Left Gastric Vein Width Is an Important Risk Factor for Exacerbation of Esophageal Varices Post Balloon-Occluded Retrograde Transvenous Obliteration for Gastric Varices in Cirrhotic Patients

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Left Gastric Vein Width Is an Important Risk Factor for Exacerbation of Esophageal Varices Post Balloon-Occluded Retrograde Transvenous Obliteration for Gastric Varices in Cirrhotic Patients

Taku Mizutani, Kazushige Nirei *, Tatsuo Kanda, Masayuki Honda, Tomotaka Ishii, Shuhei Arima, Yoichiro Yamana, Naoki Matsumoto, Shunichi Matsuoka and Mitsuhiko Moriyama

Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan; mizutani.taku@nihon-u.ac.jp (T.M.); kanda.tatsuo@nihon-u.ac.jp (T.K.); honda.masayuki@nihon-u.ac.jp (M.H.); ishii.tomotaka@nihon-u.ac.jp (T.I.); arima.shuhei73@nihon-u.ac.jp (S.A.); yamana.yoichiro@nihon-u.ac.jp (Y.Y.); matsumoto.naoki@nihon-u.ac.jp (N.M.); s.matsuoka@mitsuwadaibyoin.or.jp (S.M.); moriyama.mitsuhiko@nihon-u.ac.jp (M.M.)

* Correspondence: nirei.kazushige@nihon-u.ac.jp; Tel.: +81-3-3972-8111

Abstract: *Background and Objectives*: Balloon-occluded retrograde transvenous obliteration (BRTO) could be currently one of the best therapies for patients with gastric varices. This study examined the exacerbation rates for esophageal varices following BRTO for gastric varices in patients with hepatic cirrhosis. *Materials and Methods*: We enrolled 91 cirrhotic patients who underwent BRTO for gastric varices. In total, 50 patients were examined for exacerbation rates of esophageal varices following BRTO. Esophageal varices and their associated exacerbation were evaluated by upper gastrointestinal endoscopy. Patients were allocated into two groups according to the main inflow tract for gastric varices: (1) 37 patients in the left gastric vein (LGV) group with an LGV width of more than 3.55 mm, and (2) 13 patients in the non-LGV group who had short gastric vein or posterior gastric vein. Moreover, treatment outcomes were retrospectively analyzed. *Results*: LGV width ($p < 0.01$) was the major risk factor for the deterioration of esophageal varices post BRTO. In addition, LGV was the most common inflow tract, and the LGV group contained 74% (37/50) of patients. The exacerbation rates of esophageal varices at 1, 2, 3, and 4 years post BRTO were 40%, 62%, 65%, and 68%, respectively. The comparison of the exacerbation rates for esophageal varices following BRTO according to inflow tract showed that the exacerbation rates were significantly higher in the LGV group than those of the non-LGV group ($p = 0.03$). In more than half of the subjects, LGV was the main inflow tract for gastric varices, and this group experienced more frequent exacerbations of esophageal varices following BRTO compared to patients with different inflow tract sources. *Conclusion*: Careful attention should be paid to the LGV width when BRTO is performed for gastric varices.

Keywords: balloon-occluded retrograde transvenous obliteration; gastric varices; esophageal varices; left gastric vein

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1. Introduction

Gastric varices are serious complications that result from portal hypertension in patients with or without cirrhosis [1]. In general, it may be difficult to control extensive bleeding from gastric varices [2]. Most gastric fundic varices formed by large spontaneous shunts in either gastric or splenic veins are continuous with the left renal vein via the suprarenal (adrenal) vein [3,4]. Thus, gastric varices which are associated with porto-systemic shunt (PSS)—including gastro-renal shunt—have a five-year cumulative bleeding rate of 44% if left untreated, with a much lower survival rate associated with rebleeding [5].

Endoscopic sclerotherapy, transjugular intrahepatic portosystemic shunt (TIPS), and balloon-occluded retrograde transvenous obliteration (BRTO) [6–10] are generally used for the management of gastric variceal bleeding. BRTO is a reasonable treatment for gastric varices because the outflow route from most gastric varices connects to the left renal vein [1]. A meta-analysis demonstrated that BRTO is a safe and efficacious treatment for gastric varices and BRTO could be currently one of the best therapies for patients with gastric varices [11]. BRTO is an established treatment for solitary gastric varices and hepatic encephalopathy due to PSS and is widely applied in Japan [6,7] since the Japanese health insurance system has approved endoscopic sclerotherapy and BRTO as treatment options for the gastric varices.

There is a well-known correlation between the size and course of the left gastric vein (LGV) and esophageal varices [12]. Jogo et al. reported on the factors associated with aggravation of esophageal varices after performing BRTO for gastric varices [13]. They showed that total bilirubin and hepatic vein pressure gradients are important independent risk factors for worsening esophageal varices post BRTO [13]. Maruyama et al. reported the association between LGV width and esophageal varices with an optimal cutoff value of the LGV diameter—to identify any esophageal varices—of 3.55 mm [14].

Here, we retrospectively analyzed the responsible vessels of gastric varices using three-dimensional-computed tomography (3D-CT) and compared exacerbation rates of esophageal varices among patients with successful BRTO.

2. Materials and Methods

2.1. Patients

A total of 91 patients treated with BRTO (between 2008 and 2018) for solitary gastric varices were initially included. Seven patients who were transferred to another hospital shortly after receiving BRTO and who did not receive an endoscopic examination were excluded. A total of 34 patients who received shunt embolization for the treatment of hepatic encephalopathy were also excluded from this study. We retrospectively analyzed their data from a total of 50 cirrhotic patients (Figure 1). This study was approved by the Hospital Institutional Review Board of the Nihon University School of Medicine Itabashi (RK-200714-7) and conformed to the ethical guidelines of the Declaration of Helsinki. Participation in the study was posted on the institution's website, and informed consent was obtained from all patients.

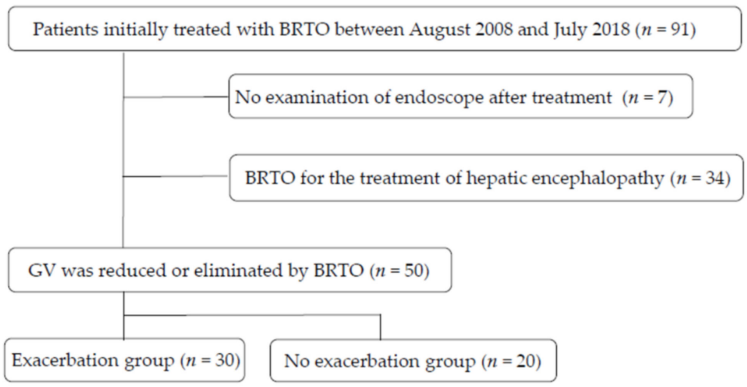


Figure 1. Flowchart showing patients enrolled in this study. BRTO: balloon-occluded retrograde transvenous obliteration; GV: gastric varices.

2.2. Eligibility Criteria of the BRTO Treatment for Gastric Varices

Eligibility criteria of gastric varices treatment were defined based on the Code for the Management of Portal Hypertension, Revised Third Edition, 2013, issued by the Japan Society for Portal Hypertension [15]. The criteria included the following: red color sign (RCS)-positive, erosion or ulcer formation on varices, engorgement classified as form F2 to

F3, tendency toward a rapid short-term increase, and residual or novel gastric varices after treatment of esophageal varices [15]. In addition, gastro-renal shunts, which were likely to be embolized, were confirmed. The status of gastric varices post BRTO was recorded as either improvement (form 1 or more) or disappearance and esophageal varices aggravation (form 1 or more), according to guidelines stipulated by the Japan Society for Endoscopic Surgery. For evaluation of esophageal varices before and post BRTO, a patient with a score that worsened or a patient who became form 1 or worse was defined as "exacerbation" (e.g., F0 to F1, F2 or F3; F1 to F2 or F3) [15]. After treatment of gastric varices by BRTO, patients whose esophageal varices worsened within 1 year or patients without exacerbation of esophageal varices were defined as the (esophageal varices) exacerbation group or as the non-exacerbation group, respectively.

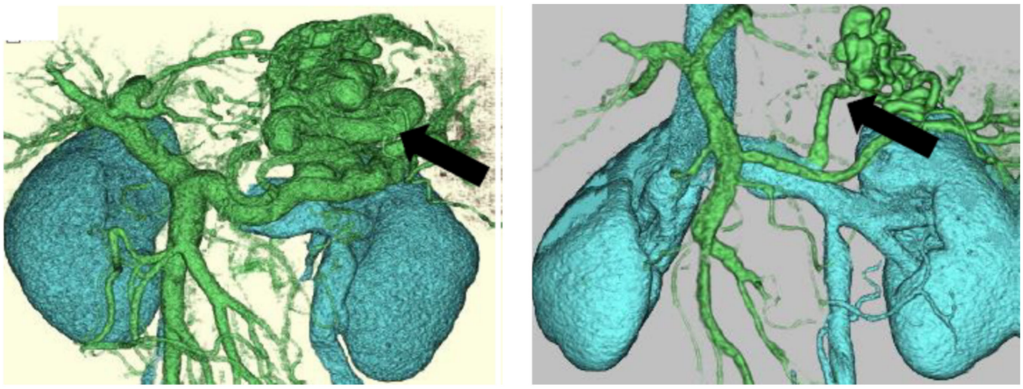
2.3. Endoscopic Grading of Esophageal, Endoscopic Examination and Treatment

Endoscopic grading of esophageal varices was defined according to the guidelines of the Japanese Research Society for Portal Hypertension [15]. Esophageal varices were classified as follows: F1—small straight varix; F2—enlarged tortuous varix occupying less than one-third of the lumen; F3—large coil-shaped varix occupying more than one-third of the lumen.

In general, we performed endoscopy within 1 to 6 months after performing BRTO. Then, endoscopy was performed every 3 to 6 months. At our hospital, endoscopic treatment is performed in patients with esophageal varices F2 or more, and in RCS-positive patients who undergo endoscopic follow-up post BRTO. Three-dimensional-computed tomography (3D-CT) was used to confirm the inflow tract for gastric varices prior to BRTO in all 50 patients (Figure 1).

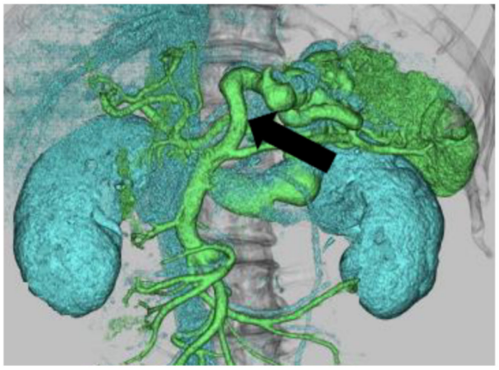
2.4. Performing Three Dimensional-Computed Tomography (3D-CT)

Prior to treatment, patients underwent plain CT and enhanced 3D-CT. Inflow tract for gastric varices was assessed by enhanced 3D-CT. The patients were divided into two groups: (1) LGV group and (2) non-LGV group. Patients with an LGV width of more than 3.55 mm were defined as the LGV group, and LGV was the main inflow tract [14]. The non-LGV group consisted of patients in which the inflow tract was from the short gastric vein (SGV) (Figure 2A) or posterior gastric vein (PGV) (Figure 2B) rather than the LGV (Figure 2C). The non-LGV group included patients with an LGV diameter of 3.55 mm or less [14].



(**A**) (**B**)

Figure 2. *Cont.*



(**C**)

Figure 2. Inflow tract for gastric varices assessed by three-dimensional-computed tomography (3D-CT). Inflow tract for gastric varices before performing balloon-occluded retrograde transvenous obliteration (BRTO) was confirmed by 3D-CT. Inflow tract for gastric varices was from (**A**) short gastric vein (SGV) (non-LGV group), (**B**) SGV and posterior gastric vein (PGV) (non-LGV group), or (**C**) left gastric vein (LGV group).

2.5. Procedure of Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

An 8 Fr-long guiding sheath (ASATO; MEDIKIT, Tokyo, Japan) was inserted from the right femoral vein into the left renal vein via the inferior vena cava (IVC) using a guidewire (PIOLAX Hydrophilic Guidewire; SURF, Yokohama, Japan). We performed BRTO using a 5 Fr guiding balloon catheter (CANDIS; MEDIKIT) or Selecon MP catheter (TERUMO, Tokyo, Japan) equipped with a balloon catheter. For the BRTO procedure, a hardening agent (5% ethanolamine oleate with iopamidol (EOI)) was infused under balloon occlusion, and a balloon catheter was placed for at least six hours. For patients who were considered to have higher blood flow, the catheter was placed overnight and haptoglobin was administered the day before and on BRTO treatment to prevent hemolysis due to the hardening agent. After treatment, antibiotics were prophylactically used to prevent infection. Complete blockage of the shunt was confirmed by 3D-CT.

2.6. Laboratory Tests

Laboratory tests were performed at least every 4 weeks before and after the BRTO procedure. Prior to starting BRTO, we measured the levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine, prothrombin time, total cholesterol, albumin levels, platelet counts, hemoglobin, and white blood cells (WBC). Hepatitis B virus (HBV) surface antigen (HBsAg) and anti-hepatitis C virus (HCV) antibodies were also measured in all patients. Diagnosis of cirrhosis and/or hepatocellular carcinoma was previously described [16].

2.7. Statistical Analysis

Statistical analyses were performed in order to determine the exacerbation rates of esophageal varices following BRTO in all patients and to compare the exacerbation rates of esophageal varices following BRTO between the LGV group and the non-LGV group. Differences between the LGV group and the non-LGV group were analyzed using the Mann–Whitney *U*-test, chi-squared test, and Wilcoxon signed-rank test.

The cumulative incidence of esophageal varices between both groups was compared using Gray's test. All statistical analyses were performed using EZR (Easy R) software, a modified version of R commander designed to add statistical functions frequently used in biostatistics. EZR is freely available at (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html, accessed on 1 December 2021), which is a modified version of R commander, designed to add frequently used statistical functions in biostatistics [16,17].

3. Results

3.1. Effects and Complications of Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

In all 50 patients, gastric varices were reduced or eliminated by BRTO. Complete blockage of the shunt was confirmed by 3D-CT within three weeks post BRTO. Although the timing of gastric varices varied among these subjects, no morphological exacerbation of gastric varices and bleeding were observed. Complications due to BRTO consisted of hemolysis caused by the hardening agent, which was observed in 4 out of 50 patients (8%); they all improved spontaneously within 24 h. Although 7 out of 50 patients (14%) experienced fever over 38 °C, all patients improved within two days. There were no serious complications (i.e., those caused by the catheterization, pulmonary embolism, bleeding, renal failure, and hepatic failure). Overall, this procedure is generally considered as safe.

3.2. Comparison of Pretreatment Factors between Esophageal Varices-Exacerbation Group and Non-Exacerbation Group

Table 1 shows the background features of patients between the esophageal varices exacerbation group and non-exacerbation group. Results from the univariate analysis demonstrated higher hemoglobin levels ($p = 0.01$) and platelet counts that tended to be lower ($p = 0.07$) in the esophageal varices exacerbation group. Moreover, we observed a higher proportion of patients with an LGV width of more than 3.55 mm in the esophageal varices-exacerbation group than in the non-exacerbation group ($p = 0.01$).

Table 1. Comparison of patients' background between the esophageal varices exacerbation and non-exacerbation groups.

	Total	Exacerbation Group	Non-Exacerbation Group	* *p*-Value
Number of patients	50	30	20	
Age (years)	67.38 ± 9.55	67.63 ± 9.47	67.00 ± 9.91	0.93
Gender (male/female)	32/18	20/10	12/8	0.63
WBC (×10/mm^3)	6.97 ± 0.63	4.40 ± 1.62	4.81 ± 2.69	0.86
Hemoglobin (g/dL)	12.09 ± 54.44	13.16 ± 6.63	10.48 ± 2.20	0.01
Platelet counts (×10^4/mm^3)	9.77 ± 4.22	8.63 ± 2.98	11.47 ± 5.23	0.07
AST (IU/L)	58.50 ± 39.16	59.96 ± 41.40	56.30 ± 36.48	0.86
ALT (IU/L)	42.40 ± 34.29	44.90 ± 34.61	38.65 ± 34.35	0.33
Total bilirubin (mg/dL)	1.17 ± 0.76	1.19 ± 0.58	1.13 ± 0.58	0.22
Total protein (g/dL)	6.96 ± 0.63	7.05 ± 0.62	6.85 ± 0.65	0.32
Albumin (g/dL)	3.42 ± 0.71	3.45 ± 0.82	3.36 ± 0.49	0.96
Creatinine (mg/dL)	0.71 ± 0.20	0.73 ± 0.17	0.68 ± 0.24	0.18
eGFR (mL/min/1.73 m^2)	80.48 ± 22.85	76.26 ± 18.66	87.52 ± 27.67	0.15
Prothrombin time (%)	83.42 ± 13.83	84.83 ± 12.57	81.30 ± 15.62	0.52
Prothrombin time (INR)	1.13 ± 0.15	1.12 ± 0.14	1.15 ± 0.16	0.64
Total cholesterol (IU/L)	148.31 ± 37.23	145.07 ± 37.01	152.85 ± 38.01	0.77
Blood glucose (mg/dL)	130.52 ± 43.12	132.0 ± 48.96	128.3 ± 33.59	0.87
NH_3 (μg/dL)	75.04 ± 35.48	72.25 ± 35.23	79.15 ± 3690	0.52
Child-Pugh A/B/C	39/11/0	24/6/0	15/5/0	0.73
HCC (±)	27/23	17/13	10/10	0.77
GV form F1/2/3	2/17/31	0/11/19	2/6/12	0.60
EV form F0/1/2/3	30/17/2/1	19/9/2/0	11/8/01	0.62
Etiology (HBV/HCV/NBNC/Alcohol)	3/28/7/12	2/20/3/5	1/8/4/7	0.27
LGV > 3.55 mm (yes/no)	37/13	26/4	11/9	0.01
Mean observation periods (months)	35.49 ± 28.28	32.73 ± 28.13	39.63 ± 28.71	0.42

Data are expressed as the mean ± standard deviation. * *p*-Value, comparison between two groups, by univariate analysis; WBC—white blood cell counts; AST—aspartate aminotransferase; ALT—alanine aminotransferase; eGFR—estimated glomerular filtration rate; HCC—hepatocellular carcinoma; GV—gastric varices; EV—esophageal varices; HBV—hepatitis B virus; HCV—hepatitis C virus; NBNC—non-HBV, non-HCV; LGV—left gastric vein.

3.3. Comparison of Pretreatment Factors between LGV Group or Non-LGV Group Patients

Next, we compared the background features between the LGV group and the non-LGV group (Table 2). The LGV group showed a lower platelet count, higher AST levels, higher ALT levels, and HCV etiology, compared to the non-HCV group (Table 2).

Table 2. Comparison of patients' background between left gastric vein (LGV) and non-LGV groups.

□	**LGV Group**	**Non-LGV Group**	***p*-Value**
Number	37	13	□
Age (years)	66.8 ± 10.2	68.8 ± 7.5	0.69
Gender (male/female)	12/25	6/7	0.50
WBC ($\times 10/mm^3$)	467 ± 232	426 ± 132	0.98
Hemoglobin (g/dL)	12.4 ± 6.2	11.2 ± 2.0	0.53
Platelet counts ($\times 10^4/mm^3$)	9.1 ± 3.7	11.6 ± 5.1	0.13
AST (IU/L)	63.8 ± 43.6	43.4 ± 14.5	0.17
ALT (IU/L)	46.9 ± 38.6	29.4 ± 38.56	0.11
Total bilirubin (mg/dL)	1.24 ± 0.85	0.95 ± 0.30	0.41
Total protein (g/dL)	7.00 ± 0.58	6.88 ± 0.77	0.65
Albumin (g/dL)	3.40 ± 0.76	3.48 ± 0.56	0.30
Creatinine (mg/dL)	0.7 ± 0.2	0.6 ± 0.2	0.80
eGFR ($mL/min/1.73\ m^2$)	80.1 ± 22.8	81.5 ± 23.9	0.89
Prothrombin time (%)	83.0 ± 13.8	84.3 ± 14.2	0.64
Total cholesterol (IU/L)	151.4 ± 39.8	138.8 ± 27.2	0.21
Blood glucose (mg/dL)	131.9 ± 46.0	126.4 ± 34.8	0.82
NH_3 (μg/dL)	75.3 ± 34.0	74.3 ± 41.0	0.66
Child-Pugh A/B/C	27/10/0	12/1/0	0.24
HCC (±)	20/17	7/6	1.0
GV form F1/2/3	1/12/24	1/5/7	0.62
EV form F0/1/2/3	23/11/2/1	7/6/0/0	0.72
Etiology (HBV/HCV/NBNC/Alcohol)	1/22/4/10	2/6/3/2	0.17
Esophagus varices exacerbation	26/37	4/13	0.02
Mean periods from BRTO to esophageal varices exacerbation (months)	17.6 ± 17.0	27.2 ± 17.3	0.06
Mean observation periods (months)	37.73 ± 28.83	29.14 ± 26.67	0.32

Data are expressed as the mean ± standard deviation. * *p*-value, comparison between two groups, by univariate analysis; WBC—white blood cell counts; AST—aspartate aminotransferase; ALT—alanine aminotransferase; eGFR—estimated glomerular filtration rate; HCC—hepatocellular carcinoma; GV—gastric varices; EV—esophageal varices; HBV—hepatitis B virus; HCV—hepatitis C virus; NBNC—non-HBV, non-HCV; LGV—left gastric vein.

The LGV group included 37 patients (74%), while the non-LGV group included 13 patients (26%). The mean follow-up periods of the LGV group and non-LGV group were 37.73 ± 28.83 and 29.14 ± 26.67 months, respectively ($p = 0.32$). Prior to BRTO treatment, the prevalence of gastric varices or esophageal varices was not statistically significant between both groups (Table 2). Exacerbation of esophagus varices post-BRTO treatment was observed to a greater extent in the LGV group than in the non-LGV group ($p = 0.02$). The mean period from BRTO to esophageal varices exacerbation tended to be shorter in the LGV group than in the non-LGV group ($p = 0.06$) (Table 2).

3.4. Esophageal Varices were Significantly Exacerbated Post-Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) in the Left Gastric Vein Group (LGV Group)

The overall exacerbation rates of esophageal varices post BRTO were: 40%, 62%, 65%, and 68% at 1, 2, 3, and 4 years, respectively (Figure 3A). Next, the exacerbation rates of esophageal varices—following BRTO according to the inflow tract of gastric varices—were examined and compared (Figure 3B). The exacerbation rates of esophageal varices at 1, 2, 3 and 4 years post BRTO were: 48%, 63%, 73% and 74%, respectively, in the LGV group; in the non-LGV group—18%, 37%, 37% and 37%. Comparing both the LGV and non-LGV groups, esophageal varices were significantly exacerbated in the LGV group (Gray test: $p < 0.03$).

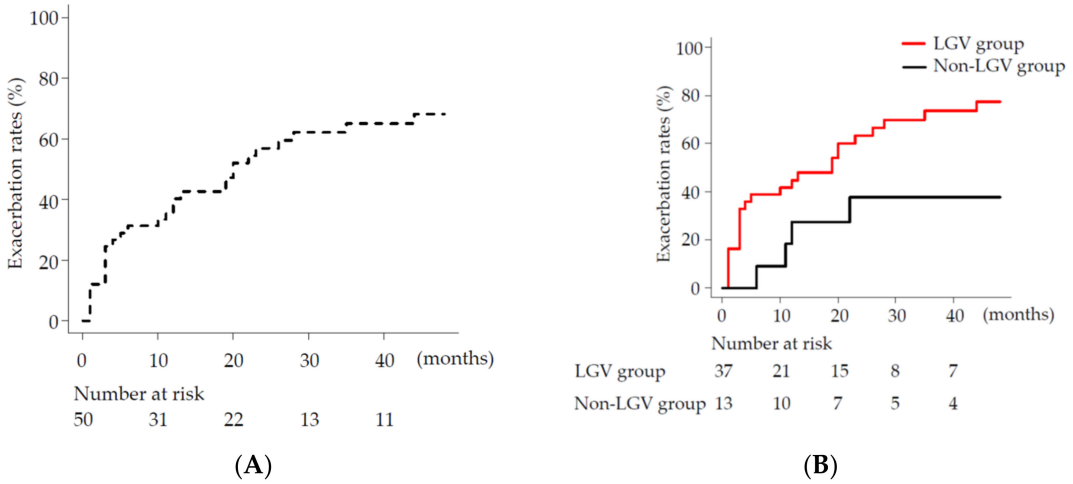


Figure 3. Exacerbation rates (%) of esophageal varices following balloon-occluded retrograde transvenous obliteration (BRTO). (**A**) Overall exacerbation rates (%) (dotted line); (**B**) exacerbation rates (%) of left gastric vein (LGV) group (red line) and non-LGV group (black line).

4. Discussion

Normal blood flow in the portal vein is antegrade and hepatopetal. However, blood vessels that form the portal venous system may become partially retrograde and show hepatofugal flow when the portal blood pressure elevates [18]. Once cirrhosis is established, collateral circulation is primarily formed as esophageal varices and gastric varices. Ruptured esophageal varices and gastric varices occasionally cause death from bleeding or hepatic failure; they are also serious complications affecting the prognosis of patients with cirrhosis. In particular, ruptured gastric varices in patients with gastro-renal shunts cause increased blood inflow and larger hemorrhages [9,19]. The cumulative incidence rates of bleeding from fundal varices within 1, 3, and 5 years have been reported as 16%, 36%, and 44%, respectively [5]. The need for prophylactic treatment of gastric varices at risk of rupture has been recognized [20,21], and BRTO is widely used in Japan as first-line therapy for fundal varices [22–24]. According to a report regarding the efficacy of BRTO with respect to bleeding, the cumulative incidence rates of bleeding within 1, 3, and 5 years were 0%, 0%, and 17%, respectively, in patients who received BRTO, and 19%, 41%, and 61%, respectively, in patients who did not [25]. Similarly, in our case, no bleeding was observed in patients. However, in the LGV group—BRTO treatment of gastric varices—esophageal varices occurred at a high rate of 74% in 4 years (Figure 3B). An LGV width of more than 3.55 mm appeared as an associated factor of exacerbation of esophageal varices.

Thus, the efficacy of BRTO has already been demonstrated. BRTO mainly interrupts the blood flow of gastro-renal shunt with a balloon and retrograde infusion of 5% EOI. The vascular endothelial cell membrane is impaired directly by ethanolamine oleate (EO), and fibrin and blood platelets attach to the endodermis, forming a thrombus [26]. This thrombus produces embolic effects and blocks the gastro-renal shunt blood flow of the

gastric varices, which leads to an improvement and the elimination of gastric varices. Early thrombogenesis causes reduced blood flow, promoting morphological changes and collapse of the gastric varices, in which, several weeks later, a reduction in the organized thrombus occurs. Thus, the therapeutic effects are mainly monitored by 3D-CT in the early stage. It was reported that, in most cases, thrombogenesis occurs a week after, as assessed by 3D-CT [27]. In comparison, elimination of gastric varices and gastro-renal shunt has also been reported as taking approximately 1–3 months, and in certain patients, a larger shunt diameter requires a longer time for blockage of the blood flow [28,29]. We also performed this method and obtained good results.

In patients successfully treated by BRTO, thrombus-mediated gastro-renal shunt occlusion was reported to effectively improve liver function by increasing blood flow through the hepatic portal vein [30,31]. However, because the portal blood pressure exiting the gastro-renal shunt increases gradually after treatment, patients often experience novel or aggravated collateral circulation, particularly esophageal varices. In general, the reported cumulative incidence of exacerbation of esophageal varices post BRTO for gastric varices ranges from 10–63% [32,33]. Our results showed similar rates (65% at three years; 68% at four years) to those reported in [32,33]. Many studies on inflow tract for gastric varices reported that gastric varices blood flow is mainly supplied by the SGV and PGV [3]. Hirota et al. described that, in general, the recurrence of esophageal varices post BRTO for grades 1 and 2 (according to Hirota's classification) is relatively low [34]. However, in our analysis, the exacerbation rates of esophageal varices following BRTO were significantly higher in the LGV group compared to those in the non-LGV group. Of note, there were no significant differences in the Child-Pugh grade between the LGV group and the non-LGV group. Therefore, further studies for portal hypertension—which seemed to be associated with exacerbation of esophageal varices, ascites, hepatic encephalopathy—are needed. Thus, we judged that it was the difference in the inflow tract for gastric varices that was associated with the exacerbation of esophageal varices post BRTO. Most inflow tracts forming esophageal varices are from the LGV. Blood flow upward from the LGV to the esophagus is increased by blocking blood flow of the gastro-renal shunt with BRTO, which seems to contribute to the exacerbation of esophageal varices. This is further supported by a report demonstrating an increase in LGV pressure and blood flow rate post BRTO using an ultrasonic autoscope [35].

Choe et al. conducted a retrospective analysis of patients with gastric varices and cirrhosis who underwent either endoscopic varicose vein occlusion (EVO) or BRTO as prophylactic treatment was observed without procedural intervention. After 35 months of observation, patients who underwent EVO or BRTO reported significantly less bleeding from gastric varices than patients with follow-up alone. Importantly, EVO and BRTO are effective and safe first-line preventive treatments that prevent bleeding from gastric varices. In particular, BRTO is superior to EVO in the complete eradication of gastric varices [36].

Furthermore, it has been noted that additional partial splenic embolization (PSE) post BRTO may reduce the incidence of esophageal varices relative to BRTO alone [37]. A previous report stated that the cumulative incidence rates of RCS-positive esophageal varices at 6 months, 1 year and 2 years were 16%, 27%, and 45%, respectively, in patients treated with BRTO alone, and 0%, 0%, and 9%, respectively, in patients treated with BRTO plus PSE [38]. Oshita et al. reported that splenectomy with gastric devascularization resulted in more effective liver function improvement than BRTO [39]. Thus, the therapeutic combination of BRTO with PSE should be considered for patients with LGV as the main inflow tract for gastric varices. We did not treat with PSE. However, if this were the case, it was theorized that the results of exacerbation of esophageal varices could be improved.

In addition, Jang et al. reported 183 cirrhotic patients who underwent BRTO for gastric varices bleeding. In their study, 52.3% of patients treated for gastric varices bleeding achieved eradication of gastric varices bleeding, along with a 72.8% reduction in gastric varices to grade 0 or 1. Postoperatively, esophageal varices occurred in 41.2% [40]. Moreover, patients who have undergone BRTO may require regular endoscopy for follow-up of

esophageal varices, with or without treatment. In our study, 68% of esophageal varices worsened in 4 years. Therefore, attention should be given to LGV as an inflow tract and LGV width.

We performed the follow-up CT in 49 of 50 patients treated with BRTO and 3D-CT in 31 of these 49 patients after the initial 3D-CT following BRTO. The development of repermeabilized vein after BRTO and other collaterals than LGV, respectively, were observed in 3 and 4 of them (Table 3). Only one patient had both the development of repermeabilized vein after BRTO and inferior mesenteric vein collaterals.

Table 3. Six patients with the development of repermeabilized vein, other collaterals other than left gastric vein, following balloon-occluded retrograde transvenous obliteration.

Case	Age (years)/Gender	Hemoglobin (g/dL)	Platelet Counts ($\times 10^4/mm^3$)	AST (IU/L)	ALT (IU/L)	Creatinine (mg/dL)	Child-Pugh A/B/C (Score)	HCC (±)
1	53/male	5.7	8	37	40	0.79	B-7	+
2	63/male	13.6	6.9	57	45	0.49	A-6	+
3	64/female	9.3	10.6	31	24	0.7	A-5	+
4	51/male	13.8	8.1	51	27	0.67	A-6	–
5	63/female	8.8	10.5	56	36	0.35	A-5	+
6	78/male	14	16.5	71	57	1.12	A-6	–

Case	GV Form	EV Form	Etiology	LGV > 3.55 mm	LGV Group (yes/no)	Esophageal Varices Exacerbation (yes/no)	Repermeabilized Vein (±)	Other Collaterals than LGV	Occurrence Following BRTO (months)
1	F3	F1	HBV	5.68	Yes	No	+	-	9
2	F2	F2	HCV	5.45	Yes	Yes	+	-	26
3	F2	F1	HCV	2.56	No	Yes	+	Inferior mesenteric vein	8
4	F2	F1	NBNC	2.55	No	Yes	-	Spleno-renal shunt	5
5	F3	F1	NBNC	3.34	No	No	-	Abdominal wall veins	24
6	F2	F0	Alcohol	5.61	Yes	No	-	Paraumbilical vein	36

AST—aspartate aminotransferase; ALT—alanine aminotransferase; HCC—hepatocellular carcinoma; GV—gastric varices; EV—esophageal varices; HBV—hepatitis B virus; HCV—hepatitis C virus; NBNC—non-HBV, non-HCV; LGV—left gastric vein.

5. Conclusions

Attention should be paid to the width of LGV, which is one of the inflow tracts for gastric varices, when BRTO is performed for gastric varices.

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【和文の要約】　水谷　卓

Left Gastric Vein Width is an Important Risk Factor for Exacerbation of Esophageal Varices Post Balloon-Occluded Retrograde Transvenous Obliteration for Gastric Varices in Cirrhotic Patients

（左胃静脈径は肝硬変患者の胃静脈瘤に対するバルーン閉塞下逆行性経静脈的閉塞術後の食道静脈瘤増悪の重要なリスクファクターである）

【目的】

胃静脈瘤は、肝硬変の有無にかかわらず、門脈圧亢進症に起因する重篤な合併症である。胃-腎シャントを含む全身シャント（PSS）を伴う胃静脈瘤は、未治療の場合、5 年間の累積出血率が 44%であり、出血により生存率を低下させることが知られている。

多くの胃静脈瘤は排出路が左腎静脈につながっているため、治療としてバルーン閉塞下逆行性経静脈的閉塞術（BRTO）が行われている。

また、左胃静脈(LGV)の径と食道静脈瘤との間には相関関係が知られている。

今回我々は LGV 径と BRTO 後の食道静脈瘤増悪との関連について、造影 CT や 3D-CT を用いて胃静脈瘤の流入路別に検討した。

【対象と方法】

当院で 2008 年～2018 年の期間に BRTO を施行した肝硬変患者計 91 名のうち、BRTO 直後に他院に転院および内視鏡検査歴のなかった患者 7 名、肝性脳症に対する治療を受けた患者 34 例を除外した、孤立性胃静脈瘤に対して BRTO を施行した計 50 例のデータを分析した。

BRTO 後の経過中に食道静脈瘤が増悪したものは、死亡例や離脱例でも、その時点で増悪群に含まれている。

BRTO 後に上部内視鏡検査を行うことなく、死亡や離脱したものは当初から今回の検討に含まれておらず、少なくとも 1 度は上部内視鏡検査を受けていることが前提になっており、死亡や離脱で内視鏡フォローが不可能となる時点までは Follow をおこない、その時点で Follow 数から除外した。

50 名全員は BRTO 施行前に CT を行い、胃静脈瘤の流入路および LGV 径の確認をおこなった。

CT 撮影に当たっては、Aquilion ONE を使用し、ヨード造影剤を 5ml/秒で静脈注射し，ボーラストラッキング法を用いた。3 相（動脈相，門脈相，平衡相）撮影をし、主には門脈層の画像から Ziostation の Workstation で 3D-CT を構築した。

血管の確認は 2D-CT（Aquilion ONE）の Axial 画像および 3D-CT（Ziostation）画像を

参考にしながら肝臓専門医 2 名で行った。2 名で行ったが、Blind ではなく、1 名が見守る中、測定をもう 1 名の人間が Workstation のメジャーで行った。
LGV の測定箇所は、2D-CT の Axial 画像（1mm スライス）の門脈相で一番径の太いところで計測を行った。
LGV 径の測定は Aquilion ONE に付属の計測ソフトウェアを使い電子カルテ上で行った。
胃静脈瘤の流入路によって 2 群に分類し、(1) LGV 径が 3.55mm 以上の患者を LGV 群（2）流入路が短胃静脈（SGV）または後胃静脈（PGV）である患者、もしくは LGV 径が 3.55mm 未満の患者を非 LGV 群に分けた。
胃静脈瘤治療の適応は、日本門脈圧亢進症学会編：門脈圧亢進症取扱い規約「改定第三版」2013 に基づいて定義した。
治療効果判定も日本門脈圧亢進症学会編：門脈圧亢進症取扱い規約「改定第三版」2013 の内視鏡所見記載基準に従いおこない、BRTO 前後で食道静脈瘤が form1 以上の増悪を認めた患者を「増悪」とした。（例：F0→F1、F2、F3、F1→F2、F3）
BRTO による胃静脈瘤治療後に食道静脈瘤が増悪した患者を増悪群、増悪のない患者を非増悪群と定義した。
BRTO は、いずれの症例も以下の通りに手技を行った。
カテーテルを排血路の奥まで進めバルーンで閉塞し、まず造影を行う。胃腎シャントから GV が一本化され、造影剤の停滞も良好であることを確認した後に、硬化剤を投与し充填する。投与量は、造影の際に造影剤が供血路に逆流し始める量を目安に決定。6 時間以上カテーテルを留置した後、カテーテルから血液の逆流がないことを確認してカテーテルを抜去した。
LGV 群と非 LGV 群の BRTO 後の食道静脈瘤の増悪率を比較するための統計解析には Mann-Whitney U-test、カイ二乗検定、Wilcoxon signed-rank 検定を用いた。
また、両群間の食道静脈瘤の累積発生率は，Gray の検定で比較した。

【結果】
BRTO はいずれの症例も上記の通りに手技を行い、術後の上部内視鏡検査で全例胃静脈瘤の縮小/消退を認めており、成功率は 100%であった。
BRTO 後の食道静脈瘤の全体的な増悪率は、1 年後、2 年後、3 年後、4 年後でそれぞれ 40%、62%、65%、68%であった。観察期間中、死亡が 10 例、離脱 29 例、4 年以上観察継続できたものが 11 例であった。
次に、胃静脈瘤の流入路別に BRTO 後の食道静脈瘤の増悪率を比較検討した。
LGV 径 3.55 mm 以上の LGV 群は 37 例、非 LGV 群は 13 例であり、LGV 群は 74%（37/50）であった。
LGV 径と体表面積（Du Bois 式）との相関係数も検討したが、相関は認めなかった。（p=0.2308）

BRTO 治療前から食道静脈瘤が存在していた症例（24 例）と存在していない症例（26 例）で、治療時の LGV 径に優位な差は認めなかった。（6.10±2.10mm　vs　5.34±2.50 mm、P=0.289）
BRTO 後 1 年後、2 年後、3 年後、4 年後での食道静脈瘤の増悪率は LGV 群 48%、63%、73%、74%、非 LGV 群-18%、37%、37%、37%であった。
LGV 群と非 LGV 群を比較すると，LGV 群では食道静脈瘤が有意に増悪していた（Gray test：p＜0.03）。

【考察】
肝硬変は、側副血行路から食道静脈瘤および胃静脈瘤を形成する。
静脈瘤とは単独に生じるものではなく、門脈圧の上昇によって生理的に発生した側副血行路の途中にできるものである。門脈血液流入量の増加と肝内血管抵抗の増加により門脈圧が上昇し、通常の静脈とは異なり逆流防止弁をもたないため、従来からある門脈系の分枝に逆流をおこし門脈－大循環系に側副血行路を生じる。側副血行路の途中に静脈瘤が発生し、供血路 → 静脈瘤 → 排出路といった血流の流れが生じる。
これらの側副血行路のうち食道・胃静脈瘤への主な供血路は左胃静脈（left gastric vein :LGV)および後胃静脈（posterior gastric vein: PGV）短胃静脈（short gastric vein: SGV）である。
胃静脈瘤の血行動態は、LGV が主な供血路となる LGV 優位群、LGV と PGV、SGV の脾静脈血流が均等な LGV・PGV＋SGV 均等群、および PGV＋SGV が優位な PGV＋SGV 優位群に分類することができる。
静脈瘤の部位別にみると、Lg-c は LGV が供血路となり食道静脈瘤と連続している場合が多く、Lg-cf は PGV および SGV、Lg-f は SGV が主な供血路となり、特に Lg-f は高率に胃腎 shunt が存在し、 食道静脈瘤との連続性はないことから孤立性胃静脈瘤とよばれる。
胃静脈瘤の破裂は、時に出血や肝不全による死亡の原因となり、肝硬変患者の予後を左右する重篤な合併症である。
1 年、3 年、5 年以内の胃静脈瘤からの出血の累積発生率は、それぞれ 16%、36%、44%と報告されている。
破裂の危険性のある胃静脈瘤に対する予防的治療の必要性が認識され、日本では胃静脈瘤に対する第一選択の治療法として BRTO が広く用いられている。
BRTO の有効性に関する報告によると、1 年、3 年、5 年以内の出血の累積発生率は、BRTO を受けた患者ではそれぞれ 0%、0%、17%であり、受けなかった患者ではそれぞれ 19%、41%、61%であった。
我々の施設では手技成功率 100%で BRTO 後に胃静脈瘤からの出血は認めなかった。
一般的な手技的成功率や胃静脈瘤の縮小・消失率は 90%以上という非常に良好な成績が報

告されており、それと相違はなかったと考える。
BRTO は主にバルーンを用いて胃-腎シャントの血流を遮断し、5%エタノールアミンオレイン酸（EO）を逆行性に注入しおこなう。EO により血管内皮細胞膜が直接障害され、フィブリンや血小板が内皮に付着して血栓が形成される。この血栓が塞栓作用をもたらし、胃静脈瘤の胃-腎シャント血流を遮断し、胃静脈瘤の改善、消失につながる。
3D-CT で評価すると、ほとんどの場合、1 週間後に血栓形成が起こることが報告されている。また、BRTO が成功した患者では、胃静脈瘤の再発は 2%程度と言われており、ほとんど再発しないと考えられており、さらに胃-腎シャント閉塞することで、門脈血流が増加し、肝機能が改善するという報告もある。
しかし、治療後、しばしば食道静脈瘤の悪化を認める。一般に、胃静脈瘤に対する BRTO 後の食道静脈瘤の増悪の累積発生率は 10～63%と報告されている。我々の結果も、同様の結果（4 年後 68%）であった。
我々の研究では、LGV 径と BRTO 後の食道静脈瘤増悪との関連についても、造影 CT や 3D-CT を用いて胃静脈瘤の流入路別に検討した。
CT での LGV 径の計測方法については上述の通りであったが、再現性・客観性を持たせるために、測定にあたっては複数名の blind で行い、その一致率を用いて評価するなど工夫が必要であったと考える。これについては将来の研究内容の課題として、 今後症例を足す際はそのような手法で行いたいと考えている。
LGV 径の Cut off 値については、既存の報告で CT での LGV 径について示すものはなかったため、別検査手法ではあるが、腹部超音波検査での Cut off 値を示した論文を参考とし、今回は 3.55mm を Cut off 値とした。
腹部超音波検査による別の報告では、被検者 187 例 86 例(46%)で LGV を同定し、その平均径は 2.4㎜ であったとしている。
BRTO 後の食道静脈瘤の増悪率は、LGV 群が 4 年間で 74%、非 LGV 群 4 年間で 37%と LGV 群で有意に高かった。（$p<0.03$）
さらに、当施設での CT 測定値に基づいた食道静脈瘤増悪に関与する LGV 径の Cut off 値を ROC 曲線で評価した。結果は 3.82mm が Cut off 値となり、カプランマイヤー曲線として腹部超音波検査と同様の結果であった。
以上から LGV 径 3.55mm 以上は食道静脈瘤増悪の関連因子と思われた。
BRTO 後の食道静脈瘤の増悪は胃静脈瘤の流入路の違いによるものと考えられた。
左胃静脈の血流方向は健常者では全て求肝性で、肝硬変患者では 72%が遠肝性であり、門脈圧が 250mmH2O を越えると 95%の症例で左胃静脈が遠肝性血流であったという報告がある。さらに食道静脈瘤の発達に伴い左胃静脈径は増大し、遠肝性の血流も高度となっていたとしている。
上記から、LGV 径が大きいということは、門脈圧が高いことを反映していると考えられるが、本研究では実際の門脈圧は測定していないため、これについては将来の研究課題と考え

る。
食道静脈瘤の流入路の多くは LGV からであり、BRTO で胃-腎シャントの血流を遮断することにより、LGV から食道への上方血流が増加し、食道静脈瘤の増悪に寄与していることが示唆された。
BRTO を受けた患者は、治療の有無にかかわらず、食道静脈瘤のフォローアップのために定期的な内視鏡検査が必要となる。
それには流入路の LGV 径に特に注意が必要である。

【結論】
胃静脈瘤に対して BRTO を行う場合、胃静脈瘤の流入路の一つである LGV 径に留意する必要がある。