ascites and variceal bleeding were successfully treated in all cases. The most frequent complication was transient encephalopathy (40%). TIPS dysfunction with reoccurrence of initial symptoms was noted in 39%, and treated successfully in all cases. 8/38 patients died during the follow up period, mostly due to progressive deterioration of liver function or to non-hepatic reasons.

CONCLUSION: In conclusion, this study confirms TIPS to be a safe and effective procedure for treatment of different complications associated to portal hypertension. Our results as well as a review of the current literature suggest TIPS to be the standard treatment in patients with refractory ascites and Budd-Chiari syndrome, and to be of emerging significance in the management of portal thrombosis. In addition, TIPS maybe of value in new indications, such as obscure non-variceal bleeding associated with portal hypertension.

© 2015 ACT. All rights reserved.

Key words: Hypertension; Portal; Portasystemic Shunt, Transjugular Intrahepatic; Liver Cirrhosis; Thrombosis; Ascites

Herzer K, Lindner D, Nolte-Ernsting C, Gerken G, Hilgard P. Patient Selection, Outcome and Clinical Efficacy of TIPS: A Single Center Experience and Review of the Literature. Journal of Gastroenterology and Hepatology Research 2015; 4(4): 1557-1564 Available from: URL: http://www.ghrnet.org/index.php/joghr/article/view/1037

INTRODUCTION

The onset of complications of cirrhosis and portal hypertension marks the transition of liver disease from a compensated to a decompensated state that is associated with a reduction in survival from a median of 12 to 2[1]. The shortage of donor organs for liver transplantation has been one driving force to develop alternative effective therapies for portal hypertension, such as surgical shunt or transjugular intrahepatic stent shunt (TIPS)[2]. Since surgery is associated with significant morbidity and mortality in patients with
decompensated liver disease, TIPS has become the treatment of choice in many clinical scenarios in which portal hypertension or portal obstruction are the key pathophysiologic factors [3].

TIPS establishes a connection between the portal vein and the right hepatic vein by introduction of an intrahepatic self-expandable stent. TIPS can achieve portal decompression and therefore prevention of variceal bleeding and an improvement of the pathologic hyperdynamic splanchnic circulation in cirrhosis and thereby has the potential to control ascites and hydrothorax. Additionally, TIPS increases glomerular filtration and urine output, promotes natriuresis, and reduces the plasma renin activity aldosterone and noradrenaline levels. As a consequence, renal function altered from advanced cirrhosis is markedly improved [4-6].

Established indications for TIPS include acute, non-controlled variceal bleeding, secondary prevention of bleeding (mainly from gastric and ectopic varices) and refractory ascites [7]. The role of TIPS in Budd-Chiari-Syndrome is meanwhile well accepted [8]. Less conventional, rare indications are acute portal vein thrombosis, hydrothorax, hepatopulmonary syndrome, hepatorenal syndrome and prophylaxis of complications in cirrhotics who need major abdominal surgery. Absolute and relative contraindications to the insertion of TIPS are heart failure (cirrhose cardiaque), severe pulmonary hypertension, severe liver failure, chronic recurrent encephalopathy, polycystic liver disease, severe obstructive arteriopathy, arterioporal fistula, liver abscess, central hepatocellular carcinoma, bile duct dilatation and chronic portal vein thrombosis with portal cavernoma [9]. A decade ago, morbidity due to hepatic encephalopathy (HE) and deterioration of liver function made the procedure less attractive [9]. However, in the meantime TIPS developed a high therapeutic significance due to advances in the pre-, intra- and post-procedural management as well as selection of the patients. Long term patency considerably improved since the introduction of polytetrafluorethylene (PTFE)-covered stent grafts and is now comparable with that of surgical shunts [10,11].

In this report, we merge our experience with TIPS and analyze the results with respect to patient selection and in particular the diversifying current indications, as well as the management of postprocedural complications.

METHODS

Patients

This retrospective study analyzes the experiences of a primary referral center with key expertise for the treatment of patients with acute and chronic end-stage liver disease and its complications. All TIPS procedures were performed together by an experienced interventional radiologist and a hepatologist. The patient cohort consisted of 38 consecutive patients between January 2010 and March 2013. During this period, 72 patients were screened for TIPS, but 34 patients were not eligible for the intervention due to contraindications (bilirubin >3 mg, previous recurrent HE) or a non-refractory clinical situation, such as adequate response of ascites to diuretic medication. Age, etiology, urgency and severity of the underlying liver disease was registered. The observation period was 3-36 months. All patients gave informed consent for the intervention and for inclusion of their clinical data into the study.

Technique

TIPS was performed under conscious sedation. Internal jugular access was obtained by ultrasound guidance. Following the selection of the right hepatic vein and introducing an Amplatz stiff wire (Cook Medical, Limerick, Ireland), the TIPS puncture needle (Cook Medical, Limerick, Ireland) was directed into the right portal vein branch under simultaneous realtime ultrasound and fluoroscopic guidance. Then, a stiff wire was inserted into the portal vein and advanced to the superior mesenteric or splenic vein. Subsequently balloon dilatation (8 mm) and measurement of the intrahepatic tract was performed, in order to select proper stent parameters. Finally, a PTFE-covered stent (10 mm Viatorr Stent, W. L. Gore & Associates, Putzbrunn, Germany) was introduced through a 10 F sheath.

According to current recommendations [8,12,13], stent diameter was not adjusted to the portal pressure, which - for this reason - was not routinely measured. Instead, post-deployment dilatation of the 10 mm stent was routinely performed only with 8 mm balloons. Sole upon clinical demand (e.g. recurrence of tense ascites) the Viatorr stent was dilated to 10 mm in a second intervention. If needed (portal vein thrombosis), the TIPS was extended by a PTFE-covered 10 mm Viabahn stentgraft (Gore, Putzbrunn, Germany) into the origin of the main stem of the vessel. If necessary, TIPS implantation was complemented by endovascular occlusion of large gastric varices by placement of an Amplatz occluder (Cook Medical, Limerick, Ireland) into the varix vessels.

All patients were observed in an intensive care unit for 24-48 hours. Patient surveillance included clinical evaluation and routine Doppler sonography to assess the symptoms of portal hypertension and stent patency at 1, 6 and 12 weeks as well as 6, 12, 18, 24 and 36 months after intervention.

RESULTS

Patient characteristics and indications

Between January 2010 and March 2013, 38 patients (median age 60, range 37-78 years) were treated with 45 TIPS procedures. TIPS was urgent in one case and elective in all of the others. 8 patients underwent a re-intervention in order to extend or reduce the lumen of the previous placed TIPS, secondary to restenosis of the TIPS tract (n=6) or development of refractory encephalopathy (n=2). Follow-up was 3-36 months.

The major clinical symptoms in our cohort leading to TIPS implantation were intractable ascites with failure of diuretics (n=34, Table 1), followed by recurrent GI-bleeding not controlled by endoscopic or beta-blocker treatment (n=3). These symptoms were the result of the following underlying liver diseases: (1) Patients with liver cirrhosis and consecutive portal hypertension without associated vessel disease (n=29), (2) Patients with chronic Budd-Chiari syndrome (n=3). (3) Patients with portal vein thrombosis (n=4). (4) Portal hypertension without signs of liver cirrhosis or thrombosis of a major hepatic vessel (n=2, 1 patient with idiopathic portal hypertension, 1 patient with heavy chemotherapy pretreatment for malignant liver disease).

Liver function was defined in all patients by Child-Pugh (CTP) and MELD score. CTP score was class A in 2 cases, B in 27 cases and C (max. 11 points) in 8 cases. The median MELD score was 12. TIPS was not performed if patients reported previous spontaneous episodes of hepatic encephalopathy and (with one exception) a bilirubin value over 3 mg/dl. The major underlying disease of the patients with liver cirrhosis was alcohol associated hepatitis, followed by viral hepatitis.

Clinical efficacy and survival after TIPS implantation

The rate of primary technical success of TIPS interventions was 98% (37/38). Only in one patient with thrombosis of the extra- and intrahepatic branches of the portal vein, stable placement of a
guidewire after puncture of the portal system failed. At 3 months, 37/38 patients were alive and shunts were patent. Accordingly, on the short term, the clinical disorders leading to TIPS implantation, such as ascites and GI-bleeding, were successfully ameliorated in all patients.

In the 34/38 patients who received TIPS for refractory ascites, 19/34 patients (56%) showed a complete response with no or minimal residual amounts of ascites. In 15/34 (44%) ascites recurred within the follow up, but was controlled in 8 of these 15 patients by small doses of diuretic medication. 7/15 patients with minor response to diuretic treatment or with suspicion of TIPS stenosis in duplex-ultrasound analysis received reintervention. In 2 patients with angiographical detectable stenosis of the outflow vein, a combination of dilation (10 mm) and extension of the TIPS to the hepatic vein ostium was performed. In the additional 5 patients, who had no detectable TIPS stenosis in angioigraphy, TIPS dilation from 8 to 10 mm was conducted without stent extension. Reintervention led to complete response in all patients during the remaining observation period.

With respect to kidney function, an improvement of serum creatinine was observed in 35/38 patients, most significant 6 months after the intervention. However, those patients with elevated preprocedural creatinine showed the most significant profit. Parameters of liver function, such as MELD and CTP score as well as other liver synthesis or detoxification parameters (albumin, ammonia) remained stable after the intervention (Table 2).

8/38 patients died during the follow up period. One patient developed disseminated intravasal coagulation after stent implantation for unknown reasons and died shortly after intervention. Death of the other 7 patients (including one case with PVT) were TIPS implantation failed, see below) was related to progressive deterioration of liver function or non-hepatic reasons. One patient with declining liver function was registered for liver transplantation, and died on the waiting list. For the other patients with deterioration of liver function, transplantation was no option due to advanced age or <6 months period of abstinence from alcohol. In the 30 patients who were alive at the last time point of data acquisition, stents were patent. This applied in particular also for the patients with portal vein thrombosis and successful TIPS implantation (n=3, see below).

### Outcome of patients with uncommon indications

6 patients in the described patient cohort received the TIPS for -to date- unproven indications, such as portal vein thrombosis (PVT, n=4) and obscure non-variceal bleeding in the presence of portal hypertension (n=2). In the 4 patients with PVT, thrombosis was associated to liver cirrhosis and diagnosed in an acute or subacute state. Therefore, the vessel was still clearly identifiable by ultrasound and portal cavernoma was excluded, although this is not an absolute contraindication for TIPS implantation anymore[14]. In one patient with subacute PVT, the intervention was not successful since stable placement of a guidewire into the splenic or mesenteric vein through the already organized thrombus failed although the portal vein was identified and punctured. To open the portal vein again, angioplasty of the occluded part was sufficient alone in one case, while the other 2 patients needed an extension of the intrahepatic stent into the distal part of the vessel (Figure 1 A-D). Remarkably, a single shot with tissue plasminogen activator (tPA) for local thrombolysis prior to deployment of the stent ineffective to lyse the thrombus was in all cases.

Figure 1A depicts the angiography of the portal vein (transjugular access) in a patient with advanced liver cirrhosis and portal vein thrombosis showing the distal end of the thrombus just proximal of the portal confluens (black arrows). In part B, the persistency of the distal part of the thrombus (black arrow) after TIPS implantation (between white arrows) and balloon dilation of the distal portal vein is shown. A large varix (*) origins from the splenic vein. Figure 1C illustrates the stent-in-stent extension of the TIPS into the distal part of the portal vein (brake). Finally, in part D of the figure the contrast enhanced CT scan post intervention shows the result of the intervention with the extended TIPS in the portal vein and embolization of the large varix by an Amplatz occluder system.

Regarding the outcome of our PVT patients, the 3 patients with successful TIPS implantation showed a survival comparable to the patients without PVT and remained alive through the entire follow up period. Correspondingly, all stents were patent and refractory ascites was successfully treated. The single patient with PVT, where TIPS implantation failed, died 4 months after the attempted intervention.

### Table 1 Patient characteristics and indications for TIPS.

| Age (years) | Median 60 (max 78, min 37) |
|-------------|----------------------------|
| Sex         | 27                         |
| Female      | 11                         |
| Indication for TIPS | 34                    |
| Refractory ascites | 1                    |
| Refractory GI-bleeding | 3 (variceal n=1/non-variceal n=2) |
| Hepatic syndrome + ascites | 1 |
| Cause of portal hypertension | 1 |
| Liver cirrhosis | 29                     |
| Budd Chiari syndrome | 3                      |
| Portal vein thrombosis + cirrhosis | 4 (in 1 patient failure of TIPS implantation) |
| Idiopathic | 1                         |
| Malgnant disease/chemotherapy | 1 |
| Etiology of liver cirrhosis (n=33) | 21 |
| Alcoholic liver disease | 4                      |
| Cholestastatic liver disease | 1                  |
| Other | 8                         |
| Liver function | 8                      |
| MELD score | 12±4.61                    |
| Child A    | 2                         |
| Child B    | 27                        |
| Child C    | 8                         |

### Table 2 Liver and kidney function parameters prior and after TIPS implantation.

| Parameter | pre Intervention | 7d after Intervention | 3m after Intervention | 6m after Intervention | 12m after Intervention |
|-----------|------------------|-----------------------|-----------------------|-----------------------|------------------------|
| MELD      | 12 (6-26)        | 12 (6-18)             | 13 (6-19)             | 13 (7-20)             | 11.5 (6-20)             |
| CHILD     | 9 (7-12)         | 7 (5-10)              | 8 (5-10)              | 7 (6-12)              | 6.5 (5-10)              |
| Bilirubin [mg/dl] | 1.4 (0.2-5.3) | 1.42 (0.2-4.1) | 1.75 (0.9-5.4) | 1.5 (0.7-4.97) | 1.55 (0.71-4.8) |
| INR       | 1.25 (0.92-1.95) | 1.25 (0.97-1.74) | 1.25 (1.0-2.36) | 1.26 (1.0-2.2) | 1.29 (1.0-1.92) |
| Creatinine [mg/dl] | 1.15 (0.57-2.9) | 0.87 (0.43-2.2) | 1.07 (0.6-1.71) | 1.0 (0.6-1.4) | 1.05 (0.5-2.05) |
| Albumine [g/dl] | 2.7 (1.5-3.8) | 2.7 (2.0-3.7) | 2.9 (1.6-3.9) | 3.1 (2.1-3.6) | 3.3 (2.4-3.9) |
| Ammonia [µmol/l] | 40 (17-137) | 52.5 (22-153) | 67.5 (44-260) | 88 (47-389) | 45 (29-131) |

Herzer K et al. Clinical Efficacy of TIPS
A further random indication for TIPS in our cohort was obscure non-variceal bleeding (n=2). Both of these patients had severe recurrent anemia with positive stool blood testing. In endoscopic evaluation of the upper and lower gastrointestinal tract no active bleeding was detected, but both patients showed slight edema of the gastric wall suggestive for portal hypertensive gastropathy. A subsequent capsule endoscopy verified stigma of portal hypertensive enteroopathy, such as mucosal edema, angiodysplasia-like lesions and scattered cherry red spots. Subsequently, portal pressure was invasively measured by hepatic vein wedge pressure and found to be significantly elevated in both cases (15 and 18 mmHg). While in one patient chemotherapy induced liver damage was suspected as the reason for portal hypertension, in the other patient it appeared to be idiopathic. However, TIPS implantation led in both cases to immediate cessation of obscure bleeding and no further anemia was detected during follow up.

Adverse events and complications
The most frequent complication after TIPS implantation in our patients was transient hepatic encephalopathy (n=15, 41%). In 1/15 patients, encephalopathy was successfully treated by a combination of orally administered lactulose and ornithine aspartate. 12 patients additionally needed intermittent administration of paromomycin or rifaximine. One patient with autoimmune hemolysis accompanying liver cirrhosis had recurrent encephalopathy despite these therapeutic measures. In this patient as well as in one further patient not responsive to medical treatment, the shunt lumen was decreased by stent-in-stent placement of a concave reduction stent (n=2; Table 3).

In one patient, prolonged bleeding at the jugular puncture site was observed, but there was no case of intraabdominal bleeding following the TIPS procedure. In addition, no cases of ischemic hepatitis or renal failure were noted.

**DISCUSSION**

**Current Indications and Clinical Benefits of TIPS implantation**

We analyzed the outcome of a series of 38 consecutive patients that received TIPS with respect to indication, patient condition, complications and survival. By far, the most frequent indication for TIPS in our cohort was refractory ascites. Although the efficacy of TIPS in the treatment of refractory ascites was demonstrated in many non-controlled studies, its advantage compared to repetitive large volume paracentesis and peritoneal-venous shunt is, due to the absence of randomized trials, not clear. As a consequence, the net effect of TIPS on overall survival in patients liver cirrhosis and refractory ascites is still questionable.

The patients in our cohort with refractory ascites treated by TIPS implantation all achieved satisfactory results on the short term. Most patients were able to significantly reduce their amount of diuretic medication needed to control ascites. In addition, the postinterventional creatinine levels indicated a preservation of kidney function by the intervention. It has been demonstrated previously that TIPS improves renal function in chronic liver disease and that patients with renal dysfunction benefit most from TIPS[15]. Therefore, impairment of renal function in association with ascites or diuretic treatment in liver cirrhosis as well as hepatorenal syndrome, respectively, are accepted main indications for implantation of the shunt[6,15-17].

The other well accepted indication for TIPS among cirrhotic patients with portal hypertension is variceal bleeding. Two patients in our cohort received TIPS due to recurrent variceal bleeding despite medical and previous endoscopic therapy. In both patients, implantation of TIPS effectively prevented recurrence of bleeding for the time of follow up. In a recent randomized controlled study, the standard combination therapy with non-selective beta-blockers and endoscopic band ligation in patients after the first episode of variceal bleeding was compared to standard therapy followed by TIPS within 72 h after the bleeding episode[18]. In this study as well as in a following post-RCT surveillance study[19], the early use of TIPS was shown to be more effective than the combination of endoscopic and medical treatment in prevention of rebleeding, translating in a significant reduction of mortality. Based on these data, TIPS could be considered earlier in the treatment algorithm for bleeding varices and may not only be reserved for cases with recurrent bleeding. However, with regard to the relatively small patient number in the mentioned

| Complication                  | n  | Treatment                                      |
|------------------------------|----|------------------------------------------------|
| Bleeding from puncture site  | 1  | Compression                                     |
| Perinterventional aspiration | 1  | Antibiotic therapy                              |
| Pain after intervention      | 0  |                                                |
| Encephalopathy               | 15 | n=1, oral lactulose + ornithine aspartate (OA)  |
|                             |    | n=12, lactulose, OA + rifaximine or paromomycin |
|                             |    | n=2, decrease of shunt volume by reduction stent|
| TIPS stenosis                | 1  | Stent dilation and extension (sten-in-stent)    |
| Recurrence of ascites        | 15 | n=8, diuretic medication only                   |
|                             |    | n=5, stent dilation 8 mm to 10 mm               |
|                             |    | n=2, stent dilation and stent extension         |
| Death during time of follow up | 10 | 1 d – 9 m post intervention                     |
| Death related to procedure   | 1  | treatment of DIC                                |
| Hepatic ischemia             | 0  |                                                |
| Renal failure                | 3  | Cessation of diuretic medication + volume i.v.  |
| (Hepato-renal-syndrome)      |    |                                                |
| Abdominal bleeding           | 0  |                                                |
trial, it is still also reasonable to perform TIPS as a second line treatment if the conventional procedures of secondary prophylaxis for variceal bleeding fail\cite{20}.

In Budd-Chiari syndrome, a recent large retrospective series demonstrated effectiveness and improved transplant-free survival following TIPS\cite{21}. Our experience with 3 patients with chronic or sub-acute Budd-Chiari syndrome complies with this result. Despite the technical difficulties usually encountered during TIPS implantation in Budd-Chiari syndrome (direct puncture of the liver parenchyma through the inferior vena cava), all of our patients that received TIPS for Budd-Chiari syndrome showed a marked and long term improvement of liver function, portal hypertension and, consecutively, quality of life. This positive long term effect of TIPS in Budd-Chiari syndrome is likely to be attributed to the interruption of the pathologic postsinusoidal pressure increase. TIPS in Budd-Chiari syndrome therefore functions, at least in part, as a causal and not only as a symptomatic treatment\cite{22}.

Acute or subacute portal vein thrombosis (PVT) with or without Budd-Chiari syndrome is another suggested, but to date unproven indication for TIPS in patients with liver cirrhosis\cite{23,24}. For the technical success of the transjugular access to the portal vein it is advantageous if PVT is diagnosed in an acute or subacute state, since the vessel is then still clearly identifiable by ultrasound, although portal cavernoma is not anymore an absolute contraindication for TIPS implantation\cite{25}. The same is true for malignant etiology of PVT, mostly caused by hepatocellular carcinoma. It is still recommended to rule cancer out prior to implantation of the intrahepatic stent, but the experience of TIPS in malignant PVT is increasing and available trials report a similar success and complication rate\cite{26}.

In our series, 4 patients with PVT in the presence of cirrhosis were treated by TIPS, in one of which the implantation technically failed. The clinical efficacy of the shunt in the remaining 3 patients was similar to the patients without PVT. Interestingly, the attempt of additional local thrombolysis prior to the stent implantation failed in all of these cases - an observation that has been described by other investigators. A greater success for elimination of the portal thrombus was reported for continuous long term infusion of urokinase, in particular if combined with catheter directed mechanical techniques and following anticoagulation\cite{27,28}.

Taken together, it can be stated that in the presence of PVT, the combination of TIPS with further mechanical and/or medical interventions to eliminate the thrombus is a promising therapeutic method and should increasingly be considered. However, the absence of larger or randomized trials and the technical difficulties accessing the portal vein have to be taken into account. Certainly questionable is the indication for TIPS in patients with idiopathic noncirrhotic PVT and portal cavernoma. In these often young patients with an underlying detectable hypercoagulability or myeloproliferative disease, a surgical shunt still has to be considered as the gold standard\cite{29-31}, although TIPS implantation recently has been reported with adequate success even in these cases\cite{32}.

Non-variceal bleeding in liver cirrhosis is still an uncommon indication for TIPS despite the fact that portal hypertensive gastropathy and in particular portal hypertensive enteropathy seems to have a very high prevalence of >60% in portal hypertension\cite{33,34}. As a consequence, data on treatment of this condition by TIPS is very limited and do not exceed single case reports\cite{35,36}. However, in the mentioned case report as well as small studies evaluating the response of portal hypertensive gastropathy to TIPS, the interventional decrease of portal pressure was, like in our patients, highly effective in the termination of chronic bleeding\cite{37}.

The cumulative survival rate in our series was due to relatively small patient number not exactly statistically estimated. However, our mortality rate of approximately 21% after 36 months following TIPS implantation complies well to published data. In a large metaanalysis, the average transplant-free survival for patients with refractory ascites, which was the main indication for TIPS in our patients, has been reported to be 75.1%, 63.1%, 49.0%, and 38.1% at 6, 12, 24, and 36 months of follow-up\cite{38}. More recent randomized trials confirmed a similar mortality rate of 30 and 40 % after 2 years after implantation of covered TIPS\cite{39,40}. The mortality of our TIPS patients may be explained by the fact that most of them classified as Child B patients, in whom mortality without TIPS and liver transplantation is as high as 30% within one year. Furthermore, the mean age of many of our patients was advanced and comorbidities may have contributed to mortality.

**Occurrence and management of complications after TIPS**

Our data confirm the results of numerous other trials in which hepatic encephalopathy (HE) was shown to be the most common obstacle after TIPS implantation, occurring in 15% to 48% of patients\cite{41}. Usually, HE after TIPS can be effectively treated, and frequency as well as intensity of encephalopathy often diminish over time, so that HE in most cases appears to be a transient phenomenon. Only 3-7% of patients after TIPS implantation show recurrent or refractory encephalopathy, in whom dietary and medical treatment alone is not sufficient and who may need occlusion or reduction of the shunt\cite{42}. The availability of an hourglass-shaped stent for such a reduction procedure marks an important technical advance, since it obviates the need for complete TIPS occlusion in most cases of refractory HE after TIPS\cite{43}. In our two patients with refractory HE the stent-in-stent deployment, decreasing the initial 8 mm TIPS lumen to 5 mm, resolved HE without recurrence of ascites.

An actual randomized trial showed no differences in the incidence of HE after implantation of bare metal and PTFE-covered stents (both ~44%)\cite{44}. Interestingly, an additional recent randomized trial, comparing the occurrence of HE after insertion of PTFE-covered TIPS grafts with different diameters independent from the portal pressure (8 or 10 mm) also demonstrated no statistical differences of the HE rate (42.6% for the 8 and 46.7% for the 10 mm device)\cite{45}.

Since concomitantly the recurrence of symptoms due to portal hypertension was much higher in the 8 mm than in the 10 mm group (see below), this trial questions - at least for PTFE-covered stents - the value of routine portal pressure measurement and of a pressure adapted TIPS diameter.

A frequent long term complication is TIPS dysfunction with consecutive recurrence of the clinical symptoms of portal hypertension. In our patients no rebleeding was observed, but the rate of patients with reoccurrence of ascites was 39% (n=15/38). Previous data, including a metaanalysis\cite{46}, showed recurrence of tense ascites in 42%. The mentioned randomized trial comparing the clinical efficacy of 8 and 10 mm PTFE-covered stents, however, demonstrated recurrence of clinical symptoms in 54.5% in the 8 mm, but only 13% in the 10 mm group\cite{47}. Therefore, the authors of this particular trial, as well as other examiners\cite{48,49,50} and ourselves follow the concept of routine employment of a 10 mm covered stent, but underlining this only to 8 mm, in order to keep the shunt associated HE as low as possible. Only upon clinical demand, the stent is dilated to the maximum of 10 mm in a second intervention.

In addition to underestimation of the required diameter, a major reason for TIPS dysfunction is the development of stenosis in the hepatic venous outflow tract, as it occurred in two patients of our
cohort. Stenosis of the hepatic vein may be prevented by positioning the distal margin of the TIPS as close as possible to the orifice of the hepatic vein before joining the vena cava\textsuperscript{[41]}. Accordingly, the interventional treatment of hepatic vein stenosis is a stent-in-stent extension of the TIPS to exactly this point, as done in our patients.

To compare TIPS with surgical shunting with respect to clinical efficacy, shunt patency and complications, different surgical procedures have been evaluated in four randomized trials against TIPS in patients with variceal bleeding. A recent metaanalysis, summarizing the results of these trials\textsuperscript{[41]} suggests a clear advantage of surgical shunting over TIPS with respect to the development of rebleeding rate and mortality. However, all of these trials have the major limitation that uncovered (bare metal) stents instead of the today state-of-the-art polytetrafluoroethylene (PTFE)-covered stents were used. The PTFE-covered stent system demonstrated in a randomized controlled trial 2004 a clear superiority over bare metal stents with respect to shunt patency, clinical relaps, rate of reinterventions and survival by inhibition of both shunt thrombosis and pseudointima proliferation while the risk of hepatic encephalopathy was not increased\textsuperscript{[41]}. The superiority of PTFE-covered stents led over the following years to an almost complete abundance of bare metal stents for TIPS implantation and their patency today seem comparable with that of surgical shunts\textsuperscript{[18,19]}

Therefore, to robustly compare TIPS with surgical shunt procedures today, a randomized trial between a PTFE-covered TIPS system and surgical shunting would be necessary, but is still missing. For the treatment of refractory ascites as the primary symptom of portal hypertension, no surgical shunting procedure is established. In children, peritoneovenous shunting have been used for the treatment of intractable malignant ascites, but the patency of this shunt system is limited\textsuperscript{[41]} and no data with cirrhotic patients were found. The role of a recently available surgically implanted automated flow pump system from the peritoneal cavity into the bladder\textsuperscript{[44]} has to be further evaluated.

An open question with respect to further optimization of TIPS dysfunction is whether patients with PTFE-covered TIPS need long term inhibition of thrombocyte aggregation with acetylic salicylic acid (ASS). Many centers, including ourselves, still administer ASS on a routine basis after TIPS implantation, thereby adapting the approach from bare metal stents, in particular, if platelet counts are>100.000/µl. This approach can be questioned, since it is well accepted that covered stents led to a significant decrease in shunt dysfunction. However, this effect of covered in comparison with bare metal stents diminishes over time, resulting in 50% shunt revisions after a 5-year follow up even in patients with covered stents\textsuperscript{[41]}. In addition, no prospective or randomized data are available to either prove continuation or discontinuation of ASS medication after implantation of covered TIPS.

In our cohort, no cases of intraabdominal bleeding, renal failure and, in particular, ischemic hepatitis were noted. Ischemic hepatitis is regarded as the single most devastating complication after TIPS, potentially leading to development of acute-on-chronic liver failure. The mechanism causing liver failure post TIPS is most likely a missing increase of blood flow into the hepatic artery that has to compensate for the shunt-induced decrease of blood supply via the portal vein\textsuperscript{[45]}. Clinical and biochemical factors that were identified to correlate with the development of post-TIPS liver failure and other complications include advanced age, elevated bilirubin level, low sodium and albumin levels, and emergent indication for TIPS\textsuperscript{[46,47]}. In addition to these single parameters, various clinical-biochemical scoring systems were also described to be helpful for the prediction of complications after TIPS\textsuperscript{[48]}. Following these recommendations, the patients we selected for TIPS had a MELD (model of end stage liver disease) score of 12.7 +/- 3.93. Consequently, none of our patients developed an acute-on-chronic liver failure after stenting.

CONCLUSION

Taken together, our study verifies TIPS treatment to be a safe and highly effective method in portal decompression in a variety of indications. Although in a relatively small cohort, we were able to show that the intrahepatic stent shunt has not only to be considered as the standard treatment in patients with refractory ascites, variceal bleeding and Budd-Chiari syndrome, but is also of emerging significance in the management of portal thrombosis. In addition, our data suggest TIPS to have a value in new indications, such as obscure bleeding in cirrhotic and non-cirrhotic hypertensive enteropathy. With respect to complications, our study confirms HE and stenosis of the TIPS outflow tract to cause the major post-procedural clinical problems, while more devastating complications became seldom. To further reduce those complications after the TIPS procedure, recent findings about patient selection and management have to be consequently applied in daily clinical practice. The use of PTFE-covered stents, placed as close as possible to the orifice of the hepatic vein, can be considered to date as state-of-the-art, but with respect to HE, new stent designs may be warranted that allow a more careful adaption of the stent width to the individual patient.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

1. Punamiya SJ, Amarapurkar DN. Role of TIPS in Improving Survival of Patients with Decompensated Liver Disease. Int J Hepatol 2011; 2011: 398291

2. Rossle M, Siegristetter V, Huber M, Ochs A. The first decade of the transjugular intrahepatic portosystemic shunt (TIPS): state of the art. Liver 1998; 18(2): 73-89

3. Riggio O, Ridola L, Lucidi C, Angeloni S. Emerging issues in the use of transjugular intrahepatic portosystemic shunt (TIPS) for management of portal hypertension: time to update the guidelines? Dig Liver Dis 2010; 42(7): 462-467

4. Palihe M, Xue H, Jha RK, Li YC, Yuan J, Wang J, Zhang M. Changes in portal hemodynamics after TIPS in liver cirrhosis and portal hypertension. Scandinavian Journal of Gastroenterology 2013; 48(5): 570-576

5. Hausegger KA, Karnel F, Georgieva B, Tauss J, Portugaller H, Deutschmann H, Berghold A. Transjugular intrahepatic portosystemic shunt creation with the Viatorr expanded polytetrafluoroethylene-covered stent-graft. Journal of Vascular and Interventional Radiology: JVIR 2004; 15(3): 239-248

6. Busk TM, Bendtsen F, Moller S. Cardiac and renal effects of a transjugular intrahepatic portosystemic shunt in cirrhosis. Eur J Gastroenterol Hepatol 2013; 25(5): 523-530

7. Goykhman Y, Ben-Haim M, Rosen G, Carmiel-Haggai M, Oren R, Nakache R, Szoold O, Klausner J, Kori I. Transjugular intrahepatic portosystemic shunt: current indications, patient selection and results. Isr Med Assoc J 2010; 12(11): 687-691

8. Rossle M. TIPS: 25 years later. Journal of Hepatology 2013; 59(5): 1081-1093

9. Peter P, Andrej Z, Katarina SP, Manca G, Pavel S. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in patients with recurrent variceal hemorrhage.
Gastroenterology Research and Practice 2013; 2013: 398172

10. Yang Z, Han G, Wu Q, Ye X, Jin Z, Yin Z, Qi X, Bai M, Wu K, Fan D. Patency and clinical outcomes of transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stents versus bare stents: a meta-analysis. Journal of Gastroenterology and Hepatology 2010; 25(11): 1718-1725

11. Rossle M, Siegerstetter V, Euringer W, Olschewski M, Kromeier J, Kurz K, Langer M. The use of a polytetrafluoroethylene-covered stent graft for transjugular intrahepatic portosystemic shunt (TIPS): Long-term follow-up of 100 patients. Acta Radiologica 2006; 47(7): 660-666

12. Riggio O, Angeloni S, Ridola L, Rossi P. Can an incomplete stent expansion modulate the effects of TIPS? J Gastroenterol 2010; 45(3): 346-347

13. Saad WE, Darwish WM, Davies MG, Kumer S, Anderson C, Waldman DL, Schmitt T, Matsumoto AH, Angle JF. Transjugular intrahepatic portosystemic shunts in liver transplant recipients: technical analysis and clinical outcome. AJR American Journal of Roentgenology 2013; 200(1): 210-218

14. Peranau JM, Baju A, D’Alteroche L, Viguier J, Ayoub J. Feasibility and long-term evolution of TIPS in cirrhotic patients with portal thrombosis. Eur J Gastroenterol Hepatol 2010; 22(9): 1093-1098

15. Anderson CL, Saad WE, Kalagher SD, Caldwell S, Sabri S, Turba UC, Matsumoto AH, Angle JF. Effect of transjugular intrahepatic portosystemic shunt placement on renal function: a 7-year, single-center experience. Journal of Vascular and Interventional Radiology: JVR 2010; 21(9): 1370-1376

16. Siramolpiwat S. Transjugular intrahepatic portosystemic shunts and portal hypertension-related complications. World Journal of Hepatology 2013; 5(8): 45-50

17. Rossle M, Gerbes AL. TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. Gut 2010; 59(7): 988-1000

18. Garcia-Pagan JC, Caca K, Bureauc C, Lalamen W, Appenrod B, Luca A, Abraldes JG, Nvens F, Vinel JP, Mossner J, Bosch J. Early use of TIPS in patients with cirrhosis and variceal bleeding. The New England Journal of Medicine 2010; 362(25): 2370-2379

19. Garcia-Pagan JC, Di Pascoli M, Caca K, Lalamen W, Bureau C, Appenrod B, Luca A, Zipprich A, Abraldes JG, Nvens F, Vinel JP, Sauerrbruch T, Bosch J. Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study. Journal of Hepatology 2013; 58(4): 545-550

20. Shi KQ, Liu WY, Fan ZZ, Lin XF, Chen SL, Chen YP, Fan YC, Zheng MH. Secondary prophylaxis of variceal bleeding for cirrhotic patients: a multiple-treatments meta-analysis. Eur J Clin Invest 2013, May 8. doi: 10.1111/eci.12115

21. Seijo S, Plessier A, Hoekstra J, Dell’era A, Mandair D, Rifai K, Seijo S, Plessier A, Hoekstra J, Dell’era A, Mandair D, Rifai K, Treibicka J, Hadengue I, Mattiacci A, Lasser L, Abraldes JG, Darwish Murad S, Gervasi VA, Kassem AM, Umegaki E, Higuchi K. Evaluation of portal hypertensive enteropathy by scoring with capsule endoscopy: is transient elastography of clinical impact? Journal of Clinical Biochemistry and Nutrition 2010; 47(1): 37-44

22. Pezzoli A, Fussetti N, Simone L, Zalenta A, Cifala V, Carella A, Gullini S. Portal hypertensive enteropathy diagnosed by capsule endoscopy and demonstration of the ileal changes after transjugular intrahepatic portosystemic shunt placement: a case report. Journal of Medical Case Reports 2011; 5: 90

23. Kamath PS, Lacerda M, Ahlquist DA, McKusick MA, Andrews JC, Nagorney DA. Gastric mucosal responses to intrahepatic portosystemic shunting in patients with cirrhosis. Gastroenterology 2000; 118(5): 905-911

24. Valero F, Campana C, Eness M, Rossle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. Gastroenterology 2007; 133(3): 825-834

25. Peranau JM, Le Gouge A, Nicolas C, d’Alteroche L, Borelaint P, Saliba F, Minello A, Anty R, Chagneau-Derode C, Bernard PH, Abergel A, Ollivier-Hourmand I, Gourjon J, Ayoub J, Gaborit C, Rusch E, Giraudoue B, group S-T. Covered vs. uncovered stents for transjugular intrahepatic portosystemic shunt: A randomized controlled trial. Journal of Hepatology 2014; 60(5): 962-968

26. Bureauc C, Pagan JC, Layrargues GP, Metivet S, Bellot P, Perreau C, Oual P, Abraldes JG, Piron JM, Rousseau H, Bosch J, Vinel JP. Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: long-term results of a randomized multicentre study. Liver International 2007; 27(6): 742-747

27. Bae M, Qi X, Yang Z, Yin Z, Nie Y, Yuan S, Wu K, Han G, Fan D. Predictors of hepatic encephalopathy after transjugular intraportal portosystemic shunt in cirrhotic patients: a systematic review. Journal of Gastroenterology and Hepatology 2011; 26(6): 943-951

28. Fanelli F, Salvatori FM, Rabuffi P, Botta E, Riggio O, Lucatelli P, Passariello R. Management of refractory hepatic encephalopathy after insertion of TIPS: long-term results of shunt reduction with pharmacologic thrombolysis for portal vein thrombosis in liver-graft recipients and in candidates for liver transplantation. Transplantation 2004; 78(6): 938-940

29. Senzolo M, T MS, Rossetto V, Boccali C, Boccali P, Gasparini D, Miotto D, Simioni P, Toschzatzis E, K AB. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. Liver International 2012; 32(6): 919-927

30. Hall TC, Garcea G, Metcalfe M, Biliku D, Dennison AR. Management of acute non-cirrhotic and non-malignant portal vein thrombosis: a systematic review. World Journal of Surgery 2011; 35(11): 2510-2520

31. Spaneder VM, van Buuren HR, Janssen HL. Review article: The management of non-cirrhotic non-malignant portal vein thrombosis and concurrent portal hypertension in adults. Alimentary Pharmacology & Therapeutics 2007; 26 Suppl 2: 203-209

32. Luo X, Nie L, Zhou B, Yao D, Ma H, Jiang M, Zhang H, Li X. Transjugular intrahepatic portosystemic shunt for the treatment of portal hypertension in noncirrhotic patients with portal cavernoma. Gastroenterology Research and Practice 2014; 2014: 659726

33. De Palma GD, Rema M, Masone S, Persico F, Siciliano S, Patrone F, Matantuono L, Persico G. Mucosal abnormalities of the small bowel in patients with cirrhosis and portal hypertension: a capsule endoscopy study. Gastrointestinal Endoscopy 2005; 62(4): 529-534

34. Abdelaal UM, Morita E, Nouda S, Kuramoto T, Miyaji K, Fukui H, Tsuda Y, Fukuda A, Murano M, Tokiwa S, Arafà UA, Kassem AM, Umegaki E, Higuchi K. Evaluation of portal hypertensive enteropathy by scoring with capsule endoscopy: is transient elastography of clinical impact? Journal of Clinical Biochemistry and Nutrition 2010; 47(1): 37-44

35. Zeppolli A, Fussetti N, Simone L, Zalenta A, Cifala V, Carella A, Gullini S. Portal hypertensive enteropathy diagnosed by capsule endoscopy and demonstration of the ileal changes after transjugular intrahepatic portosystemic shunt placement: a case report. Journal of Medical Case Reports 2011; 5: 90

36. Kamath PS, Lacerda M, Ahlquist DA, McKusick MA, Andrews JC, Nagorney DA. Gastric mucosal responses to intrahepatic portosystemic shunting in patients with cirrhosis. Gastroenterology 2000; 118(5): 905-911

37. Valero F, Campana C, Eness M, Rossle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. Gastroenterology 2007; 133(3): 825-834

38. Peranau JM, Le Gouge A, Nicolas C, d’Alteroche L, Borelaint P, Saliba F, Minello A, Anty R, Chagneau-Derode C, Bernard PH, Abergel A, Ollivier-Hourmand I, Gourjon J, Ayoub J, Gaborit C, Rusch E, Giraudoue B, group S-T. Covered vs. uncovered stents for transjugular intrahepatic portosystemic shunt: A randomized controlled trial. Journal of Hepatology 2014; 60(5): 962-968
hourglass-shaped balloon-expandable stent-graft. *AJR American Journal of Roentgenology* 2009; **193**(6): 1696-1702

39 Riggio O, Ridola L, Angeloni S, Cerini F, Pasquale C, Attili AF, Fanelli F, Merli M, Salvatori FM. Clinical efficacy of transjugular intrahepatic portosystemic shunt created with covered stents with different diameters: results of a randomized controlled trial. *Journal of Hepatology* 2010; **53**(2): 267-272

40 Clark TW, Agarwal R, Haskal ZJ, Stavropoulos SW. The effect of initial shunt outflow position on patency of transjugular intrahepatic portosystemic shunts. *Journal of Vascular and Interventional radiology: JVIR* 2004; **15**(2 Pt 1): 147-152

41 Huang L, Yu QS, Zhang Q, Liu JD, Wang Z. Transjugular Intrahepatic Portosystemic Shunt Versus Surgical Shunting in the Management of Portal Hypertension. *Chinese Medical Journal* 2015; **128**(6): 826-834

42 Bureau C, Garcia-Pagan JC, Otal P, Pomier-Layrargues G, Chabbert V, Cortez C, Perreault P, Peron JM, Abraldes JG, Bouchard L, Bilbao JI, Bosch J, Rousseau H, Vinel JP. Improved clinical outcome using polytetrafluoroethylene-coated stents for TIPS: results of a randomized study. *Gastroenterology* 2004; **126**(2): 469-475

43 Sooriakumaran P, McAndrew HF, Kiely EM, Spitz L, Pierro A. Percutaneousportosystemic shunt insertion is an effective treatment for intractable ascites. *Postgraduate medical journal* 2005; **81**(954): 259-261

44 Bellot P, Welker MW, Soriano G, von Schaewen M, Appenrodt B, Wiest R, Whittaker S, Tzonov R, Handsiev S, Verslype C, Moench C, Zeuzem S, Sauerbruch T, Guanner C, Schott E, Johnson N, Petrov A, Katzarov K, Nevens F, Zapater P, Such J. Automated low flow pump system for the treatment of refractory ascites: a multi-center safety and efficacy study. *Journal of Hepatology* 2013; **58**(5): 922-927

Patel NH, Sasadeusz KJ, Seshadri R, Chalasani N, Shah H, Johnson MS, Namyslowski J, Moreco KP, Trerotola SO. Increase in hepatic arterial blood flow after transjugular intrahepatic portosystemic shunt creation and its potential predictive value of postprocedural encephalopathy and mortality. *Journal of Vascular and Interventional Radiology: JVIR* 2001; **12**(11): 1279-1284

46 Heinzow HS, Lenz P, Kohler M, Reinecke F, Ullerich H, Domschke W, Domagk D, Meister T. Clinical outcome and predictors of survival after TIPS insertion in patients with liver cirrhosis. *World Journal of Gastroenterology: WJG* 2012; **18**(37): 5211-5218

47 Parvinian A, Shah KD, Couture PM, Minocha J, Knuttinen MG, Bui JT, Gaba RC. Older patient age may predict early mortality after transjugular intrahepatic portosystemic shunt creation in individuals at intermediate risk. *Journal of Vascular and Interventional Radiology: JVIR* 2013; **24**(7): 941-946

48 Gaba RC, Couture PM, Bui JT, Knuttinen MG, Walzer NM, Kallwitz ER, Berkes JL, Cotler SJ. Prognostic capability of different liver disease scoring systems for prediction of early mortality after transjugular intrahepatic portosystemic shunt creation. *Journal of Vascular and Interventional Radiology: JVIR* 2013; **24**(3): 411-420

Peer reviewer: Hsien Hui Chung, Institute of Basic Medical Sciences, College of Medicine, National Cheng Kung University, Tainan City, Taiwan.