

EUS in portal hypertension

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SUMMARY

Endoscopic ultrasonography (EUS) has recently emerged as a most accurate, less invasive and easily repeatable alternative means of providing data on patients with portal hypertension. It is well established that video-echo endoscopy, with combined endoscopic and sonographic examination is comparable to endoscopy in diagnosing esophageal varices, but is more sensitive in diagnosing the presence of gastric varices. Dilated venous abnormalities outside the gastroesophageal lumen, which cannot be diagnosed by endoscopy, are readily visible by means of EUS or miniature probes. In the clinical setting of portal hypertension, endoscopic ultrasonography is also useful to predict the risk of variceal recurrence or rebleeding, which cannot be reliably predicted using endoscopy alone. The introduction of echo endoscopes equipped with Doppler facilities has allowed sonographic visualization of the vessels, playing an important role in cirrhotic patients, together with the performance of hemodynamic studies. It has thus become feasible, not only to assess the vascular blood flow, but also to evaluate possible morphologic and hemodynamic changes in the vessels after endoscopic or pharmacologic therapy. It is obvious nowadays that EUS is an exciting technological advance that has established its position in the diagnosis of varices and cirrhosis; what lies ahead is for EUS to find a definite application in predicting the risk of variceal bleeding and in the management of portal hypertension.

Key words: EUS, portal hypertension, gastroesophageal varices, variceal recurrence, rebleeding, venous blood flow

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INTRODUCTION

Over the past two decades, endoscopic ultrasonography (EUS) has undergone a transition from being a novel imaging technique to a clinical diagnostic test that is necessary for the optimal management of gastrointestinal diseases. Along with established clinical indications, such as gastrointestinal and pancreatic tumor staging, differential diagnosis of submucosal lesions, evaluation of solid and cystic pancreatic masses, detection of lymph nodes and fine needle aspiration (FNA), new applications have been suggested. Of great interest has been the effort of endosonographers to define a clinical role for EUS in portal hypertension.

Since its first use in the assessment of patients with portal hypertension in the mid-1980s¹, many conflicting studies have been published, all contributing to the recognition today of a definite role for EUS in diagnosing varices and portal hypertension and, moreover, in giving credit to EUS in relation to the assessment of the risk of recurrent varices and variceal hemorrhage and the evaluation of the success of pharmacologic, endoscopic and shunt therapy for portal hypertension.

DIAGNOSIS OF VARICES, PORTAL HYPERTENSION AND CIRRHOSIS

The venous anatomy of the lower esophagus is composed of four layers: intraepithelial channels, superficial venous plexus, deep submucosal veins and adventitial veins radiating from the inner esophageal mucosa to the outer layer². The innermost venous plexus communicates with the extrinsic plexus via perforating veins³, which are commonly present 1-5 cm above the gastroesophageal junction. These, in turn, drain into the tributaries of either the portal or azygos veins. Development of portal hypertension causes diversion of blood from the drainage bed of the portal vein to that of the azygos system, causing engorgement of all the afore-

mentioned channels. Thus, the dilated deep submucosal veins are seen as variceal columns and the dilated adventitial veins form paraesophageal varices (PEV).

Currently, the most widely accepted modality for screening of gastroesophageal varices (GEV) is esophagogastroduodenoscopy (EGD), although it may be subjected to high interobserver variation in the assessment of variceal size⁴⁻⁵, it lacks sensitivity in the diagnosis of gastric varices (GV)^{6,7} and it cannot assess the variceal wall thickness. Endosonography (EUS) has been used in the evaluation of cirrhotic patients. The results with the older, large-bore fiberoptic echo endoscope, and the use of the balloon-insufflation technique, which caused esophageal wall compression resulting in lower sensitivity of EUS in detecting esophageal varices (EV), were disappointing^{7,8}. EUS was able to demonstrate only 14% of grade I, 78% of grade II and 50% of grade III esophageal varices in patients with endoscopically confirmed EV⁷, results that were confirmed in another study, which concluded that EUS could detect only 25% of grade I, 73% of grade II and 89% of grade III EV⁸. With advances in technology, the new generation video-echo endoscopes has a significantly reduced scope diameter, and an improvement in ease of scope manipulation and endoscopic image. Thus, by directly visualizing the esophageal lumen, rather than relying only on sonographic examination, the diagnosis of esophageal varices is enhanced. As was shown in a recent study⁶, EUS seems to be as good as EGD for the screening of EV, with a sensitivity, specificity, PPV and NPV of 96.4%, 95.8%, 96.4% and 95.8%, respectively (Table 1). Moreover, in the same study, the superiority of EUS in detecting gastric varices in comparison to EGD was once more demonstrated, as in previous publications⁸⁻¹⁰. Using EUS as the gold standard, the sensitivity, specificity, PPV and NPV of EGD in diagnosing gastric varices were 43.8%, 94.4%, 77.8% and 79.1%, respectively (Table 1). Finally, the use of high-frequency (20 MHz) miniature US probes can also increase the sensitivity in detecting GEV¹¹.

Apart from the gastroesophageal varices, as referred to previously, portal hypertension causes engorgement and increased blood flow in the collateral vessels surrounding the lower esophagus and proximal stomach

outside the esophageal wall. The collateral veins are divided into peri-esophageal (peri-ECV), which are located adjacent to the muscularis externa of the esophagus and para-esophageal collateral veins (para-ECV), which are external to the esophageal wall, with no contact with the muscularis externa. Similarly, collateral veins surrounding the proximal stomach are divided into perigastric (peri-GCV) and para-gastric collateral veins (para-GCV). Veins connecting peri-ECVs with para-ECVs are called connecting veins, whereas those connecting esophageal varices with peri-ECVs, are perforating veins. Although these vessels have been examined by percutaneous transhepatic portography (PTP)², this is an invasive method which is also unable to differentiate the submucosal varices from peri-ECVs. CT is highly costly and not very sensitive in detecting paraesophageal varices¹²⁻¹³. With the availability of better instrumentation, both the anatomy and physiology of the venous circulation of the esophagus and stomach can be characterized with relative clarity by endoscopic ultrasonography^{6,14-16}. Based on the venous abnormalities, it was found that the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of EUS in diagnosing portal hypertension (PHT) were 92.3%, 94.6%, 84.2% and 97.5%, respectively, whereas the sensitivity, specificity, PPV and NPV of using EGD alone in diagnosing PHT were 57.7%, 100%, 100% and 88.3% (Table 2), as EGD does not detect the extraluminal vascular changes that occur in PHT⁶. These results were echoed in another study, where the presence of peri-ECVs was 97% sensitive and 97% specific for cirrhosis, a diagnostic yield significantly better than endoscopy, which identified esophageal varices in 74% of patients with cirrhosis¹⁶. Moreover, it was shown that the higher the variceal form at endoscopy, the more readily were peri-ECVs visualized at EUS, in contrast to the situation for para-ECVs, where no significant correlation was observed between ECVs and extent of development of para-ECVs¹⁵. This is in contrast with a more recent study, where it was shown that both para-ECVs and peri-ECVs were associated with large esophageal varices⁶. This discrepancy was attributed by the writers to the large sample size and to the use of the echo endoscope rather than the miniature ultrasound

Table 1. EUS and EGD in diagnosing esophageal (EV) and gastric (GV) varices respectively

	Sensitivity	Specificity	PPV	NPV
EUS in diagnosing EV	96.4%	95.8%	96.4%	95.8%
EGD in diagnosing GV	43.8%	94.4%	77.8%	79.1%

Table 2. EUS and EGD in diagnosing portal hypertension

	Sensitivity	Specificity	PPV	NPV
EUS	92.3%	94.6%	84.2%	97.5%
EGD	57.7%	100.0%	100.0%	88.3%

probe, which may underestimate the prevalence and degree of para-ECVs due to the limited penetration depth. The latter study additionally demonstrated a positive correlation between the size of peri-ECV and para-ECV with the Child-Pugh grading of cirrhosis, and between the grade of gastric varices with the size of para-GCV and peri-GCV, and confirmed previous data about the strong association between the perforating veins and the grade of esophageal and gastric varices.

Another difference between cirrhotic and noncirrhotic patients recognized by EUS, was the thickness of gastric mucosa and submucosa, which was found to be greater in cirrhotic patients, reflecting the relative outflow obstruction of venous and lymphatic flow in these patients¹⁶.

The dilation of the azygos vein is an issue that has provoked much controversy. Although one study reported that portal hypertension causes dilation of splenic vein, portal vein and upper mesenteric vein when comparing EUS findings in cirrhotic and noncirrhotic patients, it had no significant influence on the diameter of the azygos vein⁸. This was validated in a later study, where patients with more severe liver disease did not have significantly larger azygos vein diameters¹⁷. However, other studies did show a significant dilation of the azygos vein in cirrhosis^{7,16,18}, as it constitutes the main drainage pathway for the superior portosystemic collateral circulation.

Another sign of portal hypertension, identifiable by EUS seems to be the dilation of the thoracic duct^{8,16,19}. The hepatic venous outflow obstruction and increased hepatic lymph formation cause distention of the hilar lymphatics, resulting in increase of lymph flow through the thoracic duct. Even though the dilation of the thoracic duct was found only in patients with ascites and varices in one study¹⁹, a larger sample size should be evaluated in order to identify differences between subgroups of cirrhotic patients. Nonetheless, EUS may be useful for studying the thoracic duct to determine its potential role in ascite formation.

EUS can also be used for detecting rectal varices. As was shown in one study²⁰, prevalence of rectal varices was 43.3% on endoscopy and 75% on EUS, whereas

congestive rectopathy was found in 38.3% of patients. These vascular changes seemed to be influenced by sclerotherapy, but not by the grade of esophageal varices, the etiology of portal hypertension, or severity of liver disease.

What is of great importance, is the ability of the new generation linear echo endoscopes to evaluate the vascular blood flow, by using Duplex or Doppler sonography (CD-EUS). Thus, diminished or reversed direction of vascular blood flow or even the patency of a vessel or a shunt can be recognized. Other methods used to measure the azygos blood flow are the invasive thermodilution technique²¹ and the MR angiography²², which, although noninvasive, does not allow continuous hemodynamic measurement. The hemodynamic study of the azygos vein can easily be carried out by CD-EUS, on a straight segment of the vein. Azygos blood flow (AzBF) appears as a smooth venous tracing in the spectral display with small fluctuations associated with the patient's breathing^{17,18}. Maximal blood flow velocity seems to be increased in patients with portal hypertension and gastroesophageal varices¹⁸, indicating that AzBF is related to the severity of liver disease as reflected in Child-Pugh grading¹⁷. The morphology and the blood flow of the left gastric vein (LGV) has been studied by means of Color-Doppler EUS²³ which showed that, although the diameter of the LGV trunk increased as the size of the varices increased, the increase in diameter was not statistically significant; what was more important for the development of varices was the increased hepatofugal flow velocity. Furthermore, the branching pattern of the LGV, as described in other studies using left gastric venography^{24,25}, and its relationship with topographic collateral channels was demonstrated, concluding that dominance of the anterior branch may be responsible for directing LGV blood flow toward varices at the level of the proximal stomach. Finally, Duplex endosonography can be used to identify the patency of intra-abdominal vessels, such as splenic and portal vein, or of a portosystemic shunt when transabdominal ultrasound is nondiagnostic in patients with suspected thrombosis²⁶.

ASSESSMENT OF THE RISK OF RECURRENCE OF VARICES AND REBLEEDING

As has been previously mentioned, hepatofugal blood flow velocity in the LGV trunk, and also the branching pattern, have been associated with variceal recurrence²³. Even after endoscopic variceal ligation or sclerotherapy,

the increased hepatofugal velocity and the anterior branching pattern, documented by Color Doppler EUS, were still found to be risk factors for recurrence²⁷. The detection rate and diameter of the perforating veins may also be a predictor of variceal recurrence²³.

In an early study, it was found that patients with paraesophageal varices may develop esophageal variceal recurrence more frequently after endoscopic sclerotherapy²⁸. In another prospective study, patients after receiving endoscopic variceal ligation were examined by EUS to determine the size of para-ECVs; patients with large (>5 mm) para-ECVs had a higher risk of developing recurrence of varices (93%) and bleeding (43%) than those with small or without para-ECVs (46% and 12% respectively)²⁹ (Table 3). These findings were confirmed by two subsequent studies, where, in the first, patients with large para-ECVs had a higher EV recurrence rate, irrespective of the initial treatment method³⁰ whereas in the second, it is suggested that the presence of para-ECVs or para-GCVs 5 mm or greater in diameter may be a risk factor for a first variceal hemorrhage as well¹⁶.

Severe type peri-ECVs and large perforating veins were observed when endoscopic recurrence was found in another study³¹. Moreover, these findings were also observed 3 months before endoscopic recurrence, indicating that development of peri-ECVs and large perforating veins detected by EUS may be precursors to the endoscopic variceal recurrence. Although this study showed that the veins at the esophagogastric junction had no significance for predicting variceal recurrence, the presence of multiple intramural vessels in the cardia may predict recurrence, as was demonstrated in a previous study where, as the presence of these vessels increased, the rate of variceal recurrence also increased³².

Furthermore, in assessing the risk of variceal bleeding, EUS is very useful, as it allows the evaluation of the variceal size and variceal wall thickness³³, the measurement of intravariceal pressure by direct puncture of the varices³⁴ or by using a pressure sensitive gauge³⁵ or by

Doppler-guided manometry³⁶, and the detection of high-risk stigmata of varices, such as the red hematocystic spot which can be identified by miniprobe³⁷.

EVALUATION OF THE SUCCESS OF ENDOSCOPIC THERAPY

It is well known that varices recur more commonly among patients who undergo endoscopic variceal ligation (EVL) compared with those who receive endoscopic injection sclerotherapy (EIS)^{38,39}, as EVL provokes mechanical strangulation of the varices in the mucosal and submucosal layers, leaving the perforating veins, which join the submucosal vascular channels to para-ECVs, untouched. On the other hand, sclerotherapy may be able to obliterate the perforating veins and feeding veins, while chemical irritation caused by the sclerosants induces fibrosis and thickening of the inner esophageal wall, preventing variceal recurrence.

By using miniprobes, perforating veins can be identified and bands can be applied to them, thus increasing the success of EVL⁴⁰ and the variceal recurrence-free interval⁴¹. Moreover, by using Color-Doppler EUS, the sclerosant can be injected until the varix is seen to be completely thrombosed, as indicated by the absence of flow on Doppler, or it can be directed to the level of the perforating veins⁴². Thus, the number of sessions required for obliteration of esophageal varices and the recurrence rate may be decreased. Additionally, EUS can be of value in detecting residual varices, which are less apparent in endoscopy after several sessions of sclerotherapy, because of overlying ulceration, edema and formation of pseudopolyps. The same stands for the gastric varices, which cannot be easily detected endoscopically, and then usually after cyanoacrylate injection for controlling gastric varices bleeding⁴³. EUS can easily identify residual gastric varices as submucosal anechoic vascular channels with a color Doppler signal. Persistence of blood flow as detected by CD-EUS is associated with a higher failure rate of variceal obliteration by endoscopic treatment and with a higher risk of gastric variceal recurrent bleeding compared to those without detectable blood flow⁴³. It is also noteworthy, that patients who underwent repeated EUS-guided cyanoacrylate injection had a significantly lower risk of rebleeding and the recurrent bleeding-free survival, although overall mortality was not significantly changed, was significantly improved, in comparison to the patients who received on-demand injection only at the time of recurrent bleeding⁴³.

Table 3. Risk of variceal recurrence and rebleeding according to para-ECVs' size

Size of para-ECVs	Variceal recurrence	Variceal rebleeding
>5 mm	93%	43%
<5 mm	46%	12%

EVALUATION OF THE EFFECTS OF PHARMACOLOGIC THERAPY

As has been previously mentioned, by using CD-EUS, the AzBF was found to have a positive association with the severity of liver disease as reflected in Child-Pugh grading¹⁷. A marked reduction in AzBF was documented after intravenous injections of terlipressin or somatostatin, being, in the case of somatostatin, more dramatic in the first minute after bolus injection¹⁷. These findings were confirmed in another study⁴⁴, where continuous infusion of somatostatin or octreotide was applied so as to assess the effects of these drugs in AzBF and in gastric mucosal blood flow (GMBF). An immediate and transient decrease in AzBF and GMBF was demonstrated, despite continuous infusion of either drug; in addition, somatostatin induced a significant rebound effect 60 min after administration, suggesting the existence of a desensitization phenomenon. Finally, patients on propranolol or isosorbide-5-mononitrate were examined by serial EUS and endoscopic gauge measurement to determine the effect of these drugs on variceal volume and pressure³⁵; whereas isosorbide-5-mononitrate reduced only transmural variceal pressure, in the case of propranolol, the overall reduction in the variceal wall tension exceeded that contributed by transmural pressure change, showing that propranolol reduced not only the variceal pressure but also the variceal column radius and volume.

CONCLUSIONS

The use of endoscopic ultrasonography in the assessment of patients with portal hypertension has proved to be of great value. EUS is now considered as good as endoscopy for the screening of esophageal varices with a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 96.4%, 95.8%, 96.4% and 95.8% respectively, whereas it was found to be superior to endoscopy for the detection of gastric varices. In contrast to EGD, EUS is able to detect the presence of collateral veins, such as peri-esophageal, para-esophageal collateral veins and perforating veins; thus it can accurately diagnose portal hypertension with a sensitivity, specificity, PPV and NPV of 92.3%, 94.6%, 84.2% and 97.5% respectively.

Peri-ECVs and para-ECVs diagnosed by EUS seem to be associated with large esophageal varices, gastric varices and the Child-Pugh grading, thus indicating the patients with a high risk of recurrence. Other reported EUS features of portal hypertension, such as dilatation

of the azygos vein, splenic vein and portal vein, increased diameter of the thoracic duct, thickening of gastric mucosa and submucosa, the presence of portal hypertensive gastropathy and the presence of rectal varices, can be evaluated whenever there is a suspicion of portal hypertension and, in this way, contribute to the diagnosis. Additionally, EUS allows the evaluation of variceal size, variceal wall thickness, intravariceal pressure and presence of high-risk stigmata, thus predicting the risk of recurrent bleeding.

Color-Doppler EUS (CD-EUS) is very helpful in the assessment of vascular blood flow. Studies have shown that patients who present hepatofugal blood flow in the left gastric vein and anterior-dominant branching pattern are at greater risk of developing recurrent varices. Moreover, in predicting recurrence, EUS showed that patients with recurrent varices had a significantly higher incidence of severe-type peri-ECVs, a significantly larger number and diameter of perforating veins and a higher incidence of intramural vessels in the cardia. It would thus be advisable that, when these vascular changes are detected, closer endoscopic follow-up or aggressive medical therapy be applied to these high-risk patients.

CD-EUS can also be used for the management of varices, since obliteration of esophageal varices could be achieved by direct treatment to the perforating veins rather than to the varices and obliteration of gastric varices by repeated cyanoacrylate injection in the gastric varices; the number of sessions required and the recurrence rate could then be decreased.

Finally, the combination of EUS morphologic assessment and simultaneous pressure measurement may be a useful and accurate tool in the evaluation of drug effect in the treatment of portal hypertension, helping the clinician to select appropriate drug therapy.

In conclusion, EUS is an invaluable imaging method for investigating cirrhotic patients. Although its role in the evaluation of bleeding risk and response to therapy is still not well defined, the fact is that EUS provides an accurate diagnosis of portal hypertension, identifies high-risk patients and allows the assessment of success of endoscopic and pharmacologic therapies.

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