ISSN 1948-5182 (online)

# World Journal of *Hepatology*

*World J Hepatol* 2021 June 27; 13(6): 620-716

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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Monthly Volume 13 Number 6 June 27, 2021

*World Journal of Hepatology*

**Monthly Volume 13 Number 6 June 27, 2021**

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## RESPONSIBLE EDITORS FOR THIS ISSUE

**Production Editor:** *Li-Li Wang*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Xiang Li*.

**NAME OF JOURNAL**
*World Journal of Hepatology*

**ISSN**
ISSN 1948-5182 (online)

**LAUNCH DATE**
October 31, 2009

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/1948-5182/editorialboard.htm

**PUBLICATION DATE**
June 27, 2021



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*World J Hepatol* 2021 June 27; 13(6): 650-661

DOI: 10.4254/wjh.v13.i6.650

ISSN 1948-5182 (online)

*MINIREVIEWS*

# Balloon-occluded retrograde transvenous obliteration for treatment of gastric varices

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**Author contributions:** Waguri N wrote the manuscript; Osaki A drew the illustrations; Watanabe Y reviewed the paper.

**Conflict-of-interest statement:** There are no conflicts of interest.



**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Japan

**Peer-review report's scientific quality classification**

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## Abstract

Rupture of gastric varices (GVs) can be fatal. Balloon-occluded retrograde transvenous obliteration (BRTO), as known as retrograde sclerotherapy, has been widely adopted for treatment of GVs because of its effectiveness, ability to cure, and utility in emergency and prophylactic treatment. Simplifying the route of blood flow from GVs to the gastrorenal shunt is important for the successful BRTO. This review outlines BRTO indications and contraindications, describes basic BRTO procedures and modifications, compares BRTO with other GVs treatments, and discusses various combination therapies. Combined BRTO and partial splenic embolization may prevent exacerbation of esophageal varices and shows promise as a treatment option.

**Key Words:** Gastric varices; Balloon-occluded retrograde transvenous obliteration; Balloon-occluded antegrade transvenous obliteration; Partial splenic embolization; Transjugular intrahepatic portosystemic shunt; Plug- and coil-assisted retrograde transvenous obliteration



**Core Tip:** Gastric varices (GVs) are a common complication of liver cirrhosis and their rupture is often fatal. Balloon-occluded retrograde transvenous obliteration (BRTO) has been widely adopted for treatment of GVs because of its effectiveness, ability to cure, and utility in emergency and prophylactic treatment. Various modifications of BRTO and combinations with other therapies are also beneficial. Combined BRTO and partial splenic embolization shows promise as a treatment option.

**Citation:** Waguri N, Osaki A, Watanabe Y. Balloon-occluded retrograde transvenous obliteration for treatment of gastric varices. *World J Hepatol* 2021; 13(6): 650-661

Grade A (Excellent): A, A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**Received:** February 25, 2021
**Peer-review started:** February 25, 2021
**First decision:** March 29, 2021
**Revised:** April 12, 2021
**Accepted:** May 22, 2021
**Article in press:** May 22, 2021
**Published online:** June 27, 2021

**P-Reviewer:** Chiu KW, Simón-Talero M, Xiong B
**S-Editor:** Liu M
**L-Editor:** A
**P-Editor:** Wang LL

**URL:** https://www.wjgnet.com/1948-5182/full/v13/i6/650.htm
**DOI:** https://dx.doi.org/10.4254/wjh.v13.i6.650

## INTRODUCTION

Gastric fundal varices (GVs) and esophageal varices (EVs) are two of the main presentations of cirrhosis-induced portal hypertension. Although the bleeding risk of GVs is relatively low, their rupture is associated with high mortality (14%–45%)[1-4], because of their larger shunt diameter and higher flow. Hemodynamically, the two types of varices are completely different. The left and right gastric veins comprise the inflow of EVs, with the azygos vein system serving as the outflow. In contrast, the short and posterior gastric veins comprise the main inflow of GVs, although the left gastric vein may also be involved; the gastrorenal shunt (GRS), which drains blood to the left renal vein *via* the descending branch of the left inferior phrenic veins (80%–85%), and the gastrocaval shunt (GCS), which runs below the diaphragm and drains into the inferior vena cava (10%–15%) serve as outflow[5]. Eradication of GVs is difficult endoscopically because of the large diameter and high flow velocity of the shunts. Balloon-occluded retrograde transvenous obliteration (BRTO), developed by Kanagawa in 1996, is a sclerotherapy technique that approaches the varices from the outflow side of the GRS[6]. Since then, BRTO has been widely accepted in Japan[7-9], Asia, and the United States[10,11] as an effective treatment for GVs. In Europe, however, BRTO is not well recognized and not a treatment option for GVs[12,13]. In this review, we outline the indications and contraindications for BRTO, describe basic BRTO procedures and modifications, compare BRTO with other GVs treatments, and discuss various combination therapies.

## INDICATIONS AND CONTRAINDICATIONS FOR BRTO

According to Saad *et al*[14], the two clinical indications for BRTO are bleeding GVs (active, current, prior, and impending) and refractory hepatic encephalopathy involving the portosystemic shunt that forms GVs. Contraindications include: (1) Severe uncontrollable coagulopathy associated with liver failure; (2) Splenic vein thrombosis; (3) Portal vein thrombosis; and (4) Uncontrolled bleeding from EVs. In the case of uncontrolled bleeding from EVs, BRTO is contraindicated as a sole procedure; combined transjugular intrahepatic portosystemic shunt (TIPS) and BRTO or balloon-occluded antegrade transvenous obliteration (BATO) *via* the TIPS route are recommended instead.

We use BRTO for both emergency and elective treatment of ruptured GVs as well as prophylactic treatment according to the criteria described below[15,16]. Indications for prophylactic treatment of GVs include nodular form and red color spot lesions[17], increasing size over time, and hepatic encephalopathy. However, we do not treat patients with severe hepatic dysfunction (total bilirubin ≥ 4.0 mg/dL, Child-Pugh score ≥ 13), renal dysfunction (eGFR < 30 mL/min/1.73 m$^2$), or other serious diseases with poor prognosis as well as those without a portosystemic shunt amenable to a retrograde approach[15]. We consider the presence of contrast agent flowing freely from the GRS into the portal vein on balloon-occluded retrograde venography (BRTV) a relative contraindication[16].

## ADVANTAGES OF BRTO OVER OTHER TREATMENTS

Although beta blockers are widely used to prevent bleeding in esophagogastric varices, based on a great deal of evidence[13,18], this review omits a description of them as its focus is interventional procedures.

TIPS is widely used in Western countries to treat portal hypertension in patients with esophagogastric varices and refractory ascites[19-24]. TIPS significantly reduces GVs rebleeding compared with pharmacotherapy and endoscopic treatments such as endoscopic variceal band ligation[19-21]. Although TIPS reduces portal venous pressure (PVP), GVs rebleeding and stent dysfunction are common[19-21,25]. Additionally, post-TIPS mortality is relatively high due to serious complications such as intraperitoneal hemorrhage, hemobilia, sepsis, hepatic failure, congestive heart

failure, and others[25,26]. However, the use of polytetrafluoroethylene-covered stents has improved the TIPS patency rate[27] and the complication rate has decreased in conjunction with more widespread use. Preemptive TIPS is also recommended to prevent esophagogastric varices rebleeding[13,28].

Endoscopic injection of n-butyl-2-cyanoacrylate (CA) has also been widely used to treat GVs[29]. In patients with acute bleeding, CA injection is reportedly more effective than pharmacotherapy alone[30,31] and is the therapy of choice[32,33]; however, CA injection for elective treatment is not recommended and only used when no other treatment is available[32,33].

BRTO is highly effective to eradicate GVs[6-8,15,34] and can be effective for prophylactic[7-9,34] as well as emergency bleeding treatment[15,35,36]. Several studies have shown that BRTO is superior to endoscopic interventions in terms of bleeding control and prognosis in patients with GVs[35,37,38]. Furthermore, several comparative studies have reported that BRTO has a slight advantage over TIPS in terms of rebleeding, hepatic encephalopathy, hepatic functional reserve, and survival[39-44]. These studies are summarized in Tables 1-4. Table 1 shows the study design and sample size. Table 2 summarizes the sclerosant used for BRTO, types of stents used for TIPS, and the technical success rate of each procedure. Table 3 shows the rebleeding rates of GVs and EVs. Table 4 shows the notable complications after each procedure. Recent meta-analyses[45-47] have concluded that BRTO in patients with GVs bleeding is associated with lower rates of rebleeding and postprocedural hepatic encephalopathy, as well as better survival than TIPS. Although BRTO is effective in eradicating GVs, it is associated with complications such as postprocedural EVs, ectopic varices, and intractable ascites. Further debate over the relative superiority of BRTO or TIPS is not constructive. Rather, clinicians should fully understand the characteristics, risks, and benefits of each and use them suitably according to individual patient therapeutic needs. Clinicians should also consider using them in various therapeutic combinations.

## CONVENTIONAL BRTO PROCEDURE

BRTO drug preparation and procedures have been described in detail by Hirota *et al* [16]. In Japan, BRTO using ethanolamine oleate with iopamidol (EOI) became covered by insurance in 2018 after publication of a prospective multicenter clinical trial[48].

Our conventional BRTO method is described as follows[15,49]: GRS is diagnosed by computed tomography (CT). An 8 Fr long shepherd hook-shaped (Asato; Medikit, Tokyo, Japan) or cobra-shaped (S-one sheath; Terumo Clinical Supply Co., Gifu, Japan) sheath introducer is advanced into the left renal vein *via* the right femoral or internal jugular vein, respectively. A 6 Fr catheter with a 20 mm diameter balloon or 5.2 Fr catheter with a 9 mm diameter balloon (Selecon MP Catheter; Terumo Clinical Supply Co.) is then advanced into the GRS through the introducer in a retrograde fashion. BRTV (Figure 1) is then performed to identify shunts and their inflow and outflow. Before sclerosing the GRS, the route from the GVs to the GRS needs to be simplified. We use the down-grading method [50], selective coil embolization of the minor accessory draining veins[51], and/or the stepwise injection method [51] to downgrade the target shunt vessels to a relatively simple Hirota grade 1 or 2[52] (Figure 2A-D). If the coexisting GCS has a large diameter and selective coil embolization of the left inferior phrenic vein is impossible, the GCS is occluded with another balloon catheter [53] (Figure 2E). Under temporary balloon occlusion, contrast medium is injected *via* the balloon catheter to confirm stagnation of variceal flow for ≥ 10 min and evaluate the required volume of sclerosing solution. When stagnation of the contrast medium is confirmed, the same volume (10-40 mL) of 5% EOI is injected and remains stagnant in the vessels with overnight balloon occlusion. Human haptoglobin (4000 units) is administered prior to EOI injection to prevent acute kidney injury secondary to hemolysis caused by EOI[54]. The catheter is removed after overnight occlusion. Thrombosis of the GVs-GRS outflow (therapeutic effect) and thrombus formation elsewhere in the portal system (adverse effect) are confirmed by CT 3 to 7 d after BRTO. Eradication of GVs is confirmed by endoscopy after 2 to 3 mo.

## BRTO MODIFICATIONS

BRTO is commonly performed overnight to prevent the outflow of sclerosant into the systemic circulation[15,16,48]. Alternatively, a vascular plug[55] or microcoils[56] can

**Table 1 The studies comparing balloon-occluded retrograde transvenous obliteration and transjugular intrahepatic portosystemic shunt**

| Ref. | Journal | Country | Study design | Number of cases | |
|---|---|---|---|---|---|
| | | | | BRTO | TIPS |
| Choi *et al*[39] | KJR 2003 | South Korea | RCT, Single institution | 8 | 13 |
| Ninoi *et al*[40] | AJR 2004 | Japan | Retrospective, Single institution | 77 (BRTO: 49 / PTS: 28) | 27 |
| Sabri *et al*[41] | JVIR 2014 | United States | Retrospective, Single institution | 23 | 27 |
| Kim *et al*[42] | KJR 2017 | United States | Retrospective, Single institution | 25 | 27 |
| Lee *et al*[43] | JGH 2017 | South Korea | Retrospective, Two institutions | 95 | 47 |
| Gimm *et al*[44] | Gut and Liver 2018 | South Korea | Retrospective, Single institution | 157 | 19 |

BRTO: Balloon-occluded retrograde transvenous obliteration; TIPS: Transjugular intrahepatic portosystemic shunt; RCT: Randomized controlled trial; PTS: Percutaneous transhepatic sclerotherapy.

**Table 2 Materials used and technical success rate**

| Ref. | BRTO | Tips | Technical success rate | |
|---|---|---|---|---|
| | sclerosant | Stent type | BRTO | TIPS |
| Choi *et al*[39] | EO | Bare | 8/8 | 13/13 |
| Ninoi *et al*[40] | EO | Bare | 49/58 | 27/27 |
| Sabri *et al*[41] | STS | Covered | 21/23 | 27/27 |
| Kim *et al*[42] | EO, STS | Covered | 22/25 | 27/27 |
| Lee *et al*[43] | EO, STS, polidocanol | Covered | 106/123 | 49/60 |
| Gimm *et al*[44] | EO, STS | Bare, covered | 159/166 | 19/22 |
| Total | | | 365/403 | 162/176 |
| | | | 90.6%[1] | 92.0%[1] |

[1]Not significant. BRTO: Balloon-occluded retrograde transvenous obliteration; TIPS: Transjugular intrahepatic portosystemic shunt; EO: Ethanolamine oleate, STS: Sodium tetradecyl sulfate.

be placed to occlude the GRS instead, allowing catheter system removal as soon as the treatment is complete (a single day procedure). The original methods of plug-associated retrograde transvenous obliteration (PARTO)[55] and coil-associated retrograde transvenous obliteration (CARTO)[56] (Figure 3A and B) emphasized their advantage of not requiring balloon catheters, sclerosants, or a long period of postprocedural bed rest and monitoring. However, these techniques have the disadvantage of high cost. By embolizing the small drainage vessels with gelatin particles, the selective coil embolization procedure can be omitted, and the procedure becomes easy and effective[55,57]. However, recurrence of GVs is lower when a surfactant such as sodium tetradecyl sulfate is used as a sclerosant in PARTO compared with use of gelatin alone[57]. Recurrence might be due to recanalization through the gelatin sponge which does not provide the permanent endothelial injury and thrombosis caused by sclerosants[58]. Injected gelatin has no direct effect on blood clot formation. Once the injected gelatin particles flow into the systemic circulation, they become emboli to the micro-vessels elsewhere. In contrast, sclerosant has a thrombus-forming effect on small drainage vessels, even in small amounts. However, if a small amount of sclerosant flows into the systemic circulation, it is often diluted with a large amount of blood and the effect of vascular endothelial damage can be ignored. Therefore, we believe that sclerosant should be used in BRTO rather than gelatin sponge alone.

Instead of downgrading by advancing the balloon catheter, a modified CARTO[59] in which embolization is performed using microcoils and sclerosant is injected upstream to the GVs has also been described (Figure 3C). Yamamoto *et al*[60] described CARTO-II, in which sclerosant is injected from a balloon catheter in the

**Table 3 Rebleeding rate from gastric varices and esophageal varices**

| Ref. | Rebleeding rate from GVs | | Rebleeding rate from EVs | |
|---|---|---|---|---|
| | BRTO | TIPS | BRTO | TIPS |
| Choi *et al*[39] | 0/8 | 1/13 | 0/8 | 0/13 |
| Ninoi *et al*[40] | 1/77 | 6/27 | 3/77 | 2/27 |
| Sabri *et al*[41] | 0/23 | 3/27 | 0/23 | 0/27 |
| Kim *et al*[42] | 2/25 | 2/27 | 1/25 | 0/27 |
| Lee *et al*[43] | 7/95 | 6/47 | 4/95 | 7/47 |
| Gimm *et al*[44] | 8/157 | 3/19 | | |
| Total | 18/385 | 21/160 | 8/228 | 9/141 |
| | 4.7%[1] | 13.1%[1] | 3.5%[2] | 6.4%[2] |

[1]$P$ = 0.0005.
[2]Not significant. GVs: Gastric varices; EVs: Esophageal varices; BRTO: Balloon-occluded retrograde transvenous obliteration; TIPS: Transjugular intrahepatic portosystemic shunt.

**Table 4 Complications after balloon-occluded retrograde transvenous obliteration or transjugular intrahepatic portosystemic shunt**

| Ref. | LF | | HE | | Ascites | | EVs aggravation | |
|---|---|---|---|---|---|---|---|---|
| | BRTO | TIPS | BRTO | TIPS | BRTO | TIPS | BRTO | TIPS |
| Choi *et al*[39] | 0/8 | 1/13 | 0/8 | 1/13 | 0/8 | 0/13 | 1/8 | 0/13 |
| Ninoi *et al*[40] | 3/77[1] | 10/27[1] | 0/77 | 5/27 | 6/77 | | 14/77 | |
| Sabri *et al*[41] | 0/23 | 0/27 | 0/23 | 6/27 | | | | |
| Kim *et al*[42] | 0/25 | 0/27 | 0/25 | 6/27 | 1/25 | 1/27 | 1/25 | 0/27 |
| Lee *et al*[43] | 0/95 | 1/47 | 0/95 | 14/47 | 13/95 | 2/47 | | |
| Gimm *et al*[44] | 0/157 | 0/19 | 4/157 | 0/19 | 48/157 | 1/19 | 22/157 | 1/19 |

[1]Including long-term events. BRTO: Balloon-occluded retrograde transvenous obliteration; TIPS: Transjugular intrahepatic portosystemic shunt; LF: Liver failure; HE: Hepatic encephalopathy; EVs: Esophageal varices.

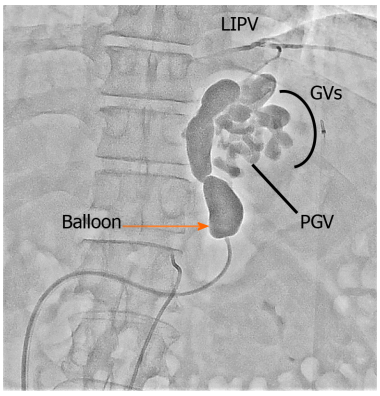


**Figure 1 Balloon-occluded retrograde transvenous venography.** When the gastrorenal shunt is balloon-occluded (arrow) and retrogradely imaged, the posterior gastric vein, which is the inflow vessel, is visualized *via* the gastric varices. A part of the left inferior phrenic vein as an outflow vessel is also demonstrated. PGV: Posterior gastric vein; GV: Gastric varices; LIPV: Left inferior phrenic vein.

same manner as conventional BRTO, coil-embolization is performed just above the balloon (Figure 3D), and the balloon catheter is finally removed. In CARTO-II, thrombosis has already occurred due to vascular endothelial damage caused by the sclerosant, and coil-embolization is performed to prevent the thrombus from flowing

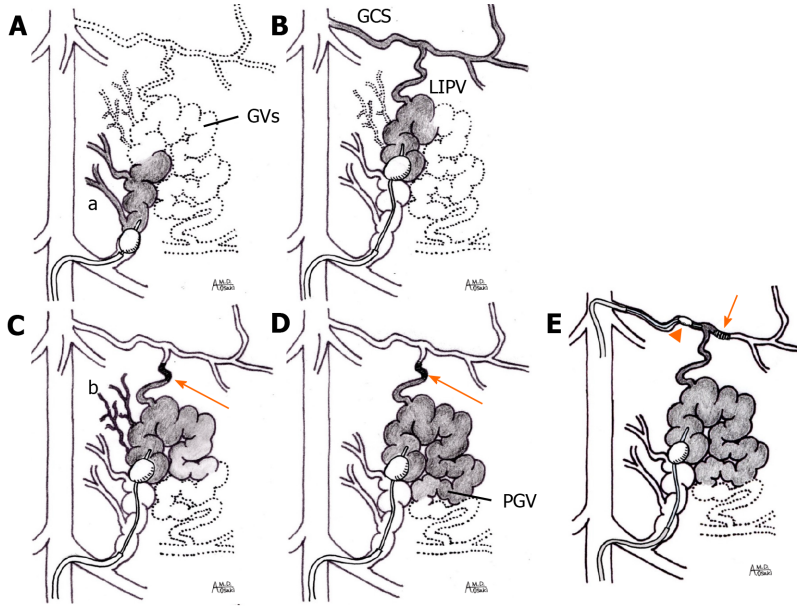


**Figure 2 Illustration of the balloon-occluded retrograde transvenous obliteration procedure.** A: Balloon-occluded retrograde transvenous venography (BRTV). The initial BRTV does not visualize the main body of the gastric varices (GVs) because multiple draining vessels are present (a); B: When the balloon catheter is advanced beyond the small drainage vessels (downgrading method), the relatively large diameter left inferior phrenic vein (LIPV) becomes visualized as another drainage route to the gastrocaval shunt (GCS); C: GVs become visualized when selective coil embolization (arrow) of the LIPV is performed. As small amounts of sclerosant are injected sequentially over time, the smaller drainage vessels (b) are gradually embolized (stepwise injection method); D: After stepwise injection, BRTV demonstrated the GVs in their entirety as well as the inflowing posterior gastric vein; E: If selective coil embolization of the LIPV is impossible, the GCS should be occluded with another balloon catheter for balloon-occluded retrograde transvenous obliteration (BRTO) (dual-BRTO). Selective coil embolization of the LIPV branch (arrow) is performed through the catheter *via* the GCS. PGV: Posterior gastric vein; GVs: Gastric varices; LIPV: Left inferior phrenic vein; GCS: Gastrocaval shunt.

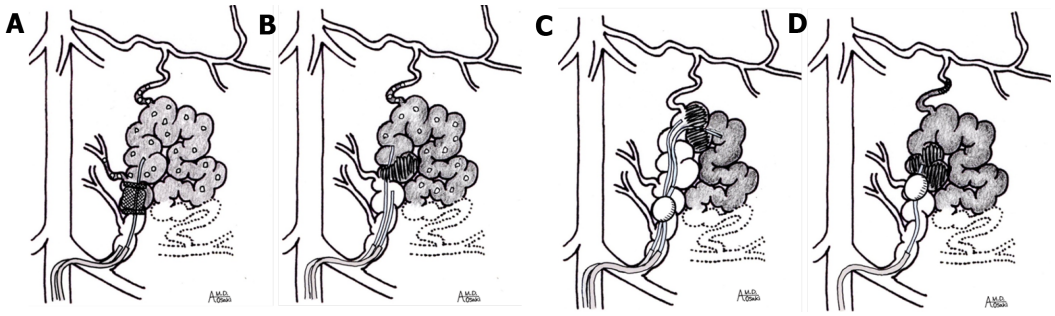


**Figure 3 Schema of balloon-occluded retrograde transvenous obliteration modified variants.** A: In plug-assisted retrograde transvenous obliteration, a vascular plug is placed instead of a balloon catheter to block shunt blood flow. In the original method, gelatin sponge suspension is injected instead of sclerosant; B: In coil-assisted retrograde transvenous obliteration (CARTO), shunt blood flow is blocked using microcoils and gelatin sponge suspension is injected to embolize the gastric varices; C: In modified CARTO, instead of downgrading by advancing the balloon catheter, embolization is performed using microcoils and sclerosant is injected upstream into the gastric varices; D: In CARTO-II, sclerosant is injected from a balloon catheter in the same manner as conventional balloon-occluded retrograde transvenous obliteration, coil embolization is performed just above the balloon, and the balloon catheter is finally removed.

to the systemic circulation after removing the balloon catheter. The same group also reported the utility of a mixture of low-dose gelatin sponge particles and 5% EOI in retrograde transvenous obliteration (GERTO)[61]. GERTO combines the advantages of gelatin particles and sclerosant, blocking small drainage vessels and causing reliable thrombosis *via* vascular endothelial damage.

Although these various BRTO modifications have appeared, their advantages and disadvantages have not yet been thoroughly evaluated. However, an advantage of both PARTO and CARTO is short indwelling balloon time; their disadvantage is high cost.

## COMBINED TREATMENT

Various additional treatments have been performed in combination with BRTO. If BRTO alone is difficult, additional embolization of gastric vein inflow may be used to completely obliterate the GVs. Percutaneous transhepatic obliteration (PTO) may be used when conditions are unsuitable for BRTO, such as GVs without GRS[40,50,62]. Combined BRTO and PTO can obstruct both the feeding and draining veins of GVs to completely retain the sclerosant with in GVs, which may provide better control of variceal blood flow than either procedure alone[63]. However, the drawback of shunt embolization, including BRTO and PTO, is an increase in PVP. Although BRTO is associated with a lower rate of GVs rebleeding than TIPS[39-44] or endoscopic intervention[37,38], the increased PVP may cause enlargement of EVs[64-66]. Saad *et al* [67] therefore proposed use of BATO *via* the TIPS route, combined TIPS and BRTO, or combined BATO and BRTO, depending on the clinical situation. A recent study[68] has proposed a modified method, balloon-assisted antegrade transvenous obliteration (BAATO), in which balloon occlusion of the GRS is performed in retrograde fashion followed by antegrade trans-TIPS catheter injection of CA rather than sclerosant. The distribution of CA in GVs can be controlled by modifying blood flow velocity *via* balloon size adjustment. Thus, BAATO might be valuable alternative option as well. Although, TIPS certainly offsets the increase in PVP caused by BATO and/or BRTO, it can cause hepatic encephalopathy. Partial splenic embolization (PSE) also has a PVP-reducing effect, although weaker than TIPS, and combination with BRTO can be effective[69]. We previously reported that PSE can diminish the increase in PVP after BRTO[49] and that combined BRTO and PSE is a safe and effective treatment for GVs [15]. PSE is technically easier than TIPS and can be performed rapidly. Furthermore, the incidence of EVs exacerbation is lower and improvement in hepatic functional reserve is greater after combined BRTO and PSE than BRTO alone[15]. Increased portal venous flow after BRTO leads to improvement in the hepatic functional reserve [65,70] and is mainly due to increased splenic venous blood flow (Figure 4A and B) without a substantial increase in hepatopetal mesenteric venous blood flow. We speculate that hepatopetal mesenteric venous blood flow increases after PSE decreases the splenic venous blood flow (Figure 4C), which results in improved hepatic functional reserve. PSE has a PVP-reducing effect and can prevent exacerbation of EVs after BRTO. However, PSE-related complications may occur. According to a systematic review of 30 articles[71], the incidence of post-embolic syndrome, pleural effusion, ascites, thrombosis (mainly portal thrombosis), splenic abscess/bacterial peritonitis, and death after PSE is 73.4%, 9.4%, 8.1%, 2.4%, 1.3%, and 1.0%, respectively. Underlying liver dysfunction and splenic infarction rate (infarcted splenic volume/total splenic volume) greater than 70% may be risk factors for major complications[71,72].

## CONCLUSION

GVs rupture is potentially fatal. Although various GVs treatments have been reported, BRTO is widely used because of its effectiveness, ability to cure, and utility for both emergency and prophylactic treatment. Recent BRTO modifications and combinations with other therapies are also beneficial. Although BRTO combined with TIPS and BRTO combined with PSE seem promising, randomized trials have not been performed and serious complications may occur. Their use should be approached with caution.

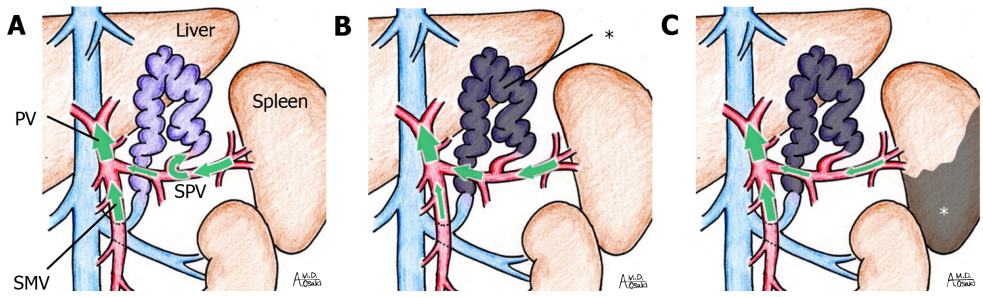


**Figure 4 Schema of changes in portal hemodynamics due to combined balloon-occluded retrograde transvenous obliteration and partial splenic embolization.** A: Before treatment, most of the splenic blood flow is short-circuited to the systemic circulation *via* the gastrorenal shunt (GRS); B: The GRS is embolized by balloon-occluded retrograde transvenous obliteration (BRTO) (black asterisk). The increase in portal venous flow after BRTO is mainly caused by increased splenic venous blood flow without a substantial increase in hepatopetal mesenteric venous blood flow; C: The lower half of the spleen is infarcted by partial splenic embolization (PSE) (white asterisk). Hepatopetal mesenteric venous blood flow increases after splenic venous blood flow is decreased by PSE. PV: portal vein, SPV: splenic vein, SMV: superior mesenteric vein.

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