Observation of immediate and mid-term effects of partial spleen embolization in reducing hepatic venous pressure gradient

Yiming Zhao, MS*a, Liangliang Guo, BSa, Qiyang Huang, MDa, Rugang Zhang, MDa, Xuyang Sun, BSa, Li Zhao, BS*a, Chao Li, BS*a, Yan Nie, MSa, Gang Sun, MDb, Jiangtao Liu, MDa,*

Abstract
Objective: To observe the immediate and mid-term effects of partial spleen embolization (PSE) in reducing hepatic venous pressure gradient (HVPG) in patients with cirrhotic esophageal gastric varices.

Methods: Patients diagnosed with cirrhosis and esophageal gastric varices in our hospital between July 2016 and March 2018 were consecutively selected. Forty-three patients were selected based on the eligibility criteria to undergo PSE. The change in HVPG 5 minutes before and after embolization, was used to determine the immediate effect of PSE on HVPG reduction. HVPG was retested after 6 months to observe the change in the antihypertensive effect along with time.

Results: Forty-three patients successfully underwent PSE and HVPG measurements. The HVPG was 17.7±3.9mmHg and 13.9±3.1mmHg before and after PSE, respectively, showing a significant decrease (21.5%, P<.05). Among them, 16 cases were retested for HVPG at 6 months after PSE, and the results showed significant differences in the HVPG levels before, immediately and 6 months after PSE. Compared with preoperative PSE, HVPG was decreased by 22.9% and 17.7% (P<0.05) immediately and at 6 months after operation, respectively. There was no significant change at 6 months after PSE when compared with immediate postoperative PSE. No serious complications were observed in patients during their postoperative hospital stay.

Conclusion: PSE immediately reduced the portal pressure, and HVPG remained stable at 6 months after surgery. PSE is considered as a safe and easy to implement method, and is expected to be one of the treatments for reducing the portal pressure.

Abbreviations: FHVP = free hepatic venous pressure, GVB = gastric variceal bleeding, HVPG = hepatic venous pressure gradient, PSE = partial spleen embolization, WHVP = wedged hepatic venous pressure.

Keywords: hepatic venous pressure gradient, partial spleen embolization, portal hypertension

1. Introduction
Portal hypertension is an independent risk factor of cirrhosis. The basic pathophysiological features included obstruction of blood flow into the portal system and/or increased blood flow, and increased pressure in the portal vein and its collateral vessels with collateral circulation. Gastroesophageal varices are the most common manifestations of portal hypertension, and are present in patients with advanced cirrhosis, accounting for an incidence rate of 7% per year. During the initial diagnosis, gastroesophageal varices were found in 50% patients with cirrhosis. The initial bleeding rate of esophageal gastric varices is 12% per year, and most of these remained dangerous. It is regarded as one of the most serious diseases of digestive system and is a leading cause of death in cirrhosis patients. Currently, vasoactive drugs combined with endoscopic treatment are considered as standard treatment approach for gastric variceal bleeding (GVB). Despite several recent treatment advances, there are still more than 20% of early rebleeding rates and had mortality within 6 weeks (with a mortality rate of up to 60% in one year). [1–3]

In addition to liver function, the prolonged increase in the portal vein pressure also has an important effect in the prognosis of GVB patients. According to a previous study, reduced portal pressure significantly reduces the risk of GVB.[4] The portal pressure can be reduced by treating with vasoactive drugs, surgical and interventional portal-systemic shunts. Vasoactive drugs such as octreotide, somatostatin, etc. reduced visceral blood flow, which thereby reduces the portal pressure, and lasts the antihypertensive effect, but its continuous effect remained unsatisfactory.[5] Another class of drugs included non-selective beta blockers (NSBB, e.g., propranolol) for reducing portal blood flow through cardiac output reduction and visceral blood vessel...
contraction. The NSBB have shown limited antihypertensive effects and remained intolerable in some populations.\cite{6} Surgical or interventional portal-body shunts were associated with problems such as trauma, hepatic encephalopathy, and liver function damage.

Liver cirrhosis is often accompanied with spleen enlargement or hypersplenism. It not only occurs as a result of portal hypertension, but also is an important factor in promoting the progression of portal hypertension. The splenic vein is the largest branch of the portal vein system, and the blood flow of it accounted for more than 60% of the total portal vein flow. In cirrhotic patients with hypersplenism, the splenic venous return volume led to portal system pressure.\cite{7,8} Partial spleen embolization (PSE) embolizes a part of splenic blood vessels by vascular intervention, causing ischemic necrosis of the corresponding splenic tissue. So, the portal vein pressure can be reduced by decreasing the splenic venous return. Clinical studies have also shown that endoscopic and interventional therapy combined with PSE significantly reduced the rate of rebleeding and improved the patient survival.\cite{9,10} However, evaluation on the exact effect of PSE in portal pressure reduction is currently rare.\cite{11,12}

Hence, this study aimed to monitor the immediate and long-term effects of PSE to reduce the hepatic venous pressure gradient (HVPG) by monitoring the levels of HVPG immediately and at 6 months after PSE, providing evidence and reference for its clinical application.

2. Materials and methods

From July 2016 to December 2017, patients diagnosed with cirrhosis and esophagogastric varices in the local hospital were prospectively collected. PSE was performed in patients with hypersplenism, and was performed in all patients within 1 week after endoscopy and treatment. This study is a part of a national key R&D program and has been approved by the Center’s Ethics Committee. All patients were informed regarding the research content and have signed the informed consent form. PSE was performed 5 days after standard therapy (endoscopy combined with drugs). PSE along with endoscopic therapy, with or without NSBB, was continued according to the secondary prevention standard scheme (Table 1).

2.1. PSE and HVPG determination methods

All interventions were performed by using Philips FD20 imaging system, and were performed sequentially in the order of first HVPG measurement, PSE, and secondary HVPG measurement. Two senior deputy chief physicians with experience in interventional therapy completed all the operations.

2.2. Baseline HVPG measurement

The right femoral vein approach was selected for measuring HVPG. The patient was placed in supine position, disinfected, draped, and administered 2% lidocaine as local anesthesia. After the right femoral vein was punctured by Seldinger technique, the guide wire was advanced into a 6F puncture sheath. The guidewire catheter was adjusted into the right hepatic vein and the exchange catheter was delivered via a guidewire to the balloon catheter (5.5F dual lumen catheter, Edwards lifesciences LLC). Free hepatic venous pressure (FHVP) was measured by connecting a pressure sensor and an accessory (Smiths Medical ASD, Inc). After the balloon was expanded into a suitable size, the end hole was smoked to confirm whether the right venous blood flow occlusion was completed with no hepatic medial branch traffic, and then the wedged hepatic venous pressure (WHVP) was measured. The measurements were taken thrice and the average value was finally obtained. If the pressure difference between any two measurements exceeded 1 mmHg, the measurement was repeated until the difference was less than 1 mmHg. The HVPG was then recorded using the formula, HVPG = WHVP - FHVP.

2.3. PSE

The right femoral artery was selected as the puncture site, and 2% lidocaine was used for local anesthesia. Seldinger technique was utilized to puncture the femoral artery, and then the 5F vascular sheath was successfully placed. The guide wire and 5F Cobra or super-sliding yasino catheter were delivered along the sheath. The spleen artery trunk that travels to the spleen was selected, and angiography was then performed to determine the size of the spleen and the number of blood vessels. The 100-300 μm microsphere embolization agent (Embosphere, BioSphere Medical SA Roissy en France-FR) was fully immersed into 160,000-unit gentamicin solution. The contrast agent was mixed in 1:1 ratio, and the spleen embolism was performed by slowly injecting the contrast agent into the splenic artery along with the catheter under fluoroscopy. During the first embolization, 1/3 amount of microspheres was administered, and then angiography was intermittently monitored until the microspheres are added until the spleen presents speckle or hazy-like appearance (Figs. 1 and 2). The embolization ratio was controlled between 40%-60% by visual inspection. After that, the embolization was stopped and then the HVPG was measured.

2.4. Secondary HVPG measurement

Five minutes after the completion of PSE, FHVP and WHVP were repeatedly measured according to the aforementioned methods to obtain HVPG, and the average value was taken after measuring thrice. After the operation, the arterial and venous sheaths were removed, the local pressure was applied for 10 minutes, followed by wrapping with sterile gauze, and placing the leg straightly on bed for 12 hours.
2.5. Follow-up
Blood routine, liver and kidney function, blood coagulation laboratory parameters and abdominal ultrasound were monitored at 3 days, 1 week, 4 weeks, 12 weeks, and 24 weeks after PSE. The number of rebleeding and mortality within 6 months were recorded. All patients were scheduled for HVPG follow-up at 6 months after surgery to confirm the maintenance of PSE antihypertensive effect.

2.6. Statistical analysis
SPSS software (version 17.0.1, Statistical Product and Service Solutions) was used for data analysis. Measurement data were expressed as mean±standard deviation. Count data was expressed as percentage±standard deviation. HVPG was compared before and after PSE by using paired t test. The HVPG was compared before and after PSE, and the variance analysis was performed at 6 months after operation. P < .05 was considered to be statistically significant.

3. Results
According to the inclusion and exclusion criteria, a total of 46 patients were enrolled in the study and HVPG measurements were obtained. Of these, 3 patients had intrahepatic venous collateral traffic during contrast agent injection, affecting the accuracy of HVPG and so were excluded from the study. Finally, a total of 43 patients who underwent PSE were included in the analysis (Table 2). Eighteen patients had follow-up HVPG measurement within 6 months.

The level of HVPG in 43 patients before and after PSE showed significant differences (Table 3). Five minutes after PSE, HVPG showed a significant decrease when compared with that before PSE, with an average decrease of 21.5%.

There were statistical differences in HVPG levels among 18 patients before, immediately, and at 6 months after PSE (Table 4). HVPG level was decreased by 22.9% and 17.7% immediately and at 6 months after PSE (P < .001), respectively. There was no significant increase in HVPG level at 6 months after PSE when compared with that of immediately after PSE (P = .779).

Among the 32 patients who underwent endoscopic follow-up at 3 to 6 months after PSE, the diameter of variceal veins was decreased in 21 patients. Of the 19 patients with portal hypertensive gastropathy, 15 patients demonstrated significant alleviation during follow-up endoscopy (Figs. 3 and 4).

WBC, PLT, and Child-Pugh Score at 6 months after PSE showed no significant changes when compared with those before PSE (Table 5).
3.1. Adverse reactions

All patients had fever during their postoperative hospital stay. The body temperature fluctuated between 37.5 and 39.0°C, and rectal antipyretic suppository was then given. The fever lasted for 2 to 10 days. All patients had pain in the upper or left abdomen, and the pain score was 2 to 8 points. In case of persistence of intolerable pain that affected the sleep, oxycodone sustained-release tablets were administered orally to relieve from pain, and the pain lasted for 2 to 8 days. Seventeen patients developed abdominal distension and constipation, and were gradually relieved after lactulose administration. No patients had serious complications such as ascites, pulmonary infection, abdominal infection, spleen abscess, and portal vein thrombosis during the 6-month follow-up period. Three patients had rebleeding at weeks 8, 13, and 20 after discharge. Two patients underwent endoscopic hemostasis to stop bleeding. One patient died due to liver failure and lung infection 2 weeks after rebleeding.

4. Discussion

This study measured HVPG levels before and after PSE, and the results showed that PSE can quickly and effectively reduced the portal pressure. After PSE, HVPG was decreased by 21.5% when compared to the baseline values. GVB showed a direct association with increased portal pressure. PSE reduced the blood flow of the spleen by embolization of spleen vessels, which thus reduced the portal pressure. HVPG accurately reflects the portal system pressure, and a close correlation was observed with the occurrence, development and outcome of varices.[15,16] A decrease in HVPG to 12 mmHg or a 20% reduction from baseline can significantly reduce the risk of variceal bleeding.[17] A similar study conducted by Chikamori et al in 2007 observed that patients with PSE have significantly lower WHVP than that before surgery,[18] and was consistent with the findings of this study, but no changes in HVPG were reported in Chikamori’s study. WHVP corresponds to the portal vein pressure, which in turn was affected by intra-abdominal pressure. The HVPG that is corrected by FHVP is considered as an internal standard and has a truly reliable clinical significance.[2,3] Helaly et al studied the hemodynamic changes of portal vein system after PSE by Doppler ultrasound, and confirmed the effect by significantly reducing the diameter of the portal vein after PSE and decreasing the

![Figure 3. Endoscopic findings pre PSE: Solid arrows showed variceal veins; hollow arrow showed obvious portal hypertensive gastropathy.](image1)

![Figure 4. Follow-up endoscopy post PSE: Solid arrows showed flattened variceal veins; hollow arrow showed alleviated portal hypertensive gastropathy.](image2)
hyperemic index. This effect was more obvious after a week[11]. This was in accordance with the results of the current study regarding the HVPG changes before and after PSE. On the other hand, Helalyy’s study showed no significant changes in the portal vein blood flow after PSE, showing inconsistencies with the angiographic findings in this study. Indirect portal angiography of splenic artery before and after embolization of the spleen was performed. The appearing time of portal vein was significantly delayed when compared with that before surgery, and the appearance was slightly changed. Most of the patients with varices that are significant before PSE became thin or even disappeared after undergoing PSE. Of the 19 cases with hypertensive gastropathy, 15 cases demonstrated significant alleviation during the follow-up endoscopy. According to Buechter et al’s study in 2017, no evidence of progression of portal hypertension is observed during the follow-up period after PSE. In some cases, distinct regression of varices was observed within 6 months after PSE. It is regarded as an evidence for the decrease of portal vein blood flow caused due to decreased splenic venous blood flow after PSE. This in turn showed that PSE could effectively reduce portal blood flow, thus reducing the effect of portal pressure. The reasons for the inconsistency with Helalyy research results are due to the use of different research methods and different content of observer’s interest. It is necessary to implement the use of Doppler ultrasound blood flow analysis in subsequent studies. Previous studies have shown that reducing HVPG to below 12 mmHg or reducing basal levels by 20% in patients with gastroesophageal varices can significantly reduce the risk of bleeding and rebleeding, risk of ascites, spontaneous peritonitis, and death.[13] In this study, by monitoring the HVPG level in real-time and controlling the volume of PSE by about 40% to 60%, HVPG can be reduced by about 20%, which subsequently assists in meeting the requirements of instant reduction of portal pressure.

In this study, HVPG retest was performed in 18 patients, and the results revealed differences in HVPG levels before, immediately and at 6 months after PSE. Compared with HVPG levels before PSE, it was decreased by 22.9% and 17.7% in immediately and at 6 months after PSE, respectively. There was no significant difference between 6 months postoperative PSE and immediate postoperative PSE. Spleen is the largest immune organ, and has strong ability to regenerate. After PSE, the spleen restores its volume and functions through regeneration. Therefore, it is generally believed that the splenic blood flow is restored with splenic regeneration and the reduced portal pressure after PSE returns to the pre-embolization level. However, this point is based on the inference from the pathophysiological theory, and there is no evidence of clinical observation. In this study, HVPG showed a slight increase in the HVPG levels at 6 months when compared to that immediately after PSE, but showed no significant differences, and still remained significantly lower than that before PSE. We speculated the existence of some complex mechanisms that are still unclear and might cause changes or remodeling of the spleen, portal vein and its branch hemodynamics after PSE, or adaptive changes of the body to postoperative portal pressure reduction after PSE. The results of mid-term HVPG monitoring have not been reported previously, and the mechanism still remained unclear. Three patients had rebled during the 6 months follow-up period (6.9%). According to Buechter et al’s study, 9 patients with PH-induced variceal bleeding underwent PSE. None of these patients were treated for PSE experienced rebleeding episodes or required blood transfusions during the follow-up period of 159 months. Further large-scale clinical trials or basic research is warranted to verify the clinical benefits.

Common adverse reactions after embolization of the spleen included fever, abdominal pain, abdominal distension, etc. Serious adverse reactions included spleen abscess, abdominal infection, and portal vein thrombosis. There were no serious adverse reactions in this study. The common reactions such as fever, abdominal pain and abdominal distension were mild and the duration remained short. The use of tiny terminal embolization agents in this group of patients might account for minor adverse reactions. Through embolization, 100 to 300μ. diameter microspheres are freely accessible into the splenic artery branch with vigorous blood flow, and evenly enter the tiny vascular end of the spleen, causing extensive micro-focal infarctions of the spleen. While reduced blood flow to the spleen avoided the occurrence of large infarctions in the spleen, minimizing the occurrence of postoperative spleen abscess. Therefore, the trunk-terminal micro-embolization method for selecting the embolization effects in PSE remained reliable and safe.

However, there are few limitations in this study, which are as follows:

1. the sample size was relatively small, especially the number of follow-up patients for undergoing retesting of HVPG levels, and this subsequently reduced the power of research conclusion to some extent;
2. the study did not include the data of survival analysis for PSE, and the clinical effect was not very convincing;
3. although early-TIPS is recommended in emergency bleeding according to the Guidelines and consensus in high-risk of rebleeding, TIPS treatment in our center is used for patients who had failed standard treatment or recurrent massive hemorrhage (salvage treatment).
4. Early-TIPS is not strictly conducted in acute hemorrhagic patients. This might weaken the generalization of the conclusion to some extent; and
5. this study was a single-arm observational study, and hence a well-designed randomized controlled study is needed to confirm its clinical effect.

5. Conclusion

In summary, PSE can immediately reduce the portal pressure, and HVPG remains at a relatively stable level at 6 months after PSE. This method of PSE is considered to be safe, associated with fewer side effects, and easy to implement. The results should be further confirmed by a large-scale clinical controlled study for considering PSE as one of the treatments for reducing portal pressure in patients with cirrhotic portal hypertension.

### Table 5

| Laboratory Index Changes Pre- and 6 months Post-PSE. | Pre-PSE | Six months Post-PSE | P value |
|-----------------------------------------------------|---------|---------------------|---------|
| WBC(10^9/L)                                         | 2.92±1.37 | 3.19±1.71           | .387    |
| PLT(10^9/L)                                         | 81±16   | 72±13               | .070    |
| Child-Pugh Score                                    | 7.3±2.5 | 7.6±2.4             | .972    |
Author contributions

Conceptualization: Gang Sun.
Investigation: Yiming Zhao, Liangliang Guo, Qiyang Huang, Rugang Zhang, Xuyang Sun, Li Zhao, Chao Li, Yan Nie, Jiangtao Liu.
Methodology: Yiming Zhao, Liangliang Guo, Qiyang Huang, Rugang Zhang, Xuyang Sun, Li Zhao, Chao Li, Yan Nie, Jiangtao Liu.
Writing – original draft: Yiming Zhao, Liangliang Guo.
Writing – review & editing: Gang Sun.

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