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Review Article

Hemodynamics and Treatment of Esophageal Varices

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Abstract

Esophageal varices are considered to be the most common complication in patients with portal hypertension. Endoscopic ultrasonography (EUS) not only visualizes the surface of the varices but also provides detailed information about their internal structure. The direction of blood flow can be determined and its velocity measured only via endoscopic color Doppler ultrasonography (ECDUS), which can show graphically esophageal varices, paraesophageal veins, and passageways. It is important to evaluate the hemodynamics of the portal venous system when treating the esophageal varices of patients with portal hypertension and ECDUS and EUS are useful modalities for the evaluation of the detailed hemodynamics of esophageal varices.

Endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL) are well-established therapies for esophageal varices. In Japan, endoscopic therapy has become the first choice for the treatment of esophageal varices. Recently, combination therapies of EIS and EVL or EVL and argon plasma coagulation were found to be more effective than EIS or EVL alone.

Keywords: Color Doppler; Endoscopic Ultrasonography; Endoscopic Injection Sclerotherapy; Endoscopic Variceal Ligation; Esophageal Varices; Hemodynamics; Portal Hypertension

Introduction

Portal hypertension induces the development of porto-systemic collateral vessels. Esophageal varices are considered to be the most common complication in patients with portal hypertension. Surgery was the only treatment for esophageal varices in 1950s and 1960s and endoscopic treatments were developed in the 1980s. EIS [1] and EVL [2] are effective treatments for variceal bleeding. These endoscopic therapies are important tools for the prevention of esophageal varices. In Japan, there appears to be controversy in deciding which of the two is the best therapy for elective and prophylactic cases. Therefore, it is important to evaluate the hemodynamics of the portal venous system when determining the optimal choice of treatment for patients with portal hypertension. In this article, we review the hemodynamics of esophageal varices due to portal hypertension and describe the usefulness of EUS and endoscopic management of esophageal varices.

Portal Hypertension

Portal hypertension is defined as a pathological increase in the portal venous pressure or an increase in the hepatic venous pressure gradient (HVPVG) above the normal range (1-5 mmHg). It induces the development of porto-systemic collateral vessels and the increased intrahepatic and extrahepatic vessel resistance leads to hepatofugal flow in the collateral veins (left gastric vein, short gastric vein, and pos-

terior gastric vein). Hepatofugal flow in the collateral veins is involved in the formation of esophageal varices. Esophageal varices are the most relevant because their rupture results in variceal hemorrhage, which is the most common lethal complication of cirrhosis. The left gastric vein is the major site of esophageal varices in patients with portal hypertension. The morphological changes of the left gastric vein in portal hypertension have been elucidated by angiographic examinations [3-5]. Matsutani et al. reported that hepatofugal blood flow in the left gastric vein increased in direct correlation with enlargement of the size of the varices and a high flow velocity in the left gastric vein was strongly associated with variceal bleeding [6]. It is generally thought that the blood flow in the left gastric vein may change from a hepatopetal to a hepatofugal direction in liver cirrhosis.

The palisade zone corresponds to the abdominal esophagus, beginning at the gastro-esophageal junction and extending superiorly for 4-5 cm [7]. The veins in this zone were distributed uniformly, in close proximity to each other and running parallel and longitudinally as a palisade. Palisade veins, which are normally seen in the lamina propria at the lower end of the esophagus, are called sudare like veins. The palisade veins run through the lamina propria and most end draining to the submucosal veins at the critical area. Noda et al. stated that the ruptured veins were situated in the lamina propria and the rupture points were located near the area where the varicosed palisade veins connected to the submucosal varices [8]. Arakawa et al. noted that marked dilatation of the veins in the submucosa is more common in patients with well-developed varices than in those without varices via the palisade zone, and they classified these cases into two groups: those with sudare like veins, and those with vascularity in which one or two large dilated vessels run through the submucosa [9]. Hashizume et al. classified the sudare like veins as a palisading type and the dilated vessels as a bar type and reported that palisading type veins in the lamina propria were dilated leading into the muscularis mucosae and were observed circumferentially in the submucosa [5, 10].

The routes 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. There is little information in the literature regarding perforating veins [10-12].

Diagnosis of Portal Hypertension

Computed tomography (CT) and magnetic resonance (MR) angiography are reliable modalities for examining the entire portal venous system [13-15]. Esophageal varices appear on CT scans as well-defined, round, tubular, or serpentine structures that are smooth and have homogeneous attenuation. In particular, 320-row multi-detector CT is useful for the detection and grading of esophageal varices and for evaluating esophageal varices to predict the risk of hemorrhage [16]. Unfortunately, detailed hemodynamic studies of the vascular anatomy of the lower esophagus and upper stomach are not feasible with CT or MR angiography.

The gold standard in the diagnosis of esophageal varices remains esophagogastroduodenoscopy (EGD); this is a useful modality for diagnosing and observing esophageal varices of a certain size and extent, and has a very sensitive predictive value for variceal hemorrhage. The endoscopic findings of esophageal varices may be evaluated according to the grading system outlined in'The General Rules for Recording Endoscopic Findings of Esophago-gastric Varices 'prepared by the Japanese Research Committee on Portal Hypertension [17]. In this system, esophageal varices are classified according to their color (white or blue), form (small and straight, F1; enlarged and tortuous, F2; large and coil-shaped, F3; or no varices after treatment, F0) and red color sign (RC), which refers to dilated, small vessels or telangiectasia on the variceal surface.

RC indicates a high risk of variceal bleeding, based on endoscopic findings (RC0-3). Bleeding is classified as gushing, spurting and oozing. The following images show blue color and red color-positive enlarged and tortuous esophageal varices with a red plug (Figure 1).

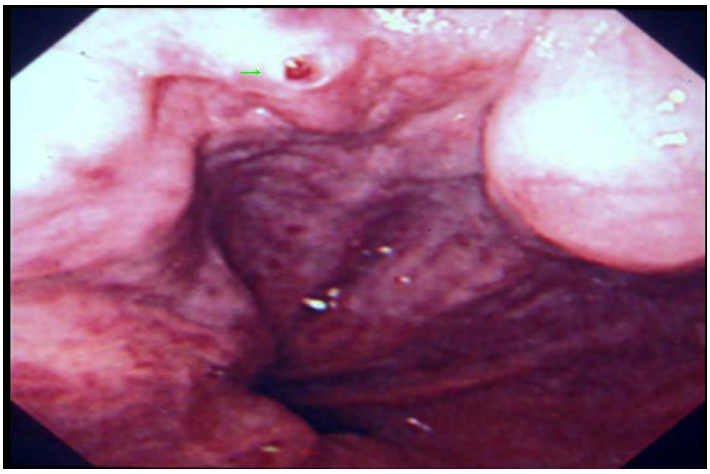

Figure 1: Esophagogastroduodenoscopy show blue color and red color-positive enlarged and tortuous esophageal varices with a red plug (arrow).

EUS has become a very useful modality for the diagnosis of esophageal varices [18-20]. EUS not only visualizes the surface of the varices but also provides detailed information regarding their internal structure. In particular, it is suitable for visualizing the collateral channels that surround the distal esophagus and upper stomach. EUS features a 20 MHz ultrasound catheter probe and also has been shown to provide clear images of esophageal collateral veins [21,22], allowing detailed evalua-

tion of esophageal variceal hemodynamics.

By applying EUS with Doppler capabilities, ECDUS allows the sonographic visualization of the vessels, as well as evaluation of vascular blood flow and morphology. ECDUS is better than conventional EUS for observing the detailed hemodynamics of esophageal varices better.

Evaluation of Esophageal Varices Using Ecdus

Intially, the identification of esophageal varices was made by B-mode scanning followed by color flow mapping. On B-mode scanning, submucosal esophageal varices and periesophageal collateral veins were visualized as hypoechoic vessels within the esophageal wall and spaces exterior to the adventitia of the esophageal wall. ECDUS is a method for detecting color flow images in blood vessels and evaluating the flow pattern using fast Fourier transform (FFT) analysis. FFT analysis can indicate the flow pattern and calculate the velocity of blood flow. This modality can show graphically esophageal varices, paraesophageal veins, and passageways. Sato et al. have reported previously on the usefulness of convex type ECDUS for evaluating the hemodynamics of esophageal varices [23-25]. Hino et al. analyzed the morphology and hemodynamics of the left gastric vein using ECDUS to evaluate the development of esophageal varices [26]. They reported that the hepatofugal blood flow velocity in the left gastric vein trunk increased with the size of the varices. The left gastric vein bifurcates into anterior and posterior branches and, as the size of the varices enlarged, the branch pattern was more likely to be anterior branch dominant. EIS is recommended as the better choice of endoscopic treatment for anterior branch-dominant esophageal varices. The image shows anterior branch-dominant esophageal varices observed with ECDUS (Figure 2-a).

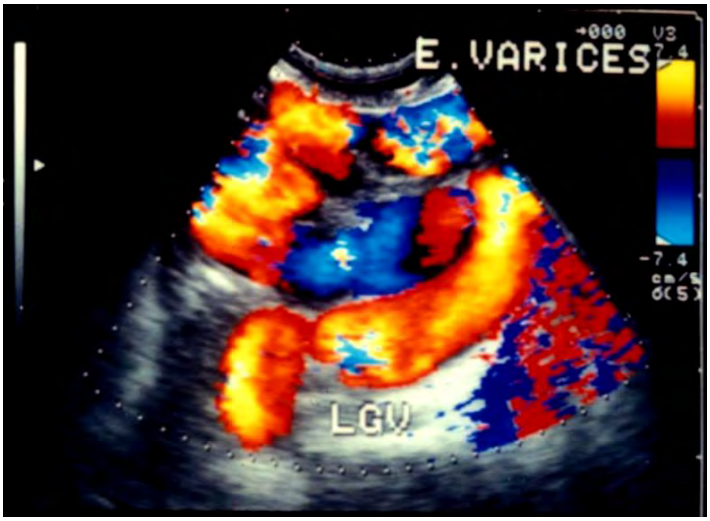

Figure 2-a: Endoscopic color Doppler ultrasonography shows anterior branch dominant color flow images of the left gastric vein (LGV) and esophageal varices.

Vessel images of the palisade veins running parallel and longitudinally around the gastro-esophageal junction were made with ECDUS. Observation of color flow images of palisade veins by ECDUS is difficult because of the fine vessels with low velocity [27]. Sato et al. reported the usefulness of a new electronic radial ECDUS, in comparison with convex type ECDUS, for evaluating the hemodynamics of esophageal varices and color flow images of palisade veins were obtained in 12 of 26 (46.2%) cases using electronic radial ECDUS. In addition, the detection rate of palisade veins with electronic radial ECDUS was significantly higher than that with the convex type ECDUS [28].

Perforating veins are defined as communicating vessels between esophageal varices and paraesophageal veins. It is not possible to detect perforating veins via CT scans or MR angiography. Perforating veins can be visualized via EUS, but the direction of the blood flow within them cannot be determined by this method. The direction of blood flow in perforating veins can only be shown qualitatively by ECDUS [29]. Choudhuri et al. reported on perforating veins that connect the submucosal and paraesophageal collateral venous channels in the lower esophagus using EUS; these were observed in 15% of patients with small varices and 70% with large varices [19]. The perforating veins detected by ECDUS were classified into three types according to the flow direction. Type 1 showed inflow from the paraesophageal veins to the esophageal varices (Fig.2-b), Type 2 showed outflow from the esophageal varices to the paraesophageal veins and Type 3 was a mixed type that featured both inflow and outflow [29].

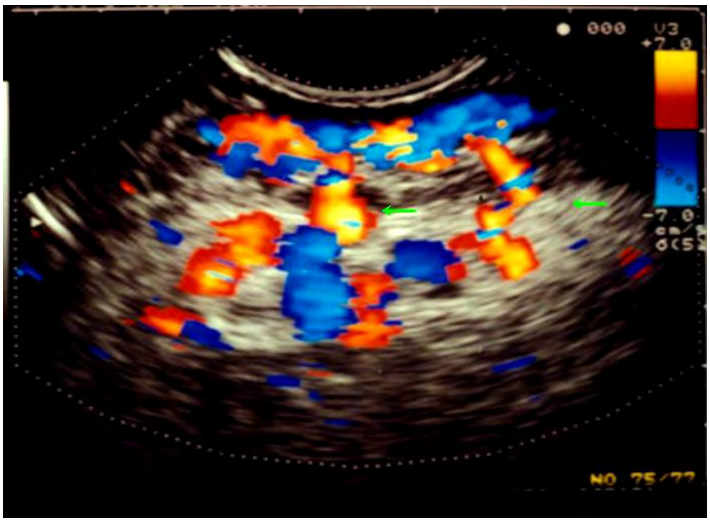

Figure2-b: Endoscopic color Doppler ultrasonography show inflow from the paraesophageal veins to the esophageal varices (arrow).

The direction of blood flow in perforating veins is an important consideration for the therapeutic management of esophageal varices and, therefore, we should perform EIS on Type 1 in order to obliterate esophageal varices and perforating veins. On the other hand, Type 2 is associated with diversion of esoph-

ageal variceal blood flow into the paraesophageal veins and is effectively equivalent to an extra-esophageal shunt [30]. One must use great caution in performing EIS on Type 2 and Type 3 variceal patients and EIS should be performed at the inner side of out-flowing perforating veins. EVL may be the optimum treatment for varices of this type [31].

Treatment of esophageal varices

Endoscopic therapy is considered the optimal treatment for acute variceal bleeding and is also performed to prevent initial variceal hemorrhage and to prevent variceal recurrence. EIS is now a standard procedure for treatment of esophageal varices [1]. Currently, EVL also is widely used to treat esophageal varices [2]. EIS and EVL are effective treatments for variceal bleeding, and in Japan, there appears to be controversy in deciding which is the best therapy for elective or prophylactic cases. Therefore, it is important to evaluate the hemodynamics of the portal venous system in patients with portal hypertension when determining the optimal choice of treatment.

EIS

EIS not only blocks esophageal varices but also scleroses the passageways to esophageal varices (left gastric vein, short gastric vein, palisade vein, and perforating veins) and is therefore an effective therapy for developed esophageal varices. It is also safe because of the use of endoscopic varicealography during injection sclerotherapy.

Various sclerosants, such as sodium nitrate, polidocanol, alcohol, sodium tetradecyl sulfate, and ethanolamine oleate (EO), have been widely used for EIS [32, 33]. In Japan, EIS is performed frequently using EO as the sclerosing agent. EO is injected via a catheter through the working channel of the endoscope to target esophageal varices. This harsh chemical agent acts by denaturing biologic tissue, bringing about complete endothelial destruction and fibrosis following injection into a vein [34]. Ten percent EO is mixed with an equal volume of iopamidol as the contrast medium, resulting in a 5 % EO-iopamidol (5% EOI) mixture. EO is hemolytic, and the resultant free hemoglobin may cause renal failure if large amounts are used [35]. Injection of less EO is advisable to minimize the renal risk.

In our institute, EIS for esophageal varices was performed weekly using 5% EOI, which was injected gradually into the esophageal varices under fluoroscopic guidance. The procedure was performed using a flexible gastrointestinal endoscope with a transparent hood attached to the tip (Fig.3-a). Until the disappearance of all varices was confirmed by endoscopy, EIS was repeated weekly using a 23 or 25-gauge injection needle placed into the varix using the free-hand method (Fig.3-b). To determine the extent of the varices, fluoroscopic observation was performed using a balloon attached to the endoscope to guide and control the infusion of 5% EOI (Fig.3-c). The amount of 5%EOI injected was determined based on the depiction of vessels feeding the esophageal varices. After EIS, antibiotic therapy was administered to all patients to reduce the risk of infection. EIS is an effective therapy for esophageal varices and is less invasive than surgery. However, several complications have been reported, such as pleural effusion, pulmonary failure, renal failure, and esophageal stricture [36-40]. In addition, gastric ulcer is a rare complication after EIS for esophageal varices [41]. There are two possible causes, either sclerosant flowing into the left gastric artery via arterio-venous anastomoses or direct injection of the sclerosant into the artery. With repeated sessions, EIS promotes inflammation of the vascular wall and variceal obliteration. There are some technical variations associated with EIS [42].

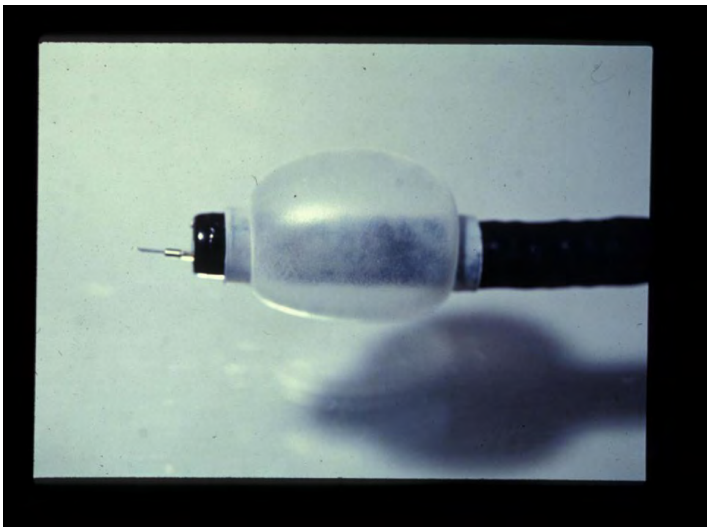

Figure 3-a: Endoscopic injection sclerotherapy was performed using a flexible gastrointestinal endoscope with a transparent hood attached to the tip.

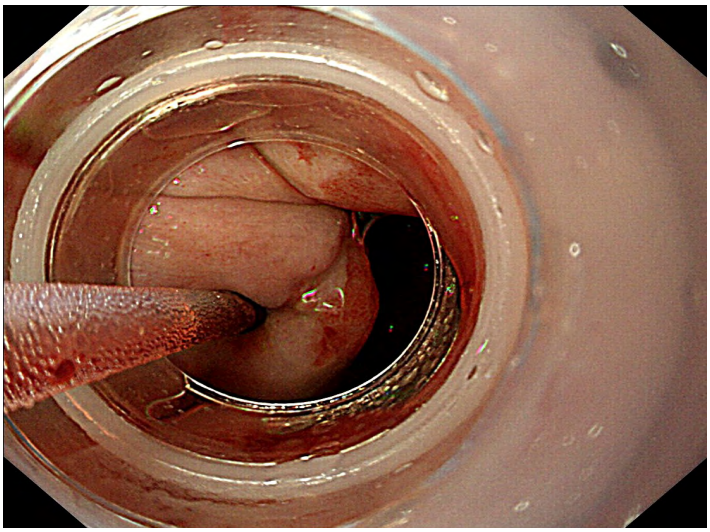

Figure3-b: Injection needle placed into the varix using the free-hand method.

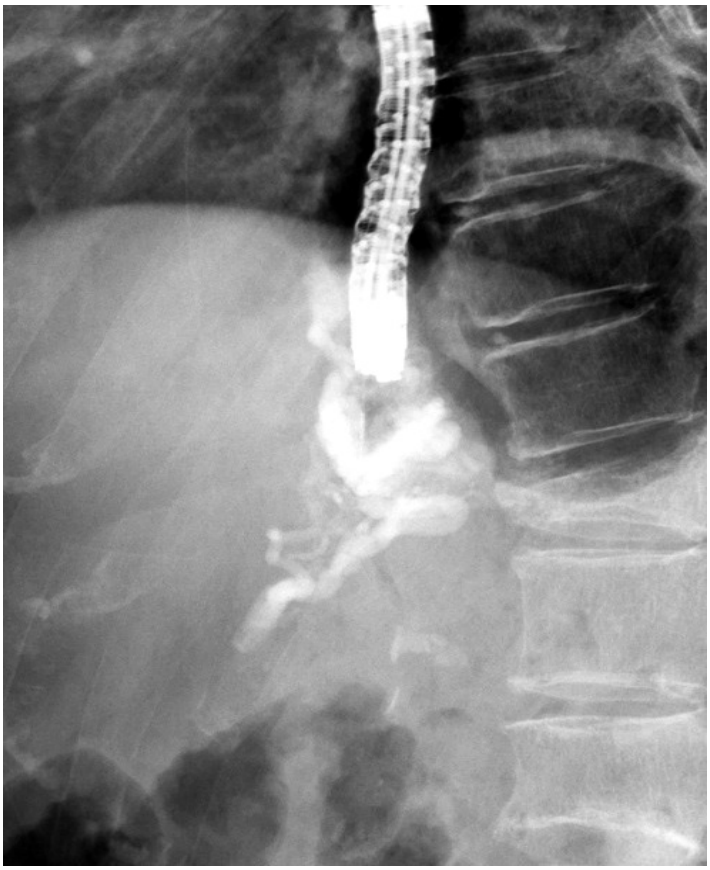

Figure 3-c: Determining the extent of the varices, fluoroscopic observation was performed using a balloon attached to the endoscope to guide and control the infusion of 5% ethanolamine oleate with iopamidol.

EVL

EVL is widely used as an effective and standard treatment for esophageal varices by obliteration of the submucosal varices using a rubber band [2]. EVL is especially effective for actively bleeding esophageal varices, by attaching the rubber band at the bleeding point, and it is the first-choice treatment because of its ease and safety.

Eradication of esophageal varices is achieved in approximately 90% of patients, however, the recurrence rate is high [43]. Yoshida et al. reported that the recurrence rate of varices is lower after repeated ligation [44]. Laine et al. have shown by meta-analyses that EVL is well suited to the treatment of acute bleeding and was associated with fewer adverse events and improved the mortality, compared to EIS [45].

Currently, EVL is considered the gold standard for variceal ligation worldwide, however, it is not acceptable because of the high rate of recurrence associated with the technique. This is explainable by the fact that EVL does not obliterate the passageways of varices and perforating veins [46].

On the other hand, APC is a new modality of non-contact electrocoagulation that applies high frequency electronic energy into the tissue to cause defined thermal effects and which can be used for thermal devitalization of the tissue, as well as hemostasis. Grund et al. have reported the first experiences with APC as an option for the treatment of gastrointestinal hemorrhage [47]. Some results indicate that EVL combined with APC is superior to EVL alone [48, 49].

APC can be used for mucosal fibrosis therapy for the complete elimination of esophageal varices.

Nishikawa et al. compared EIS alone and an EIS procedure with ligation (EISL), in which EIS and EVL are performed simultaneously, and for EISL, fewer treatment sessions and less sclerosant were sufficient, because the sclerosants were more effective with blockage of variceal blood flow by the ligation [50].

Conclusion

It is important to evaluate the hemodynamics of the portal venous system when treating the esophageal varices of patients with portal hypertension. ECDUS or EUS are useful modalities for the evaluation of the detailed hemodynamics of esophageal varices.

In Japan, endoscopic therapy has become the first choice for the treatment of esophageal varices. Recently, combination therapies of EIS and EVL or EVL and argon plasma coagulation were evaluated and found to be more effective than EIS or EVL alone.

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