separated patients into three groups with significantly different survival rates (Table 4) and confirmed that the model also predicted mortality in a separate series of patients.

Malinchoc et al. [150] studied 231 patients electively treated with TIPS and obtained a risk score combining the four independent predictors of survival: serum bilirubin and creatinine, international normalized ratio for prothrombin time and cause of liver disease. This score was used to predict survival at a given time. The model was validated in

Table 4. Predictors of survival after TIPS placement [144]

Variable	0 points	1 point	2 points
Emergency TIPS	No		Yes
Alanine aminotransferase (IU/L)	<100	>100	
Bilirubin (mg/dL)	<3	>3	
Pre-TIPS encephalopathy	No	Yes	

Low risk: 0 points, 1-year survival 67–70%.

Medium risk: 1–3 points, 1-year survival 43–49%.

High risk: 4–5 points, 1-year survival 10–30%.

Table 5. Model for end-stage liver disease (MELD) [145]

MELD =	$3.8^* \log_e(\text{bilirubin [mg/dl]})$ $+ 11.2^* \log_e(\text{INR})$ $+ 9.6^* \log_e(\text{creatinine [mg/dl]})$ $+ 6.4$ (if non-alcoholic/noncholestatic cirrhosis)
MELD	≤ 9 : 3-month mortality rate 1–8% 10–19: 3-month mortality rate 5.6–26% 20–29: 3-month mortality rate 50–76% 30–39: 3-month mortality rate 66–83% ≥ 40 : 3-month mortality rate 100%

an independent series of 71 patients. Recently, a slight modification of this risk score called MELD has been studied on four independent series of cirrhotic patients (more than 2,000 patients) (Table 5). It was very useful in predicting 3-month mortality rates [151].

Concluding Remarks

Since the insertion of the first TIPS in 1989 [5] much has been learned about this therapeutic procedure. It has an established role for the treatment of some complications of portal hypertension: prevention of recurrent variceal bleeding and rescue of patients with acute uncontrollable variceal bleeding. In addition TIPS is useful for Budd-Chiari syndrome, refractory ascites and hepatorenal syndrome, although its specific role in these indications remains to be definitively established. However, the decrease in sinusoidal

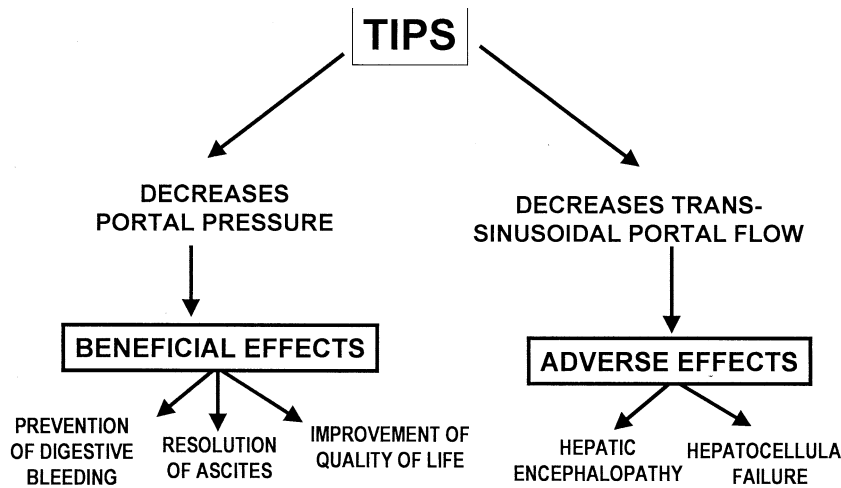


Fig. 17. Summary of the beneficial and adverse effects of TIPS.

blood flow induced by TIPS can lead to the patient developing hepatic encephalopathy and liver failure (Fig. 17). Therefore, TIPS should be used with caution in patients with very poor liver function.

From a technical point of view, successful placement of TIPS is achieved in more than 98% of cases by experienced groups. At present, evaluation of TIPS dysfunction based on morphology probably leads to an overdiagnosis of this complication since most of these cases are not associated with clinical manifestations (recurrent bleeding or refractory ascites). The major disadvantage of TIPS remains its poor long-term patency requiring a mandatory surveillance program. The indicator for shunt function/malfunction should be the portosystemic pressure gradient, which is best assessed by intravascular measurements. Shunt obstructions may be prevented or reduced by the use of stent-grafts in the future.

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