

ORIGINAL CONTRIBUTIONS

Incidence, Natural History, and Risk Factors of Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt With Polytetrafluoroethylene-Covered Stent Grafts

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BACKGROUND AND AIMS: The aim of this study was to assess the incidence, natural history, and risk factors of hepatic encephalopathy (HE) after transjugular intrahepatic portosystemic shunt (TIPS) with the new polytetrafluoroethylene (PTFE)-covered stent grafts in cirrhotic patients.

PATIENTS AND METHODS: Seventy-eight cirrhotic patients treated by TIPS with PTFE-covered stent grafts and followed by the same medical team—according to a prospective protocol for diagnostic workup and surveillance strategy—were reviewed. The follow-up was 19.9 ± 20.6 months.

RESULTS: At least one episode of HE occurred in 35 of 78 (44.8%) patients. The probability of remaining free of HE was 53.8% (95% confidence interval [CI] 41.4–66.2) at 1 yr and 50.9% at 2 yr (95% CI 38.2–63.8%). The total number of HE episodes was 89. Fifty-five percent of the episodes were grades III–IV. The occurrence of HE tended to be constant during the follow-up, probably because of the very low incidence of shunt dysfunction (13.6% at 2 yr). Moreover, in six patients, a refractory HE required the reduction of the shunt diameter. One patient died due to variceal bleeding after this procedure. At a multivariate analysis, an older age, high creatinine levels, and low serum sodium and low albumin values were shown to be independent factors for the occurrence of HE. Serum creatinine level was the only variable related to the development of refractory HE at the logistic multivariate analysis.

CONCLUSIONS: HE after TIPS with PTFE-covered stent grafts is frequent; its incidence is not confined to the first post-TIPS period, but it has the tendency to be frequent over time. Refractory HE occurred in 8% of patients and may be successfully managed by reducing the stent diameter. The selection of patients undergoing TIPS placement should be very accurate, especially for those subjects with abnormal creatinine level.

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INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is presently used in the treatment of complications of portal hypertension in cirrhotic patients (1–9). This procedure, however, involves two main drawbacks: the occurrence of shunt dysfunction and hepatic encephalopathy (HE), reported respectively in 30–70% (1, 4, 10–13) and 30–55% (14–19) of patients within the first year. Recently, the use of a new generation of covered stents overcame the problem of shunt dysfunction, with consequent significantly improved patency and clinical efficacy (20–30). Some authors (31, 32), however, despite these favorable results, suggested their cautious

use, as an uninterrupted shunt patency might also increase the risk of HE. The data available in the literature are few and the only published and recently updated randomized controlled trial (RCT) (28, 33) actually reported a lower incidence of HE in patients treated with covered stents as compared with those treated with conventional bare stents. A similar incidence of HE was observed in other series of patients (26, 29). No study investigated the risk factors for HE after TIPS with covered stents.

The aim of the present study was to evaluate the incidence, the characteristics, the natural history, and the risk factors of HE in a group of 78 patients treated by TIPS with the new polytetrafluoroethylene (PTFE)-covered stent grafts.

Table 1. Demographic, Clinical, and Biochemical Characteristics of the Patients

	Patients
N	78
Sex (M/F)	48/30
Age (yr)	56.9 ± 9.9
Child-Pugh class (A/B/C)	21/44/13
Alcoholic origin (no/yes)	50/28
MELD score	11.4 ± 7.2
Indication for TIPS: bleeding/ascites	49/29
Elective/emergency TIPS	70/8
Creatinin (mg/dL)	1.08 ± 0.74
Serum sodium (mEq/dL)	136.9 ± 4.3
HE before TIPS (no/yes)	66/12
Ascites before TIPS (no/yes)	25/53
Portosystemic pressure gradient pre-TIPS (mmHg)	20.3 ± 4.8
Portosystemic pressure gradient post-TIPS (mmHg)	6.8 ± 2.5
Venous ammonia (μg/dL)	54.3 ± 34.5
TMT-A Z-score	1.4 ± 1.1
Duration of follow-up (months)	19.9 ± 20.6

Values are expressed as mean ± SD.

PATIENTS AND METHODS

Seventy-eight consecutive cirrhotic patients referred to our Unit in whom TIPS was carried out with PTFE-covered stent-grafts (Gore Viatorr TIPS endoprosthesis, W.L. Gore & Associates, Inc., Flagstaff, AZ) from January 2000 to September 2006, were included in the study. All the subjects were evaluated and followed by the same medical team by a prospective protocolized diagnostic workup and a surveillance strategy. All the procedures were carried out by the same radiology team. A written informed consent was obtained from all the patients before the TIPS procedure. The demographic, clinical, and biochemical characteristics of the patients are reported in Table 1. The indications for TIPS were acute or recurrent variceal bleeding refractory to conventional therapy in 49 patients (39 with esophageal and 3 with gastric varices, 6 with portal hypertensive gastropathy, and 1 with rectal varices), refractory ascites in 27 patients, and hepatic hydrothorax in 2 patients. The mean follow-up was 19.9 ± 20.6 months (range 0.03–72.9 months).

DEFINITIONS

Shunt dysfunction – evidence of a portosystemic pressure gradient of more than 12 mmHg and an angiographic finding of stenosis or occlusion of the shunt.

Hepatic encephalopathy – diagnosed and graded according to the “West Haven criteria” (34) as moderate (grades I–II) and severe (grades III–IV). *Episodic hepatic encephalopathy* – defined as the sporadic occurrence of alteration in the neuropsychiatric function that develops over a short period of time. *Refractory hepatic encephalopathy* – occurrence of a recurrent HE, defined as at least three episodes of nonprecipitant-induced severe encephalopathy requiring hospitalization in the last 3 months despite continuous treatment

with nonabsorbable disaccharides; or a persistent HE, defined as the presence of a continuously detectable altered mental state with further episodic deterioration despite protein restriction and treatment with nonabsorbable disaccharides.

PROCEDURES AND FOLLOW-UP

The anesthesiologic procedure (4, 35) and the technical details of TIPS with 10-mm PTFE-covered stent grafts implantation were previously described (29, 36). Before TIPS, the patients’ medical histories were collected; physical examinations, calculations of Child-Pugh’s (37) and model end-stage liver disease (MELD) (38) scores, Doppler ultrasonographies, and upper gastrointestinal endoscopies were performed.

Shunt Reduction Technique

This procedure was performed only in the patients with persistent or recurrent HE not responding to the medical therapy.

Under sterile conditions, the right jugular vein is punctured through an anterior approach with an 18-G needle; a 10-F introducer sheath, 25 cm in length (St. Jude Medical Division, Inc., Minnetonka, MN), is then advanced into the inferior vena cava and maneuvered into the hepatic vein. An angled, 0.035-inch, hydrophilic guidewire (Terumo Co., Tokyo, Japan) is subsequently advanced through the TIPS shunt and then into the superior mesenteric vein. A portography is performed with a pigtail catheter placed into the portal region, and the portosystemic pressure gradient is measured. Shunt reduction is performed by implantation of a PTFE-covered balloon-expandable stent graft Jostent (Abbott Laboratories, Abbott Park, IL) inside the shunt. A reabsorbable 3–0 suture line (Vicryl, Ethicon Products, Johnson & Johnson Intl., Sommerville, NJ) is tied in the middle portion of a 10-mm × 4-cm balloon catheter (Wanda, Boston Scientific Inc., Natick, MA). The central ligature of the balloon allows the dilatation of both ends of the stent only, thus conferring an “hourglass” appearance. The balloon is then inflated with saline to verify the correct position of the suture line with dilatation of both ends only. A large (6–12 mm ø) Jostent, 38 mm long, is manually crimped on the balloon. The Jostent is a nonmounted balloon-expandable stent graft with a sandwich design, characterized by a thin layer of PTFE placed between two stainless steel (316 L) stents; it presents a very high radial strength, a low profile, and a good flexibility. It is currently available in the European market in two diameters (4–9 mm and 6–12 mm) and different lengths (17, 28, 38, 48, and 58 mm). The stent graft, mounted on the balloon catheter, is advanced inside the sheath into the Viatorr stent graft until the desired position is reached. The sheath is then pulled back, and the balloon is inflated. The proximal and distal portions of the balloon are completely dilated up to 10 mm, while the central portion is only partially expanded due to the presence of the suture line. After removal of the 10-mm balloon, a 5-mm balloon catheter is inserted to dilate

the middle portion of the stent graft to the desired inner diameter. A portogram is performed to analyze the residual flow inside the shunt, and the portosystemic pressure gradient is measured.

Follow-Up

One month after the procedure and every 3 months thereafter, or whenever needed, a clinical examination, blood chemistry, and an assessment of HE were carried out. Ultrasonography was performed 1 and 4 wk after TIPS, at 3 and 6 months post-TIPS, and at 6-month intervals thereafter, or in case of recurrent bleeding or ascites. Ultrasonography included an assessment of the shunt patency with color and/or power-Doppler, a measurement of the mean flow velocity and direction within the shunt at three sites (proximal, medial, and distal portions), in the portal vein and in the intrahepatic portal branches. The diameters of the stent, the portal vein, and the spleen were also measured. The patients underwent upper gastrointestinal endoscopy 1 wk and 1 month after TIPS placement and then at 6-month intervals, or whenever clinically necessary. The size and location of esophageal varices were recorded using the Italian Liver Cirrhosis Project criteria (39). Venography and portosystemic pressure gradient measurement were performed only if the patients had clinical evidences of shunt dysfunction (recurrence of ascites/hydrothorax or gastrointestinal bleeding due to portal hypertension). Venography was also performed in case of recurrences or enlargement of varices in addition to one of the following ultrasonography findings: (a) absent flow in the shunt, and (b) presence of a significant increase in flow velocity in the stent lumen, together with the normalization of flow direction into the main portal branches, or a significant decrease in the mean flow velocity in the portal vein, or an increase in the splenic longitudinal diameter. The follow-up was measured in months from the date of successful TIPS procedure until death, liver transplantation, or most recent clinical examination. The patients were considered lost to follow-up if they did not show up at two consecutive 6-month clinical examinations.

Evaluation of HE

The day before the procedure, a basal evaluation of HE including examination and grading of the patients' mental state, asterixis, and psychometric performance (trail-making test-A, TMT-A), as well as their venous blood ammonia determination were carried out. The evaluation of the degree of HE was based on the alteration of the patient's mental state using modifications of the West Haven Criteria (34). The mental state was assessed in each patient by the same investigator using standardized tests and questions. One of the four variations, of equal difficulty, of the TMT-A was used when the test was repeated for re-evaluation of the neurological symptoms. The TMT-A results were expressed as Z-score, adjusted for the main confounders (age and education) according to Amodio *et al.* (40). Both the patients and their families were instructed about the importance to contact immediately the

medical staff should any alteration in the mental state occur in between the scheduled visits. In particular, the family was instructed to refer the occurrence of lethargy, apathy, obvious personality change, and inappropriate behavior or disorientation for time and place that correspond to the occurrence of a grade II alteration in the patient's mental state. In this case, the HE evaluation, including the psychometric performance, was repeated to confirm and stage the degree of HE. The patients with an overt episode of HE were then managed as in- or out-patients, depending on the severity of the HE episode. None of the patients received any pharmacological treatment to prevent the occurrence of HE. Once developed, HE was treated with an oral administration of nonabsorbable disaccharides or nonabsorbable antibiotics. In some patients with recurrent or persistent HE, the protein content of the diet was restricted to 1 g/kg of body weight. All potential HE-precipitating events were treated and, when possible, avoided.

STATISTICAL ANALYSIS

The results are expressed as mean \pm standard deviation (SD). The comparisons among groups were performed for quantitative data by an analysis of variance (ANOVA) or, when appropriate, by an unpaired Student's *t*-test. The χ^2 test was used to determine the differences in proportions. The incidence of the first episode of HE after TIPS was calculated by the Kaplan-Meier method (41).

As for each patient, there was the possibility of observing more than one HE episode over time; the study of time to any HE episode cannot be performed by means of the standard Kaplan-Meier or Cox model analysis. Instead, a multiple events per subject Cox model was fit, and the Aalen method was used to plot the survival curve (42). The response was the time between HE events for each patient. The observed time is right-censored whenever the patient experienced no events or whenever there was no further HE event for a patient.

The demographic and clinical parameters (age, gender, origin of liver cirrhosis, Child-Pugh's class, MELD score, and history of HE), biochemical parameters (albumin, bilirubin, creatinine, and sodium), ultrasonography findings (spleen, liver, portal vein, and stent diameter, portal vein and stent flow velocity, portal vein flow direction, flow direction in the intrahepatic portal vein branches), portosystemic pressure gradient before and immediately after TIPS, ammonia, and TMT-A Z-score were recorded in each patient at entry and analyzed as the possible predictors of HE. Some of these parameters have shown to be useful in predicting the occurrence of HE in patients treated with bare stents. Two separate analyses were performed to establish the possible predictors of the development of HE and refractory HE. The factors associated with the development of HE were initially evaluated using a univariate modeling (by means of the log-rank test) and then included in a multivariate analysis (according to a multiple events per subject Cox regression model, defined as described before). The factors associated with refractory HE

were initially evaluated by a univariate analyses (ANOVA or χ^2) and then included in a logistic multivariate analysis. The response was whether a patient is affected by refractory HE or not. This analysis was chosen because refractory HE is not a time-dependent event but rather a continuous state that can or cannot occur after a TIPS. In the multivariate analyses, model selection was performed using a stepwise method based on the Akaike Information Criterion (AIC) (43). All the variables finally included in the models were significant at a 5% level.

Refractory HE was analyzed also by means of a Classification Tree Analysis (C&RT) as a backup analysis, which also has the additional feature to rank the predictors in order of importance with respect to the HE outcome and derive optimal cutoffs for numeric variables for classification and prediction (44). At each node of the tree a predictor is selected which best separates the two groups. The output is a tree with nodes and leaves in which a frequency table for the response in each leaf is reported. At each step, the best predictor is selected and optimally split into subsets if it is a numerical predictor, according to a χ^2 -based criterion. Finally, the tree can be used to predict the response, with patients falling into one leaf according to the measured predictors and assigned to the most likely class in the leaf. Classification Tree Analysis provides a sensitivity/backup/confirmation analysis of the results of the logistic model. The Number Cruncher Statistical System software (NCSS, Kaysville, UT), SPSS 15.0 (SPSS, Chicago, IL), and R (R development core team, 2007) were used for the computations.

RESULTS

TIPS was successfully implanted in all the 78 patients. After placement, the portosystemic pressure gradient decreased from 20.3 ± 4.8 mmHg (range 9.8–35.7 mmHg) to 6.8 ± 2.5 mmHg (range 1.4–13.0 mmHg) ($P < 0.01$). The cumulative

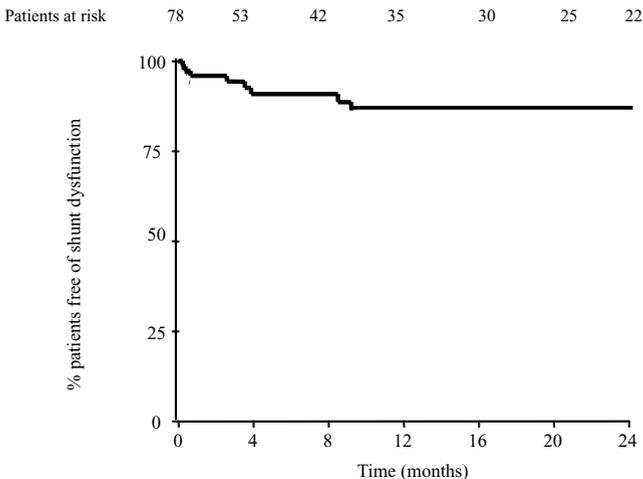


Figure 1. Cumulative incidence of shunt dysfunction in the 78 patients submitted to TIPS with PTFE-covered stent grafts.

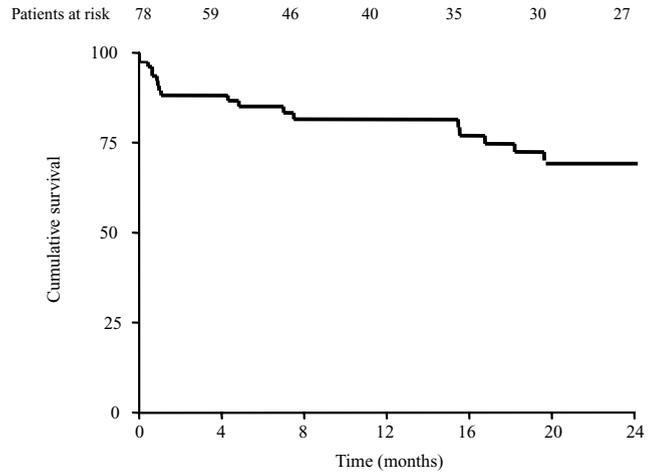


Figure 2. Cumulative survival in the 78 patients submitted to TIPS with PTFE-covered stent grafts.

incidence of shunt dysfunction and the cumulative survival are reported in Figures 1 and 2, respectively.

At least one episode of HE occurred in 35 of the 78 patients. The probability of remaining free of HE was 53.8% (95% confidence interval [CI] 41.4–66.2) at 1 yr and 50.9% at 2 yr (95% CI 38.2–63.8%) (Fig. 3). The total number of HE episodes in 35 of 78 patients during the whole follow-up period was 89. Fifty-five percent of the episodes were graded as severe. The estimated cumulative number of HE events over time in the patients with at least one episode of HE is shown in Figure 4. HE is not confined only in the first postoperative period and does not decrease with time, but also has the tendency to be frequent during the whole follow-up. For patients with an initial HE episode, HE events tend to happen repeatedly over time. For instance, as shown in Figure 4, it is expected that about three additional events will happen

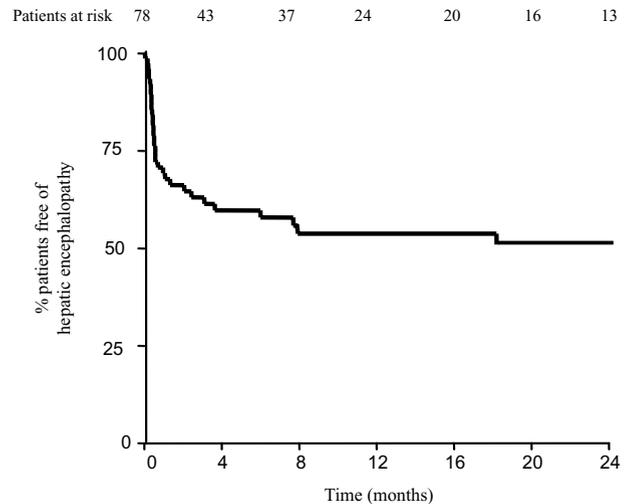


Figure 3. Cumulative incidence of hepatic encephalopathy (initial episode) in the 78 patients submitted to TIPS with PTFE-covered stent grafts.

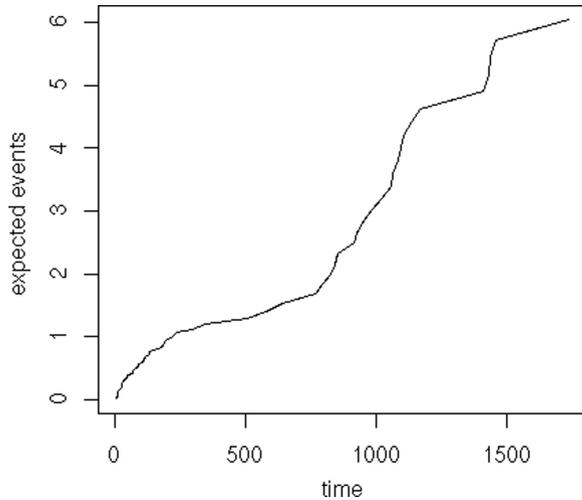


Figure 4. Estimated cumulative number of HE events over time in the patients with an initial HE episode. On the y-axis is shown the expected number of events for each individual having experienced an HE event at an observation time of days on the x-axis. For instance, it is expected that about three additional events will happen within the 1,100th day, and an additional six events within the end of the follow-up.

within the 1,100th day, and an additional six events within the end of the follow-up.

Moreover, 6 of 35 patients had a refractory HE that did not respond to the medical therapy and required a reduction of the shunt diameter. Some clinical data, including the reasons for shunt reduction and the outcomes after the procedure, are summarized in Table 2. At the time of shunt reduction, mean portosystemic pressure gradients were 5.5 ± 2.1 mmHg and 14.7 ± 1.9 mmHg (range 11.9–16.8 mmHg) before and after TIPS reduction, respectively. The procedure was carried out within 3 months after TIPS in 2 patients, after 10 months post-TIPS in 1, and after more than 2 yr of follow-up in the remaining 3 patients. HE improved in all the patients after shunt reduction, but complications related to portal hypertension recurred in two subjects (recurrence of ascites in one case and recurrence of variceal bleeding in the other one): one patient was successfully transplanted, while the other died due to variceal bleeding. Three other patients died several months after shunt reduction due to liver failure. The last patient is alive and free of complications due to portal hypertension.

A series of clinically relevant parameters (see the “Materials and Methods” section) were analyzed to identify variables significantly associated with the occurrence of HE and the development of refractory HE. As shown in Table 3, an older age, a higher creatinine level, and a lower serum sodium and albumin level were the factors independently associated with the development of HE at the multivariate analysis (according to multiple events per subject Cox regression model).

Serum creatinine level was the only variable selected by the AIC criterion as related with the development of refractory HE at the logistic multivariate analysis, with the high levels

Table 2. Clinical Data of Patients Who Underwent Shunt Reduction

Pts	Reason for Shunt Reduction	TIPS Indication	Time to Shunt Reduction (Months)	PPG Pre-Reduction (mmHg)	PPG Post-Reduction (mmHg)	HE Amelioration	Relapsed Complication	Outcome (Months After Shunt Reduction)
1	5 HE episodes (III–IV grades) in 2 months + persistent HE	Ascites	2.4	5.6	16.8	Yes	Ascites	OLT (8.2)
2	5 HE episodes (III–IV grades) in 3 months	Variceal bleeding	28.6	9.1	15.4	Yes	Variceal bleeding	Death due to variceal bleeding (13.8)
3	13 HE episodes in 17 months + persistent HE	Ascites	37.5	3.5	11.9	Yes	No	Alive
4	4 HE episodes (III–IV grades) in 4 months + persistent HE	Variceal bleeding	33.7	4.5	13.3	Yes	No	Death (39.2)
5	3 HE episodes (2 of III–IV grades) in 3 months + persistent HE	Ascites	10.6	5.6	16.8	Yes	No	Death (6.1)
6	4 HE episodes in 3 months + persistent HE	Ascites	3.2	4.9	14	Yes	No	Death (11.2)

Table 3. Factors Associated With the Development of HE at the Multivariate Analysis (According to Multiple Events per Subject Cox Regression Model)

	Hazard Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	P
Age	1.086	1.05	1.13	0.000002
Creatinine	1.516	1.02	2.26	0.041
Albumin	0.352	0.19	0.67	0.001
Sodium	0.926	0.87	0.98	0.016

associated with a higher probability of developing refractory HE (odds ratio 4.63; 95% confidence limit 1.1–19.3, $P = 0.04$). Due to the low number of events, as the backup analysis, a classification tree was used. The C&RT is shown in Figure 5 and confirms the relevance of high levels of creatinine in discriminating between developers and nondevelopers of refractory HE. The optimal cutoff is determined as 1.1 mg/dL, with patients above that threshold having a probability 12.05 times higher than that of developing refractory HE. Five out of 6 patients developing refractory HE had creatinine value above 1.1 mg/dL. If this criterion is used for classifying a patient as high-risk for developing refractory HE, it is expected that 83.3% of true developers will be correctly identified, and 25% of patients who would have not developed the refractory HE will be wrongly classified as high-risk. In other words, the sensitivity is 83.3%, and the specificity is 75%. A summary is given in Table 4.

Table 4. Predictive Value of Creatinine for Identifying Patients With Refractory HE

Observed Refractory HE	Predicted Refractory HE		Specificity/sensitivity
	No	Yes	
No	54	18	75.0%
Yes	1	5	83.3%

DISCUSSION

With the use of new PTFE-covered stents, the problem of post-TIPS shunt insufficiency is successfully managed. With the new endoprostheses, in fact, the number of shunt stenoses is reduced, and the incidence of events related to the recurrence of portal hypertension is significantly less than that occurring with traditional bare stents (28, 33). The efficacy of TIPS with this new device has, therefore, increased, and studies aimed at re-evaluating the role of this procedure in the treatment of portal hypertension are in progress. However, the uninterrupted patency of the shunt may also have some drawbacks, and the possible increase in the risk of HE related to the use of covered stents has been suggested (31, 32). HE incidence in TIPS patients with traditional bare stents occurs in almost 50% of cases and is not easily prevented (45); it, however, tends to be particularly frequent during the first months after TIPS and to become less common with time. This behavior is thought to be due to the development of shunt stenosis, which, even when not clinically overt (in this case, in fact, the shunt is usually revised), reduces the amount of the portal blood shunted. The concern about the new endoprostheses, therefore, regards not only the incidence of post-TIPS HE (which has been showed to be actually reduced (28, 33) or, at least, not increased (26, 29) when compared with traditional stents), but also the possibility of an increased number of patients with recurrent or persistent HE, or the possibility that the occurrence of HE is not only confined to the first postoperative period. The data of all our patients treated with TIPS with covered stents—followed up according to a prospective protocol—were then reviewed, with the specific purpose of studying post-TIPS HE. To our knowledge, this is the first study aimed at establishing the characteristics of HE after TIPS with covered stents, its natural history, and the factors associated with its development.

Our main observations can be summarized as follows: using PTFE-covered stents, post-TIPS HE is regrettably frequent, occurring in almost half of the patients and is not confined to the first postoperative period; HE refractory to standard treatments occurs in a minority of patients (8%) and may be managed by reducing the stent diameter; the risk factors associated to HE are an older age, high creatinine levels, and low serum sodium and albumin values.

The cumulative incidence of HE, in our series, is about 49% at 2 yr, similar to that reported in the literature with traditional bare stents. Our data are different than those reported in the only available RCT comparing covered and uncovered

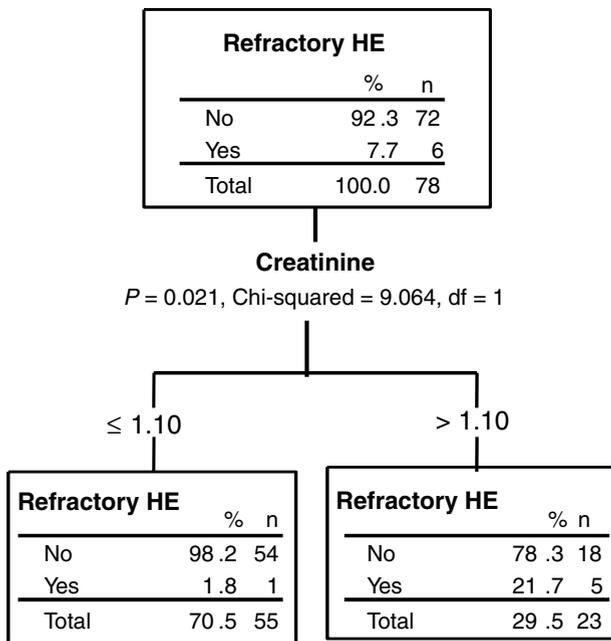


Figure 5. Classification tree analysis for refractory hepatic encephalopathy. Five out of 6 patients developing refractory HE had creatinine value above 1.1 mg/dL.

stents, which showed a cumulative HE incidence of 33% at 2 yr for TIPS with covered stents. The difference between the present study and the Bureau *et al.* study (33) cannot be easily explained. In fact, the two series were similar in terms of gender, mean age (58 yr vs 55 yr), Child-Pugh's score (8 vs 9), post-TIPS gradient (8 mmHg vs 7 mmHg), number of patients with alcoholic origin, active alcoholism, and refractory ascites. However, a higher number of patients at risk for post-TIPS HE might have been included in our cohort. In fact, those patients with a history of episodic HE prior to TIPS were included in our series and not in the Bureau *et al.* study.

In order to test the hypothesis that an uninterrupted patency of the shunt may maintain the patients at risk of HE during the follow-up, we analyzed the variations of HE frequency along time by using a multiple events per subjects Cox model. According to this analysis, the estimated cumulative number of HE events in the patients with an initial HE episode (Figure 4) remains constant over time. This behavior seems to be different from what has been described in patients submitted to TIPS with traditional bare stents in whom HE episodes are usually confined only in the first postoperative period and tend to disappear over time.

In our study, a minority of patients (8%) experienced a severe form of HE refractory to standard treatments. The characteristics of HE in the six patients with recurrent/persistent symptoms were completely different. In three of them, HE occurred soon after TIPS and did not tend to disappear with time, but in the remaining three patients, a recurrent/persistent HE developed for the first time after 20–31 months. Although in these cases liver deterioration might have contributed to the onset of HE, the reduction of the shunt diameter led to its resolution in these patients also. In one of them, HE recurred again after almost 18 months. The shunt was again revised, but the portosystemic gradient was high (18.2 mmHg) and the diameter was not reduced. Unfortunately, although the procedure adopted for the reduction of the diameter permits the portal pressure modulation, it is very difficult to establish which portosystemic pressure gradient values should be reached to avoid further episodes of HE as well as events related to the recurrence of portal hypertension. In those patients with a clinically evident recurrence of portal hypertension, in fact, the portosystemic pressure gradient was similar to that achieved after the shunt reduction of those patients with no further complications (Table 2). We never tried to occlude the shunt; this procedure was recently described in 29 out of 38 patients with post-TIPS refractory encephalopathy, but involved a higher risk of complications and deaths as compared with shunt reduction (46). Moreover, despite the fact that the risk of bleeding from varices was assessed in all the patients undergoing shunt reduction, and endoscopy was always repeated after shunt revision, one patient died of variceal bleeding 13.8 months after the procedure (this patient had shown small varices at the endoscopy performed 1 month after shunt reduction). In another subject, ascites recurred after shunt reduction and became again re-

fractory to the medical therapy; this patient was successfully transplanted 8.2 months after shunt reduction.

A number of clinical, biochemical, and ultrasonographic parameters were included in the multivariate analyses to identify those factors associated with the occurrence of HE and the development of refractory HE. Some of the selected parameters, such as a low post-TIPS portosystemic pressure gradient, an abnormal psychometric performance, an older age, etc., were related to HE after TIPS with conventional stents (15–18). Hepatofugal portal flow before TIPS—suggested to protect from HE (47)—was observed in two patients only, and thus, not included in the analysis. The flow direction in intrahepatic portal vein branches was reversed in the majority of patients independently on the development of HE, indicating that the persistence of some degree of portal perfusion to the liver does not seem to be a protective factor for HE.

At the multivariate analysis, an older age, high creatinine levels, and low serum sodium and albumin values were the parameters related to the development of post-TIPS HE during the follow-up. A high creatinine level was the only parameter independently related to refractory HE. Previous HE—suggested to be a risk factor for HE after TIPS with traditional stents (17)—was not associated to post-TIPS HE. In our series, TIPS was not performed in patients with recurrent HE, and only 12 out of 78 patients had a history of episodic HE before the procedure.

In conclusion, HE in cirrhotic patients after TIPS with PTFE-covered stents is still a problem, as it was with traditional bare stents. We think that, once the decision to perform a TIPS has been carefully taken, the patient should be informed that HE is likely to occur during the follow-up, but that this complication is episodic and can be managed successfully. However, a severe persistent HE can also rarely occur, and that this form of HE may need the reduction of the stent diameter, although this maneuver is not without risks. A special caution is necessary in patients with creatinine level higher than 1.1 mg/dL. In these patients, the use of smaller stents (8 mm \varnothing) could also be proposed.

STUDY HIGHLIGHTS

What Is Current Knowledge

- The use of a new generation of polytetrafluoroethylene (PTFE)-covered stents for TIPS overcame the problem of shunt dysfunction, with consequent significantly improved patency and clinical efficacy.
- However, the uninterrupted patency of the shunt may also have some drawbacks, and the possible increase in the risk of hepatic encephalopathy (HE) related to the use of covered stents has been suggested.
- To date, data available in the literature on the incidence, natural history, and characteristics of hepatic encephalopathy after TIPS with the new covered stents in cirrhotic patients are small and controversial.

What Is New Here

- Our study shows that using PTFE-covered stents, post-TIPS HE is regrettably frequent, occurring in almost half of the patients, and is not confined to the first post-operative period, but has the tendency to be frequent over time.
- HE refractory to standard treatments occurs in a minority of patients (8%) and may be managed by reducing the stent diameter.
- The risk factors associated to HE are an older age, high creatinine levels, and low serum sodium and albumin values.

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CONFLICT OF INTEREST

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