Transjugular Intrahepatic Portosystemic Shunts and Liver Transplantation in Patients With Refractory Hepatic Hydrothorax

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Hepatic hydrothorax is a relatively infrequent but potentially serious complication of cirrhosis resulting from the accumulation of ascitic fluid in the chest cavity. Medical management is initially directed at controlling ascites formation, but invasive therapeutic procedures may be required if symptoms persist. The aim of this study was to report on the long-term efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPS) placement to reduce portal hypertension in 12 consecutive subjects with refractory hepatic hydrothorax. Most subjects had evidence of advanced cirrhosis of varying causes (Child-Pugh class A, 1; B, 5; C, 6). Mean subject age was 54 years, and subjects were followed up for a mean of 173 days (range, 7-926 days). The portosystemic pressure gradient after TIPS was reduced to <12 mmHg in all cases. Periprocedural morbidity was noted in 2 subjects, and 30-day survival after TIPS placement was 75%. Overall, 58% of sub-jects experienced either a complete or partial response following TIPS placement. Subject response did not correlate with age, baseline creatinine clearance, or Child-Pugh score. Cumulative subject survival was 42%, and 4 of the 5 long-term survivors required eventual liver transplantation. Subject age >65 years was associated with early mortality after TIPS placement, but this trend was not statistically significant. All 4 subjects undergoing liver transplantation required perioperative pleural fluid drainage, but only 1 subject has experienced recurrent effusion. We conclude that TIPS may be a safe and effective temporizing treatment for carefully selected patients with refractory hepatic hydrothorax. However, patient survival is limited after TIPS and is primarily determined by availability of liver transplantation. *Copyright © 1998 by the American Association for the Study of Liver Diseases*

H epatic hydrothorax is defined as the accumulation of ascitic fluid in the pleural cavity. Hydrothorax is an infrequent complication of cirrhosis that occurs in approximately 5% of patients with cirrhotic ascites.[1] The effusion is typically transudative and is localized to the right hemithorax in the majority of cases. The proposed mechanism of hepatic hydrothorax formation includes the transdiaphragmatic flow of ascitic fluid across a pressure gradient from the abdominal cavity to the pleural space through small eventrations in the diaphragm.[2,3] Ascites is typically present to a variable extent, but in a small proportion of patients it may not be detectable because of the preferential flow of ascitic fluid into the pleural space.[4] When attempting to establish a diagnosis of hepatic hydrothorax, one must exclude other common causes of transudative pleural effusion. Nuclear scintigraphic techniques can be useful in confirmation of a diagnosis of suspected hepatic hydrothorax.[5]

The clinical management of hepatic hydrothorax is similar to that of ascites and is usually symptom driven. Initial efforts are directed at achieving a negative sodium balance via the restriction of sodium intake and the use of diuretics. Because of the slow rate of fluid mobilization from the pleural space, these therapies may lead to the development of intravascular volume depletion, prerenal azotemia, electrolyte disturbance, and hepatic encephalopathy with little or no improvement in symptoms. Although therapeutic pleurodesis and surgical interventions have been reported in small series of patients, success may not be durable, and serious complications have been noted.[3,6-9] Portal decompression via the creation of a transjugular intrahepatic portosystemic shunt (TIPS) has recently been proposed as a means of treating patients with refractory ascites.[10-13] In

addition, several reports of the beneficial effect of TIPS in treatment of patients with refractory hepatic hydrothorax have recently been published.[14,15] In one series, a beneficial response was observed in 79% of treated patients, but substantial early and late mortality was also encountered.[15]

The aim of this longitudinal study was to report on the long-term efficacy and safety of TIPS for refractory hepatic hydrothorax in 12 consecutive subjects treated at a single center. A secondary aim of our study was to identify potential clinical predictors of a therapeutic response as well as possible contraindications to TIPS for hepatic hydrothorax. Lastly, we also set out to determine the impact of TIPS in liver transplant candidates with hepatic hydrothorax and the incidence and type of cardiopulmonary complications in those patients undergoing subsequent liver transplantation.

Patients and Methods

Patient Population

Between June 1993 and May 1997, a total of 181 TIPS procedures were performed at our institution: 115 for control of variceal bleeding, 52 for control of refractory ascites, 12 for hepatic hydrothorax, and 2 for other indications. The medical records of the 12 patients undergoing TIPS for refractory hepatic hydrothorax were retrospectively reviewed. The cause of liver disease was established by review of medical history, clinic notes, serological tests, liver biopsy, and imaging studies. Clinical data, including the indication, clinical characteristics, procedural details, and subsequent outcome, were recorded. All identified subjects were then followed up until their most recent clinical encounter, liver transplantation, or death, with a mean subject follow-up of 173 days (range, 7-926 days).

All 12 consecutive subjects with hepatic hydrothorax had become refractory to standard medical management with sodium restriction and high-dose diuretic therapy. Paracentesis was ineffective in controlling respiratory symptoms in subjects with concomitant ascites. All subjects required numerous hospitalizations due to intractable respiratory symptoms with an associated decline in their functional status despite frequent thoracentesis or chest tube drainage prior to TIPS placement. Subjects with known heart failure, hepatocellular carcinoma, alcoholic hepatitis, and intrinsic renal disease were denied TIPS for hepatic hydrothorax over the study period. Surface or stress dobutamine echocardiography was performed before TIPS placement in 11 of 12 subjects. Estimated creatinine clearance (C_{cr}) at the time of TIPS was calculated using the Cockroft-Gault equation.[16] Global liver function was assessed objectively by calculation of the the Child-Pugh (CP) score.[17]

TIPS Placement

Blood products were administered to subjects with severe coagulopathy and thrombocytopenia as needed before the TIPS procedure. In addition, prophylactic parenteral antibiotics were administered to all subjects before and immediately after the procedure. A 10-mm-diameter Wallstent (Schneider USA, Minneapolis, MN) was placed in all subjects via a transjugular approach.[18] During TIPS placement and all subsequent revisions, portal and systemic hemodynamic pressure measurements were recorded. These measurements included inferior vena cava and portal vein pressures, from which a portacaval pressure gradient was calculated. TIPS patency was assessed immediately after placement with a baseline ultrasound Doppler examination of the shunt. Shunt patency was then followed by screening ultrasound Doppler examinations every 3 months. Subjects with absence of flow by both color and power Doppler interrogation indicative of shunt thromboses and those with shunt velocities below 50 cm/s underwent angiographic revision. Other subjects with an interval change in shunt velocity of 50 cm/s, a relative decrease of 30% compared with normal baseline, or evidence of reversal of flow in peripheral portal veins were referred for angiographic revision.

Outcomes

Clinical response was determined 1 month or more after TIPS placement. A complete response was defined as an improvement in respiratory status with no further thoracentesis required. A partial response was defined as an improvement in respiratory status with a reduction in the frequency of thoracentesis after TIPS. A nonresponse was defined as a lack of improvement in respiratory status or the need for thoracentesis. All subjects who died or underwent liver transplantation less than 30 days after TIPS did not have an adequate follow-up period for reliable assessment of their potential response and were classified as nonresponders. Intraoperative events and the clinical course after liver transplantation were assessed retrospectively.

Complications potentially attributable to TIPS placement were defined as either procedural, early (1-30 days), or late (>30 days). Hepatic encephalopathy was considered a complication of TIPS if it had not been previously noted or had increased in frequency or severity from baseline within 30 days of TIPS.

Statistics

Standard descriptive statistics for clinical variables are reported. Pearson's chi-squared and two-tailed *t* tests were used for statistical calculations with SPSS for Macintosh v6.1.1 software (SPSS Inc., Chicago, IL). The survival of subjects undergoing transplantation and other eligible subjects who did not undergo transplantation were determined using the Kaplan-Meier method

Table 1. Clinical Characteristics of Subjects (n = 12)

Mean age	54.5 yr (range, 41–72)
Sex	4 male, 8 female
Cause of liver disease	
Viral	5
Cryptogenic	5
Autoimmune	2
Child–Pugh class	A = 1, B = 5, C = 6
Liver transplant candidates	8 (67%)
Ascites before TIPS	
Moderate-marked	6
Small	4
Not detectable	2
Hydrothorax characteristics	
Right/left-sided	10/2
Transudate/exudate	11/1

and compared using the log-rank test. $P < .05$ was considered statistically significant.

Results

Clinical Characteristics

All 12 subjects who underwent TIPS for refractory hepatic hydrothorax over the study period met the identified inclusion and exclusion criteria, and they form the basis of this report. The mean duration of subject follow-up after initial TIPS placement to death, liver transplantation, or last follow-up was 173 days (range, 7 to 926 days).

Four subjects were followed up for less than 30 days because of early death in 3 cases and liver transplantation in another. Clinical characteristics of the study population are summarized in Table 1. Mean subject age was 54.5 years, and 3 subjects were over age 65. The majority of subjects had decompensated chronic liver disease of various causes with markedly abnormal CP scores. Of note, none of the subjects in this series carried a diagnosis of alcoholic hepatitis or known active alcohol use within 1 year of TIPS placement. Eight of the 12 subjects (67%) were on the liver transplant waiting list before TIPS.

As expected, the majority of pleural effusions were right-sided and transudative in nature. A single subject (subject 5) had an exudative pleural effusion clinically consistent with hepatic hydrothorax. An extensive evaluation, including repeated pleural fluid analysis and culture as well as a pleural biopsy, did not show other contributing causes. Results of preprocedural cardiac studies were unremarkable in 11 subjects. Estimated C_{cr} immediately before the procedure varied from less than 10 to 123 mL/min (Table 2) and 4 of the subjects had moderate to severe renal impairment with estimated C_{cr} <50 mL/min. A diagnosis of functional renal impairment in the setting of cirrhosis was established by a lack of known chronic renal insufficiency, no evidence of structural or intrinsic renal disease by renal ultrasound, the presence of a benign urinary sediment, a low urinary sodium concentration, and a lack of im-

Table 2. Clinical Outcomes

No.	Age/Sex	C_{cr} (mL/min)	CP Score	Hydrothorax Response	Outcome (d)
1	41/M	49	13/C	None	OLT (112)
2	53/F	37	10/C	Complete	Died (308)
3	52/F	103	9/B	None	OLT (10)
4*	70/F	59	8/B	None	Died (18)
5	44/M	127	6/A	Complete	OLT list (926)
6*	57/F	69	11/C	Complete	Died (200)
7*	72/F	36	9/B	None	Died (7)
8	47/F	93	12/C	None	Died (29)
9	50/F	53	10/C	Partial	Died (119)
10	45/M	<10	12/C	Partial	OLT (39)
11*	69/F	22	9/B	Complete	Died (60)
12	54/M	77	8/B	Complete	OLT (252)

Abbreviation: OLT, orthotopic liver transplant.
*Not a transplant candidate before TIPS.

provement with volume expansion. A single subject (subject 10) had advanced hepatorenal syndrome at the time of TIPS with a serum creatinine level of 4.5 mg/dL and marked oliguria.

TIPS Placement

A TIPS stent was successfully placed with a residual portosytemic pressure gradient of <12 mmHg in all 12 subjects (Table 3). The stents were initially dilated to 10-mm diameter in all but 1 elderly subject (subject 7) whose stent was intentionally dilated to only 8 mm. A single stent was placed in 10 subjects, and 2 subjects required two stents in series to create an adequately functioning shunt. Seven shunt revisions were required in 4 subjects over the course of this study.

Clinical Response

A complete or partial response was seen in 7 of 12 subjects (58%) (Table 2). Five subjects had a complete response without further requirement for therapeutic thoracentesis or chest tube drainage. The 2 subjects with a partial response had required therapeutic thoracentesis every 2 to 3 days in addition to supplemental oxygen and intensive care unit monitoring because of respiratory compromise before TIPS. After TIPS, both of these subjects were treated successfully outside of the intensive care unit and required a total of 3 (subject 9) and 2 (subject 10) thoracenteses over 119 and 39 days, respectively. Subject 10 required peritoneal dialysis because of advanced hepatorenal syndrome shortly after TIPS placement. With improvement in his respiratory and functional status, he then underwent successful liver and kidney transplantation on day 39 after TIPS.

Concomitant detectable ascites of variable severity was noted in 10 of the 12 subjects at the time of TIPS placement. Ascites subsequently improved or became undetectable in all 8 subjects who were followed up more than 30 days after TIPS. Surprisingly, this was not associated with a reduction in diuretic dose. In fact, 5 of the 8 subjects were able to tolerate higher doses of diuretics to maintain fluid balance after the procedure. Seven of the 8 subjects (88%) followed up for more than 30 days experienced a significant improvement in respiratory status. However, a consistent objective improvement in liver function as measured by CP scores was not observed among the responders during follow-up (data not shown).

Three of the 5 nonresponders were followed up for less than 30 days because of incipient death. Because 30 or more days after TIPS may be required for the beneficial neurohumoral and cardiovascular changes that lead to a natriuresis, it is difficult to determine whether any of these subjects may have derived a clinical benefit.[19,20] In 2 of our subjects (subjects 4 and 7), death was possibly hastened by TIPS placement as evidenced by the development of progressive hepatic encephalopathy and coagulopathy. In the other subject (subject 8), the development of renal failure and pneumonia after-TIPS placement precluded her from undergoing subsequent transplantation, and she died of infectious complications on day 29. There was no apparent relationship between clinical response and subject baseline C_{cr}, age, portosystemic pressure gradient, and CP score ($P > .10$).

Cumulative subject survival was 42% over the study period. Late deaths in 4 subjects (subjects 2, 6, 9, and 11) were related to complications of advanced liver disease. Subject survival was independent of baseline C_{cr}, CP score, or age, although age greater than 65 did show a trend toward statistical significance ($P = .11$) . Overall subject survival was most greatly influenced by access to liver transplantation. Of the 8 subjects who were eligible and listed for transplantation, 4 underwent the procedure after TIPS placement. The transplant group did not differ from eligible subjects who did not receive transplants in regard to baseline clinical characteristics or hepatic hydrothorax response. Median survival for the transplanted group was 773 days, compared with 214 days for the others. Using the Kaplan-Meier survival analysis method,

Table 3. Procedural Outcomes and Portal Hemodynamic Measurements (n = 12)

Technical success	12/12
Portosystemic pressure gradient	
Pre-TIPS	19.6 (± 5.8) mmHg
Post-TIPS	7.7 (± 2.6) mmHg
% Reduction	60.3 (± 8.5)
Shunt revisions	7 (in 4 subjects)
Occlusion*	3
Stenosis†	4

*Shunt occlusion prompted revision in subject 4 at days 1 and 7 and in subject 5 at day 5.
†Shunt stenosis prompted revision in subject 2 on day 162, subject 5 on day 377 and day 784, and in subject 12 on day 56.

there was a statistically significant difference between the two groups ($P = .0401$) by the log-rank test. Only 1 subject (subject 5) experienced long-term survival (926 days) without liver transplantation. Overall, 4 of the 5 subjects who responded to TIPS but did not undergo transplantation died within 1 year of complications of their liver disease (Table 2).

Complications

Major procedural complications included a single case of hemoperitoneum. This subject (subject 2) required blood transfusions but recovered completely without other sequelae. Another subject (subject 9) required short-term mechanical ventilation because of fluid overload associated with TIPS placement, which responded to diuretics.

The most frequent early (<30 days) complication after TIPS placement was the development of new or worsening hepatic encephalopathy in 4 of the subjects (33%). The encephalopathy readily responded to medical management in 3 subjects. In a single elderly subject (subject 4), severe hepatic encephalopathy developed in association with progressive liver failure that resulted in death 18 days after TIPS. Another elderly subject (subject 7) developed ischemic liver injury and progressive coagulopathy with multiorgan failure following TIPS which also led to a fatal outcome at 7 days.

Other early complications included three episodes of shunt occlusion in 2 subjects. Subject 4 developed shunt thromboses at both day 1 and day 7, requiring shunt revision. No apparent anatomic abnormality could be identified. Subject 5 developed shunt thromboses on day 5, and the shunt was sucessfully revised.

Late complications (>30 days) after TIPS placement included symptomatic shunt stenoses on four occasions in 3 subjects (see Table 2). In all four instances, the subjects presented with either recurrent pleural effusion or respiratory symptoms with worsening ascites. A suspicion of shunt stenoses was confirmed by ultrasound Doppler, and the TIPS device was successfully revised angiographically with a decrease in residual portosystemic pressure gradient to <12 mmHg and an associated improvement in respiratory status in all 4 cases. Subject 5 required two late shunt revisions; on day 377, a parallel stent was placed after a persistent gradient could not be reduced by angioplasty, and then on day 784, the parallel shunt was revised.

Liver Transplant Recipients

The operative course and cardiopulmonary morbidity of 4 subjects who underwent transplantation are reviewed in Table 4. All subjects required perioperative drainage of the hydrothorax. Diaphragmatic defects were identified and repaired in a single subject. All 4 subjects were successfully extubated within 3 days of transplantation, but 1 subject required reintubation for several days. Interestingly, this subject developed rapidly reaccumulating ascites and pleural effusions immediately after transplantation that has persisted for more than 2 years. The remaining 3 subjects are alive and well at a mean of 519 days after liver transplantation.

Discussion

Hepatic hydrothorax represents the accumulation of ascitic fluid in the pleural space primarily because of the flow of ascitic fluid through small diaphragmatic defects under a pressure gradient. This complication has been reported to occur in approximately 5% of patients with cirrhosis and ascites.[1] Clinical management of this entity is driven by the development of respiratory symptoms and related morbidity. As with ascites, initial therapy is directed toward improvement of fluid balance via sodium and fluid restriction and the use

Table 4. Pulmonary Morbidity After Liver Transplantation

No.	Operative Management	Days to Extubation	Long-Term Outcome (Days Post-OLT)
1	Chest tube (×7 days)	2, 6	Recurrent ascites, pleural effusion (1015)
3	Fenestration closed, chest tube (×4 days)	2	No effusion (704)
10	None; chest tube (days 1–5)	3	No effusion (792)
12	None; thoracentesis (day 9)	2	Minimal effusion (61)

Abbreviation: OLT, orthotopic liver transplant.

of diuretics. Unfortunately, a minority of patients will have persistent symptoms with rapid re-accumulation of pleural fluid despite optimal medical therapy. Reducing concomitant ascites by large volume paracentesis will not reliably benefit these patients because even small amounts of ascitic fluid can cross the diaphragm and cause respiratory symptoms.

The contribution of previously unrecognized pulmonary, cardiac, and pleural diseases as well as compliance with diet and medication should be evaluated in all patients with worsening hepatic hydrothorax. When the effusion becomes refractory to medical management, a therapeutic thoracentesis may be required to relieve the respiratory symptoms. However, the long-term treatment of these patients with percutaneous drainage is problematic because these therapies can lead to protein depletion and electrolyte imbalance as well as serious infectious and bleeding complications.[9] Treatment with peritoneovenous shunts has been limited to a few reports with variable results.[7,8,19] Successful outcomes have also been reported with pleurodesis with or without diaphragmatic repair.[3,6-8] However, most patients with hepatic hydrothorax have advanced liver disease, which may prohibit surgical intervention.

Portal decompression via creation of a TIPS has recently been proposed as a means of treating patients with refractory ascites as well as hepatic hydrothorax.[10-14] TIPS for refractory ascites has lead to an improved control of ascites in as many as 50% to 80% of treated patients. The neurohumoral and cardiovascular changes after TIPS placement and their association with clinical response are currently under investigation.[11,12,20,21] From these studies, the importance of recognizing concomitant organ dysfunction such as cardiac and kidney disease in prediction of a poor response to TIPS for fluid management is becoming apparent. In fact, some authors have suggested that these factors may represent relative to absolute contraindications to TIPS placement for fluid control. In addition, patients with more advanced liver disease and advanced age appear to be at increased risk for worsening liver function and early death after TIPS, which may occur in as many as 7% to 45% of treated patients.[10,22]

Currently, information on the use of TIPS for refractory hepatic hydrothorax is limited to several small series.[14,15] In the earliest series, a clinical benefit was demonstrated in all 5 treated subjects.

The importance of reducing the portosystemic pressure gradient to <12 mmHg was also noted in that 3 of the subjects with shunt stenoses developed recurrent symptomatic effusions that resolved rapidly upon shunt revision. However, the long-term success of TIPS in this patient population remains unknown.

In our series, a TIPS device was successfully placed in all 12 subjects with a residual portosystemic pressure gradient of <12 mmHg. A clinical benefit from TIPS placement was realized in 58% of treated subjects and in 88% of subjects followed up more than 30 days. The duration of clinical benefit after TIPS placement varied from 39 to 926 days in the 7 responders (mean, 272 days). Not surprisingly, control of concomitant ascites was improved as well. Subject age, baseline C_{cr}, and CP score failed to predict a response to TIPS or overall patient survival. In contrast to other recent reports, the CP score of responders did not improve in our subjects during follow-up.[15] Long-term subject survival was principally determined by their transplant status in that only 1 subject survived without a liver transplant.

A lack of clinical improvement in respiratory status or the need for thoracentesis was noted in 5 of the 12 subjects. Advanced age may have been a factor in that all 3 subjects older than 65 years of age tolerated this intervention poorly and died within 60 days. Impaired compensation in hepatic arterial blood flow and a poor natriuretic effect in elderly subjects after TIPS have both been implicated in the poor response observed in this subgroup.[21] In our series, the majority of subjects had only mild to moderate renal insufficiency at the time of TIPS. Preprocedural estimated C_{cr} did not predict clinical response, although the number of patients studied is small. Regarding other contributing factors, none of the nonresponders had demonstrable heart disease by history or physical examination or on preprocedural echocardiography. Furthermore, unrecognized shunt malfunction is unlikely to have been a factor because periodic ultrasound Doppler examination of the TIPS device was performed in all subjects, and shunt revision led to prompt improvement in all identified cases. It is certainly possible that the persistence of other factors contributing to hepatic hydrothorax formation such as anatomical defects of the diaphragm, hypoalbuminemia, and poor lymphatic drainage from the liver, which are not improved by TIPS placement, may explain some of

the limitations of this technique. In addition, impaired pleural fluid dynamics that can develop in the setting of a chronic pleural effusion may play an important role.[23]

The clinical outcomes of subjects undergoing liver transplantation in our center have generally been good. No technical difficulties caused by problematic positioning or migration of the stent were encountered at the time of surgery. All subjects required some form of perioperative pleural fluid drainage. The short duration of intubation and the lack of other associated cardiopulmonary morbidity suggest that TIPS placement before surgery may have been beneficial. As already noted, 1 subject (subject 1) developed rapid reaccumulation of ascites and pleural effusions shortly after transplantation. It is possible that this subject's persistent ascites and pleural effusion resulted from peritoneal dissection and lymphatic disruption at the time of transplantation or the persistence of diaphragmatic defects not corrected at the time of surgery.[24]

Our results are similar and yet unique in several aspects compared with the series of Gordon et al.[15] Although our series had fewer patients, the overall clinical benefit observed (58% and 79%), the early mortality following TIPS (25% and 21%), and the low incidence of periprocedural complications are remarkably similar. In contrast, our surviving patients did not experience an improvement in CP scores or serum albumin levels. This may relate in part to differences in patient selection in that none of our subjects had a history of alcoholic liver disease, whereas 67% of their population had a component of alcoholic liver disease. It is possible that their patients had marked improvement in portal hypertension and ascites formation with ongoing abstinence and improved nutrition. Nonetheless, overall patient survival in both series was poor without transplantation (8% and 17%).

In summary, we conclude that 58% of subjects undergoing TIPS for refractory hepatic hydrothorax derived a clinical benefit during follow-up. However, even in responders, long-term survival was primarily determined by availability of liver transplantation. Periprocedural morbidity was acceptable, although decompensation of liver function was noted in 17% of subjects within 30 days of TIPS placement. The "malignant" nature of refractory hepatic hydrothorax and the poor prognosis associated with this complication are highlighted by the observation that overall patient survival without liver transplantation was only 8%. Therefore, TIPS for refractory hepatic hydrothorax may be a useful "bridge" to transplantation as opposed to a "replacement" for eventual transplantation.[25] Subjects who went on to liver transplantation had a low rate of perioperative and long-term cardiopulmonary complications and have derived an excellent long-term benefit.

We propose that patients with cirrhosis and confirmed hepatic hydrothorax should initially be treated with medical therapy whenever possible. For the minority of patients that require repeated thoracenteses for persistent respiratory symptoms, exclusion of secondary causes should be undertaken. Portal decompression via TIPS placement may provide clinical benefit in carefully selected patients without significant concomitant organ dysfunction such as cardiac or intrinsic kidney disease. Because overall survival without liver transplantation is limited, the application of this technique to elderly subjects and other patients who are not transplant candidates should be approached with great caution.[25] Future studies to identify potential predictors of response and associated physiological changes are needed. Establishment of a multicenter group and/or database may be warranted to further investigate the outcomes with TIPS in this infrequent but clinically problematic condition.

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