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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Small-diameter TIPS combined with splenic artery embolization in the management of refractory ascites in cirrhotic patients

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PURPOSE
Maximally decreasing portal pressures with transjugular intrahepatic portosystemic shunt (TIPS) is associated with improved ascites control but also increased encephalopathy incidence. Since splenic venous flow contributes to portal hypertension, we assessed if combining small-diameter TIPS with splenic artery embolization could improve ascites while minimizing encephalopathy.

METHODS
Fifty-five patients underwent TIPS creation for refractory ascites. Subjects underwent creation of 8 mm TIPS followed by proximal splenic artery embolization (group A, n=8), or of 8 mm (group B, n=6) or 10 mm TIPS (group C, n=41) without splenic embolization. Data were retrospectively reviewed.

RESULTS
In group A, median portosystemic gradient decreased from 19 mmHg to 9 mmHg after TIPS, and 8 mmHg after subsequent splenic artery embolization. In groups B and C, gradient decreased from 15 mmHg to 8 mmHg and 16 mmHg to 6 mmHg. All patients except for one in group A and two in C had greater than 50% reduction in the number of paracenteses in 3 months. Any postprocedural encephalopathy incidence was 62%, 50%, 83% in groups A, B, and C, respectively. Overall, 20% of subjects with 10 mm TIPS required TIPS reduction/closure compared to 7% of subjects with 8 mm TIPS.

CONCLUSION
We found that 8 mm diameter TIPS provided similar ascites control compared to 10 mm TIPS regardless of splenic embolization. While more patients with 10 mm TIPS required reduction/closure for severe encephalopathy, the study was underpowered for definitive assessment. Splenic embolization might have the potential to further decrease portosystemic gradient and ascites as an alternative to dilation of TIPS to 10 mm minimizing the risk of encephalopathy, but larger studies are warranted.

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Transjugular intrahepatic portosystemic shunt (TIPS) placement to manage refractory ascites in patients with cirrhosis is effective and associated with increased survival (1–3). This, however, comes at the cost of increased hepatic encephalopathy (3). While maximizing shunting with larger diameter stent-grafts (for example 10 mm) is associated with higher incidence of encephalopathy (4, 5), smaller stent-grafts (such as 8 mm) may be insufficient to fully control ascites (6). Optimal shunt diameter therefore remains controversial.

Since ascites is directly related to increased portal pressure (7, 8), other options to decrease it might be considered in addition to TIPS placement, rather than increasing shunt diameter. Proximal splenic artery embolization has been demonstrated to lower portal pressure (9) and therefore could also help managing refractory ascites. We hypothesize that the addition of proximal splenic artery embolization to 8 mm diameter TIPS has the potential for improving ascites control while minimizing the incidence of hepatic encephalopathy. Avoiding overshunting from TIPS could also minimize the risk for cardiac and hepatic decompensation considering the interplay between decompensated cirrhosis and associated cardiac dysfunction (10).

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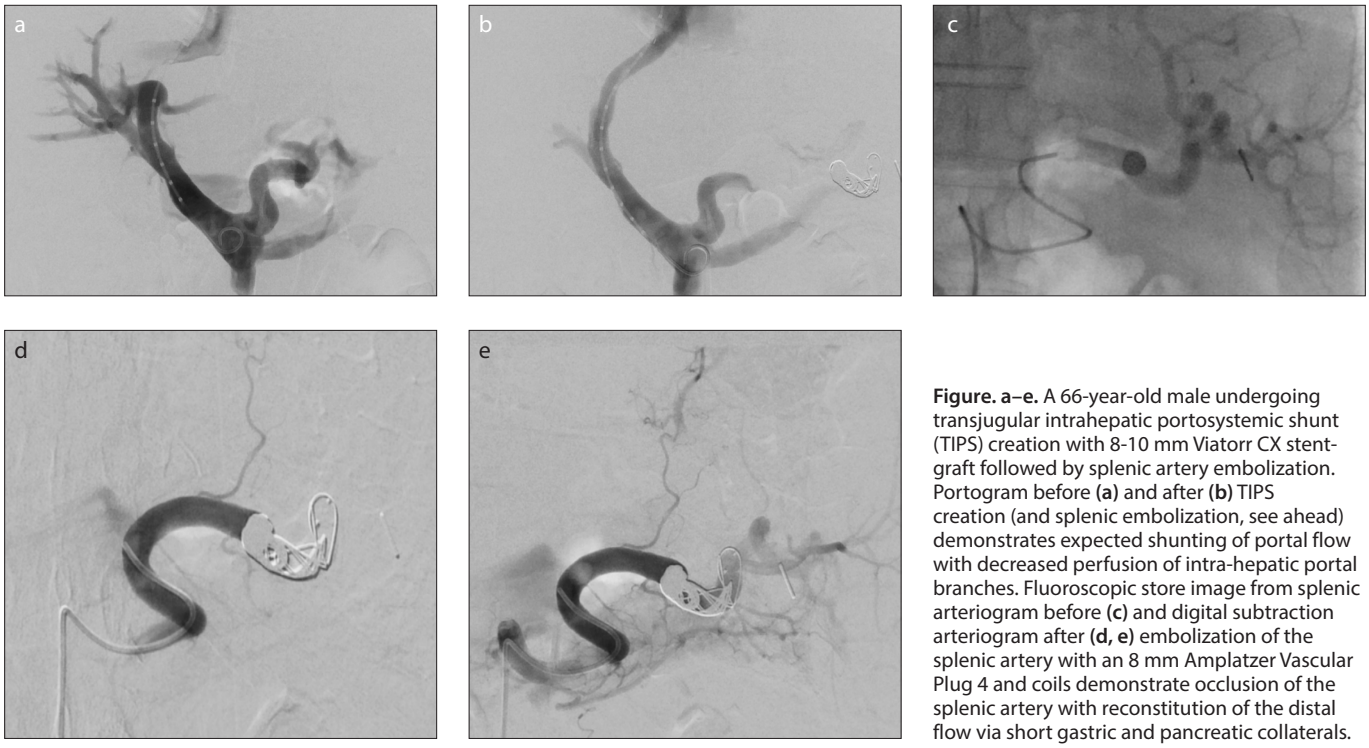

Figure. a–e. A 66-year-old male undergoing transjugular intrahepatic portosystemic shunt (TIPS) creation with 8-10 mm Viatorr CX stent-graft followed by splenic artery embolization. Portogram before **(a)** and after **(b)** TIPS creation (and splenic embolization, see ahead) demonstrates expected shunting of portal flow with decreased perfusion of intra-hepatic portal branches. Fluoroscopic store image from splenic arteriogram before **(c)** and digital subtraction arteriogram after **(d, e)** embolization of the splenic artery with an 8 mm Amplatzer Vascular Plug 4 and coils demonstrate occlusion of the splenic artery with reconstitution of the distal flow via short gastric and pancreatic collaterals.

This exploratory study describes the experience of combining 8 mm TIPS with proximal splenic artery embolization for managing refractory ascites and compares it to controls that had 8 mm or 10 mm TIPS placement with no splenic embolization.

Methods

Study design and population

An Institutional Review Board-approved retrospective review of medical records at an academic medical center was performed (protocol number 2018P001921). The requirement for written informed consent for the research study was waived; consent was obtained for each procedure as per standard clinical practice. Sixty-one cirrhotic subjects who underwent elective TIPS placement for management of refractory ascites between February 2015 and October 2018 were identified. Subjects were excluded if there was no follow-up of at least one month after the procedure (n=6).

Subjects who underwent placement of an 8 mm diameter TIPS followed by proximal splenic artery embolization were identified as the study group (group A). These comprised eight patients (five male and three female patients), median age 67 years (interquartile range [IQR], 63–68 years), median Model for End Stage Liver Disease (MELD) score 11 (IQR, 9–14). Splenic craniocaudal diameter on these patients ranged from 12.2–20.7 cm (median, 15.3 cm; IQR, 13.35–15.3 cm). Data on these subjects were compared to controls who underwent creation of TIPS of 8 mm (group B, n=6) or of 10 mm (group C, n=41), without splenic embolization. Demographics and clinical data are described in Table 1. Data from group A were compared to that of groups B and C.

Procedural technique

TIPS placement was performed as previously described (11–14). Once available at our institution, 8–10 mm Controlled Expansion (CX) Viatorr stent-graft (Gore & Associates) was the stent of choice, while previously nonconstrained 8 or 10 mm Viatorr stent-grafts were used. In groups A and B, 8 mm diameter TIPS were created (either with 8–10 mm CX Viatorr or with nonconstrained 8 mm Viatorr stent-grafts dilated to 8 mm). In group C, 10 mm diameter TIPS were created, either with 8–10 mm CX Viatorr dilated to 10 mm or with nonconstrained 10 mm Viatorr stent-grafts, regardless of the diameter they were dilated to at the time of the procedure, since that stent-graft is known to gradually open to its nominal size of 10 mm over time (15); one patient (2%) had the stent dilated to 7 mm, 19 patients (46%) had it dilated to 8 mm, and 21 patients (51%) had it dilated to 10 mm. Decision for creation of an 8 or 10 mm TIPS was based on operator's preference and could not be evaluated on this retrospective study. In group A, embolization of the splenic artery proximal to its hilar branches was then performed during the same procedure. Devices included Amplatzer Vascular Plug 4 (AGA Medical), MicroVascular Plug (Medtronic), 0.035-inch Nester coils (Cook), 0.035-inch Azur Detachable HydroCoils (Terumo Medical Corp), and 0.018- and 0.035-inch Interlock fibered detachable coils (Boston Scientific) according to sizing availability and operator's preference (Fig.). Since splenic embolization was

Main points

- There is no consensus on portosystemic pressure gradient target when creating TIPS for refractory ascites; increasing diameter of TIPS and therefore reducing the pressure gradient might improve ascites control but is generally associated with increased incidence of encephalopathy.
- In this study, proximal splenic artery embolization was combined with small diameter (8 mm) TIPS creation. This was shown to be safe and provide good ascites control with low incidence of hepatic encephalopathy.
- Unfortunately, no statistical comparisons were made due to small sample sizes. However, in this study less subjects with 8 mm TIPS required TIPS reduction due to severe hepatic encephalopathy, and all study groups had good ascites control.
- Larger prospective studies are warranted.

Table 1. Demographics and clinical data

	A: 8 mm TIPS + splenic embolization n=8	B: 8 mm TIPS (no embolization) n=6	C: 10 mm TIPS (no embolization) n=41
Male sex, % (n/n)	62 (5/8)	83 (5/6)	63 (26/41)
Age (years)[a]	67 (63–68)	65 (58–69)	59 (53–66)
Etiology of cirrhosis, % (n/n)			
Alcoholic	12 (1/8)	17 (1/6)	32 (13/41)
NASH	25 (2/8)	17 (1/6)	22 (9/41)
HCV/HBV	0 (0/8)	34 (2/6)	7 (3/41)
Multiple	50 (4/8)	33 (2/6)	22 (9/41)
Other	12 (1/8)	0 (0/6)	17 (7/41)
Prior liver transplant, % (n/n)	25 (2/8)	0 (0/6)	2 (2/41)
Prior encephalopathy, % (n/n)	38 (3/8)	67 (4/6)	51 (21/41)
Prior variceal bleeding, % (n/n)	38 (3/8)	33 (2/6)	32 (13/41)
MELD score[a]	11 (9–14)	11 (9–16)	12 (11–15)
Total bilirubin (mg/dL)[a]	1.00 (0.70–1.25)	0.45 (0.32–1.10)	1.10 (0.60–1.70)
Creatinine (mg/dL)[a]	1.17 (0.94–1.68)	1.35 (1.10–1.79)	1.19 (0.88–1.44)
INR[a]	1.20 (1.20–1.20)	1.15 (1.10–1.35)	1.30 (1.20–1.40)
Initial PSG (mmHg)[a]	19 (17–20)	15 (15–18)	16 (13–21)
Final PSG (mmHg)[a]	8 (4–10)	8.0 (7–9)	6 (4–8)

TIPS, transjugular intrahepatic portosystemic shunt; NASH, nonalcoholic steatohepatitis; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, model for end-stage liver disease; INR, international normalized ratio; PSG, portosystemic pressure gradient.
[a]Continuous variables are summarized as the median (interquartile range).

Table 2. Clinical outcomes

	A: 8 mm TIPS + splenic embolization n=8	B: 8 mm TIPS (no embolization) n=6	C: 10 mm TIPS (no embolization) n=41
Number of paracenteses in 3 months prior to TIPS[a]	8 (3–13)	12 (8–14)	6 (4–12)
Number of paracenteses in 3 months after TIPS[a]	0 (0–2)	0 (0–1)	0 (0–1)[b]
Ascites control, % (n/n)			
Complete	62 (5/8)	67 (4/6)	62 (23/37)[b]
Partial	25 (2/8)	33 (2/6)	32 (12/37)[b]
No	12 (1/8)	0 (0/6)	5 (2/37)[b]
Overall encephalopathy, % (n/n)	62 (5/8)	50 (3/6)	83 (34/41)[b]
Severe encephalopathy requiring TIPS reduction or closure, % (n/n)	12 (1/8)	0 (0/6)	20 (8/41)
Length of follow-up (days)[a]	105 (85–141)	421 (190–608)	394 (244–532)

TIPS, transjugular intrahepatic portosystemic shunt.
[a]Continuous variables are summarized as the median (interquartile range). [b]4 subjects who died or had transplant within one month of procedure were excluded.

performed proximally, with no expectation of causing substantial splenic infarction, patients were not vaccinated for encapsulated organisms prior to the procedure (16); no prophylactic antibiotics were administered. Portosystemic pressure gradient (PSG) was measured between the portal vein and the right atrium (17).

Patients were followed with clinic visits, laboratory evaluation and Doppler ultrasonography 2 weeks after the procedure and subsequently every 3–6 months.

Data collection

Medical records were reviewed for clinical notes, procedural imaging and reports, and laboratory data. Ascites was assessed by determining the number of therapeutic paracenteses performed in the 3 months before and after TIPS creation. Ascites control was graded as no improvement (less than 50% reduction in number of paracenteses), partial improvement (at least 50% reduction), and complete improvement (no further paracenteses) (18, 19).

Encephalopathy during follow-up was classified as absent, mild (no need for admission), severe requiring admission, or severe requiring TIPS reduction or closure. The West Haven Criteria (20) was not used as it could not be consistently characterized on this retrospective evaluation of medical records.

Patient charts were reviewed up to date of liver transplant, death, or last follow-up. Subjects who were transplanted or passed away within one month from TIPS creation were excluded from the analysis of ascites control but included in the encephalopathy analysis.

Continuous variables were described as median (IQR). Due to the descriptive nature of this study, inferential group comparisons were not performed.

Results

Group-specific demographics are detailed in Table 1. Overall, there were 36 males and 19 females, median age was 62 years (IQR, 56–68 years), median MELD was 12 (IQR, 10–15), and 51% of subjects had history of hepatic encephalopathy prior to TIPS creation.

Initial PSG was similar in all groups: group A, median 19 mmHg (IQR, 17–20 mmHg); group B, 15 mmHg (15–18 mmHg); group C, 16 mmHg (13–21 mmHg). In group A, median PSG decreased to 9 mmHg (5–10 mmHg) after TIPS creation, and then to 8 mmHg (4–10 mmHg) after proximal splenic artery embolization. Final PSG decreased to 8 mmHg (4–10 mmHg) in group A, 8 mmHg (7–9 mmHg) in group B, and 6 mmHg (4–8 mmHg) in group C.

All procedures were completed with no immediate complications. No patients in group A developed splenic abscesses; three of them had computed tomography done for clinical reasons unrelated to the TIPS and one was found to have small splenic infarcts, from which he was asymptomatic.

Group-specific clinical outcomes are detailed in Table 2. Postprocedural follow-up in group A (range, 53–225 days; median, 105 days; IQR, 85–141 days) was shorter than in groups B (range, 105–624 days; median, 421 days; IQR, 190–608 days) and C (range, 2–1359 days; median, 394 days; IQR, 244–532 days). No patients in groups A or B were transplanted or deceased during follow-up. In group C, 5 (12%) patients were transplanted (median 135 days after the procedure; IQR, 120–230 days) and 11 (27%) passed away (median 301 days after the procedure; IQR, 62–612 days).

Postprocedure, median number of paracentesis in 3 months decreased to zero in all groups. Ascites control was complete or partial in all patients except for one patient (13%) in group A and two patients (5%) in group C.

Postprocedural encephalopathy was seen in 5 patients (62%) of group A, 3 patients (50%) in group B, and 34 patients (83%) in group C. One patient (12%) in group A required TIPS reduction or closure, compared to none in group B and 8 (20%) in group C.

During the follow-up, one patient (13%) required TIPS thrombectomy in group A, no patients required re-intervention in group B, and 4 patients (10%) required TIPS thrombectomy and 4 other patients (10%) required TIPS dilatation in group C.

Discussion

When a TIPS is placed for refractory ascites, the ideal shunt diameter remains controversial with potential compromise between improved ascites control and increased risk for encephalopathy. This retrospective study aimed to assess whether combining proximal splenic artery embolization and a smaller shunt diameter (8 mm) could provide good ascites control (defined as a 50% decrease in number of paracentesis) with lower incidence of encephalopathy. Data showed that subjects that underwent creation of TIPS with 8 mm stents, including the 8 subjects that also had splenic embolization, had overall good ascites control. Encephalopathy incidence and severity appeared increased with 10 mm stent-grafts as hypothesized, with more patients requiring TIPS reduction. The addition of proximal splenic artery embolization was safe and associated with further decrease in PSG in this small cohort.

Multiple risk factors account for encephalopathy after TIPS, including increased age, worse liver function, low serum sodium concentration, and prior encephalopathy (4, 17). From a procedural perspective, decreased shunting and decreased PSG reduction should result in lower incidence of encephalopathy (21). However, this comes with the drawback of potentially worse ascites control. Given insufficient data, while there is consensus that TIPS created for variceal bleeding should target PSG less than 12 mmHg (21, 22), no such goal has been established for refractory ascites (23).

In the absence of established PSG reduction targets, it is worthwhile to review studies that have compared different diameters of stents for TIPS. Rowley et al. (4) retrospectively studied patients undergoing urgent TIPS for bleeding, identifying increased incidence of refractory encephalopathy requiring TIPS reduction in patients with stents larger than 8 mm (18.5% vs. 3.4%)—similar to our results of 20% vs. 7%. However, Miraglia et al. (24) identified similar incidence of encephalopathy in 8 and 10 mm TIPS (41% and 44%), with greater need for paracentesis in the 8 mm group (58% vs. 31%), in a retrospective study of TIPS for ascites.

Only two prospective randomized studies have compared 8 mm and 10 mm stent-grafts in TIPS. Riggio et al. (6) included 45 patients with ascites. The study was prematurely stopped due to insufficient control of portal hypertension complications in the 8 mm shunt arm (83% vs. 42% at one year), before possible differences in the incidence of encephalopathy could be detected (50% and 48%); however, the ammonia levels significantly increased only in the 10 mm stent group. On the other hand, a more recent study by Wang et al. (25) including 127 patient with variceal bleeding showed similar good shunt function with 8 and 10 mm stent-grafts but decreased incidence of overt encephalopathy with 8 mm stent-grafts (27% vs. 43%)—interestingly, with no correlation with PSG. Similarly, a prospective nonrandomized study by Schepis et al. (5), including TIPS created for ascites or bleeding, compared 53 patients who had TIPS stent-grafts dilated to their nominal 8 or 10 mm diameters to 100 patients with underdilated (6 or 7 mm) stent-grafts and found that underdilated shunts provided similar control of portal hypertension complications with less encephalopathy (27% vs. 54%); in this case, underdilated shunts were also associated with lower decrease of PSG.

The recent availability of controlled expansion covered stent-grafts now allows an easy and reliable creation of smaller 8 mm diameter shunts, hoping for decreased encephalopathy, but with the possibility of subsequent dilatation to 10 mm in case of insufficient clinical response (26). However, other measures that could improve ascites control without further increasing the risk of encephalopathy could still provide value, such as proximal splenic artery embolization.

As ascites is directly related to increased portal pressure (7, 8), associating measures to decrease the portal pressure appears reasonable. Proximal splenic artery embolization has been successfully performed in patients with liver transplant for suspected splenic artery syndrome and recurrent ascites. Pravisani et al. (9) retrospectively assessed 23 such patients who underwent proximal splenic artery embolization and observed resolution of ascites in all. While the physiopathology of ascites in those patients might be more complex, involving decreased arterial and/or excessive portal perfusion to the transplanted liver, splenic embolization significantly reduced portal vein velocities and wedged hepatic venous pressures. The effect of splenic artery interruption in portal venous flow has also been demonstrated in native livers: Akamatsu et al. (27) studied an *in vivo* model in patients undergoing pancreaticoduodenectomy and demonstrated 10%–16% decreased portal venous flow with splenic artery clamping.

At least one study assessed the combination of TIPS with splenic embolization. Wan et al. (28) retrospectively compared the outcomes of 16 patients who underwent TIPS and splenic embolization for recurrent bleeding with 32 matched controls with no embolization. Splenic embolization was indicated for severe hypersplenism (leukopenia or thrombocytopenia) and was performed by coiling distal splenic artery branches to infarct 50% of the spleen. While it is not clear why patients who underwent splenic embolization had a higher 5-year primary shunt patency (56.8% vs. 32.8%), the incidence of portal vein thrombosis, encephalopathy, and survival were similar in both groups. Two subjects in the embolization group developed splenic abscesses. We did not observe any infectious complications in our study, though follow-up was limited to a median of 105 days.

Splenic embolization by itself has also been used to manage bleeding complications from portal hypertension. Buechter

et al. (29) performed partial splenic embolization on 9 patients who were not TIPS candidates and had failed medical and endoscopic therapy for gastrointestinal bleeding with no significant rebleeding during a mean follow-up of 18 months. On that case, however, embolization was also performed distally with the objective of infarcting approximately 60% of the spleen, unlike our study. This also supports the hypothesis that splenic embolization decreases portal pressure and can be potentially useful in the management of its complications, including ascites as evaluated in the current study. Recent studies have assessed splenic stiffness with ultrasound elastography and found positive correlation between PSG and splenic stiffness, both in the setting of screening for esophageal varices (30, 31) and of assessment of hemodynamic changes after TIPS (32); unfortunately splenic elastography is not routinely performed at the authors' institution and therefore could not be assessed in this study, but future research evaluating for changes in splenic stiffness after splenic embolization could further support its use as an ancillary or alternative therapy for managing portal hypertension complications.

Splenic embolization has potential risks, the main ones including splenic infarcts and abscesses. These are more associated with distal rather than proximal embolization, which preserves collateral flow to the spleen (16). That is the main reason for proximal, rather than distal, embolization in the current study, and probable explanation why no patients developed abscesses despite no prophylactic antibiotics having been administered systematically. Since most patients in this study did not undergo dedicated imaging after TIPS combined with splenic embolization, the incidence of splenic infarcts cannot be calculated. However, only one of three patients who did undergo computed tomography after the procedure was found to have splenic infarcts, and these were small and asymptomatic.

This study has several limitations. The retrospective nature limits available data and the comparability of the groups. The small sample size and lack of statistical analyses preclude drawing definitive conclusions. Patients who received 8 mm TIPS without splenic embolization had overall good ascites control, making it difficult to detect further benefit of embolization. The study assumes that all unconstrained 10 mm Viatorr stent-grafts spontaneously expanded to 10 mm regardless of initial dilatation and that there are no other differences between unconstrained and constrained stent-grafts. The shorter follow-up of the subjects who underwent TIPS and splenic embolization also partially limits comparisons.

In conclusion, in this retrospective study, 8 mm diameter TIPS provided good ascites control compared to 10 mm TIPS, regardless of association with proximal splenic embolization. Combining 8 mm TIPS with proximal splenic artery embolization was safe. The 10 mm TIPS was associated with worse encephalopathy. Associating splenic embolization to 8 mm TIPS might have the potential to further improve ascites control when needed, as an alternative to dilatation of the TIPS to 10 mm, so as to keep the incidence of encephalopathy low, but this needs to be confirmed in larger prospective studies.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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