—Commentary—

# EUS-guided vascular interventions

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## INTRODUCTION

EUS-guided therapeutic interventions are evolving in multiple different directions, affording therapy for various gastrointestinal (GI) conditions. High resolution imaging of mediastinal and abdominal vascular structures from the GI tract create an opportunity for precise vascular access and therapy. This chapter will provide an overview of the current clinical literature regarding EUS-guided vascular interventions, including management of nonvariceal and variceal GI bleeding, EUS-guided portal vein (PV) access and therapeutic implications, and EUS-guided cardiac access and therapy.

## MANAGEMENT OF NONVARICEAL GASTROINTESTINAL BLEEDING

Endoscopic therapies for nonvariceal GI bleeding are well established and entail epinephrine injection,[1,2] contact coagulation,[3,4] clipping,[5] and band ligation.[6] While successful in most cases, treatment may fail in up to 15% of cases.[7,8]

The first report of EUS-guided therapy used a radial scanning echoendoscope to inject epinephrine/polidocanol through a standard sclerotherapy needle to treat a Dieulafoy's lesion.[9] Levy *et al.* used a curved linear array echoendoscope to treat refractory bleeding in a case series of five patients with hemosuccus pancreaticus, duodenal ulcer, and GI stromal tumors.[10] Patients presented with an average of three bleeding episodes requiring multiple transfusions and had failed multiple endoscopic and radiographic interventions. EUS was able to delineate the bleeding vessel, and alcohol or cyanoacrylate (CYA) was delivered through a 22-gauge fine-needle aspiration (FNA) needle. The absence of postinjection flow indicated hemostasis of the bleeding vessels, which was achieved in all cases without any complications or rebleeding over a mean follow-up of 12 months. Gonzalez *et al.*[11] described a case series involving five patients with arterial GI bleeding, all refractory to previous endoscopic hemostasis attempts, from Dieulafoy's lesions, pancreatic tumor, pseudoaneurysm secondary to acute pancreatitis, and an arterial anomaly after pancreaticoduodenectomy. EUS-guided CYA or polidocanol injection achieved immediate control of hemorrhage, visualized by Doppler. One patient rebled, necessitating repeat EUS-guided therapy, and the remainder experienced no rebleeding during 9 months of follow-up. EUS-guided CYA injection into the distal arm of the splenic artery achieved successful hemostasis in a patient with life-threatening intracystic hemorrhage of a splenic

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pseudoaneurysm injured during EUS-guided pseudocyst drainage.[12] Additional case reports describe the treatment of arterial pseudoaneurysms,[13-15] Dieulafoy's lesions,[16,17] and a bleeding GI stromal tumor.[18]

In a large series of 17 patients with nonvariceal bleeding,[19] multiple modalities were used to achieve EUS-guided hemostasis, including coil embolization, band ligation, and injection of epinephrine, ethanol, hyaluronate, or CYA. For band ligation, EUS was used to mark the site of the vessel with a subepithelial tattoo. Before EUS, 16 of the 17 patients underwent a median of 2.5 esophagogastroduodenoscopies, 4 had prior unsuccessful radiologic interventions, and 3 had prior surgical interventions. Ten patients with available blood transfusion data received a median of 11 packed red blood cells units. Doppler confirmed either complete cessation or a marked decrease in flow in all patients receiving EUS-guided therapy. The procedure was performed with no adverse events. There was no recurrent bleeding in 15 patients during a median follow-up of 12 months. One patient with a gastric Dieulafoy's lesion needed one additional EUS-guided therapy after 38 months, and another patient with a rectally invasive prostate cancer continued to bleed.

To summarize, EUS-guided therapy of nonvariceal bleeding has been shown to be feasible and safe for peptic ulcer disease, Dieulafoy's lesions, bleeding tumors, and pseudoaneurysms. The abilities to directly visualize and target the bleeding vessel with a specific therapy and subsequently confirm hemostasis with real-time Doppler ultrasound are significant advantages of EUS-guided therapy. These advantages have translated into treatment success in patients with recurrent refractory bleeding.

## MANAGEMENT OF ESOPHAGEAL VARICEAL BLEEDING

Band ligation is the preferred technique for primary and secondary treatment of esophageal varices.[20] Recurrent bleeding rates of 15%–65% have been reported[21,22] and are thought to be secondary to treatment failure of the perforating veins and collateral vessels feeding the esophageal varices.[23,24]

Lahoti *et al*. were the first to describe the use of EUS-guided endoscopic sclerotherapy for esophageal varices.[25] Sodium morrhuate was injected into the perforating vessels until cessation of flow. A mean of 2.2 sessions was required to completely eradicate the esophageal varices. No rebleeding or complications were recorded over a 15-month follow-up. de Paulo *et al*. described a cohort of 50 patients with bleeding esophageal varices, randomized to conventional endoscopic sclerotherapy and EUS-guided sclerotherapy.[26] No difference was found in the number of sessions to vessel obliteration or in rebleeding rates between the two groups. Rebleeding was significantly associated with the presence of collateral vessels.

The theoretical advantage of EUS-guided therapy for esophageal varices is the ability to identify and target collateral vessels. Further studies are needed to assess the practical clinical benefit, either in terms of reduction of a number of sessions to achieve vessel obliteration or reduction of rebleeding rates.

## MANAGEMENT OF GASTRIC VARICEAL BLEEDING

Gastric varices (GVs) may be present in up to 20% of patients with portal hypertension, with up to a 65% bleeding rate over 2 years.[27] GVs in connection with esophageal varices (gastroesophageal varices [GOVs]) are located along the lesser curve (GOV1) or at the cardia (GOV2). Isolated GVs (IGVs) are either in the fundus (IGV1) or sporadic, usually around the antrum or pylorus (IGV2). Endoscopic sclerotherapy of GVs is discouraged due to reports of prohibitive rates of adverse events including gastric ulceration, perforation, and rebleeding in 37%–53% of cases.[27,28] Band ligation is also discouraged due to the larger size of GVs, coupled with a thick overlying mucosa, making suction of the entire varix into the bander difficult. If the contralateral wall of the varix is not captured, postbanding ulceration may lead to catastrophic bleeding.[29] Endoscopic CYA injection for GVs, first described in 1986,[30] has become the treatment of choice for GVs.[31] Hemostasis rates of 58%–100% and rebleeding rates of 0%–40% have been reported.[32] The major and most serious adverse event associated with CYA therapy is systemic embolization,[33] including pulmonary embolism, cardiac embolism, splenic artery embolism, and paradoxical cerebral embolism in patients with foramen ovale. Additional complications include splenic vein thrombosis, renal vein thrombosis, entrapment of the needle in the varix by CYA and damage to the endoscope.[33]

EUS has many conceptual diagnostic and therapeutic advantages in the management of GV. First, the

detection rate of GV is increased, as reported by Boustière *et al.* (six-fold increase in detection rate).[34] GV is located deep in the submucosa and therefore can be mistaken as thickened folds on endoscopy. Second, Doppler ultrasound can confirm posttreatment cessation of blood flow in real time. This advantage has clinical prognostic implications since residual patency of treated varices has been shown to correlate with rebleeding risk.[35] Third, EUS-guided treatment lacks dependency on direct varix visualization, which may be impaired by retained food or blood in the stomach. Fourth, EUS guidance enables accurate delivery of the hemostatic agent into the varix lumen, avoiding paravariceal injection, which can occur in up to 60% of injections.[36] Finally, the main deep "feeder" vessel may be visualized. Targeting the feeder may enable more effective treatment with a lesser quantity of the hemostatic agent. This may reduce embolization risk when using CYA, as suggested by Romero-Castro in a small pilot study[37] using a mixture of CYA and lipiodol.

As an alternative to glue injection that risks glue embolization, the deployment of stainless steel coils has been reported. The first case was described by Levy *et al.*, treating a refractory ectopic choledochojejunal variceal bleed.[38] Rebleeding occurred, though in the repeat EUS the treated varices were thrombosed. Additional coils were deployed into previously untreated varices. Romero-Castro *et al.* treated four patients with GVs, with successful obliteration in three patients.[39]

Coils are made of metal alloy and contain radially extending synthetic fibers, which induce clot formation and hemostasis. Coils are 2–15 mm in length and loops are 2–20 mm in diameter. Coil selection is based on the size and diameter of the varix. Coils can be deployed through a 22-gauge needle (0.018" coil) or a 19-gauge needle (0.035" coil). The needle stylet is used to push and deploy the coil into the varix.

A retrospective trial comparing EUS-guided coil deployment to EUS-guided CYA injection found no difference in obliteration rate, number of sessions or rebleeding rate over a 17-month follow-up.[40] Eleven out of 19 patients in the CYA group had adverse events, significantly more than in the coil group (58% *vs.* 9%, $P = 0.01$), 9 of whom had asymptomatic pulmonary embolism, found on computed tomography (CT), which was performed routinely for all patients postprocedure. Coil deployment was significantly more expensive than CYA injection; however, the hospital stay was longer in the CYA group.

The deployment of coils followed by immediate CYA injection [Figure 1] can offer three potential advantages over CYA injection alone: (1) the contribution of each method to hemostasis and varix obliteration may be additive; (2) the coil may concentrate the glue at the coil site, thus reducing the CYA volume needed for obliteration; (3) the coil can act as a scaffold to retain CYA within the varix, thus reducing the risk of embolization.

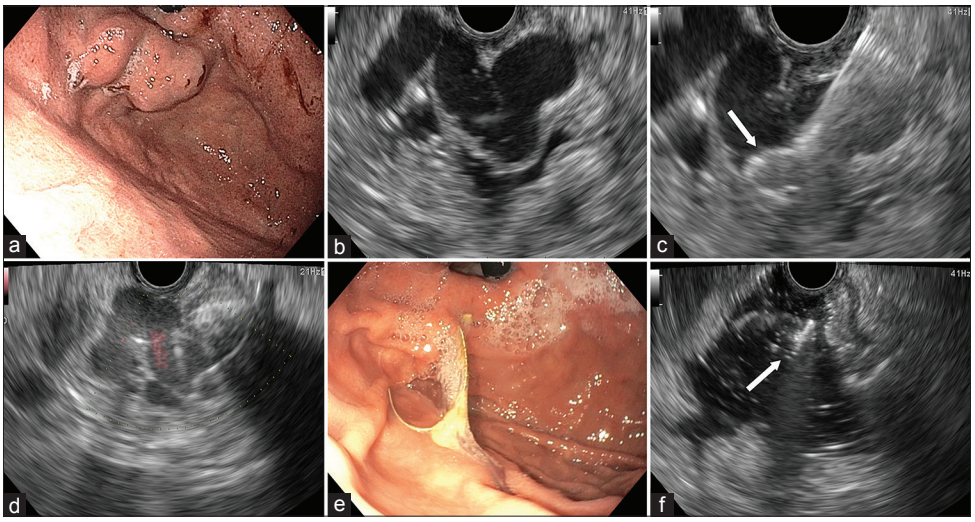


**Figure 1.** (a) Type I isolated gastric variceal conglomerate in a patient with a history of bleeding. (b) Sonographic image of the 2.5 cm variceal conglomerate. (c) Deployment of a coil through a 19-gauge needle (arrow pointing to coil). (d) Coil and glue complex (creating acoustic shadow) with nearly no flow confirmed by Doppler. (e) Varix obliterated with coil extruding. (f) No varix seen on sonography with the coil visible in the gastric lumen (arrow)

We first reported combined coil and glue treatment in 30 patients with recent bleeding from large GVs who were poor candidates for transjugular intrahepatic portosystemic shunt (TIPS).[41] After coil deployment, a mean of 1.4 mL of CYA per patient was injected. Rebleeding occurred in 16.6%, with one rebleed attributed to GVs. Among 24 patients with follow-up, GV remained obliterated in 23 after a single session. There were no complications. We later published a larger series of 152 patients with a mean follow-up of 436 days.[42] Of 100 patients, who had a follow-up EUS, 93% had confirmed varix obliteration. Recurrent bleeding attributed to GVs occurred in 10 out of 125 patients, of whom five had repeat EUS-guided therapy. Forty patients out of the total group had high-risk GVs with no history of bleeding and underwent prophylactic treatment. Obliteration of targeted GVs was achieved in 96% of patients; bleeding occurred in two patients from new varices, both successfully treated endoscopically. These data support consideration of primary prophylaxis of high-risk GV using combined EUS coil deployment and glue injection.

On a technical note, we approach GVs transesophageally with the echoendoscope in an orthograde position. This "retrograde" approach avoids puncture through the mucosa overlying the GV. When anatomically feasible, we include the thick fibromuscular diaphragmatic crus in the needle path. The rationale is that the crus serves as a stabilizing backboard to prevent back-bleeding. The transesophageal approach has the additional advantage of not being hindered by gastric contents, which tend to accumulate in the gastric fundus.

## MANAGEMENT OF ECTOPIC VARICEAL BLEEDING

Bleeding from ectopic varices account for 1%–5% of all variceal bleeding.[43] The most frequent site of bleeding is the duodenum, particularly the duodenal bulb, with mortality rates reaching up to 40%.[44] Other anatomical sites are the small bowel, colon, rectum, and peristoma.

### *Duodenal varices*

In a 2014 review of the literature, duodenal varices were treated with TIPS in 11 cases, balloon-occluded retrograde transvenous obliteration in 14, ethanolamine sclerotherapy in 1, endoscopic band ligation in 6, and CYA injection in 16.[45] The same group reported on a patient with a refractory bleeding duodenal varix after endoscopic sclerotherapy treated with EUS-guided coil placement followed by glue injection.[45] Additional cases of EUS-guided coil placement ± CYA injection of patients with bleeding duodenal varices have been reported.[46,47]

### *Rectal varices*

Rectal varices occur in 44%–89% of cirrhotic patients and are a significant cause of lower GI bleeding in patients with portal hypertension[48-50] although they pose a smaller risk of bleeding than gastroduodenal varices. Massive bleeding is reported with a frequency of 0.5%–3.6%.[51-53] It has been shown that EUS can detect the presence and number of rectal varices better than endoscopy.[54] The intramural rectal varices, perirectal collateral veins, and the communicating veins between them could be clearly observed with an ultrasonic microprobe.[55] Sharma *et al.* described a series of five patients with lower GI bleeding, two of whom required EUS to identify the inevident rectal varices.[56]

We and others have reported EUS-guided coiling and/or CYA injection for rectal varices.[57-59] EUS-guided CYA injection has also been used for peristomal varices.[60] EUS was postulated to have the advantages of inevident varix visualization, perforating vein identification, precise delivery of treatment directly into the varix, ability to target therapy unhindered by luminal contents, and confirmation of the absence of flow after therapy using Doppler imaging.

## EUS-GUIDED PORTAL VENOUS ACCESS AND THERAPY

### *Portal vein access and pressure measurements*

PV angiography with pressure measurements can add important information for the management of patients with chronic liver disease and portal hypertension. Transcutaneous portal venography and pressure measurements are not performed in clinical practice due to technical difficulties and a high rate of complications.[61] Currently, portal pressure is measured indirectly as the wedged hepatic portal venous pressure gradient, which is an unreliable surrogate in cases of prehepatic, presinusoidal, and posthepatic portal hypertension.

The PV can be easily identified by EUS, permitting access, contrast injection, and pressure measurement using a standard FNA needle. These were first performed in the porcine model using a 22-gauge needle by the tranduodenal extrahepatic route.[62] In 15% PV pressure

measurements were not attainable, most probably due to the small needle caliber and difficulty holding a stable needle position within the PV for continuous monitoring. Complications such as intraperitoneal bleeding in 1 pig out of 19 and subserosal hematoma formation in all pigs were described. A different group demonstrated a good-quality portal angiography, enabling continuous portal pressure measurements over 1 h, with consistent results and minimal variability, achieved by the transhepatic route with a modified catheter.[63] Animal respiratory motions and movements of the endoscope operator did not influence the stability of the catheter within the PV. The transhepatic route is thought to prevent postprocedure hemorrhage due to a tamponade effect of the hepatic parenchyma on the needle and catheter track.

Huang *et al*. published the first study to measure the portal pressure gradient (PPG), the pressure gradient between the PV and the inferior vena cava (IVC)/hepatic vein (HV) in humans.[64] They used a 25-gauge needle passed either through the transduodenal extrahepatic or the transgastric intrahepatic routes. A 100% procedural success with no complications was reported. Patients with cirrhosis had significantly higher PPG. In further analysis, PPG had excellent correlation with the presence of varices, portal hypertensive gastropathy, and thrombocytopenia. Tsujino *et al*. combined EUS-guided liver biopsy and PPG measurements.[65] Adequate samples were obtained in 73% and recovery time was significantly shorter for the EUS procedure compared with percutaneous liver biopsy, with no reported complications. These studies establish the feasibility, efficacy, and accuracy of EUS-guided portal pressure measurement, aiding in diagnosis and management of portal hypertension. It also provides an accurate measurement of presinusoidal portal hypertension, as HV pressure gradient is not reliable in this setting.

### *EUS-guided FNA of portal vein thrombus*

PV thrombosis (PVT) is a common complication of hepatocellular carcinoma (HCC). Venous thromboembolism is also a frequent complication of pancreaticobiliary tumors, occurring in 20%–36%.[66-68] A malignant thrombus cannot be accurately distinguished from a bland thrombus by imaging studies, such as sonography, the usual modality used to detect a vascular thrombus.[69] Transabdominal US-guided sampling of a PV thrombus may lead to false-positive results if traversing through liver tumor tissue and potentially can cause serious biliary or other vascular injuries. Furthermore, HCC can be diffusely infiltrating without an obvious mass. EUS-guided FNA of PVT may overcome these limitations by enabling direct access to the PV. A few studies have reported EUS-guided FNA of PVT to be safe and provide sufficient tissue for the diagnostic staging of HCC.[70-73] The transduodenal approach to the extrahepatic PV is best suited for direct access to the PV without passing through liver tissue. EUS-guided FNA of PVT has also been described in patients with tumors other than HCC.[74] In addition to reports of EUS-guided FNA of PV thrombus, EUS-guided FNA of IVC thrombus to diagnose adrenocortical adenocarcinoma[75] and a pulmonary artery thrombus to diagnose a synchronous lung adenocarcinoma in a patient with pancreatic cancer[76] have been described.

EUS-guided FNA of remote malignant thrombi was reported in a large cohort study.[74] Cytology was positive or suspicious for malignancy in 12 out of 17 patients. Three patients were upstaged and two patients converted from a resectable to nonresectable disease. This study highlights the ability of EUS to detect and diagnose occult tumor thrombi, which impacts cancer staging.

### *EUS-guided portal venous blood sampling*

An additional role for EUS-guided diagnosis can be the collection of circulating tumor cells (CTCs) from portal venous blood. This is of particular interest in pancreaticobiliary tumors, CTCs of which are theoretically sequestered in portal circulation and filtered in the liver, thus possibly explaining their inconsistent detection in peripheral blood.[77] This has been demonstrated in a study by Catenacci *et al*., in which CTCs were found in significantly more patients in the PV than in peripheral blood. Furthermore, a significantly higher number of CTCs were found in portal blood than in peripheral blood,[78] sufficient enough to perform genomic and proteomic profile of the CTCs.

### *EUS-guided portal vein embolization*

Selective PV embolization has been performed in animals before liver lobectomy to induce affected lobe atrophy and hypertrophy of the functional liver remnant.[79,80]

### *EUS-guided liver-directed chemotherapy and radiotherapy*

With limited treatment options, patients with diffuse liver metastasis resort to palliative systemic

chemotherapy. However, hepatic tissue drug levels may be suboptimal, limited by concurrent systemic toxicities, driving the need for targeted liver therapy. Transarterial microbead injection into the hepatic artery affords higher hepatic drug levels with lower systemic levels, but risks ischemic biliary strictures, as the bile duct blood supply relies on the hepatic artery. EUS-guided PV injection of chemotherapy has been described in animal models.[81,82] Drug-eluting microbeads or nanoparticles were successfully injected with resultant significantly higher liver levels and lower systemic levels, in comparison to the levels achieved by systemic injection. These trials are encouraging as a new modality for hepatic metastases treatment while decreasing the systemic toxicity and biliary tract sclerosis rate associated with hepatic artery infusion therapy.

CT-guided implantation of iodine-125 seeds into PV tumor thrombi has been reported by Zhang *et al.*[83] Out of 10 patients with PV tumor thrombosis secondary to HCC, five patients responded completely, five patients had a partial response, and 1 patient had a stable disease course. An EUS-guided approach would have theoretical advantages of more direct access with a decreased risk of vessel injury and malignant cell seeding.

### *EUS-guided creation of intrahepatic portosystemic shunt*

TIPS is a well-recognized and frequently used treatment of portal hypertension and its complications, mainly for the prevention of acute or recurrent variceal bleeding and refractory ascites.[84-86] Buscaglia *et al.* described the first EUS-guided creation of an intrahepatic portosystemic shunt in a live porcine model.[87] Under EUS guidance, the HV and the PV were sequentially punctured, contrast was injected to confirm needle location within the PV, after which a guidewire was advanced through the needle to the PV, the needle was then removed and the stent was inserted over the wire with its distal end in the PV and its proximal end in the HV. There were no complications, including a 2-week survival period in two pigs.

Binmoeller *et al.* used a similar technique to deploy a fully covered lumen-apposing metal stent (LAMS) in a porcine model.[88] Necropsy confirmed successful stent placement between the PV and the HV with no tissue injury or hematomas. Schulman *et al.* successfully deployed a LAMS for the creation of TIPS in five pigs.[89] Placement of LAMS addressed the concern of stent migration. Technical success was 100%, with no bleeding on necropsy, but with two pigs developing partial in-stent thrombosis. Long-term data, with refinements of devices and tools, are required before these procedures can be implemented in humans.

### *EUS-guided cardiac intervention*

The heart's proximity to the esophagus makes it accessible to EUS, as routinely used in cardiology. Fritscher-Ravens *et al.* performed porcine EUS-guided puncture of the heart, in which a 22- or a 19-gauge needle was introduced into the left atrium, left ventricle, coronary arteries, and aortic valve.[90] While under cardiac monitoring, the authors injected contrast agents, performed radiofrequency ablation of the aortic valve and inserted pacing wires. No arrhythmias during the procedure were recorded; no cardiac abnormalities before euthanasia and no bleeding or hematomas in necropsy were noted. Subsequently, the same group performed pericardial fluid aspiration in two patients and FNA of a 5 cm left atrial mass in a third patient with no adverse events. Larghi *et al.* described EUS-guided drainage of a pericardial cyst[91] with no complications. Romero-Castro *et al.* described EUS-guided FNA of a pericardial tumor.[92] No arrhythmias were noted. A stable 6-mm hyperechoic lesion at the puncture site, consistent with a hematoma, was noted after FNA. EUS-guided cardiac puncture of a right atrial tumor was recently described with no adverse event during the following 72 h.[93]

## CONCLUSION

The GI tract provides an excellent window to access vascular structures in the abdomen and mediastinum. Interventional EUS continues to evolve, offering new exciting diagnostic and therapeutic options. We can deliver sclerosants, CYA and coils into bleeding vessels, measure PV pressures, biopsy intravascular thrombus, collect circulating cells, and potentially access the heart and pericardium, all through a standard FNA needle. Data are still limited to either small numbers of patients or animal experimental studies. Clinical effectiveness and safety data are awaited from larger prospective controlled trials.

### *Conflict of Interest*

There are no conflicts of interest.

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