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RESEARCH ARTICLE

Endoscopic Ultrasound-Guided Portal Pressure Gradient Measurement, Is It Ready for Prime Time?

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ABSTRACT

Portal hypertension is a serious complication of advanced liver disease. Portal pressure gradient measurement accurately determines severity of portal hypertension, prognosis, and guides medical therapy. Conventionally, interventional radiology-guided hepatic venous portal gradient measures portal pressure gradient indirectly using specialized balloon catheter. Recent advances in endoscopy have paved the novel method of endoscopic ultrasound-guided direct portal pressure gradient measurement to evaluate portal hypertension with equivalent safety in both animal models and humans studies. With the expansion of Endo-Hepatology practice, a concept of "one stop shop" is becoming more popular which is a comprehensive endoscopic approach in the evaluation of chronic liver disease. During the same endoscopic procedure, patients could be evaluated for esophageal or gastric varices, portal hypertensive gastropathy, EUS-guided elastography, EUS-guided portal pressure measurement and EUS-guided liver biopsy when suspecting advanced liver disease or diagnosis remains uncertain. This article focuses on the overview of portal hypertension and EUS-guided interventions such as EUS-guided portal pressure measurement, EUS-guided elastography and EUS-guided liver biopsy in the evaluation of individuals with advanced liver disease.

Keywords: Endoscopic ultrasound, Fine needle biopsy, Portal hypertension, Portosystemic pressure gradient measurement, Hepatic venous pressure gradient, Cirrhosis

Introduction

Portal hypertension (PH) is an increase in portal venous pressure due to high resistance of hepatic sinusoidal blood flow. Cirrhosis is one of the most common intrahepatic causes of PH which is associated with high morbidity and mortality from associated complications including bleeding from esophageal varices, severe portal hypertensive gastropathy, ascites and hepatic encephalopathy[1]. Common non-cirrhotic etiologies of PH are pre-hepatic causes due to vasculature disruption proximal to the liver (portal vein thrombosis, splenic vein thrombosis, splanchnic arteriovenous fistulas), post-hepatic causes due to disruption of vasculature distal to the liver such as hepatic vein (HV) or inferior vena cava (IVC) obstruction such as Budd-Chiari syndrome, pulmonary hypertension, and cardiac diseases (right-sided heart failure, restrictive cardiomyopathy and constrictive pericarditis). Given these debilitating complications and mortality due to untreated PH, defining the severity of PH is critical for the staging, management, and prognosis of patients with chronic liver disease. Furthermore, if uncertainty exists in patients without a history of cirrhosis or preexisting risk factors, portal pressure gradient (PPG) measurement can confirm the diagnosis and aid in treatment. Recent advances have paved the way for endoscopic ultrasound-guided portal pressure gradient (EUS-PPG) measurement with promising results both in animal models and humans studies[2-5].

Pathophysiology of portal hypertension

The structural or dynamic changes of hepatic circulation results in PH. Alteration of hepatic microcirculation due to hepatic fibrosis, nodularity, vascular obstruction, or angiogenesis causes structural changes. Dynamic changes result from imbalance of vasoconstrictive and vasodilator cytokines. An overproduction of vasoconstrictive cytokines (such as norepinephrine, endothelin, angiotensin II, thromboxane A2) and underproduction of vasodilators (nitric oxide) results in contraction of activated stellate cells and myofibroblasts lining the inner surface of hepatic sinusoids and vascular smooth muscle cells. This effect creates an increased resistance of blood flow through hepatic vasculature resulting in PH. With sustained PH, blood flow to splanchnic circulation increases due to splanchnic vasodilator (nitric oxide, endothelial growth factors), rendering underfilling of systemic vasculature resulting in systemic hypotension that activates the renin-angiotensin system to increase cardiac output through systemic vasoconstriction and volume expansion.

Hepatic venous pressure gradient

Hepatic venous pressure gradient (HVPG) is an indirect method to measure PPG that was first used in 1950's to evaluate the severity of PH[6]. The utility of HVPG has expanded to large tertiary centers due to clear benefits of this modality in the clinical assessment of advanced liver disease[6]. PH is defined as a HVPG >5 mmHg. Mild PH is defined as a HVPG 6-9 mm Hg, whereas clinically significant PH (CSPH) is defined as a HVPG of

10-12 mm Hg or greater or presence of PH complications such as ascites, esophageal or gastric varices, and bleeding varices[6,7]. Recently, Rodrigues *et al.* evaluated correlation of HVPG with histological features of cirrhosis on liver biopsy[7]. In patients with HVPG ≥10 mm Hg, 16% did not have evidence of cirrhosis on liver biopsy, however, HVPG value ≥12 mm Hg correlated with histological features of cirrhosis with 92% specificity[7]. Esophageal varices developed with HVPG >10-12 mmHg[8]. In a randomized control trial, Groszmann *et al.* have shown an association of esophageal varices hemorrhage in patients with PPG > 12 mmHg[9]. Reduction of PPG to <12 mmHg or by 20% with pharmacological therapy prevented esophageal varices bleeding, decreased risk of recurrent hemorrhage, and reduced mortality[9-11].

Principles and methods of hepatic venous pressure gradient measurement

Traditionally, HVPG measurement is performed by interventional radiology (IR) using a balloon-tipped catheter, a quartz pressure transducer and pressure tracing recorder. Using local anesthesia or under sedation, a catheter introducer is placed into the internal jugular, antecubital or femoral vein[12,13]. Then, a balloon-tipped catheter is introduced through the catheter sheath and slowly advanced through IVC and HV under fluoroscopy while injecting contrast agent[12,13]. Once final position of catheter tip is confirmed at desired position in the HV, an occluded hepatic vein pressure (OHVP), also known as wedge pressure, is obtained with inflated catheter balloon. Pressure tracing values are measured for 45-60 seconds to obtain a sustained pressure reading through transducer attached to the catheter. After achieving stable pressure tracing, three measurements of OHVP are recorded. A mean value of three pressure readings is used as final OHVP. This is followed by recording of free hepatic vein pressure (FHVP) by deflation of balloon using similar technique. HVPG is obtained by subtracting FHVP from OHVP. Factors including patient's movements, coughing, and posing catheter tip too proximal in the HV to acquire FHVP may result in false readings. Measurement of HVPG is an invasive procedure, currently performed in only high-volume centers requiring specially trained expertise.

Endoscopic ultrasound-guided portal pressure gradient measurement

Portal pressure gradient (PPG) represents a direct method for the assessment of hepatic perfusion pressure which is measured as a pressure gradient between the portal vein (PV) and the HV (or the IVC when access to HV is difficult due to altered anatomy)[14]. A wide availability of endoscopic ultrasound and recent advances in endoscopic tools has enabled a novel technique of direct PPG measurement using specialized needle with digital display (figure 1)[2-5].

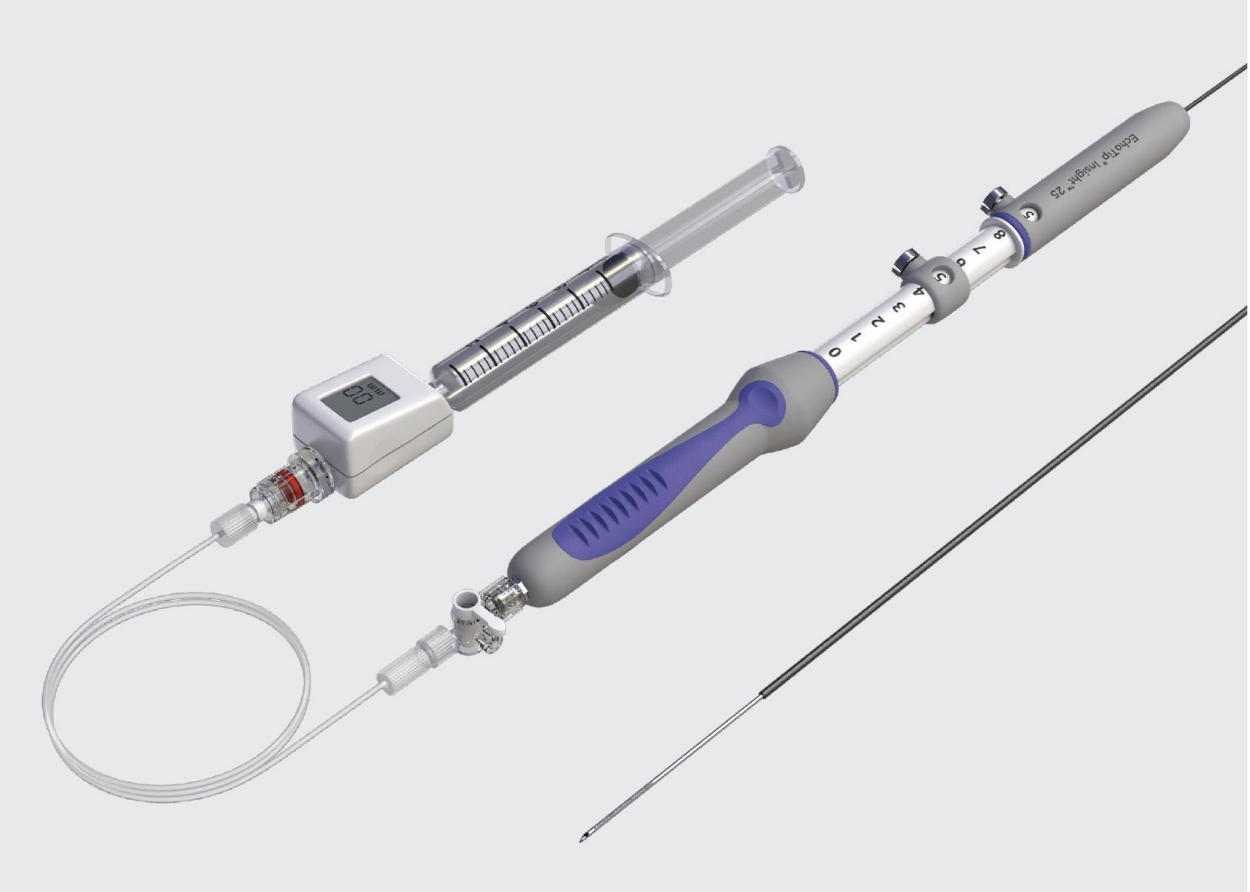

Figure 1: Portosystemic pressure gradient measuring system including a 5.2 French transducer sheath, 25-gauge (G) fine needle aspirate (FNA) needle, 8 cm adjustable needle extensions, compact manometer and noncompressible connecting tube. (Courtesy of Cook Medical USA).

Device/Apparatus

The apparatus for EUS-PPG measurement includes a forward viewing endoscope (GIF - 190 HQ, Olympus, Tokyo, Japan), a linear echoendoscope (GF-UC140P-AL5; or GF-UC180O-AL5; Olympus, Tokyo, Japan), EchoTip Insight portosystemic pressure gradient measuring system including a 5.2 French transducer sheath, 25-gauge (G) fine needle aspirate (FNA) needle (Cook Medical, Winston-Salem, NC, USA), 8 cm adjustable needle extensions, self-calibrated pressure transducer, compact manometer and 90 cm noncompressible connecting tubing (Cook Medical, Bloomington, Ind, USA). The compact manometer can display pressure range from -199 to +999 mm Hg on a 2 cm × 3 cm × 2 cm digital display. It is FDA approved and commercially available since 2020 (figure 1).

Principles and methods of endoscopic ultrasound-guided portal pressure gradient measurement

Endoscopic ultrasound-guided PPG measurement is a unique procedure and should be performed by specially trained therapeutic endoscopist. Under general

anesthesia, an esophagogastroduodenoscopy (EGD) is performed with a forward viewing endoscope for evaluation of clinical features of portal hypertension such as esophageal or gastric varices, and portal hypertensive gastropathy which is commonly seen in patients with cirrhosis. After EGD exam, EUS is performed using an echoendoscope to assess vascular anatomy of liver, parenchymal tissue, and morphological changes of liver due to cirrhosis such as hepatic surface nodularity, dilated splenic vein or portal vein, presence of collaterals, and ascites. A standardized technique for EUS visualization of HV is to trace IVC with positioning of linear echoendoscope in the gastric cardia[15]. From proximal to distal scanning of IVC from stomach, right hepatic vein (RHV) comes off first, followed by middle and left hepatic vein (LHV)[15]. Middle hepatic vein (MHV) looks like an elephant trunk when it comes off from IVC. It is the preferred target of EUS-guided hepatic venous pressure because of its wider caliber lumen and straight trajectory of the needle on linear EUS. Doppler flow of HV branches shows classic pulsatile triphasic flow signals as opposed to PV which illustrates typical venous "hum" like monophasic flow signals.

Steps to setup portal pressure gradient measurement apparatus

Initially, pressure transducer is turned on. A 10 ml sterile heparinized saline syringe is attached to the luer lock located at the proximal end of transducer and proximal (female) end of non-compressible tubing at distal end of transducer secured with the luer lock. The other end of the connecting tube attaches to the inlet of FNA needle and secured with tightly fitted luer lock. The system is flushed with heparinized saline to remove air bubbles. The setup of the apparatus is simple, and usually takes less than 5 minutes. While portosystemic pressure gradient system is prepared by an assistant, the endoscopist may perform EUS-guided shear wave elastography for assessment of liver stiffness measurement (LSM) and steatosis which may aid in the diagnosis of advanced liver fibrosis (figure 2).

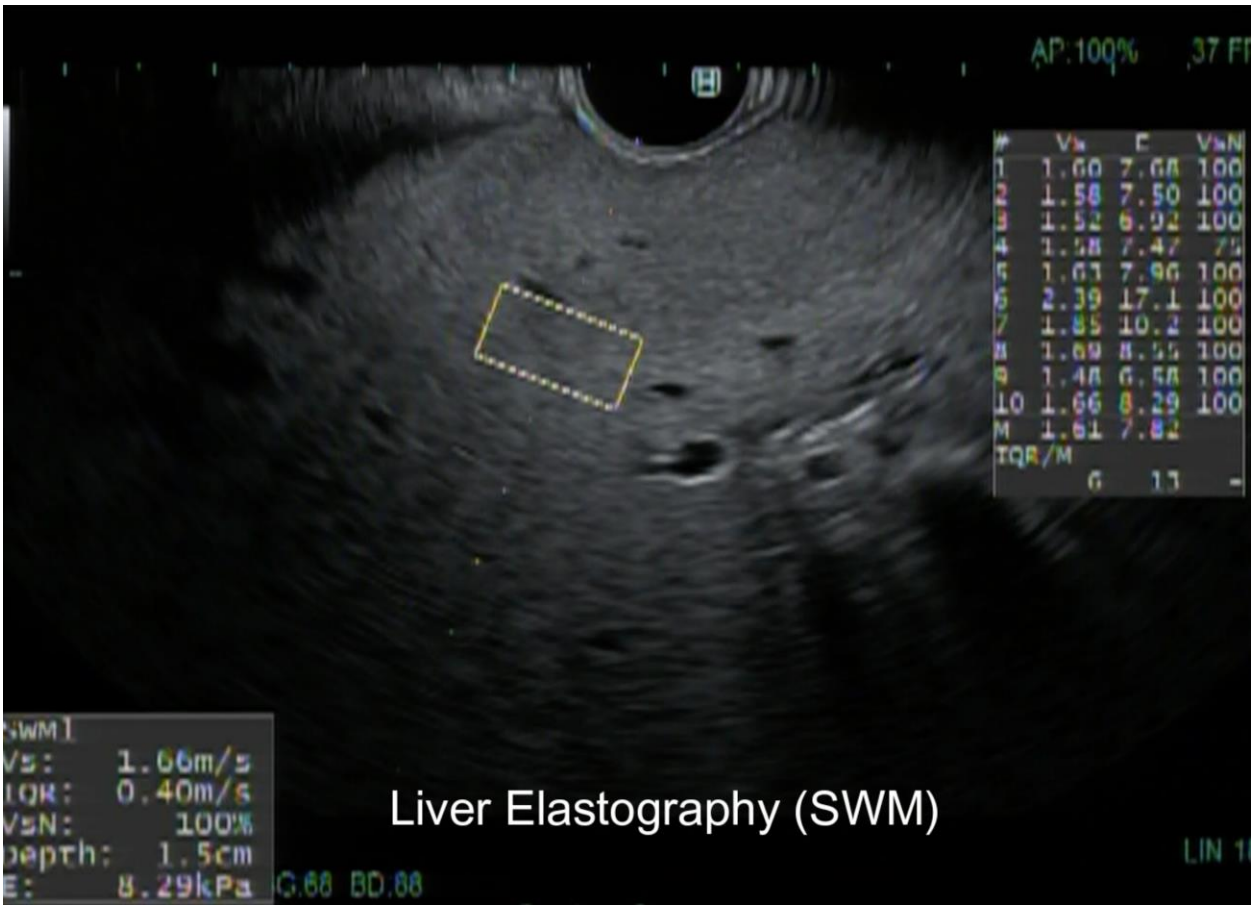

Figure 2: EUS-guided shear wave elastography to assess liver stiffness measurement and steatosis

Technique to measure endoscopic ultrasound-guided portal pressure gradient measurement

The technique has been described previously by Huang *et al*[4,5]. In preparation for EUS-PPG measurement, the patient is positioned supine. Before insertion of echoendoscope, the manometer is set to zero by holding it along left mid-axillary line at the level of heart. EUS with doppler is used to identify hepatic vein and to interrogate for significant doppler signals in needle path (figure 3). After confirming positioning of MHV (or LHV in some cases), hepatic vein is punctured with 25-G FNA needle through transgastric transhepatic approach (figure 4). A small amount of saline (usually 1ml) is flushed through the needle which produces visible bubbles to confirm position of needle tip in the lumen of vessel. This results in transient rise in pressure reading on digital manometer which drops to a sustained pressure state in 45-60 seconds. A sequential of three steady state pressure readings are measured and average of these readings is calculated as a final reading of hepatic venous pressure to minimize the variation or errors. Then FNA needle is slowly taken out from the HV and liver parenchyma back to the needle sheath. The needle tract is observed with EUS doppler

to ensure no significant blood flow signals which could be a sign of active bleeding. A gentle pressure by the tip of the echoendoscope at the site of puncture can be applied if significant flow signals are seen.

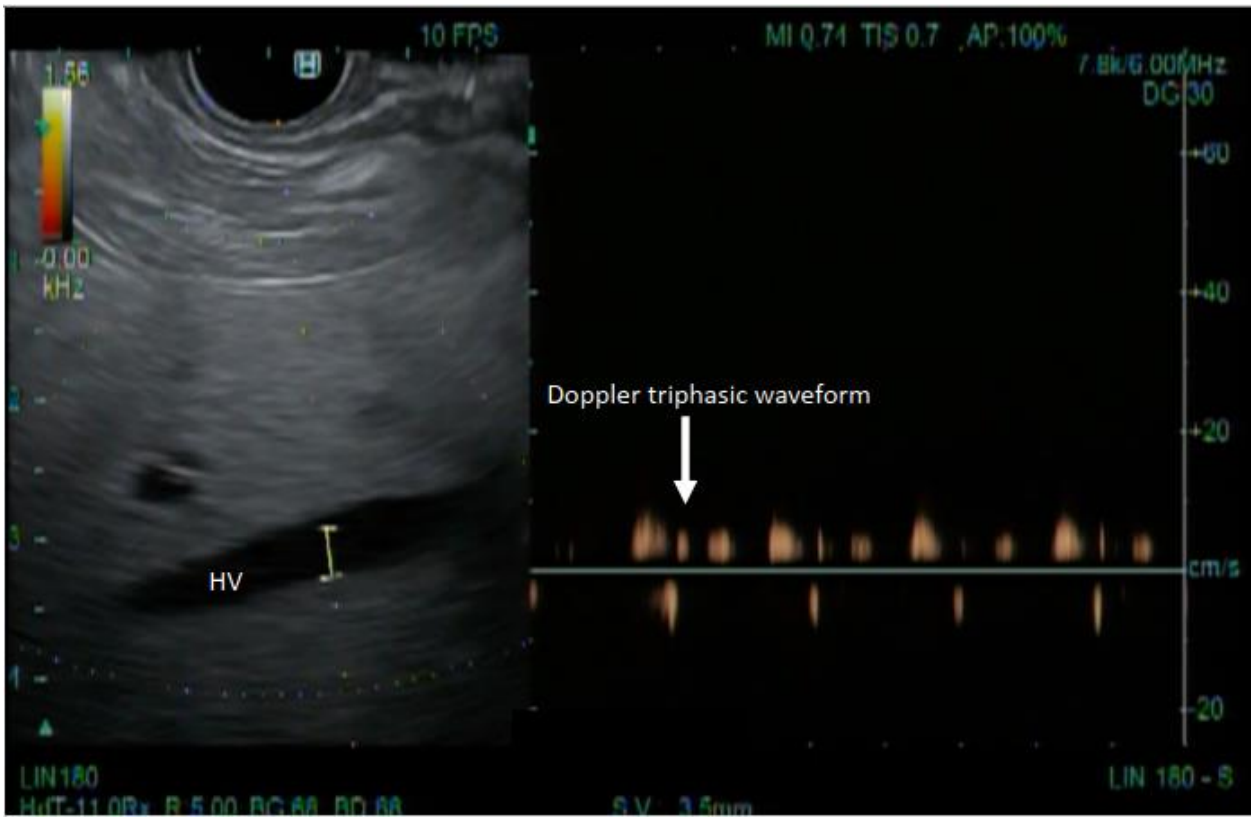

Figure 3: EUS doppler flow signals of middle hepatic vein (HV) demonstrating typical triphasic waveform

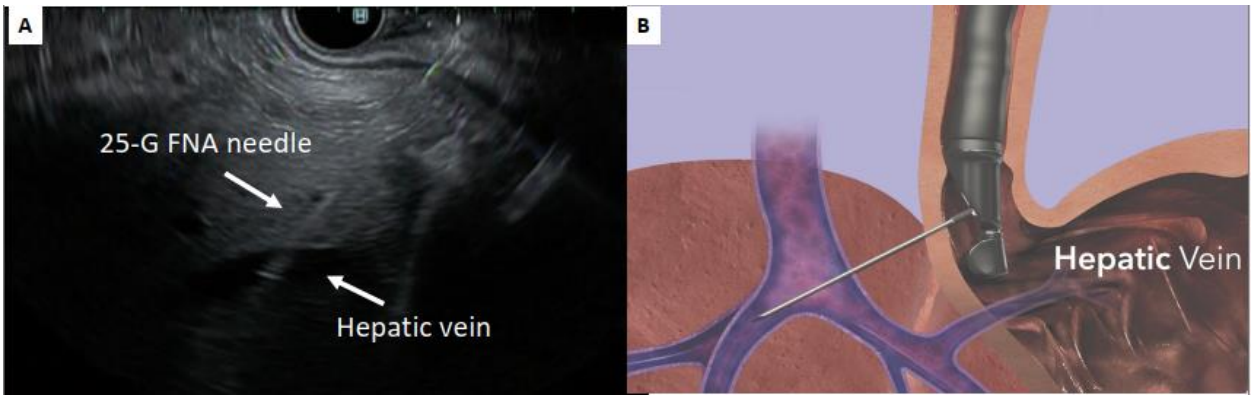

Figure 4: EUS-guided puncture of middle hepatic vein with 25-G FNA needle (panel A and B), Diagram in panel B adopted from Cook Medical USA.

To obtain portal vein pressure (PVP), the umbilical portion of left portal vein is preferred target which is identified using EUS doppler signals with typical monophasic

waveform (figure 5). Left Portal vein is punctured with 25-G FNA needle through transgastric transhepatic approach (figure 6). In cases of difficult access to left PV due to altered anatomy, access to right portal vein obtained through transduodenal approach. A small amount of saline (usually 1 ml) is flushed through the needle which produces visible bubbles to confirm position of needle tip in the lumen of vessel. This results in transient rise in pressure reading on digital manometer which drops to a sustained pressure state in 45-60 seconds. A sequential of three steady state pressure readings are measured and average of these readings is calculated as a final reading of PVP to minimize the variation or errors. Then FNA needle is slowly taken out from PV and liver parenchyma back to the needle sheath. The needle tract is observed with EUS doppler to make sure no blood flow signals due to active bleeding. EUS-PPG is calculated by subtraction of PVP from hepatic venous pressure. In certain cases, FNA needle access to HV is difficult due to its narrow caliber or inadequate window because of anatomical reasons. In such cases, IVC pressure is used to calculate PPG. If indicated, EUS-guided liver biopsy (EUS-LB) could be performed after PPG measurement to evaluate for advanced liver disease. Post-procedural antibiotics are recommended for 5 days. Patients are generally discharged on the same day after the procedure if vital signs are stable and recovery is uneventful.

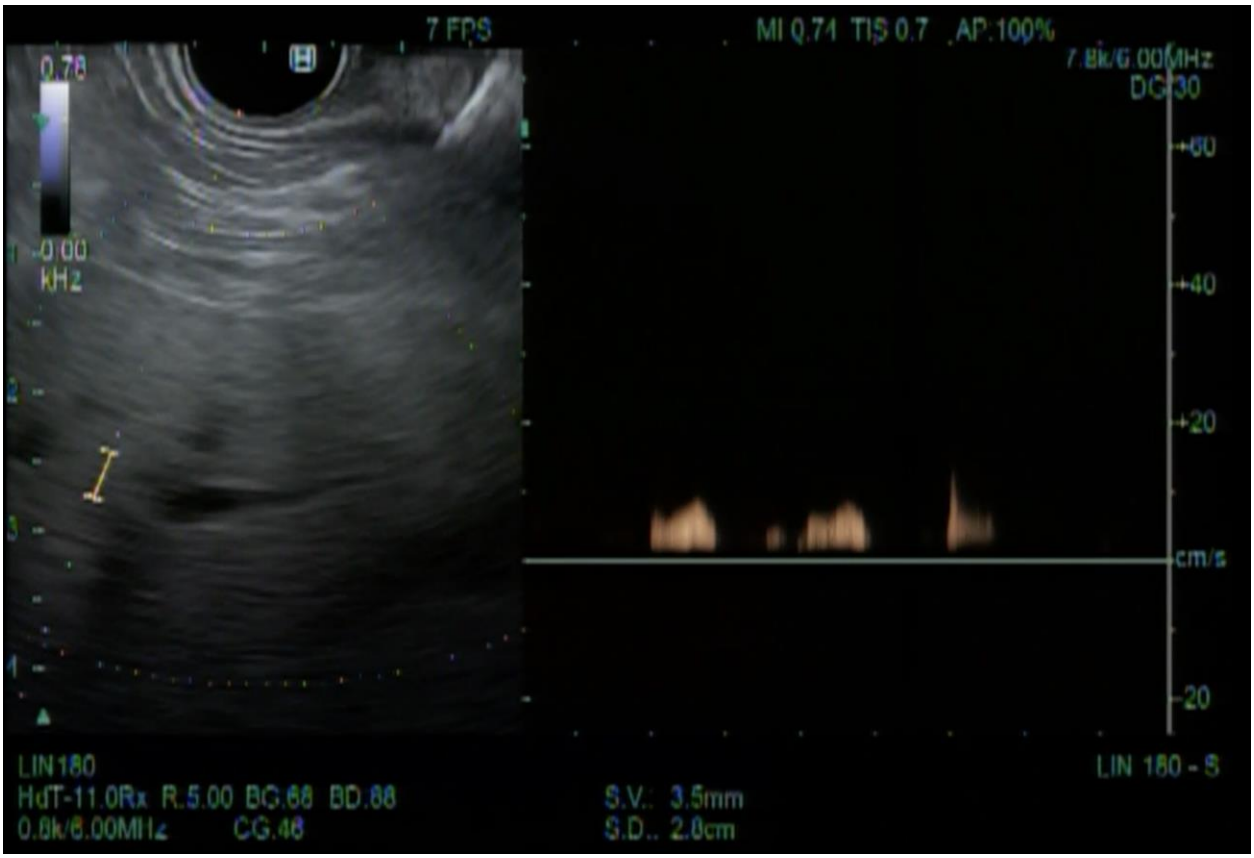

Figure 5: EUS doppler flow signals of portal vein (PV) demonstrating typical monophasic waveform

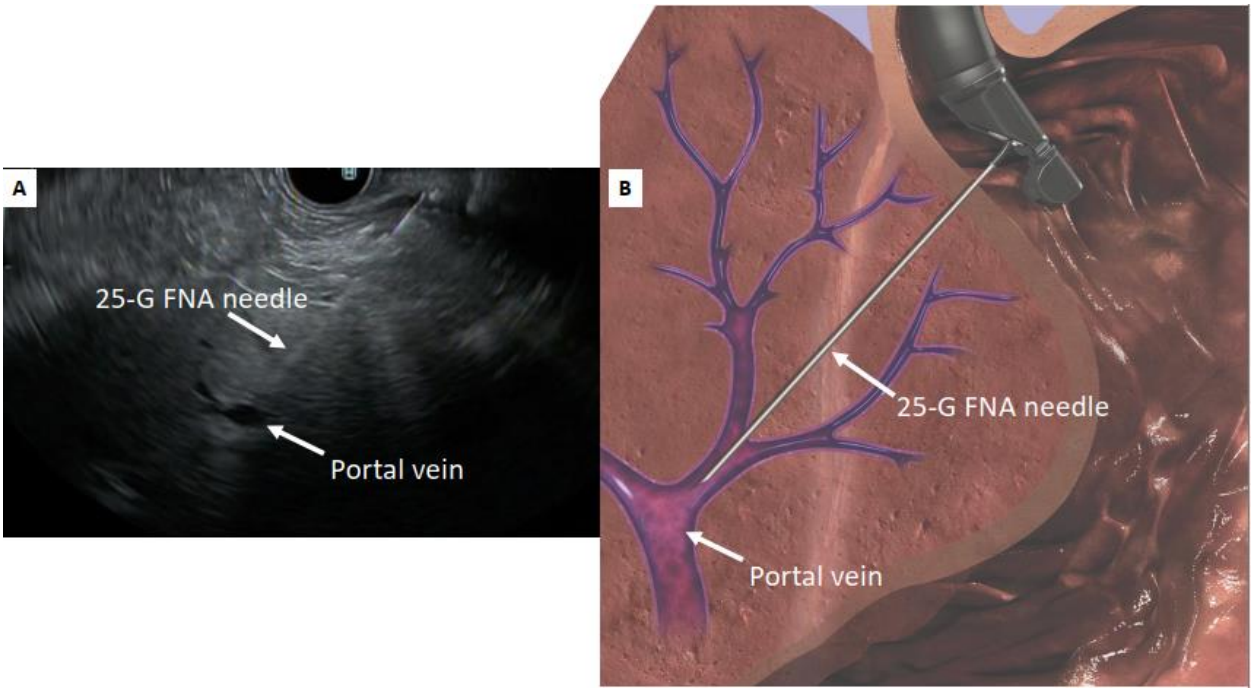

Figure 6: EUS-guided puncture of left portal vein with 25-G FNA needle (panel A and B), Diagram in panel B adopted from Cook Medical USA.

Feasibility and safety of endoscopic ultrasound-guided portal vein pressure measurement in animal models

In the past decade, the feasibility and safety of EUS-PPG measurement has been well established in animal models (Table1)[2,16-20]. In 2004, Lai *et al.* established a novel technique of EUS-PVP measurement for the first time in an animal model[16]. Feasibility of EUS-guided PV catheterization was evaluated in this pilot study using 21 farm swine that were divided into three groups including 7 normal, 7 with PH and 7 having both PH and coagulopathy. PH and coagulopathy were created by injecting polyvinyl ethanol particles and combining it with heparin injection respectively. The success rate of EUS-guided PV catheterization was 100% (21/21 pigs) using 22G FNA needle through transduodenal approach, while it was 64% (9/14) with transhepatic approach using transabdominal ultrasound. High quality PVP tracings were achieved in 86% (18/21) of pigs with EUS transduodenal approach and 64% (9/14) through transhepatic approach with strong correlation of PVP tracing between two approaches (r = 0.91). Obstruction of FNA needle with thrombosis was the proposed reason of failed EUS-PVP measurement. At necropsy, minor subserosal hematoma was noted at FNA puncture site in all pigs. Only one pig in the anticoagulation group had 25 ml hematoma between duodenum and liver with EUS-transduodenal approach.

Endoscopic ultrasound-guided transhepatic approach seems favorable since it was associated with minimal risks of hemorrhage and liver damage. Giday *et al.* assessed the feasibility of EUS-PVP through transgastric transhepatic approach in porcine model using

25-G FNA needle, and carbon dioxide (CO2) contrast agent[17]. Portal venography was performed in 6 pigs using iodinated contrast and CO2 contrast agent. The technical success rate of EUS-PV catheterization was 100% with no evidence of bleeding, hepatic or intra-abdominal organ damage at necropsy 30 minutes after the procedure. Opacification of PV with CO2 contrast agent was significantly better than viscous iodinated contrast (visualization score 4.33 ± 0.52 vs 1.33 ± 0.52; $p < 0.0001$) and longer opacification time (19.83 ± 1.68 vs 6.02 ± 1.15 seconds; $p < 0.0001$)[17].

Buscaglia *et al.* investigated the impact of different endoscopic procedures on PV, IVC and systemic pressures in porcine model with 19-G FNA needle through transhepatic approach using EUS and modified tapered tip catheter under fluoroscopy guidance and modified ERCP technique[18]. There was no significant increase in PV, IVC and systemic pressure during EGD and colonoscopy, however, with ERCP, a threefold increase in PVP was noted compared to baseline pressure (39.0 ± 15.2 mm Hg vs 13.4 ± 3.6 mm Hg; $p = 0.006$) that start rising with canulation, contrast injection into common bile duct and reached to peak pressure value at the time of sphincterotomy. The technical success rate of procedure was 100% in all (5/5) pigs. At necropsy, there was no evidence of complications such as damage to PV, IVC, bile duct, liver, surrounding organs and hemorrhage at sphincterotomy site.

In 2016, Schulman *et al*, established a novel technique of EUS-guided direct PVP measurement and compared the accuracy of PVP measurements with conventional transjugular HVPG[19]. EUS-guided PV access was confirmed with venogram using 22-G FNA needle. Direct PVP was measured by advancing a specialized wire into PV that is loaded with digital pressure sensor (3 cm from tip of wire) and transmitter enabling wireless transmission of real time pressure data on digital display. The technical success rate of procedure was 100%, baseline PVP ranged from 5 to 10 mm Hg and total procedure time was <5 minutes (range 2.3-4.7 minutes) in all 5 Yorkshire pigs. Compared to control transjugular HVPG, difference of EUS-PVP was ±1 mm Hg. There were no post procedural adverse events such as intra-peritoneal hemorrhage or PV thrombosis. In a later study, Schulman *et al.* evaluated the safety and feasibility of serial measurements of direct EUS-PVP compared with transhepatic access of first order venule using same device in a porcine model[20]. The technical success rate of procedure was 100% in all 5 Yorkshire pigs, mean baseline PVP ranged from 3 to 11 mm Hg (6.1 mm Hg), and mean procedure time was 3.6 minutes. All pigs survived for 2 weeks. EUS-PVP measurements on day 14 were comparable with baseline values. Post-mortem examination did not reveal hemorrhage, or vascular thrombosis.

Huang and colleagues demonstrated a novel technique of EUS-PPG measurement using 25-G FNA needle, compact manometer, and non-compressible tubing in a swine model[2]. Pressure measurements were obtained from PV, HV, IVC with EUS-transgastric transhepatic and conventional transjugular approach in 3

Yorkshire pigs at baseline and after induction of PH with rapid infusion of Dextrain-40. The technical success rate of vascular access and PPG measurement was 100% with a strong Pearson's correlation (r = 0.985-0.99) of pressure gradients between the two approaches. No adverse events were noted after either EUS or transjugular approach in all pigs.

Taken together from six animal studies including 45 pigs (weight range 40-55 Kg), the overall technical success rate of EUS-guided portal vein catheterization and PVP measurement is 100% (Table1)[2,16-20]. Transgastric transhepatic approach to access PV, HV or IVC is favored over transduodenal approach due to less risks of complications. Hematoma between duodenum and liver was reported in one study after transduodenal approach in a pig with PH and coagulopathy[16]. The safety profile of EUS-PVP measurement is excellent regardless of size of FNA needle (22-G vs 25-G vs 19G) [2,16-20].

Table 1: Feasibility of endoscopic ultrasound guided portal pressure measurement in animal models

Study Author (year)	Total subjects	Subjects	Subjects Weight (Kg)	Needle type	Approach	Catheter used	Technical success rate	Complications
Lai *et al.*[16] 2004	21	Pigs	40-50	22-G FNA	Transduodenal and transhepatic	NA	100%	Hematoma between liver and duodenum
Giday *et al.*[17] 2007	6	Pigs	50	25-G FNA	Transgastric transhepatic	NA	100%	None
Buscaglia *at al.*[18] 2008	5	Pigs	50	19-G FNA	transhepatic	Modified tapered–tip ERCP catheter	100%	None
Schulman *et al.*[19] 2016	5	Yorkshire pigs	40-55	22-G FNA	Transgastric transhepatic	Digital pressure sensor wire	100%	None
Huang *et al.*[2] 2016	3	Yorkshire Swine	43.5-48	25-G FNA	Transgastric transhepatic	Compact manometer with pressure transducer and non-compressible tubing	100%	None
Schulman *et al.*[20] 2017	5	Yorkshire pigs	40-55	22-G FNA	Transgastric transhepatic	Digital pressure sensor wire	100%	None

FNA; Fine needle aspiration, G; Gauge, NA; Not available, Kg; Kilogram

Feasibility and safety of endoscopic ultrasound-guided portal pressure gradient measurement in Human studies

Several studies have proven the feasibility and safety of EUS-PPG measurement in humans (Table 2)[5,21-27]. Currently, EUS-PPG measurement is being performed in selected large tertiary care centers with expertise to perform this procedure. The first human case report of EUS-PPG was published in 2004 by Fujii-Lau *et al.* for evaluation of PH and arteriovenous malformation resulting in recurrent upper gastrointestinal bleeding in a 27-year-old man with Noonan syndrome[21]. EUS-PPG was measured with 22-G FNA needle and arterial catheter. EUS-PPG of 1 mm Hg (PVP 11 mm Hg – MHV pressure 10 mm Hg) strongly correlated with IR-guided HVPG. Post-procedural hospital course remained uneventful without evidence of hemorrhage.

Huang *et al.* performed first prospective pilot study of EUS-PPG measurement using 25-G FNA needle, compact manometer, with pressure transducer and non-compressible tubing system in 28 patients (11 male) with known or suspected cirrhosis[28]. EUS-PPG was measured through transgastric transhepatic approach with similar techniques as described above. The technical success rate of EUS-PPG was 100%, average PPG 8.2 mm Hg (range 1.5-19 mm Hg), without evidence of major adverse events. CSPH was seen in 66.7% (11/28) patients which correlated with EGD findings of esophageal/gastric varices (p = 0.0002), portal hypertensive gastropathy (p = 0.007), and thrombocytopenia (p = 0.36). Logistic regression analysis demonstrated the odds of having thrombocytopenia and cirrhosis 6.1 (95% Confidence interval (CI), 1.19-38.38) and 18.7 (95% CI 2.97-180.66) folds higher with a PPG of 5 mm Hg or greater[28].

Zhang and colleagues prospectively compared efficacy and safety of HVPG with EUS-PPG measurement in 12 patients (9 male) with acute and subacute PH[22]. Rather than 25-G FNA needle, they used 22-G FNA needle with portosystemic pressure transducer system via transgastric transhepatic approach[22]. The technical success rate of EUS-PPG was 91.7% (11/12 patients), with comparable mean EUS-PPG 18.07 ± 4.32 mm Hg and HVPG 18.82 ± 3.43 mm Hg demonstrating an excellent Pearson's correlation r = 0.923 (p < 0.001) between two modalities. EUS-PPG measurement was unsuccessful in one patient due to failed access to narrow caliber IVC. Mean procedure time of EUS-PPG vs HVPG methods was 38.33 ± 15.41 vs 37.22 ± 6.18 minutes respectively (p = 0.862). Overall, there were no procedure rated complications. In a single center observational study of 26 patients with suspected cirrhosis, Martínez-Moreno *et al.* demonstrated 92.3% (24/26 patients) success rate of EUS-PPG measurement using 22-G FNA needle[23]. Failed procedure in two

patients was due to inadequate sedation in one patient and poor vascular access to HV and IVC in the setting of liver transplant in the other patient. A subgroup of the patient also underwent IR-guided HVPG. Mean EUS-PPG 17.2 ± 5.2 mm Hg was comparable with mean HVPG 18.1 ± 3.9 mm Hg with strong correlation (r = 0.75) between the two methods. Mean time to perform EUS-PPG measurement was 25.6 ± 12.7 minutes. Upper gastrointestinal hemorrhage was the only adverse event noted in one patient that was managed endoscopically.

Feasibility and safety of concomitant endoscopic ultrasound-guided portal pressure gradient measurement and endoscopic ultrasound-guided liver biopsy

With the expansion of Endo-Hepatology practice, a comprehensive approach of endoscopic evaluation of chronic liver disease (CLD) is becoming more popular. During the same endoscopic procedure, patients could be evaluated for esophageal or gastric varices, portal hypertensive gastropathy, EUS-guided elastography, EUS-PPG measurement and EUS-LB; a concept of "one stop shop" evaluation of cirrhosis or suspected advanced liver disease when diagnosis remains uncertain. In a large retrospective study including 83 patients (61% male), Choi and colleagues investigated the correlation of clinical markers of PH with EUS-PPG and feasibility of concomitant EUS-LB during same session[24]. EUS-PPG measurement was performed using 25-G FNA needle and compact manometer using same technique as previously described[2,28]. After PPG measurement, EUS-LB was performed in 71 patients using 19-G (straight FNA needle in 38 patients, core type needle in 33 patients) with either dry suction with slow pull or wet suction technique. The technical success of EUS-PPG and EUS-LB was 100%. The correlation of PPG and clinical markers of cirrhosis was excellent with higher PPG noted in patients with esophageal or gastric varices (13.88 vs 4.34 mm Hg, $p < 0.0001$), thrombocytopenia (9.25 vs 4.71 mm Hg) and in patients with cirrhosis (9.46 vs 3.61 mm Hg, $p < 0.0001$). Logistic regression analysis determined a PPG cutoff 10 mm Hg or greater (vs less than 10 mm Hg) predicted 12 folds higher risks of cirrhosis (OR 12, 95% CI 3.14-79.26, $p = 0.001$), 32 folds increased risk of esophageal or gastric varices (OR 31.8, 95% CI 9.38-130.28, $p < 0.0001$), 16 fold risk of portal hypertensive gastropathy (OR 15.71, 95% CI 5.11-56.67, $p < 0.001$), and 5 fold higher risk of thrombocytopenia (OR 5.04, 95% CI 1.75-16.93, $p = 0.004$). Total procedure time was <60 minutes. EUS-LB specimen was adequate (greater than 10 portal tracts) in 98.6% patients to establish histological diagnosis. There were no major adverse events. Eight patients reported sore throat and mild abdominal pain that was managed conservatively. In a later retrospective study of 64 patients with CLD, the same group of authors established correlation of EUS-PPG with histological stage

of liver fibrosis and clinical outcomes of cirrhosis[25]. Similar to prior study by same group of authors, success rate of procedure was 100%. EUS-PPG of 5 mm Hg or greater was found in 45.3% patients that correlated with histological findings of stage 3 fibrosis on concomitant EUS-LB (likelihood ratio (LR) 27.0, 95% CI 1.65-360.59, $p = 0.004$). Patients with EUS-PPG 5 mm Hg or greater (vs PPG < 5 mm Hg) demonstrated significant clinical features of advanced liver disease such as clinical PH (41.4% vs 8.6% $p = 0.002$), compensated cirrhosis (72.4% vs 28.6% $p = 0.0001$), decompensated cirrhosis (40.9% vs 5.9% $p = 0.013$), thrombocytopenia (60.0% vs 16.7% $p = 0.001$), AST to platelet ratio index (APRI) score greater than 1 (58.3% vs 16.7% $p = 0.001$), fibrosis-4 (FIB-4) score greater than 3.25 (58.3% vs 16.7% $p = 0.001$), and histologic stage 3 (F3) or stage 4 (F4) fibrosis on EUS-LB (78.6% vs 27.6% $p = 0.02$). EUS-PPG cutoff 5 mm Hg or greater was found to be 57.9% sensitive, 87.5% specific with 78.6% positive predictive value and 72.4% negative predictive value to predict stage 3-4 liver fibrosis. Mild abdominal pain and sore throat were reported by 6 patients predominately after EUS-PPG and concomitant EUS-LB.

Hajifathalian *et al.* performed the first prospective pilot study to evaluate feasibility, and safety of EUS-PPG with EUS-LB in a cohort of 24 patients (5 males) with suspected advanced liver disease or cirrhosis using 25-G FNA needle, compact manometer, non-compressible tubing, and 19-G core biopsy needle respectively[26]. The success rate of EUS-PPG and EUS-LB was 96% and 100% respectively. EUS-PPG measurement was unsuccessful in one patient due to lack of feasible window to access narrow caliber HV. There was a significant correlation between PPG and clinical markers such as transient elastography LSM ($r = 0.31$, $p = 0.011$), APRI score 0.58 ± 0.42 ($r = 0.26$, $p = 0.013$), and FIB-4 score ($r = 0.21$, $p = 0.026$). As opposed to previous studies, no signification correlation was found between EUS-PPG measurements and stage of liver fibrosis[24,25]. EUS-PPG >5 mm Hg was found in only 21 % (5/23) patients with biopsy proven F3 or F4 fibrosis. A PPG of 5-10 mm Hg and >10 mm Hg was found in seven and one patients that demonstrated stage 0 fibrosis (F0) on LB. The potential reasons of these disparities are variability in HV and PV pressure measurements, Type II error, and low powered study due to small sample size. Only 1/23 patient required ER admission due to abdominal pain that was managed conservatively.

In a large multicenter retrospective study of 159 patients with suspected CLD, the technical success rate of EUS-PPG measurement with concurrent EUS-LB was 98.1% (156/159)[27]. EUS-LB was performed in 49% (78/159) patients[27]. The mean PPG was 5.73 mm Hg (range 0-26 mm Hg). EUS-PPG >5 mm Hg was found in 43% patients that

correlated with histological findings of F3-F4 fibrosis on concomitant EUS-LB (OR 6.043, 95% CI 1.797-22.582). There was strong correlation between EUS-PPG and APRI score (r= 0.30, p = 0.0003), FIB-4 score (r= 0.484, p < 0.01), MELD score (r= 0.28, p = 0.006), however a weak correlation with transient elastography LSM (r= 0.05, p = 0.54). Higher PPG (vs low) predicted esophageal or gastric varices (11 mm Hg vs 2.75 mm Hg, p < 0.01), gastropathy (10.5 mm Hg vs 4.3 mm Hg p < 0.01), thrombocytopenia (8.27 mm Hg vs 3.99 mm Hg p < 0.01).

Our group evaluated the correlation of EUS-guided liver transient elastography (EUS-LE), EUS-PPG values with stages of liver fibrosis in patients who underwent concomitant EUS-LB (unpublished data). All procedures were performed by an experienced endosonographer. EUS-LE was performed initially in all patients using shear wave measurement. EUS-PPG measurement was performed using a therapeutic linear echoendoscope, compact manometer with a 25-G needle targeting the hepatic and portal veins through transgastric transhepatic approach using established technique as described above. EUS-LB was performed using 19-G Franseen or Fork-tip biopsy needle. Seventeen patients, 59% (n=10) male, mean age 57 ± 11 years, mean BMI 36.4 ± 13.2, mean MELD-Na score of 9 ± 3 underwent EUS-PPG measurement and EUS-LB. Two patients did not undergo EUS-E. Indications of the procedure were clinical concerns for advanced liver disease. The technical success rate of EUS-PPG and EUS-LB was 100% with mean procedure time 54 ± 15 minutes. Franseen needle was used in 94% patients. Mean maximum length of specimen was 2.03 ± 0.64 cm with adequate number of portal tracts to establish a histological diagnosis. Significant fibrosis (SF) defined as F2-F4 was seen in 65% patients. Overall, mean EUS-LE measurement was 25.92 ± 15.4 kPa, and PPG was 4.54 ± 3.42 mmHg. PH was found in 41% patients and CSPH in 12% (n=2) patients with endoscopic findings of portal hypertensive gastropathy. PPG was significantly higher in patients with SF compared to non-significant fibrosis (F0-1) group (5.2 ± 2.5 vs. 3.34 ± 4.7 mmHg, respectively; p = 0.04). Patients in SF group tended to have higher LSM (31.46 ± 11.4 kPa) compared to non-SF group (17.63 ± 17.78 kPa; p = 0.13). There were no adverse events such as pain, bleeding, or perforation during or after the procedure at 24-48 hour follow up. A series of retrospective and prospective human studies including 414 patients with CLD, or suspected advanced liver disease have shown promising feasibility and safety of EUS-PPG measurement (Table 2)[5,21-27]. The majority of patients are aged 50-60 years, with comparable male to female ratio. All studies have shown technical success rate of EUS-PPG measurement over 91% (range 91.7% to 100%). Transgastric transhepatic approach to access PV, HV or IVC is favored over

transduodenal approach due to less risks of complications. Commonly used FNA needle was 25-G over 22-G in most of studies, however there was no difference between two in terms of feasibly, technical success rate and adverse events. Three patients had post-procedural hemorrhage, one of them required endoscopic management. Abdominal pain, sore throat are other common adverse events in small proportion of paints that were managed with medical therapy. A higher EUS-PPG correlated well with clinical features of PH including esophageal or gastric varices, portal hypertensive gastropathy, thrombocytopenia. Most studies have shown a cutoff value of PPG cutoff 5 mm Hg or greater predicted clinical features of PH and advanced liver disease, however heterogenicity exists among retrospective and prospective studies. Hajifathalian and colleagues have shown no signification correlation between EUS-PPG >5 mm Hg and stage of fibrosis on concomitant EUS-LB as only 21 % (5/23) patients with biopsy proven F3 or F4 fibrosis had PPG > 5 mm Hg, while 30% patients has shown no fibrosis in patients with PG of 5-10 mm Hg (7 patients) and >10 mm Hg (1 patient). This study also showed a significant correlation between PPG and transient elastography LSM (p = 0.011) in their prospective study, however, a poor correlation was reported between PPG and transient elastography LSM (r= 0.05, p = 0.54) in a recent large multicenter retrospective study[26,27]. Large multicenter randomized clinical trials are required to further investigate these issues.

Table 2: Feasibility of endoscopic ultrasound guided po`rtal pressure gradient measurement in human studies

Study Author (Year)	Total patients	Male	Female	Age	Needle type	Approach	Catheter used	Procedure time (minutes)	Technical success rate	PPG* (mm Hg)	Adverse events
Fujii-Lau *et al.*[21] 2014	1	1	0	27	22-G FNA	Transgastric transhepatic	Arterial catheter	NA	100%	1	None
Huang *et al.*[5] 2017	28	18	10	63	25-G FNA	Transgastric transhepatic and transduodenal (4 cases)	Compact manometer with pressure transducer and non-compressible tubing	NA	100%	8.2	None
Zhang *et al.*[22] 2021	12	9	3	63	22-G FNA	Transgastric	Compact manometer with pressure transducer and non-compressible tubing	EUS PPG: 38.33 HVPG: 37.22	91.7%	EUS-PPG 18.07 HVPG 18.82	None
Martínez-Moreno *et al.*[23] 2022 **	26	-	-		22-G FNA	NA	NA	25.6	92.3%	17.2	Upper gastrointestinal bleed (1)
Choi *et al.*[24] 2022	83	50	33	59.4	25-G FNA, 19-G FNA or core needle ***	Transgastric transhepatic and transduodenal (less often)	Compact manometer with pressure transducer and non-compressible tubing	<60	100%	7.06	Mild abdominal pain and sore throat (8)

Study Author (Year)	Total patients	Male	Female	Age	Needle type	Approach	Catheter used	Procedure time (minutes)	Technical success rate	PPG* (mm Hg)	Adverse events
Choi *et al.*[25] 2022	64	40	24	57.5	25-G FAN	Transgastric transhepatic and transduodenal (less often)	Compact manometer with pressure transducer and non-compressible tubing	<60	100%	6.21	Mild abdominal pain (3) and sore throat (3)
Hajifathalian *et al.*[26] 2022	24	5	19	53	25-G FNA	Transgastric	Compact manometer with pressure transducer and non-compressible tubing	NA	EUS-PPG =96% EUS-LB = 100%	7.5	Abdominal pain (1)
Monachese *et al.*[27] 2022**	159	74	85	56	25-G FNA	Transgastric transhepatic	Compact manometer with pressure transducer and non-compressible tubing	NA	98.1	5.73	Hemorrhage after LB (2)
Yousaf *et al.* 2022 **	17	10	7	57	25-G FNA	Transgastric transhepatic	Compact manometer with pressure transducer and non-compressible tubing	54	100	4.54	None
Total	414	-	-								

FNA; Fine needle aspiration, G; Gauge, NA; Not available, EUS; endoscopic ultrasound, PPG; portal pressure gradient, LB; liver biopsy

(*) Mean value

(**) Abstract

(***) Needle used for liver biopsy

Conclusions

Endoscopic ultrasound-PPG measurement and concomitant EUS-LB during single session is a feasible and safe alternative approach offering a comprehensive endoscopic assessment of patients with advanced liver disease as opposed to standard of care. EUS-PPG provides an excellent correlation with clinical markers of PH and histological stage of fibrosis. Although, an EUS-PPG of 5 mm Hg or greater demonstrated significant features of PH, however, this cutoff value needs to be refined with large multicenter prospective clinical trials as a subset of patients with histological evidence of advanced liver disease exhibited low PPG < 5 mm Hg, and vice versa.

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Conflict of Interest Statement

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