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Perforating veins in recurrent esophageal varices evaluated by endoscopic color Doppler ultrasonography with a galactose-based contrast agent

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Background. We evaluated the usefulness of endoscopic color Doppler ultrasonography (ECDUS) with Levovist, a galactose-based contrast agents, for detecting perforating veins in the esophageal wall in patients with recurrent esophageal varices after endoscopic therapies. ***Methods.*** We compared vessel images detected prior to the use of contrast with those detected by enhanced ECDUS in 29 patients with recurrent esophageal varices. After the pre-contrast ECDUS examination, all 29 patients received Levovist intravenously, at a concentration of 300 mg/ml. A 7.5-ml dose of the contrast agent was injected at a slow infusion rate, of 1 ml/min. The perforating veins detected by ECDUS were classified, according to flow direction, into three different types. Type 1 showed inflow from the paraesophageal veins to the esophageal varices. Type 2 showed outflow from the esophageal varices to the paraesophageal veins, while type 3 was a mixed type with both inflow and outflow. For comparison, 26 patients without recurrent esophageal varices were studied. ***Results.*** Color flow images of perforating veins were obtained in 9 (31.0%) of the 29 patients with recurrent esophageal varices with pre-contrast ECDUS. The detection rate of perforating veins in the patients with recurrent esophageal varices (31.0%) was significantly higher than that in patients without recurrent esophageal varices (0 of 26; 0%) with pre-contrast ECDUS. Color flow images of perforating veins were detected in 22 (75.9%) of the 29 patients with recurrent esophageal varices after Levovist contrast. On the other hand, color flow images of perforating veins were not detected in any of the 26 patients without recurrent esophageal varices after Levovist contrast. Type 1 perforating veins were recognized in 6 (20.7%) of the 29 patients, type 2 in 2 (6.9%) of the 29, and type 3 in 1 (3.4%) of the 29 prior to the use of contrast. After the enhanced ECDUS, type 1 perforating veins were recognized in 13 (44.8%) of the 29 patients, type 2 in 6 (20.7%) of the 29, and type 3 in 3 (10.3%) of the 29. All color-flow images detected with pre-contrast ECDUS were enhanced after Levovist contrast. ***Conclusions.*** Perforating veins can be detected at a high rate by ECDUS with Levovist in patients with recurrent esophageal varices after endoscopic therapy.

Key words: recurrent esophageal varices, perforating veins, galactose-based contrast agent, endoscopic color Doppler ultrasonography

Introduction

Endoscopic injection sclerotherapy (EIS) is now a standard procedure for the treatment of esophageal varices.[1] Recently, endoscopic variceal ligation (EVL) has been widely applied to treat esophageal varices.[2] Endoscopic treatment is safe and popular, but recurrence of varices has become a serious problem. Intramucosal venous dilatation (IMVD) of esophageal varices has been frequently observed in follow-up endoscopy after endoscopic therapies.[3] IMVD has been evaluated as the regional tortuous dilatation of varices and indicates a risk of bleeding.

Endoscopic color Doppler ultrasonography (ECDUS) is a useful method of obtaining color flow images of blood vessels. We previously reported the usefulness of ECDUS in patients with esophago-gastric varices.[4,5] We have been able to obtain color flow images that graphically show esophageal varices, paraesophageal veins, and perforating veins in patients with esophageal varices.

Levovist (Schering, Berlin, Germany) is a microbubble echo-enhancing agent which improves Doppler

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ultrasound examinations by increasing the intensity of the Doppler signal. We have previously reported that the use of Levovist contrast can improve the diagnostic quality of ECDUS in patients with esophageal varices, yielding a much clearer picture of the hemodynamics.[6] Perforating veins can be detected at a high rate by ECDUS in patients with recurrent esophageal varices after endoscopic therapy.[7] The purpose of this study was to confirm the usefulness of ECDUS with Levovist for detecting perforating veins in the esophageal wall in recurrent esophageal varices after endoscopic therapies.

Subjects and methods

Patients

Twenty-nine patients with recurrent esophageal varices after endoscopic therapy were studied. The subjects included 19 men and 10 women, ranging in age from 46 to 72 years (mean, 59.6 years). The underlying pathology of portal hypertension was liver cirrhosis in 19 patients (including primary biliary cirrhosis in 2) and cirrhosis associated with hepatocellular carcinoma in 10 patients (19 Child-Pugh class A, 5 class B, and 5 class C). The etiologies of liver diseases were as follows: hepatitis B surface antigen (HBs Ag)-positive in 2 patients, anti-HCV antibody-positive (HCV) in 12, alcoholic liver diseases in 12, primary biliary cirrhosis in 2, and unknown in 1.

Endoscopic findings

Endoscopic findings of esophageal varices were evaluated according to the grading system outlined in *The general rules for recording endoscopic findings of esophageal varices* prepared by the Japanese Research Society for Portal Hypertension.[8] The form (F) of the varices was classified as either small, straight (F1); enlarged, tortuous (F2); or large, coil-shaped (F3). Variceal location (L) was classified as either locus superior (Ls), when located above the level of the tracheal bifurcation; locus medialis (Lm), when located at or near the level of the tracheal bifurcation; or locus inferior (Li), when located within the area encompassing the abdominal and lower thoracic esophagus. The fundamental color of the varices was classified as either white (Cw) or blue (Cb). The red color sign (RC) referred to dilated, small vessels or telangiectasia on the variceal surface. Risky intramucosal venous dilatation (IMVD) was observed in the esophagus of 6 of the 29 patients with recurrent esophageal varices. Li, F1, Cb, and RC-positive varices were observed in 18 of the patients. The other 5 patients had Lm, F2, Cb, and RC-positive varices.

Prior endoscopic therapies in patients with recurrent esophageal varices

The prior endoscopic therapies performed were as follows: EIS and heat-probe coagulation treatment (HPT) in 20 patients; EVL, EIS, and HPT in 4 patients; and EIS only in 5 patients. EIS was performed by intravariceal sclerosant injection using 5% ethanolamine oleate under X-ray fluoroscopy. HPT was performed to obtain fibrosis in the lower esophagus. EVL was completed with the use of a pneumo-activated EVL device (Sumitomo Bakelite Tokyo, Japan). Endoscopic findings were F0: varices were not observed, and RC-negative in all 29 patients after the prior therapies.

Group without recurrent esophageal varices

Twenty-six patients who had been treated endoscopically, and were without recurrent esophageal varices, were studied for comparison. The subjects included 18 men and 8 women ranging in age from 46 to 76 years (mean, 61.5 years). The underlying pathology of portal hypertension was liver cirrhosis in 21 patients (including primary biliary cirrhosis in 2), cirrhosis associated with hepatocellular carcinoma in 3 patients, and idiopathic portal hypertension in 2 patients. There were 22 patients in Child-Pugh class A, 3 in class B, and 1 in class C. The etiology of liver disease was as follows: HBs Ag-positive in 4 patients, HCV-positive in 9, alcoholic liver diseases in 8, primary biliary cirrhosis in 2, and unknown in 1. Endoscopy showed no evidence of recurrent esophageal varices in any of the 26 patients.

ECDUS

The ECDUS was performed with the following specifications: Pentax FG-36UX (forward-oblique viewing), 7.5 MHz, convex type (Pentax, Tokyo, Japan). A Hitachi EUB 525 (Hitachi, Tokyo, Japan) was used for the display. ECDUS provides a color display of blood flow, and evaluates the flow pattern, using fast-Fourier transform (FFT) analysis. We monitored the color flow images of esophageal varices, paraesophageal veins, and perforating veins from the gastro-esophageal junction to approximately 7 cm proximally towards the oropharynx. Perforating veins were defined as communicating vessels between esophageal varices and paraesophageal veins. The perforating veins detected by ECDUS were classified, according to flow direction, into three different types. Type 1 showed inflow from the paraesophageal veins to the esophageal varices. Type 2 showed outflow from the esophageal varices to the paraesophageal veins (Fig. 1). Type 3 was a mixed type that revealed both inflow and outflow. The color gain was adjusted to eliminate background noise.

Levovist

Levovist is a suspension of monosaccharide microparticles (galactose in sterile water stabilized with palmitic acid). These microbubbles are stable enough to pass through capillary beds and produce useful systemic enhancement after intravenous injection. After the pre-contrast ECDUS examination, all 29 patients received Levovist intravenously, at a concentration 300 mg/ml. A 7.5-ml dose of the contrast agent was injected at a slow infusion rate, of 1 ml/min. We compared vessel images detected by pre-contrast ECDUS with those detected by enhanced ECDUS. The examination was recorded on videotape and showed the Doppler signal enhancement returning to pre-contrast levels. The Doppler settings were kept constant prior to and after the injection of contrast. The following parameters were recorded: (1) the detection rates of color flow images prior to and after Levovist injection, and (2) the signal intensity, graded as (a) for no signal enhancement and (b) for positive signal enhancement.

Informed written consent was obtained from all patients prior to the procedure.

Statistical analysis

The χ^2 test was used for statistical analysis of comparisons between frequencies in the two groups. A P value of less than 0.05 was considered to be statistically significant. The quality of perforating veins detected by ECDUS was graded on a scale of 1–3 (1, not visible; 2, good; 3, excellent). Kappa values were calculated to measure concordance between observers in the detection of perforating veins during ECDUS.[9] Kappa values were classified as follows: greater than 0, positive agreement; less than 0.2, positive but poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and greater than 0.81, excellent agreement.

Results

Color flow images of recurrent esophageal varices by pre-contrast ECDUS were obtained in 26 (89.7%) of the 29 patients. Color flow images of paraesophageal veins were obtained in 27 (93.1%) of the 29 patients, and those of perforating veins were obtained in 9 (31.0%) of the 29 patients with pre-contrast ECDUS (Table 1). The perforating veins detected by ECDUS were classified into three types according to flow direction. Perforating veins of type 1 were recognized in 6 (20.7%) of the 29 patients, type 2 in 2 (6.9%) of the 29, and type 3 in 1 (3.4%) of the 29 (Table 2). The color flows of perforating veins showed a continuous wave on FFT analysis.

Table 1. Detection rates of color flow images with ECDUS

	Pre-contrast	Post-contrast
EV	26/29 (89.7%)	29/29 (100%)
PEV	27/29 (93.1%)	29/29 (100%)
PFV	9/29 (31.0%)	22/29 (75.9%)

EV, esophageal varices; PEV, paraesophageal vein; PFV, perforating vein; ECDUS, endoscopic color Doppler ultrasonography

Table 2. Evaluation of perforating veins with ECDUS

	Pre-contrast	Post-contrast
Type 1	6/29 (20.7%)	13/29 (44.8%)
Type 2	2/29 (6.9%)	6/29 (20.7%)
Type 3	1/29 (3.4%)	3/29 (10.3%)

Type 1, inflow-type perforating veins; type 2, outflow-type perforating veins; type 3, type 1 + type 2

Color flow images of the esophageal varices and the paraesophageal veins were obtained in all 29 (100%) of the 29 patients by enhanced ECDUS using Levovist (Table 1). Color flow images of perforating veins were detected in 22 (75.9%) of the 29 patients after Levovist contrast. Perforating veins were delineated in 13 patients after the administration of Levovivst contrast; these were not detected otherwise with pre-contrast ECDUS. Seven of these 13 patients had inflowing (type 1) perforating veins, and 4 had outflowing (type 2) perforating veins. The other 2 patients had mixed (type 3) perforating veins. After enhanced ECDUS, perforating veins of type 1 were recognized in 13 (44.8%) of the 29 patients, type 2 in 6 (20.7%) of the 29, and type 3 in 3 (10.3%) of the 29 (Table 2). After the Levovist contrast, the color flow images detected with pre-contrast ECDUS were enhanced in all patients (positive enhancement). In accordance with the ECDUS findings, we performed EIS and HPT for type-1 recurrent varices, and EIS, EVL, and HPT for type 2 and type 3. Twenty-one of these 22 patients had experienced no recurrence of esophageal varices 1 year later.

As a control, 26 patients without recurrent esophageal varices were examined by ECDUS. Color flow images of perforating veins were not obtained in any of these 26 patients. The detection rate of perforating veins in the patients with recurrent esophageal varices (9 of 29 patients; 31.0%) was significantly higher than the rate in those without recurrent esophageal varices (0 of 26 patients; 0%) with pre-contrast ECDUS ($P < 0.001$). Color flow images of the perforating veins were not detected in any of these 26 patients after the administration of Levovist contrast.

Next, Kappa values were calculated to measure concordance between observers in the detection of perforating veins during ECDUS (Table 3, pre-contrast; Table 4, after Levovist contrast). The agreement values

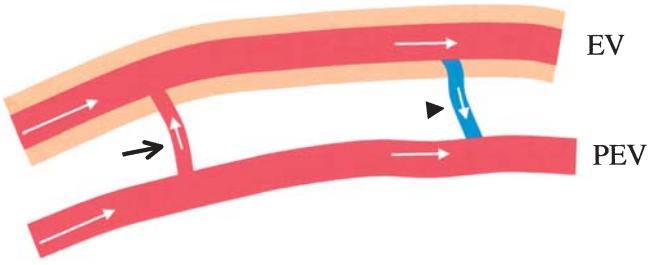

Fig. 1. Schematic view of the scanning of the lower esophagus with endoscopic color Doppler ultrasonography. *EV*, esophageal varices; *PEV*, paraesophageal vein. *black arrow*, inflow-type perforating vein; *black arrowhead*, outflow-type perforating vein

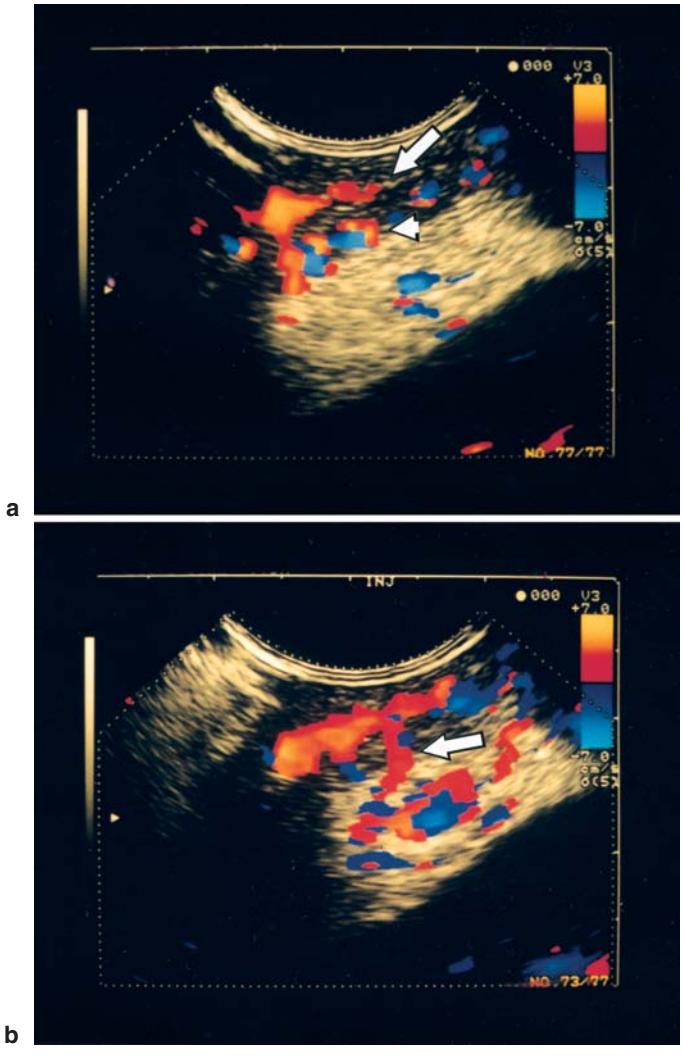

Fig. 2. **a** Vessel images of esophageal varices (*arrow*) and paraesophageal veins (*arrowhead*) are detected via pre-contrast endoscopic color Doppler ultrasonography. **b** Color flow image of inflow-type perforating vein (*arrow*) is clearly detected after administration of Levovist contrast

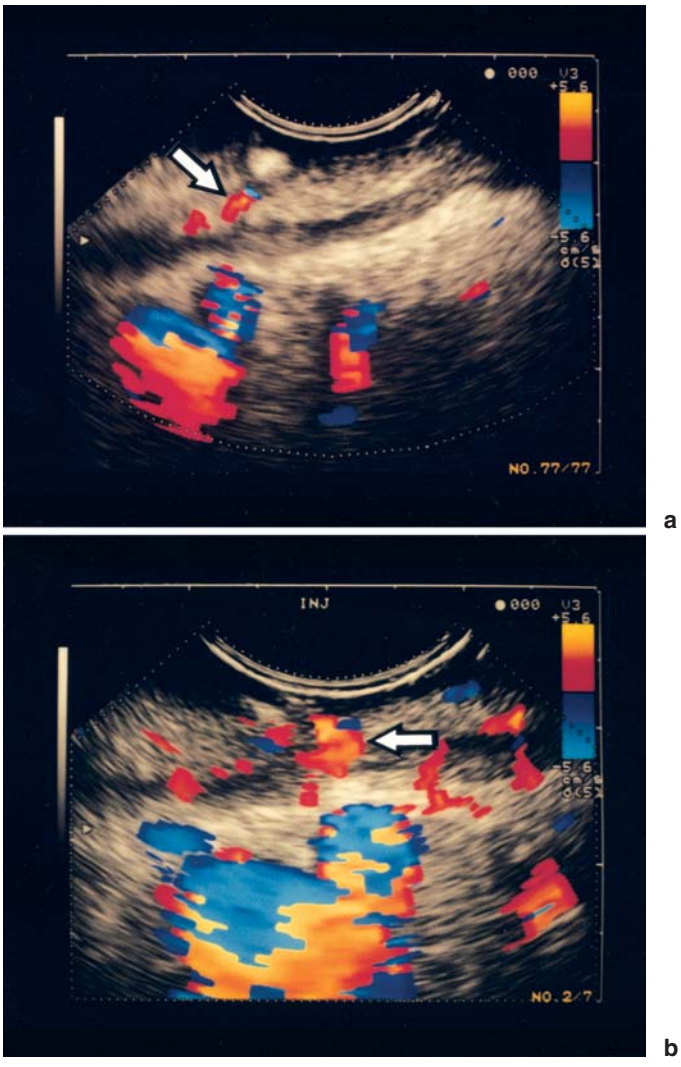

Fig. 3. **a** Vessel images of esophageal varices (*arrow*) and paraesophageal veins are detected via pre-contrast endoscopic color Doppler ultrasonography. **b** Vessel image of inflow-type perforating vein (*arrow*) can be discerned with endoscopic color Doppler ultrasonography after administration of Levovist contrast

between observer A and observer B for depicting perforating veins were excellent (pre-contrast, Kappa value, 0.84; after Levovist contrast, Kappa value, 0.92).

Case presentations

Case 1

A 63-year-old woman had primary biliary cirrhosis associated with Lm, F2, Cb, RC-positive esophageal varices, which were treated with prophylactic EIS. This patient experienced recurrence of esophageal varices 2 years later, when endoscopy revealed F1 RC-positive type. Vessel images of esophageal varices and

Table 3. Subjective image quality of perforating veins with pre-contrast ECDUS

A	Image quality score			
B	1	2	3	Overall
1	20	0	0	20
2	0	0	1	1
3	0	1	7	8
Overall	20	1	8	29

A, observer A; B, observer B; Image quality score: 1, not visible; 2, good; 3, excellent

Table 4. Subjective image quality of perforating veins with enhanced ECDUS

A	Image quality score			
B	1	2	3	Overall
1	7	0	0	7
2	0	0	0	0
3	0	1	21	22
Overall	7	1	21	29

A, observer A; B, observer B; Image quality score: 1, not visible; 2, good; 3, excellent

paraesophageal veins were detected via pre-contrast ECDUS (Fig. 2a). After administration of Levovist contrast, a color flow image of the perforating vein (type 1) was clearly detected (Fig. 2b). We performed EIS on the type-1 vein for the purpose of obliterating esophageal varices and the perforating vein, and this patient had experienced no recurrence of esophageal varices 1 year later.

Case 2

A 58-year-old man had liver cirrhosis (hepatitis C) associated with Lm, F2, Cb, RC-positive esophageal varices, which were treated with prophylactic EIS and HPT. This patient experienced recurrence of esophageal varices 1 year later, when endoscopy revealed F1 RC-positive type. Vessel images of the esophageal varices and the paraesophageal veins were detected via pre-contrast ECDUS (Fig. 3a). After administration of Levovist contrast, color flow images of the esophageal varices and the paraesophageal veins were enhanced. An image of the perforating vein (type 1) could then be discerned with ECDUS (Fig. 3b). We performed EIS on the type-1 vein for the purpose of obliterating esophageal varices and the perforating vein, and this patient had experienced no recurrence of esophageal varices 1 year later.

Discussion

Evaluating the hemodynamics of the portal venous system with portal hypertension is important for determining the optimal choice of treatment. Angiography is a useful method of assessing hemodynamics in portal hypertensive patients, but it cannot distinguish intramural vessels from extramural vessels of the esophagus. It is impossible to discern perforating veins via computed tomographic scans or magnetic resonance (MR) angiography. Endoscopic ultrasonography (EUS) has become a useful modality for the diagnosis of esophagogastric varices.[10] Perforating veins can be visualized via EUS, but the direction of blood flow in perforating veins cannot be detected with this method. The direction of blood flow in perforating veins can only be qualitatively demonstrated by ECDUS. There is little information in the literature on perforating veins.[5,11–14]

Color Doppler is based on the mean Doppler frequency shift and therefore is a measure of the directional component of the blood velocity moving through the sample volume. Power Doppler, on the other hand, is based on the integrated Doppler power spectrum, and the power in the Doppler signal is related to the number of red blood cells producing the Doppler shift.[15,16] We previously reported our evaluation of color flow images in patients with esophagogastric varices with EUS, using power Doppler in comparison with ECDUS (EUS using color Doppler). EUS using power Doppler was better than ECDUS in depicting variceal blood flow.[17] However, it was impossible to visualize the direction of blood flow in perforating veins with EUS using power Doppler. This is a weak point of EUS using power Doppler for imaging blood flow. Therefore, we expect improvement in the capability of depicting variceal blood flow with ECDUS.

The present study was designed to evaluate ECDUS findings of recurrent esophageal varices. In particular, the detection rate, and the direction of blood flow, in the perforating veins were examined by ECDUS. Passageways of esophageal varices are mainly associated with gastric-wall blood flow (left gastric vein, short gastric vein, and palisade vein), and perforating veins are recognized as additional passageways.

Choudhuri et al.[18] demonstrated perforating veins that connected the submucosal and paraesophageal collateral venous channels in the lower esophagus by EUS; these veins were observed in 15% of patients with small varices and in 70% with large varices. In this study, color flow images of perforating veins were obtained in 9 (31.0%) of the 29 patients with pre-contrast ECDUS, and the detected perforating veins had an inflowing pattern from paraesophageal veins to esophageal varices in 6 of the 9 patients.

Levovist is an ultrasound echo-enhancing agent that increases the echo signal intensity of the body blood pool following intravenous injection. It is made up of granules that are 99.9% galactose and 0.1% palmitic acid. Multiple, small, stabilized, air microbubbles are produced, with a mean diameter of 2–3 μm. The echo-enhancing effect depends on the dose used and individual patient parameters. Several reports in the literature have reported that Levovist increases the sensitivity of color Doppler flow imaging of liver tumors.[19,20] In a phase III trial, Levovist had an excellent safety record, and there have been no serious reactions to the agent.[21] Our results revealed that color flow images of perforating veins were detected in 22 (75.9%) of our 29 patients with recurrent esophageal varices after Levovist contrast. After the enhanced ECDUS, perforating veins were delineated in 13 patients in whom these veins were not previously detected with pre-contrast ECDUS. Therefore, the sensitivity of ECDUS for the detection of perforating veins rose from 31.0% to 75.9% after Levovist contrast. After the contrast ECDUS, the perforating veins were reclassified as follows: perforating vein of type 1 in 13 of the 29 patients; type 2 in 6 of the 29; and type 3 in 3 of the 29. The direction of blood flow in perforating veins is an important consideration in the therapeutic management of esophageal varices. Therefore, we should perform EIS on type 1 veins for the purpose of obliterating esophageal varices and perforating veins. On the other hand, the type 2 vein is associated with diversion of esophageal variceal blood flow into paraesophageal veins, and is thus equivalent to an extraesophageal shunt.[22] One must observe great caution in performing EIS for patients with type 2 and type 3 varices, and EIS should be performed at the anal side of outflowing perforating veins on purpose of blocking the diversion of sclerosant on EIS; EVL may be the optimal treatment for this type of varices.[23] Of note, color-flow images of the perforating veins were not detected in any of the 26 patients without recurrent esophageal varices either before or after Levovist contrast. These results reveal that perforating veins may play an important part in recurrent esophageal varices.

The images of the perforating veins were greatly changed when compared before and after the injection of Levovist. Enhanced color Doppler images have been observed to be bigger than the true vessel images, due to "blooming" artifact around the blood vessels. In this study, Levovist was injected at a slow infusion rate, of 1 ml/min, to extend the duration of enhancement and to reduce "blooming" artifacts.

Endoscopic coagulation therapy is a useful treatment for high-risk IMVD. Nevertheless, coagulation therapy for IMVD and EVL for F1 or F2 recurrent esophageal varices leads to incomplete results, because of the presence of remaining passageways (including perforating veins); therefore, EIS should be performed for the purpose of obliterating passageways.[24]

ECDUS is a useful modality for the evaluation of the hemodynamics of recurrent esophageal varices. Levovist contrast provides further refinement in the quality of the ultrasound images. ECDUS with Levovist contrast can improve the diagnostic quality of the hemodynamics of recurrent esophageal varices. Perforating veins can be detected at a high rate by ECDUS with Levovist in patients with recurrent esophageal varices after endoscopic therapy.

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