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Embolization of Large Spontaneous Portosystemic Shunts for Refractory Hepatic Encephalopathy: A Multicenter Survey on Safety and Efficacy

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Refractory hepatic encephalopathy (HE) remains a major cause of morbidity in cirrhosis patients. Large spontaneous portosystemic shunts (SPSSs) have been previously suggested to sustain HE in these patients. We aimed to retrospectively assess the efficacy and safety of patients treated with embolization of large SPSSs for the treatment of chronic therapy-refractory HE in a European multicentric working group and to identify patients who may benefit from this procedure. Between July 1998 and January 2012, 37 patients (Child A6-C13, MELD [Model of Endstage Liver Disease] 5-28) with refractory HE were diagnosed with single large SPSSs that were considered eligible for embolization. On a short-term basis (i.e., within 100 days after embolization), 22 out of 37 patients (59.4%) were free of HE ($P < 0.001$ versus before embolization) of which 18 (48.6% of patients overall) remained HE-free over a mean follow-up period of 697 ± 157 days ($P < 0.001$ versus before embolization). Overall, we noted improved autonomy, decreased number of hospitalizations, and severity of the worst HE episode after embolization in three-quarters of the patients. Logistic regression identified the MELD score as strongest positive predictive factor of HE recurrence with a cut-off of 11 for patient selection. As to safety, we noted one major nonlethal procedure-related complication. There was no significant increase in *de novo* development or aggravation of preexisting varices, portal hypertensive gastropathy, or ascites. *Conclusion*: This multicenter European cohort study demonstrated a role for large SPSSs in chronic protracted or recurrent HE and substantiated the effectiveness and safety of embolization of these shunts, provided there is sufficient functional liver reserve. (HEPATOLOGY 2013;57:2448-2457)

Hepatic encephalopathy (HE) is a major complication of cirrhosis and refers to potentially reversible alterations in autonomy, consciousness, behavior, and psychomotor functions related to an accumulation of toxins due to hepatocellular dysfunction and portosystemic shunting.[1-5] While in some patients HE is initiated abruptly by a precipitating event such as infection or gastrointestinal bleeding (the so-called episodic HE), other patients have persistent HE characterized by continuous high levels of ammonia, chronic electrophysiological abnormalities, and recurrent or persistent incapacitating alterations in mental status, often without evident precipitating events.[1,3,4] In this latter group, medical treatment is

Abbreviations: EASL-CLIF, European Association for the Study of the Liver - Consortium on Chronic Liver Insufficiency; HE, hepatic encephalopathy; MELD, Model of Endstage Liver Disease; mRS, modified Rankin Scale; SPSS, spontaneous portosystemic shunt; SRS, splenorenal shunt; TIPS, transjugular intrahepatic portosystemic shunt.

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usually unsatisfactory, with subsequent need of frequent hospitalization.[1,6] This impacts not only the quality of life of these patients but also puts a weight on health economics due to significant resource use.[6] Moreover, some of these patients may paradoxically present with a relatively mild degree of hepatocellular insufficiency, that is, without ascites and/or esophageal varices and/or jaundice, which makes them unlikely to be priorized for transplantation in the current Model of Endstage Liver Disease (MELD) era.

Previous reports have suggested that 46%-70% of patients with refractory HE show large spontaneous portosystemic shunts (SPSSs) upon radiological screening.[7–9] Therefore, the presence of a SPSS not only provides an explanation for the persistence or recurrence of HE despite an acceptable liver function, it might also represent a therapeutic target. Although this latter concept seems straightforward, an extensive literature search has resulted in only a few reports that have either occluded SPSSs surgically or radiologically by means of embolization.[10-15] Due to the anecdotal nature of these reports (largest radiological series n = 11) and heterogeneous selection of patients between series, it is hardly possible to draw any firm conclusion with regard to overall efficacy.[11-15] Moreover, concerns about potential aggravation of portal hypertension and procedure-related thrombosis have been stated but remain unopposed, which sustains the high-risk label associated with this procedure.[16,17]

Using this background and to overcome these shortcomings, we aimed to assess the efficacy and safety of embolization of large SPSSs for the treatment of chronic therapy-refractory HE in a European multicentric working group and to identify patients that may benefit or not from this procedure.

Patients and Methods

Patient Characteristics. This project was a retrospective, multicenter cohort study of a group of patients with cirrhosis and refractory chronic hepatic encephalopathy with large SPSSs amenable to angiographic embolization in six European liver units.

Refractory chronic HE was defined as recurrent episodes of HE (≥grade 2 according to the West Haven classification) without clear identifiable precipitant and with at least two hospital admissions because of HE after the start of standard therapy or as persisting HE 30 days after the start of medical therapy and requiring continuous hospital admission.[18,19] Standard medical therapy consisted of maximally tolerated daily lactulose/lactitol with or without add-on of selective intestinal decontamination using neomycin or rifaximin, according to the discretion of the treating physician.

SPSSs were identified by angio-computed tomography (CT) and/or magnetic resonance imaging (MRI) and included splenorenal shunt (SRS), recanalized (para) umbilical veins, portocaval, or mesorenal/caval shunts.

Exclusion criteria for further study involved absence of cirrhosis (clinically, radiologically, or histologically proven), the presence of a surgical shunt or transjugular intrahepatic portosystemic shunt (TIPS)-graft, portal vein thrombosis, preexisting hepatocellular carcinoma, absence of follow-up data, and a Child-Pugh class >C13.

Procedural Characteristics. Depending on the anatomy of the targeted SPSS and preference of the interventional radiologist, the approach and occlusive type of intervention was determined. In case of recanalized paraumbilical veins, the approach was mainly percutaneous (occasionally transhepatically) and under local anesthesia, whereas for SRS, mesenterico-renal, or -caval shunts, the access was primarily transhepatically or less frequently by way of the femoral vein and under general anesthesia. In any case, the SPSS was first confirmed and evaluated by way of conventional angiography. Embolization was subsequently performed using either coils, amplatzer plugs or matrix, or a combination of these latter. Occlusion was angiographically confirmed at the end of the procedure.

Analysis and Outcome Parameters. In patients fulfilling inclusion and lacking exclusion criteria, medical history, demographic and biochemical characteristics, drug history, specifics of the SPSS, details of the embolization procedure including potential associated complications, immediate and long-term outcome, and survival were reconstructed and completed according to medical records and clinical databases and/or by contacting the general physician in charge of the

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patient. The data were retrieved per center by way of a standardized case-report form and centrally processed.

Efficacy was evaluated by direct (primary) and indirect (secondary) outcome parameters. The primary outcome measure was to evaluate the number of patients free of HE within 100 days pre- and postintervention (short-term efficacy) and during overall time of follow-up pre- and postintervention (long-term efficacy). Secondary parameters involved assessment of the worst grade of encephalopathy, number and days of hospitalizations because of HE, changes in medical therapy, and the degree of disability on a short- and long-term basis, as defined above. The degree of disability or dependence in daily activities was assessed through the modified Rankin Scale (mRS).[20]

Safety was assessed by evaluating immediate postprocedural complications (bleeding, thromboembolic events, infection, anaphylaxis, hypotension, etc.) and in the long-term by monitoring portal hypertensive complications: *de novo* occurrence or aggravation of preexisting gastroesophageal varices or portal hypertensive gastropathy (with or without bleeding), ascites (with or without need of paracentesis), or spontaneous bacterial peritonitis. Changes in liver function were assessed by alterations in the MELD score.

Statistical Analysis. Statistical analysis was performed using MedCalc Statistical Software. Data are given as mean ± standard error of the mean (SEM) or as range between brackets. The paired Student's *t* test was used for pairwise comparison between pre- and postinterventional data, whereas for comparison of two independent samples the unpaired Student's *t* test was applied. The Fischer's exact or chi-square test was used for evaluation of categorical data. To assess independent variables predicting recurrence of HE, logistic regression analysis was performed. Before entering independent variables in the logistic regression model, multicollinearity was excluded by evaluating correlation matrices between different independent variables and univariate analysis was performed to weigh the different variables. The discrimination ability of prognostic score systems to predict HE recurrence was evaluated using the area under a receiver operating characteristic (ROC) curve. The Youden index (sensitivity + specificity-1) was used to capture the best cutoff point. $P \leq 0.05$ was considered statistically significant.

Results

Patient Characteristics Pre-SPSS-Embolization

Forty-one patients were identified between July 1998 and January 2012 as potential candidates for study, of which 37 were finally found eligible for analysis according to the preset inclusion and exclusion criteria. Reasons for exclusion of four patients related to absence of follow-up data in two, presence of a TIPS graft in one, and failure to angiographically characterize the portosystemic shunt in one patient. The demographics of the remaining included 37 patients are listed in Table 1. All patients had a long-standing diagnosis of cirrhosis and the average length of follow-up prior to SPSS embolization was 79 ± 13 months (range 5-328 months). Patients with underlying alcoholic liver disease were abstinent for at least 3 months before considering embolization. The preprocedural biochemistry is reviewed in Table 1. Of the 37 patients, 18 patients had concomitant comorbidities such as diabetes mellitus (n = 18), epilepsy (n = 3), congestive heart failure (n = 3), arterial hypertension (n = 11), and chronic renal insufficiency without need of dialysis (n = 3). All of these comorbidities were

Table 1. Patient Demographics and Baseline Clinical and Biochemical Characteristics

Number of patients	37
Age at SPSS embolization (years)	61 ± 2 (29-83)
Sex (male/female)	21/16
Etiology cirrhosis	
- alcoholic	17
- hepatitis C	13
- non alcoholic fatty liver disease	3
- primary biliary cirrhosis	2
- autoimmune	1
- cryptogenic	1
Hemoglobin (g/dL)	11 ± 0.4 (7.5-15.3)
White blood cell count (10^9/L)	4.5± 0.4 (1.7-14.5)
Thrombocytes (10^3/L)	103 ± 8.6 (19-256)
Bilirubin (mg%)	1.8 ± 0.2 (0.5-6.3)
Albumin (g/L)	2.9 ± 0.1 (1.5-4.2)
PT (%)	62.2 ± 2.8 (30-88)
INR	1.5 ± 0.1 (0.4-4.2)
Creatinin (mg%)	1.1 ± 0.1 (0.4-4.2)
Sodium (mEq/L)	138.1 ± 0.7 (129.2-148)
Child-Pugh score pre-SPSS embolization	7.9 ± 0.3 (6-13)
MELD pre-SPSS embolization	13.2 ± 0.9 (5-28)
Gastroesophageal varices within 100 days pre-SPSS embolization	
- Esophageal varices	17
- Grade 1/2/3 oesophageal varices	11/6/0
- Varices (GOV1/GOV2/IGV1)*	18 (16/1/1)
- Portal hypertensive gastropathy (mild/severe)	13 (9/4)
- History of variceal bleeding	0
Ascites within 100 days pre-SPSS embolization	
- ascites (grade 1/2/3)†	13 (3/7/3)
- need of large volume paracentesis	1
- spontaneous bacterial peritonitis	2

Data are expressed as mean ± SEM with range in parentheses.
*Classification according to Sarin.[21]
†According to EASL guidelines.[22] SPSS, spontaneous portosystemic shunts; GOV1, gastroesophageal varices type 1; GOV2, gastroesophageal varices type 2; IGV1, intragastric varices type 1.

Table 2. Features of HE Pre-SPSS Embolization

During overall follow-up pre-SPSS embolization	
Worst grade HE*	3.3 ± 0.1 (range 2-4)
Number of hospitalizations for HE	3.8 ± 0.4 (range 1-10)
Number of days of hospitalization for HE	41 ± 5.7 (range 8-166)
Within 100 days pre-SPSS embolization	
Worst grade HE*	2.9 ± 0.2 (range 0-4)
Number of hospitalizations for HE	1.7 ± 0.2 (range 0-4)
Number of days of hospitalization for HE	19 ± 3.3 (range 0-100)
Degree of disability†	
- autonomous (mRS 0-1)	9/37
- limited activities (mRS 2-3)	25/37
- disability (mRS 4-5)	3/37

Data are expressed as mean ± SEM with range in parentheses.
*According to West Haven classification (18).
†According to the modified Rankin Scale (mRS) (20).

medically controlled and were stable prior to SPSS embolization. With regard to portal hypertensive complications preembolization, out of 37 patients, 18 showed gastroesophageal varices and 13 portal hypertensive gastropathy at the most recent screening endoscopy within 3 months before embolization. Four patients had a history of variceal hemorrhage but none of the patients had experienced a variceal hemorrhage within 100 days preembolization. Twelve patients were on beta-blockers for prophylaxis of variceal bleeding. One patient received endoscopic band ligation in primary prophylaxis because of intolerance to beta-blockers, whereas the four patients with previous bleeding were on combined medical-endoscopic treatment. Seventeen patients had experienced episodic or continuous presence of ascites previous to embolization, which was controlled with diuretics in 16 patients and with combined large-volume paracentesis and diuretics in one patient.

The characteristics of HE with regard to severity (worst grade, number, and days of hospitalization) and impact on physical abilities are summarized in Table 2. All except one intolerant patient were on maintenance therapy with nonabsorbable disaccharides (26 on lactulose with an average daily dose of 79 ± 8 mL [range 30-160 mL] and 10 on lactitol with an average dose of 35 ± 5 mL [range 20-60 mL]). Seventeen patients additionally used nonabsorbable antibiotics (neomycine, n = 13, rifaximin, n = 4) as selective gut decontaminants.

Procedural Characteristics

The interval from the time of onset of HE until diagnosis of SPSS as a possible etiological factor for HE was 13.3 ± 3.3 months (range 0.5-79). Large SPSSs were diagnosed either by CT or MRI scan and included: 20 SRS, seven mesenterico-caval, nine periumbilical, and one mesenterico-renal shunt.

Thirty-seven procedures were performed in which the considered culprit SPSS was embolized with either coils (n = 22), Amplatzer plugs (n = 13), matrix (n = 1), or a combination of coils and Amplatzer plugs (n = 1). The approach was transhepatic in seven patients, percutaneous in six others, or by way of the femoral or jugular vein in the remaining 23. Complete occlusion was demonstrated by angiography at the end of the procedure and additionally confirmed by angio-CT in some cases. Sonography after the procedure was performed according to local customs or upon clinical suspicion. Two exemplary angiographic procedures are depicted in Fig. 1.

Because of clinical recurrence of HE, secondary procedures were performed in four patients after identification of a revascularized SPSS despite previous occlusion (n = 3) or of a novel shunt (n = 1). The average time to reintervention was 311 ± 131 days (range 89-631) after index embolization.

Outcome Parameters: Efficacy and Safety

Primary and Secondary Endpoints. The overall follow-up period from diagnosis of first HE episode until embolization was 659 ± 129 days, which was comparable to the follow-up postembolization (697 ± 157 days, $P = 0.385$). On a short-term basis (i.e., within 100 days after embolization), 59.4% of patients (22/37) were free of HE ($P < 0.001$ versus before embolization) of which 18 (or 48.6% of patients overall) remained HE-free over a mean period of follow-up of 697 ± 157 days ($P < 0.001$ versus before embolization) (Fig. 2). In the 19 patients with relapse of HE, the average time to reappearance of HE was 74.2 ± 21.5 days (range 2-365): 15 patients of these 19 showed recurrence of HE within 7 days after index embolization, whereas a minority (n = 4) experienced HE several months later.

With regard to the secondary outcome parameters of response, defined as either improved autonomy (according to mRS), decreased number of hospitalizations or severity of the worst HE episode according to West Haven score, 29 out of 37 patients (78.4%) improved in comparison to preembolization. The specific changes pre- versus postembolization in terms of the severest HE grade, number of hospitalizations, and days of hospitalization because of HE and autonomy grades are depicted in Figs. 3A-C and 4, respectively. The intake of lactulose after embolization decreased to 60 ± 7 mL ($P = 0.04$ versus before embolization). Eight patients of 37 were still in need of nonabsorbable antibiotics compared to 17 before

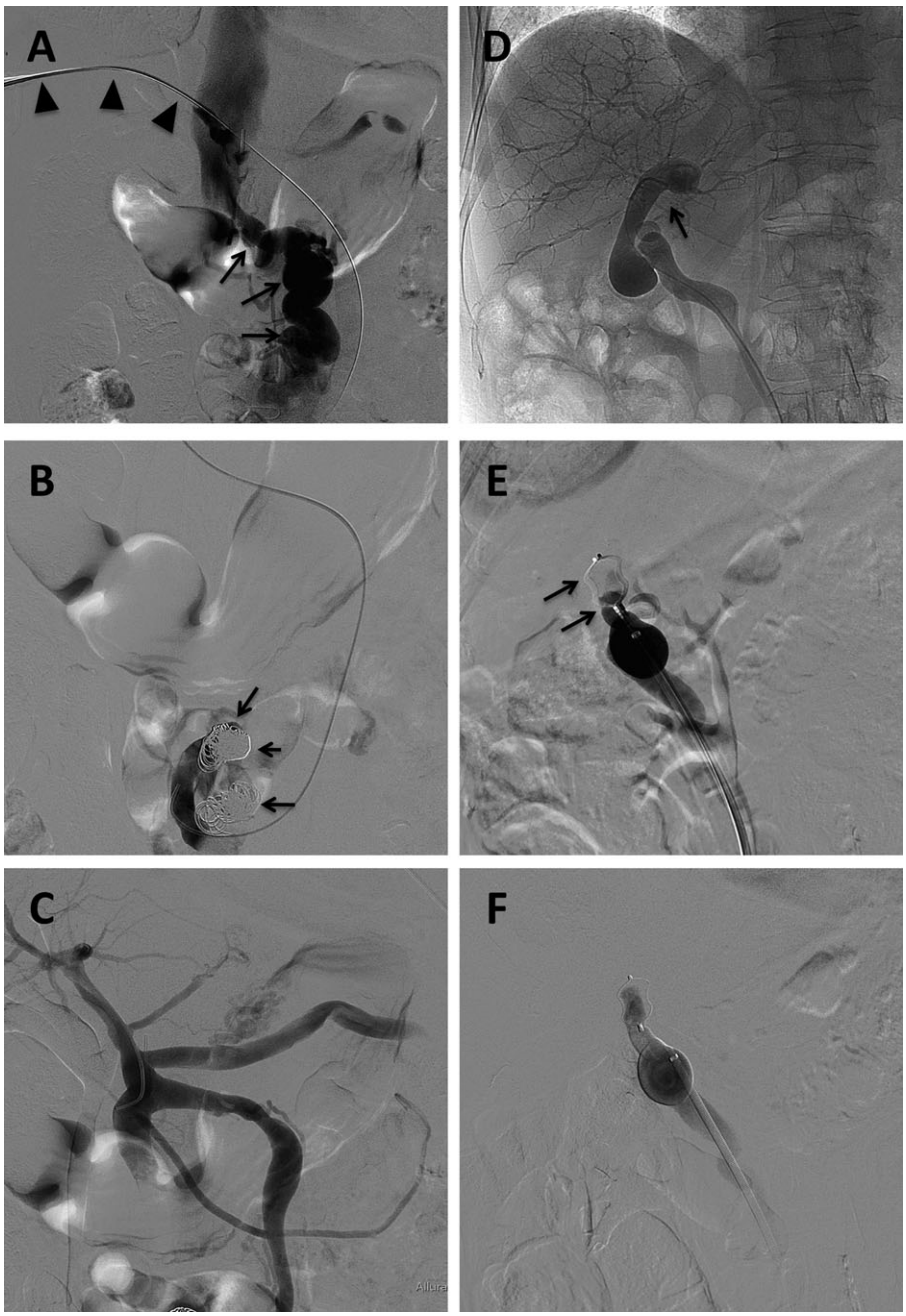

Fig. 1. Exemplary procedure of embolization of a portocaval shunt (A-C) and a periumbilical shunt (D-F). (A) Contrast injection through a sheath (arrowheads) placed in the portal vein main branch reveals hepatofugal flow with early drainage of contrast medium through a large portosystemic shunt (arrows). (B) After coiling (arrows) of the shunt, no contrast opacification of the inferior vena cava could be demonstrated and (C) contrast medium injection through the catheter placed at the confluence of the portal vein shows antegrade flow into the narrowed main portal vein and right and left endbranches. Note also discrete retrograde opacification of both the superior mesenteric and splenic veins. (D) After ultrasound-guided puncture of a paraumbilical, collateral vein in the anterior abdominal wall, a catheter is navigated through the spontaneous shunt located between the left portal vein and the large paraumbilical vein. Contrast injection demonstrates clear opacification of the left portal vein endbranches as well as opacification of the shunt and the large, paraumbilical collateral. (B) This large collateral is occluded with use of a vascular plug (arrows). (C) Venography after plug-occlusion shows absence of portal vein opacification and stasis of contrast medium in the paraumbilical vein.

embolization. One patient was successfully transplanted after embolization because of persisting bouts of encephalopathy.

Predictors of Outcome. Univariate analysis of a wide spectrum of biochemical and clinical parameters identified sex, time interval between diagnosis of HE and SPSS, serum albumin, International Normalized Ratio (INR), the presence of ascites preembolization, hemoglobin level, Child and MELD score (all with $P < 0.05$) as predictors of HE recurrence post-SPSS-embolization. After weighing these different variables to exclude multicollinearity, logistic regression ascertained the following parameters to be predictive of HE recurrence postembolization: sex (odds ratio [OR] 0.06, 95% confidence interval [CI] 0.005-0.971, $P = 0.048$) and MELD preembolization (OR 1.52, 95% CI 1.073-2.180, $P = 0.019$).

We further evaluated the discrimination ability of the MELD score in predicting HE recurrence after SPSS embolization by using the area under ROC curve. The MELD score showed good accuracy to discriminate between patients with recurrence or not (95% CI = 0.637- 0.914, $P < 0.0001$). Using the Youden index, the best cutoff point for the MELD score was 11 with a sensitivity and specificity of 68.4% and 77.6%, respectively (Fig. 5).

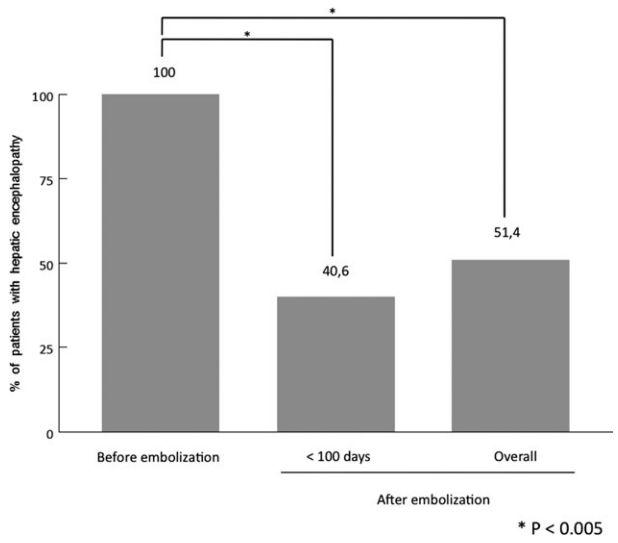

Fig. 2. Short- and long-term efficacy of SPSS-embolization in the occurrence of HE.

Safety. Overall there were eight early procedure-related complications, of which seven were mild and symptomatically treated (one cutaneous infection at the puncture site, one contrast-induced nephropathy, three hematomas limited to the puncture site, and two self-limiting episodes of fever). One patient had a capsular bleeding due to a transhepatic approach complicated with hypovolemic shock for which surgical hemostasis was needed. All complications were nonlethal and without permanent injury or morbidity.

With regard to long-term complications, we observed no significant aggravation of portal hypertension during follow-up. More specifically, there was no increase postembolization in the number of patients with gastroesophageal varices (48.6 versus 52%, $P = 0.94$) or with portal hypertensive gastropathy (50 versus 66%, $P = 0.18$). Two patients developed *de novo* esophageal varices (grade 1 and grade 2, respectively). Overall, one patient with preexisting varices experienced a nonfatal variceal bleeding at 55 months postembolization which was managed by combined pharmacological and endoscopic intervention. There was no difference with respect to the number of patients with ascites (13/37 pre- and 15/37 postembolization, $P = 0.92$). In the postembolization group, 6 of 15 patients developed *de novo* ascites (of which five were patients with recurrent HE). From these 15 patients, seven were in need of large-volume paracentesis (of which six were also nonresponders to embolization) and two developed spontaneous bacterial peritonitis during follow-up. In four patients (10.8%), a thrombosis of the portal vein (n = 1) or one of its branches (n = 3) was diagnosed upon ultrasound surveillance (range 1-1,670 days). Two were treated with low molecular weight heparin (LMWH), resulting in recanalization of the thrombosis. None of these led to thrombosis-related clinical manifestations during overall follow-up. Three of these four patients, including the two LMWH-treated patients, were responders during overall follow-up. The patient with recurrence of HE had a thrombosis of a side-branch of the portal vein and experienced a new bout of HE 2 days after embolization (baseline MELD 35).

The impact on liver function in the overall group, as evaluated by the MELD score, showed no statistically significant differences (before: 13.2 ± 0.9 versus after: 15.2 ± 1.5). However, we observed a significant deterioration of the MELD score in the nonresponder group (i.e., with recurrence of HE), whereas this was not the case for the responder group (i.e., HE-free) (Fig. 6A,B). Direct comparison of the responder and nonresponder group using delta-MELD values pre- versus postembolization showed that nonresponders had a significant increase (4.2 ± 1.9 versus 0.2 ± 0.7, $P = 0.05$) (Fig. 6C).

Discussion

In this multicenter European study, we assessed the efficacy and safety of embolization of large SPSSs for the treatment of chronic therapy-refractory HE and tried to identify patients who had benefited following this procedure. Our analysis showed that embolization of dominant single large SPSSs in this specific group of patients is relatively safe and effective over an average follow-up of almost 2 years, provided that the preprocedural MELD score was 11 or less.

Like variceal hemorrhage, ascites, and jaundice, HE is one of the cardinal features heralding hepatic decompensation, and therefore influences the prognosis of a patient with cirrhosis.[1,6,23-26] More than the other complications, HE threatens patients' self-reliance, physical condition, quality of life, and tranquility of patient surroundings given the often unpredictable and daunting nature of encephalopathic episodes.[25,26] As a result, HE is the most common cause of protracted hospitalization and readmission and therefore is a major cause of expensive resource use.[6,24] A recent review in the United States of this matter showed that HE comprised only 0.33% of all hospitalizations but was responsible for an overall related total national cost of 5,888 million Euros in 2009, which had increased by 2,086 million Euros compared to 2005.[6] This predicament originates in part due to the fact that therapy for overt HE is not always

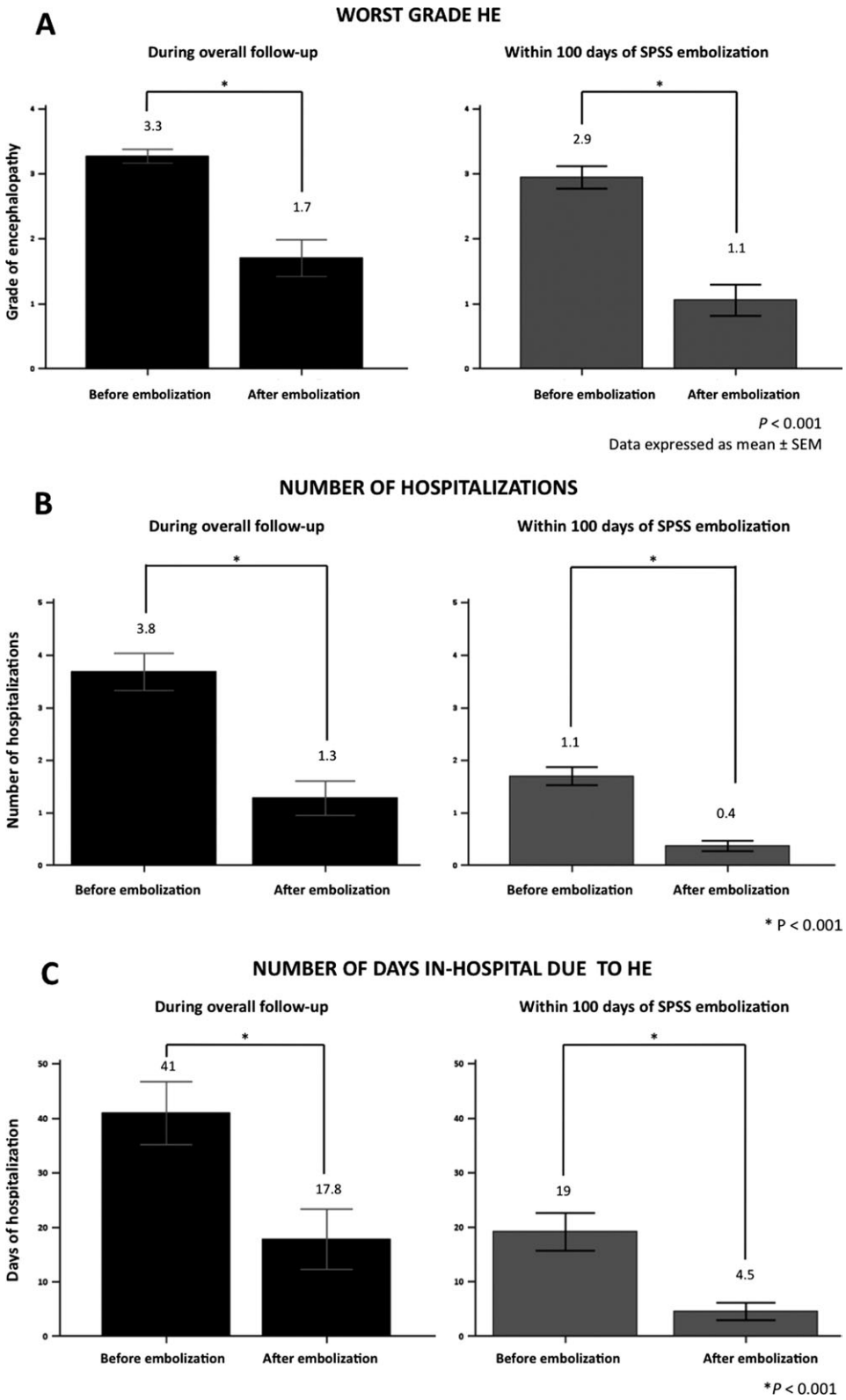

Fig. 3. Short- and long-term changes pre- versus postembolization in terms of the most severe grade of HE (A), number of hospitalizations (B), and days spent in the hospital (C) because of HE.

straightforward, since its course is highly variable between different patients and even within the same individual. In addition, the currently available therapeutic armamentarium for HE is far from optimal. Most therapies for HE focus on treating episodic bouts and are directed at reducing the nitrogenous load in the gut. This approach is based on the historical premise that HE results from the systemic accumulation of gut-derived neurotoxins, in particular ammonia, due to impaired liver detoxification.[1,3,19,26] The

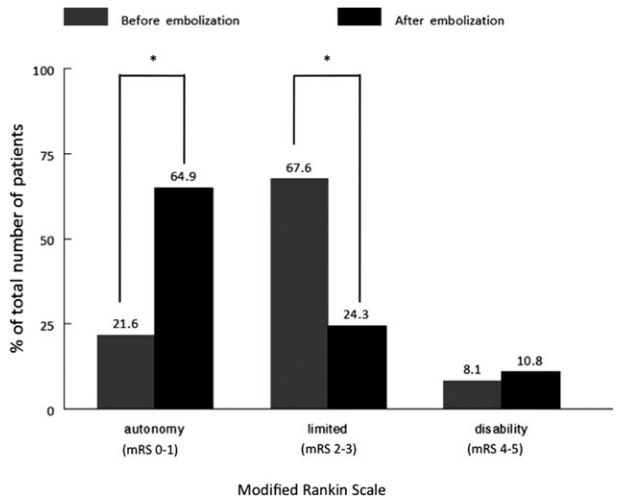

Fig. 4. Comparison of the degree of disability or dependence in daily activities according to the mRS,[20] before and after SPSS embolization.

current standard of care therefore relates to decreasing either the absorption of ammonia by using nonabsorbable disaccharides or either its production by reducing urease-producing bacteria by nonabsorbable antibiotics.[26,27] Recent innovations, such as rifaximin or liver dialysis, are either not universally licensed for use or hampered because of lack of direct applicability.[28-30] The ultimate solution remains liver transplantation but this implies relentless liver and renal insufficiency to become priorized in the current MELD era.

Recently, large SPSSs were described to be highly prevalent (46%-71%) in patients with refractory HE. These latter might not only explain the refractoriness of HE but also serve as a therapeutic target.[7-9,12,16,31,32] Nevertheless, the diagnosis of large SPSSs is often delayed and controversy still prevails whether SPSSs might be therapeutically targeted for HE.[11,15] To elaborate further on these issues, we pooled the datasets of six different European liver units concerning 37 patients whose data were collated into a preset

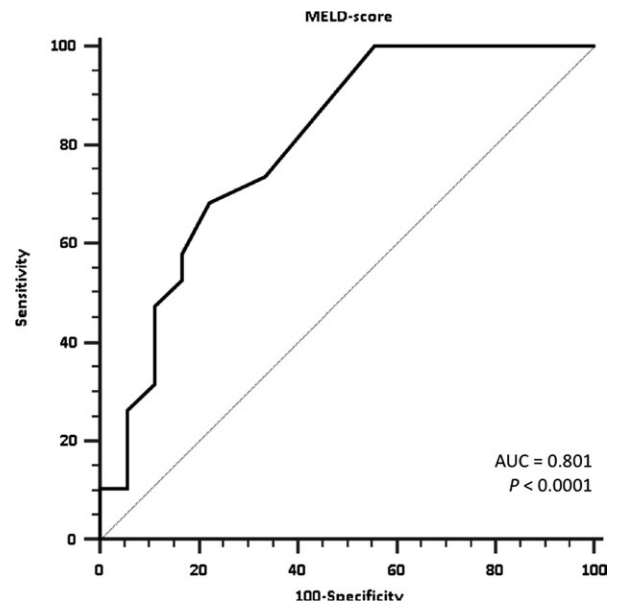

Fig. 5. Prediction of HE recurrence by way of the MELD score, using area under ROC curves. The best cutoff point for the MELD score was 11 with a sensitivity and specificity of 68.4% and 77.6%, respectively.

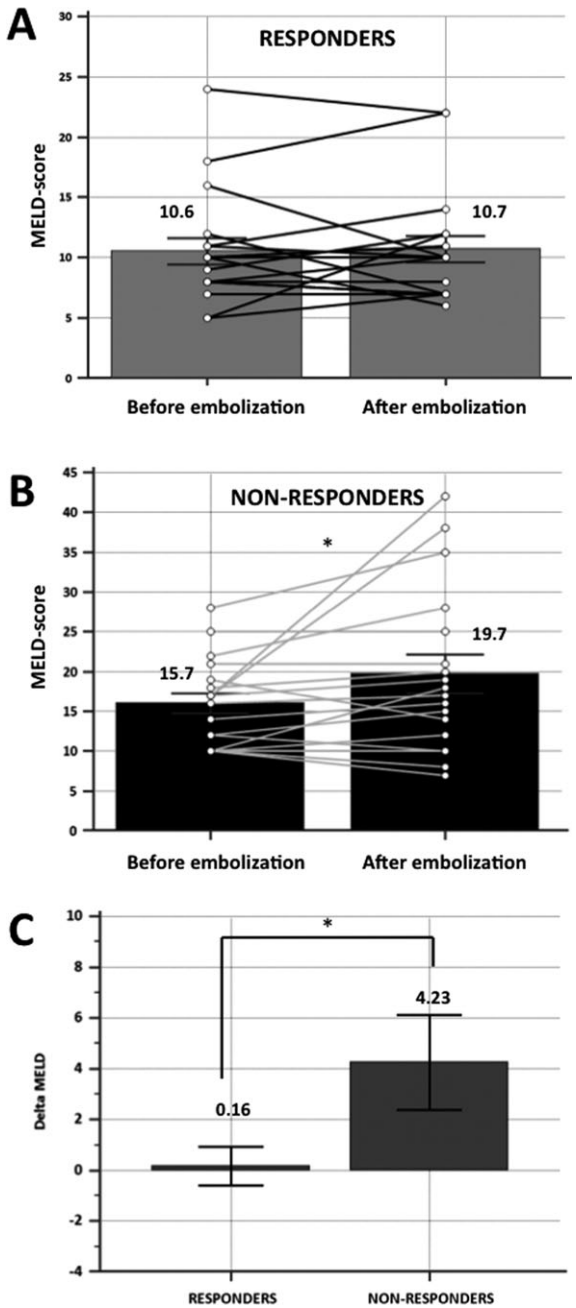

Fig. 6. Comparison of the MELD score before and after embolization according to outcome (i.e., responders being free of HE [A] and nonresponders [B]). The responder and nonresponder groups were compared directly by using delta-MELD values pre- versus postembolization (C).

standardized case-report form. Our analysis not only confirms a delayed diagnosis, as in our series the diagnosis of SPSS was made on average 13 months after onset of HE, but more importantly substantiates the therapeutic effectiveness of embolization of the considered culprit SPSSs once the diagnosis is made. More specifically, almost 50% of the treated patients became HE-free during an average follow-up of more than 2 years. Considering secondary parameters of success, defined as either improved autonomy (objectively using mRS[20]), or decreased number of hospitalizations or severity of the worst HE episode after embolization, an improvement was observed in three-quarters of the patients. More specifically, autonomy was improved 3-fold and as such the hospitalization rate and in-hospital stays were similarly significantly reduced. Even more important, the need for liver transplantation could theoretically be reduced in a large portion of these patients, as HE was the sole presenting symptom in a substantial proportion. It was impossible to retrospectively determine if all patients had been suitable for transplantation at the time of embolization. On the other hand, if eventually deemed necessary, as was the case in one patient, embolization did not technically compromise liver transplantation.

If HE recurred nevertheless, it occurred either within days after index embolization (2-7 days, n = 15) or several months later (n = 4). Given angiographic confirmation of complete occlusion of the SPSS at the end of the procedure, the early occurrence presumably relates to insufficient remnant critical functional liver mass (cfr, the higher baseline MELD of nonresponders Fig. 6B), whereas late recurrences were all based on the development of novel or recanalization of previous occluded SPSSs.

In addition to efficacy, the procedure also showed to be relatively safe on both a short- and long-term basis. Except for one major procedure-related complication (bleeding due to a transhepatic approach), no other short-term problems within 48 hours after embolization were noted. The concern of generating or aggravating portal hypertension due to occlusion of an "escape" or decompressive shunt, as reported in some previous anecdotal series,[11-15] was not substantiated in this large cohort. More specifically, there was no significant increase in *de novo* development or aggravation of preexisting varices, portal hypertensive gastropathy, or ascites. One patient experienced a variceal bleeding but this was felt unrelated to the SPSS embolization, occurring more than 4.5 years after embolization. Procedure-related thrombosis of the portal vein or one of its branches, on the other hand, was observed in 10% of patients under ultrasound surveillance but remained without clinical consequence due to early intervention with anticoagulants. Albeit rare, potential portal hypertensive and thrombotic complications should be actively monitored, given their severity and impact.

How to define, then, patients who might benefit the most? Logistic regression identified the MELD score as the strongest positive predictive factor of HE recurrence. This is not surprising, since a critical functional liver mass is needed to assure detoxification of the increased toxin load presented to the liver after shunt occlusion, as previously discussed and also suggested by Zidi et al.[12] By using the Youden index, a surrogate approximation of this minimal "critical functional liver mass" was a MELD score of 11 or less. In addition, the procedure should be avoided in completely disabled patients (mRS 4-5) since none of them improved overall in our series. Of further note in our study is that the effect of embolization is irrespective of the type of shunt, which opposes a hierarchy of the type of SPSSs in the development of HE and the suggestion that patency of the umbilical vein is not associated with HE.[33,34]

Our analysis has some shortcomings. First, the analysis was retrospective. However, given the infrequent undertaking of this procedure, a prospective trial would be difficult to perform. Second, a type 2 statistical error cannot be excluded, but this is the largest cohort so far reported. Third, a selection bias different in every center with regard to only considering patients in whom the procedure was tried cannot be ruled out.

In conclusion, this multicenter European cohort study demonstrated a role for large SPSSs in chronic protracted or recurrent HE and substantiated the effectiveness of embolization of these shunts provided there is sufficient functional liver reserve.

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References

1. Cordoba J, Minguez B. Hepatic encephalopathy. Semin Liver Dis 2008;28:70-80.
2. Laleman W, Van Landeghem L, Wilmer A, Fevery J, Nevens F. Portal hypertension: from pathophysiology to clinical practice. Liver Int 2005; 25:1079-1090.
3. Shawcross DL, Olde Damink SW, Butterworth RF, Jalan R. Ammonia and hepatic encephalopathy: the more things change, the more they remain the same. Metab Brain Dis 2005;20:169-179.
4. Cordoba J. New assesment of hepatic encephalopathy. J Hepatol 2011; 54:1030-1040.
5. Witters P, Maleux G, George C, Delcroix M, Hoffman I, Gewillig M, et al. Congenital venovenous malformations of the liver: widely variable clinical presentations. J Gastroenterol Hepatol 2008;23:390-394.
6. Stepanova M, Mishra A, Venkatesan C, Younossi ZM. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. Clin Gastroenterol Hepatol 2012;10:1034-1041.e1.
7. Lam KC, Juttner HU, Reynold TB. Spontaneous portosystemic shunt: relationship to spontaneous encephalopathy and gastrointestinal hemorrhage. Dig Dis Sci 1981;26:346-352.
8. Ohnishi K, Sato S, Saito M, Terabayashi H, Nakayama T, Saito M, et al. Clinical and hemodynamic features in cirrhotic patients having a large spontaneous splenorenal and/or gastrorenal shunt. Am J Gastroenterol 1986;81:450-455.
9. Riggio O, Efrati C, Catalano C, Pediconi F, Mecarelli O, Accornero N, et al. High prevalence of spontaneous portal-systemic shunts in persistent hepatic encephalopathy: a case control study. HEPATOLOGY 2005; 42:1158-1165.
10. Kato K, Kondo S, Hirano S, Omi M, Ambo Y, Okushiba S, et al. Surgical closure of the gastrorenal shunt with distal splenorenal shunt operation for portosystemic encephalopathy. Hepatogastroenterology 2001;48:840-841.
11. Henderson JM. Treatment portal systemic encephalopathy by embolization of the shunt. HEPATOLOGY 1989;9:164-165.
12. Zidi SH, Zanditenas D, Gelu-Simeon M, Rangheard AS, Valla DC, Vilgrain V, et al. Treatment of chronic portosystemic encephalopathy in cirrhotic patients by embolization of portosystemic shunts. Liver Int 2007;27:1389-1393.
13. Uflacker R, Silva Ade O, d'Albuquerque LA, Piske RL, Mourao GS. Chronic portosystemic encephalopathy: embolisation of portosystemic shunts. Radiology 1987;165:721-725.
14. Boixadera H, Tomasello H, Quiroga S, Cordoba J, Perez M, Segarra A. Succesful embolization of a spontaneous mesocaval shunt using the Amplatzer Vascular Plug II. Cardiovasc Interv Radiol 2010;33: 1044-1048.
15. Fukuda T, Hirota S, Sugimura K. Long-term results of balloon-occluded retrograde transvenous obliteration for the treatment of gastric varices and hepatic encephalopathy. J Vasc Interv Radiol 2001;12: 327-336.
16. Caturelli E, Pompili M, Squillante MM, Sperandeo G, Carughi S, Sperandeo M, et al. Cruveilhier-Baumgarten syndrome: an efficient spontaneous portosystemic collateral preventing oesophageal varices bleeding. J Gastroenterol Hepatol 1994;9:236-241.
17. Hsieh JS, Wang JY, Huang CJ, Chen FM, Huang TJ. Effect of spontaneous portosystemic shunts on hemorrhage from esophagogastric varices. World J Surg 2004;28:23-28.
18. Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. A controlled, double-blind clinical trial. Am J Dig Dis 1978;23:398-406.
19. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy — definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna 1998. HEPATOLOGY 2002;35: 716-721.
20. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991;54:1044-1054.
21. Sarin SK. Long-term follow-up of gastric variceal sclerotherapy: an eleven-year experience. Gastrointest Endosc 1997;46:8-14.
22. European Association for the Study of the Liver. EASL Clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53: 397-417.
23. Gines P, Quintero E, Arroyo V, Terés J, Bruguera M, Rimola A, et al. Compensated cirrhosis: natural history and prognostic factors. HEPATOLOGY 1987;7:122-128.
24. Volk ML, Tocco RS, Bazick J, Rakoski MO, Lok AS. Hospital readmissions among patients with decompensated cirrhosis. Am J Gastroenterol 2012;107:247-252.
25. Cordoba J, Garcia-Martinez R, Simon-Talero M. Hyponatremic and hepatic encephalopathies: similarities, differences and coexistence. Metab Brain Dis 2010;25:73-80.
26. Morgan M, Blei A, Grüngreiff K, Jalan R, Kircheis G, Marchesine G, et al. The treatment of hepatic encephalopathy. Metab Brain Dis 2007; 22:389-345.
27. Agrawal A, Sharma BC, Sharma P, Sarin SK. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy. Am J Gastroenterol 2012;107:1043-1050.
28. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010; 362:1071-1081.
29. Nevens F, Laleman W. Artificial liver support devices as treatment option for liver failure. Best Pract Res Clin Gastroenterol 2012;26: 17-26.
30. Hassanein TI, Tofteng F, Brown RS Jr, McGuire B, Lynch B, Mehta R, et al. Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. HEPATOLOGY 2007; 46:1853-1862.
31. Watanabe A. Portal-systemic encephalopathy in noncirrhotic patients: classification of clinical types, diagnosis and treatment. J Gastroenterol Hepatol 2000;15:969-979.
32. Maleux G, Heye S, Verslype C, Nevens F. Management of transjugular intrahepatic portosystemic shunt induced refractory hepatic encephalopathy with the parallel technique: results of a clinical follow-up study. J Vasc Interv Radiol 2007;18:986-992.
33. Del Piccolo F, Sacerdoti D, Amodio P, Bombonato G, Bolognesi M, Mapelli D, et al. Central nervous system alterations in liver cirrhosis: the role of portal-systemic shunt and portal hypoperfusion. Metab Brain Dis 2002;17:347-358.
34. Takashi M, Igarashi M, Hino S, Takayasu K, Goto N, Musha H, et al. Portal hemodynamics in chronic portal-systemic encephalopathy. J Hepatol 1985;1:467-476.