Reduced Stents and Stent-Grafts for the Management of Hepatic Encephalopathy after Transjugular Intrahepatic Portosystemic Shunt Creation

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ABSTRACT

Hepatic encephalopathy (HE) is a common complication encountered by patients after transjugular intrahepatic portosystemic shunt (TIPS) creation. Although most patients respond well to conservative medical therapy, up to 7% of patients do not and require more invasive therapeutic approaches. One option is emergent liver transplantation; however, most patients are not suitable candidates. During the past decade, various percutaneous techniques have been described that alter the hemodynamics through the TIPS by occluding it with coils or balloons or by reducing its diameter using constrained stents or stent-grafts. These endovascular techniques have produced symptomatic improvement in many patients with refractory HE, with either complete resolution or substantial reduction of HE symptoms that can be controlled with additional medical therapy. Unfortunately, despite all attempts, some patients remain incapacitated and ultimately die. Further research is necessary to improve our understanding of HE after TIPS creation so that less invasive and safer procedures can be developed to treat this difficult clinical problem.

KEYWORDS: Hepatic encephalopathy, hypertension—portal, liver—interventional procedure, shunts—portosystemic

Objectives: Upon completion of this article, the reader should be able to (1) understand the proposed pathophysiology that leads to hepatic encephalopathy after TIPS, (2) review the management options for patients who develop hepatic encephalopathy after TIPS, and (3) describe numerous endovascular techniques that can be performed for patients whose hepatic encephalopathy is refractory to medical management.

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Transjugular Intrahepatic Portosystemic Shunts: An Update; Editors in Chief, Brian Funaki, M.D., Peter R. Mueller, M.D.; Guest Editor, Hector Ferral, M.D. *Seminars in Interventional Radiology*, volume 22, number 4, 2005. Address for correspondence and reprint requests: David C. Madoff, M.D., Department of Diagnostic Imaging, Interventional Radiology Section, Unit 325, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4009. ¹Department of Diagnostic Radiology, Section of Interventional Radiology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas. Copyright © 2005 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662. 0739-9529,p;2005,22,04,316,328,ftx,en;sir00332.

Hepatic encephalopathy (HE) is a common complication following the creation of a transjugular intrahepatic portosystemic shunt (TIPS). This condition is characterized by confusion, disorientation, obtundation, abnormal sleep patterns, and overall alterations in quality of life.¹ New or worsened HE after TIPS placement has been reported to occur in up to 35% of patients, but conservative medical therapy usually is sufficient to reverse the problem.² HE that is refractory to conservative therapy develops in up to 7% of patients,³ for whom further intervention, including shunt reduction or occlusion and potentially emergent liver transplantation, may be required.

Various percutaneous techniques used to treat refractory HE alter the hemodynamics through the shunt by occluding or reducing its diameter. Although effective in reversing HE, complete shunt occlusion, using balloons or coils, may have abrupt, life-threatening hemodynamic consequences.⁴⁻⁶ Other techniques that attempt to reduce flow by creating turbulence within the shunt rely on the placement of constrained bare stents within the TIPS lumen.^{3,7-9} This latter approach is unpredictable, and several days may be required for the portosystemic gradient (PSG) to increase and stabilize. More recently, stent-grafts constrained to a predetermined diameter have shown promise as an effective means of shunt reduction, resulting in immediate and measurable hemodynamic responses.¹⁰

In this article, we review the proposed pathophysiology that leads to HE after TIPS placement and the medical management options available for patients who develop HE after TIPS. In addition, endovascular techniques that can be performed for patients in whom HE is refractory to conservative therapy are presented, as are the advantages, disadvantages, and potential consequences of these novel approaches. Importantly, some of the endovascular devices used for the management of refractory HE are, at present, considered "off-label" by the Food and Drug Administration.

HE AFTER TIPS CREATION

The exact pathophysiology of HE is complex and at present, poorly understood. However, the current belief is that central nervous system disturbances occur when intestinally derived compounds requiring hepatic detoxification bypass the liver and remain within the systemic circulation.^{1,3,11,12} Which toxin or toxins lead, directly or indirectly, alone or in combination, to the development of HE after TIPS creation is controversial.¹³ The most widely accepted theory is that nitrogenous compounds such as ammonia access the systemic circulation as a result of diminished hepatic function or by portosystemic shunting. Once within the brain parenchyma, these compounds cause alterations in neurotransmission, which lead to fluctuations in behavior and consciousness. Addi-

tional substances have been proposed to cause HE including γ -aminobutyric acid/benzodiazepines, neurotransmitters (e.g., glutamate, norepinephrine, and dopamine), short- and medium-chain fatty acids, mercaptans, phenols, serotonin/tryptophan, manganese, and endogenous opioids. These chemicals may interact with ammonia to result in additional neurological alterations.¹⁴

The pathogenesis of HE after TIPS creation is related to the combination of excessive bioavailability of gut-derived toxins and portal hypoperfusion.^{13,15} Two phenomena are believed to contribute to diminished portal flow: portal flow diversion from the liver and, secondarily, "sinusoidal steal" that results in additional cellular compromise in the face of preexisting hepatocellular dysfunction.¹¹

MEDICAL MANAGEMENT OF HE

Episodes of HE that occur within weeks of TIPS creation are often induced by specific precipitating factors (e.g., dietary protein indiscretion, gastrointestinal bleeding, sepsis, dehydration, hypokalemia, hypoxia, constipation, or use of sedatives or psychoactive medications), particularly in patients with ascites and in patients who remain on diuretics after TIPS creation.^{1,12} Post-TIPS diuresis associated with rapid weight loss may result in electrolyte imbalance and intravascular volume depletion that may precipitate HE. In cirrhotic

Figure 1 Schematic illustration of coil embolization (arrows) to permanently and completely occlude a TIPS. Note the enlarged esophageal varix.

Figure 2 Schematic illustrations of a method of temporary TIPS occlusion. (A) Occlusion balloon (arrowhead) is seen within the TIPS with development of a thrombus (arrow) below (portal side). (B) The thrombus (arrows) remains within the intraparenchymal tract following removal of the occlusion balloon. (C) If necessary, recanalization can be performed to reestablish flow through the TIPS.

patients, acute deterioration of liver function leading to HE may also result from alcoholic hepatitis or the development of an acute circulatory disturbance such as portal vein thrombosis.¹⁴

HE after TIPS creation may forecast the development of chronic recurrent encephalopathy. Some precipitating factors for this condition are reversible and

might be successfully treated with protein-restricted diets, nonabsorbable disaccharides (e.g., lactulose), and/or antibiotics (e.g., neomycin, metronidazole). Furthermore, drugs that affect neurotransmission may have a therapeutic role in selected patients.

The medical management of HE following TIPS creation is similar to that of HE in the absence of TIPS

Figure 3 Schematic illustration shows constrained Wallstent (black arrowhead) placed within a TIPS. A suture (white arrowhead) was threaded through the stent mesh and tied with multiple knots to reduce the stent lumen at its midportion. Small curved arrows demonstrate turbulent blood flow within the shunt.

creation. In the absence of other precipitating factors, TIPS should be evaluated and a search for large splenorenal or gastorenal shunts should be performed. The classic cornerstone of therapy for acute HE has been dietary protein restriction to less than 0.5 g/kg/d, with incremental increases to assess clinical tolerance.¹⁴ The dietary management of HE also includes increasing dietary fiber to promote catharsis. Unfortunately, the overall nutritional status of these already malnourished patients may worsen, adding to the morbidity of liver transplantation should that option become available. Importantly, a positive nitrogen balance will have favorable effects on HE by promoting liver regeneration and improving the muscles' ability to detoxify ammonia. The decision to use severe dietary protein restriction requires weighing the risks of worsening HE without such restriction against the risk malnutrition with it.¹⁶ Branched-chain amino acids may provide a better-tolerated source of protein.¹⁷ However, because of their high costs and limited therapeutic value, branched-chain amino acids should be reserved for patients with HE refractory to maximal medical therapy.

Another option to reduce the nitrogenous load from the gut is by bowel cleansing. HE itself may result in slow transit time, and colonic cleansing with various laxatives and enemas, or irrigation with a 5-L isotonic mannitol solution, has been used to reduce intraluminal

ammonia, intraluminal bacterial content, and blood ammonia.^{14,18–20} Nonabsorbable disaccharides such as lactulose have also been advocated, but their precise mechanisms of action are unknown. They have been thought to work by causing catharsis and acidification of the colon.²¹ Catharsis assists in the removal of neurotoxins from the gut. Acidification of the colon occurs as colonic bacteria ferment the nonabsorbable disaccharide into acetic acid and lactic acid, which leads to ammonia passing from the bloodstream into the colonic lumen. Lactulose may be administered orally or rectally, depending on the patient's mental status and gastrointestinal integrity. The dose of orally administered lactulose is titrated to achieve two to three semiformal bowel movements per day (generally 15 to 45 mL every 8 to 12 hours).¹⁴ If administered rectally, lactulose (300 mL in 1 L of water) is retained for 1 hour with the patient in the Trendelenburg position to increase access to the ascending colon.²² However, side effects include volume depletion from diarrhea, electrolyte imbalances, and renal insufficiency, all of which may worsen HE.

For patients not responding to lactulose, non-absorbable antibiotics may be used. Neomycin has been used to reduce the population of urease-containing bacteria in the colonic lumen during acute HE episodes.^{23,24} A drawback to this approach, however, is that although neomycin is poorly absorbed, up to 3% reaches the systemic circulation and may lead to neurotoxicity, ototoxicity, and renal failure. Neomycin also affects the small bowel mucosa, impairing the activity of glutaminase in the intestinal villi, resulting in intestinal malabsorption and diarrhea. For these reasons, neomycin should not be used long term to treat patients with HE. An alternative antibiotic, metronidazole, may be used but its long-term benefit is also limited by its potential to cause irreversible neuropathy.^{14,25,26}

Lastly, HE may be treated by drugs that affect neurotransmission such as flumazenil and bromocriptine, based on the hypothesis that γ -aminobutyric acid (GABA) transmission is enhanced in HE development.^{14,27} Agents that bind to GABA_A receptors have direct neuroinhibitory effects on the brain, leading to HE symptoms.²⁸ Because flumazenil was found to have only modest effectiveness in one large clinical trial,²⁹ and has been reported occasionally to cause seizures, the use of this drug to treat HE cannot be recommended.¹⁴

In some cases, the treatments mentioned above may be gradually tapered off during follow-up as HE improves. Gradual improvement may be, in part, related to progressive TIPS stenosis. HE that occurs in the presence of shunt stenosis and recurrent variceal hemorrhage poses a clinical dilemma. If HE is disabling, an endovascular approach to manage variceal hemorrhage and prevent the worsening of HE may be considered and could include variceal embolization without shunt

Figure 4 Schematic illustrations showing Forauer-McLean reduction method. (A) A Wallstent is placed within a 15-mm Palmaz stent (black arrowhead). (B) If necessary, the constrained stent can be expanded in stepwise fashion. Immediately after balloon dilatation (white arrowhead), the constrained shunt diameter is wider (black arrowhead).

revision. Alternatively, endoscopic treatment or liver transplantation can be used depending on the severity of the liver dysfunction.¹

ENDOVASCULAR THERAPIES FOR HE

A small but important subset of patients who do not respond to medical management will require more invasive approaches.^{1,30} Endovascular treatment for these patients is directed toward reducing the amount of portal venous blood diverted from the liver by occluding or reducing the diameter of the existing TIPS.

Permanent shunt occlusion has been used to treat postprocedure HE and fulminant liver failure.^{4,31} In 1984, Potts et al³¹ used detachable balloons to occlude a surgically created splenorenal shunt. Following shunt occlusion, the authors reported a reduction in cardiac output and an increase in vascular resistance and hepatic perfusion, along with improved hepatocyte function. Based on this study, interventional radiologists have used embolic agents (stainless steel coils and detachable balloons) for permanent TIPS occlusion (Fig. 1).

Despite the successful use of shunt occlusion, several later reports described life-threatening sequelae of this approach. Aside from the sudden increase in portal pressure and risk of recurrent variceal hemorrhage, other severe hemodynamic consequences have been encountered. In 1994, Paz-Fumagalli et al⁴ reported a

Figure 5 Schematic illustration of Ethibloc embolization (arrows) of space between the outer TIPS stent and the reducing stent.

Figure 6 Coil embolization of the "dead space" between inner and outer stents. (A) Schematic illustration of the location of coils (arrow) used for "dead space" embolization. The constrained stent is shown with arrowhead. (B) Anterior-posterior fluoroscopic image demonstrating the constrained stent (arrow) within the TIPS (arrow). (C) Large coils (arrow) placed between the inner and outer stents. (D) TIPS venography performed immediately after coil deployment demonstrates flow throughout the original TIPS lumen. Thrombus has not yet formed within the "dead space."

Figure 7 Schematic illustration of the use of stent-graft technology within a TIPS shunt. The stent-graft (arrow) is constrained with a suture (arrowhead).

case of intentional TIPS occlusion using coils that resulted in death. Although no postmortem evaluation was performed, death was believed to have resulted from sudden, severe hemodynamic alterations that resulted in decreased cardiac output, hypotension, and metabolic acidosis. The insertion of a permanent foreign object such as a detachable balloon or coils into TIPS to reverse shunt-related complications may pose a problem should variceal hemorrhage recur. In such cases, shunt recanalization might not be feasible and creation of a new TIPS might be required.

Intentional reversible occlusion of the shunt has also been described as a way to treat refractory HE. Kerlan et al⁶ and Haskal et al⁵ reported seven total cases of successful reversible thrombosis achieved by placing completely occlusive latex balloons (Meditech/Boston Scientific, Natick, MA) within the midportion of a TIPS for up to 48 hours (Fig. 2). The technique has been used to thrombose the transparenchymal portion of a TIPS below the balloon and has the advantage of its being reversible should ascites and/or variceal bleeding recur. If recanalization is needed, a smaller diameter shunt may be used to reduce the risk of recurrent HE. Nevertheless, like other techniques that abruptly occlude the shunt, this approach increases the risk of recurrent variceal hemorrhage and may produce life-threatening hemodynamic changes.^{4-6,32} Further, this technique poses the theoretical risk of thrombus propagation either proximally or distally into the portal or hepatic vein and the

potential for balloon migration to the right side of the heart, or balloon rupture. Various techniques have been used to avoid potential complications from this approach such as periodic radiographic imaging during the balloon inflation process.⁵

More recently, several methods of shunt reduction that diminishes flow by creating turbulence within the shunt lumen have been used to overcome the problems associated with complete shunt occlusion. Haskal and Middlebrook⁷ reported clinical improvement in a patient with refractory HE using a standard, uncovered Wallstent (Boston Scientific, Natick, MA) that was constrained to a diameter of 5 mm using a silk suture tied within its midportion to create an hourglass-shaped stent. Their technique (Fig. 3) involved the transjugular insertion of a 12-Fr sheath through which a 40-cm-long 9-Fr sheath was then backloaded onto the Wallstent delivery system. The stent was then partially deployed to expose the leading half of the stent so that a 3-0 silk suture could be woven through the meshwork of the stent and tied, creating a waist in the stent. The partially deployed stent and its delivery system were then withdrawn into the 9-Fr sheath, and the entire unit was advanced into the shunt and deployed with the waist positioned within the parenchymal tract. The authors attributed the improved clinical outcome to reduced flow (by increased turbulence and friction) created by the interposed stent mesh within the TIPS lumen. Modifications of this technique using sutures to constrain bare stents have been reported.³³

Forauer and McLean³ reported an alternative approach using balloon-expandable stents to constrain the Wallstent for HE management (Fig. 4). A 10-mm diameter, 42-mm-long Wallstent was deployed within a 15-mm-long Palmaz stent (P154M; Johnson & Johnson, Warren, NJ). A 5-0 braided polyglactin suture (Vicryl; Ethicon, Somerville, NJ) was used to tie and anchor the two stents together. The stents were then loaded into a 10-Fr sheath, deployed within the shunt, and dilated to a 4-mm diameter with a balloon catheter. The advantage of using a balloon-expandable stent to constrain the Wallstent is the ability to further dilate the stent should sequelae of portal hypertension recur.

A major limitation of these uncovered constraining stent techniques is the difficulty of accurately regulating blood flow across the shunt and the ability to control and immediately measure the PSG elevation. It is uncertain whether thrombus will form within the dead space surrounding the constrained portion of the stent and alter the flow dynamics sufficiently to reverse HE. Patients are usually reexamined several days after stent placement to confirm hemodynamic success.

The evolution of the constrained Wallstent technique continued with adjunct embolization of the dead space surrounding the constrained portion of the stent. In 1998, Gerbes et al⁹ reported their experiences with

reducing blood flow through TIPS in three patients. In their first patient, a constrained bare stent failed to produce alterations in shunt velocity, and the HE did not resolve. In an attempt to solve this problem, the space between the two stents (outer TIPS stent and reducing stent) was filled with the embolic emulsion Ethibloc (Ethicon, Norderstedt, Germany) (Fig. 5). The PSG immediately increased from 10 to 23 cm H₂O, the shunt velocities decreased from 85 to 25 cm/s, and the HE completely resolved. In the subsequent two cases, Palmaz stents were placed into curved-shaped TIPS stents. To avoid displacement, the distal ends of the Palmaz stent were dilated to 6 mm and the proximal end was dilated to 10 mm. Flow velocity decreased from 90 to 70 cm/s as the HE resolved in one patient. In the other patient, Ethibloc embolization around the Palmaz stent was required to cause an immediate increase in PSG. Alternative embolic agents like Gianturco coils have been used in a similar fashion (Fig. 6).

Technological advances have recently brought stent-grafts to the forefront as an attractive alternative to existing techniques of shunt reduction. Using a constrained stent-graft offers a controlled means of shunt

lumen reduction with an instantly measurable increase in PSG (Fig. 7). Initially, "homemade" endografts were used, but these have largely been replaced by commercially available stent-grafts (Fig. 8).

In 2003, we¹⁰ first described the effective use of constrained stent-grafts (Wallgraft, Boston Scientific) to treat six patients with refractory HE after TIPS creation. The approach was similar to that of the initial reports of constrained Wallstents (Fig. 9). In our series, a 10- or 12-mm Wallgraft was fully deployed and the trailing end of the stent-graft covering was removed to reduce the risk of hepatic vein thrombosis. An angioplasty balloon (6- to 8-mm diameter) or dilator (18- to 24-Fr) was then used as a template to form a waist with a purse-string 3-0 silk suture (Ethicon) approximately one-third the distance from the leading end of the stent-graft. The constrained diameter was chosen based on the initial TIPS diameter and the severity of the HE. The modified stent-graft was then loaded into the tip of a 35-cm-long, 9- or 10-Fr sheath and deployed within the existing shunt.

Shunt reductions were technically successful in all six patients, with an immediate mean PSG increase of

Figure 8 Method of "homemade" reduced stent-graft construction for placement within TIPS. (A) A 4-mm thin-walled PTFE covering was attached to a Palmaz 394 stent. (B) Graft material was sewn to the cross-struts at both ends with 5-0 prolene after the graft was predilated to 6 mm. (C) Stent was crimped on a 6 mm × 8 cm Opta-LP balloon (Cordis, Miami Lakes, FL) and placed through an 11-Fr peel-away sheath into a 35-cm-long 10-Fr sheath. (D) A 30-cm-long 12-Fr sheath (arrows) was then manipulated through the TIPS.

Figure 8 (continued) (E) Preloaded stent (advanced to the front of the 10-Fr sheath) (arrows) was then placed so that the leading end of the graft would be near the portal-vein entry site. (F,G) The entire device was dilated to 6 mm in this location, and then a 10 mm × 2 cm balloon was used to flare the leading and trailing ends until a seal was obtained. (H) TIPS venography through the sheath demonstrates an hourglass stent-graft configuration with the "dead space" (arrows) entirely excluded. Accurate PSG measurements were subsequently obtained.

9.3 mm Hg. Clinical improvement (complete resolution of HE [$n = 4$] and partial resolution of HE [$n = 1$]) was achieved within 72 hours of reduction. The remaining patient continued to decline and died 3 weeks later, at least partially because of a comorbid process, thrombotic thrombocytopenic purpura, which also causes symptoms that mimic HE. Shunt occlusion occurred in two patients within 8 months. It is unclear whether the polyethylene terephthalate (PET) graft material in the Wallgraft endoprosthesis played a role in shunt occlusion or whether the final shunt diameters (6-mm) and intimal hyperplasia played a dominant role. One of the shunt occlusions occurred after 6 months, leading us to favor the latter hypothesis.

Additional modifications have been made to the constrained stent-graft technique.¹⁰ York³⁴ partially deployed the Wallgraft endoprosthesis short of the "point of no return," so that the device could be recaptured in its own delivery system after the constraining suture was placed. The benefit of this modified technique is that it is fast, easy to learn and perform, and requires no addi-

tional supplies. The only downside is the accuracy of the final stent-graft diameter. When the Wallgraft endoprosthesis is in a partially deployed state, it is difficult to gauge the true residual lumen of the stent-graft. Though in most situations, this approach is adequate, for patients who may require additional shunt reductions (i.e., from the initial diameter of 12 mm to 8 mm and subsequently to 5 mm), the technique may not be optimal. The original technique we described¹⁰ allows more accurate titration of the shunt diameter downward. However, the initial technique also involved cutting away the trailing end of the stent-graft to avoid coverage of the hepatic veins. This is no longer believed to be necessary because covering the hepatic veins has been well tolerated and even recommended for TIPS to improve patency with the use of the recently Food and Drug Administration–approved VIATORR[®] stent-graft (W. L. Gore & Associates, Flagstaff, AZ).³⁵

Controversy exists as to what stent-graft is best suited for treating refractory HE resulting from TIPS creation. Many authors agree that PET-covered

stent-grafts such as the Wallgraft endoprosthesis are not appropriate for creating de novo TIPS because of concerns of early shunt occlusion. In fact, studies performed in a porcine model demonstrate superior patency rates when stents were covered with polytetrafluoroethylene (PTFE) material rather than with PET, because PET produced thrombogenic and inflammatory responses that led to earlier shunt occlusion.^{36,37} In addition, a

recent report³⁸ described three patients in whom TIPS created with PET-covered stents became occluded but were successfully salvaged using PTFE stent-grafts. However, it remains unclear whether shunt occlusions are caused by the apposition of and interaction between the PET material and the traumatized surface of hepatic parenchyma or whether there is inherent thrombogenicity of the material itself.³⁹ If the inherent

Figure 9 Method of constrained Wallgraft endoprosthesis placement within a TIPS. (A) Anterior-posterior fluoroscopic image from a normal shunt venogram through a 9-Fr vascular sheath. (B) A Wallgraft endoprosthesis was deployed on a table. A dilator was used as a template to determine the desired endograft diameter for reduction. A purse-string suture was woven through the stent mesh and graft material, approximately one-third the distance from the leading end, to create a constrained diameter. (C,D) The trailing end covering of the endograft was removed to prevent occlusion of the hepatic vein following deployment.

Figure 9 (continued) (E,F) The stent-graft was then loaded into a new 9-Fr curved sheath, with the trailing end resheathed first. (G) Anterior-posterior image from a shunt venogram after deployment of the constrained Wallgraft endoprosthesis. Contrast material is seen within the constrained endograft (white arrow), indicating instantaneous reduction of the shunt diameter. The TIPS stent is indicated by the black arrow. Postprocedure venography showed an hourglass waist, and PSG measurements were obtained. (H) If necessary, an additional constrained endograft (white arrow) may be deployed within the preexisting constrained endograft (black arrow) to further reduce the shunt lumen.

problem is related to the PET material's interaction with the exposed parenchyma, shunts created with PTFE stent-grafts may negate this problem, allowing the use of PET for subsequent shunt reduction. It is quite clear that the optimal device has yet to emerge for this particular application.

Stent-graft modification using a similar technique has been deployed successfully to reduce shunt flow, immediately increase PSG, and improve the clinical status of a patient with TIPS-induced HE and hepatic failure.⁴⁰ Quaretti et al⁴⁰ used a PTFE-covered balloon expandable endograft, available currently only outside the United States, that was altered by targeted balloon expansion at each end of the device. At the 7-month follow-up, the shunt was patent and the liver failure had completely resolved. A more recent study (2004) compared five different TIPS reduction techniques (one patient per technique), including using two parallel stents with subsequent coil embolization of one stent; a balloon-expandable bare stent placed within the shunt; a balloon-expandable stent-graft placed within the shunt; a suture-constrained self-expanding stent-graft placed within the shunt; and a self-expanding stent-graft placed within the shunt with a parallel balloon-expandable bare stent extrinsically constraining the diameter of the stent-graft.⁴¹ In this series, all procedures were technically successful, resulting in increased PSGs and decreased symptoms and none of the patients experienced recurrent variceal hemorrhage or ascites in short-term follow-up. As could be predicted, the stent-graft technique had the advantage of immediate exclusion of blood flow outside the reducing stent, resulting in an immediate reduction of the caliber of the shunt.

CONCLUSION

TIPS-related HE is a difficult clinical problem that is usually managed conservatively. When HE is refractory to conservative treatments, more invasive techniques are often required. The innovative percutaneous interventions described herein have only recently become available. Further refinement of these techniques and materials used for shunt reduction are still needed. Additional study of this complex topic is mandatory so that patients with TIPS-related HE can be offered even more ideal treatments.

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