

# Endohepatology in clinical practice: EUS-guided portal pressure measurement combined with EUS-guided liver biopsy and variceal screening and treatment in outpatients

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## ABSTRACT

**Background and Objectives:** EUS-guided portal pressure gradient (PPG) is a novel technique that permits a true, direct measure of portal vein pressure and hepatic vein pressure. This article details our experience and lessons learned from 20 consecutive outpatient EUS-PPG procedures performed at a single center, along with simultaneous EUS-guided liver biopsy, variceal screening, and variceal banding.

**Methods:** Data on the first 20 patients who underwent EUS-PPG at a single center were retrospectively viewed and analyzed. The effects of various liver diseases or other patient-related factors on the clinical and technical success of EUS-PPG measurements, as well as EUS-guided liver biopsy (EUS-LB), were evaluated. During the procedure, if esophageal varices were encountered, they were assessed, and if felt to be clinically indicated, endoscopic variceal ligation was performed.

**Results:** The 20 patients included 10 male and 10 female patients. All procedures were technically successful. In all patients, the portal vein and hepatic veins could be easily identified. One adverse event of bleeding occurred during the EUS-PPG measuring procedure. All 20 EUS-LBs were technically successful and yielded adequate samples for histological evaluations, with an average of 25 complete portal tracts per sample. Among patients with esophageal varices, 40% of patients underwent banding. The mean EUS-PPG among 5 patients with esophageal varices was 11.6 mm Hg, compared with 3.2 mm Hg among 15 patients without esophageal varices.

**Conclusion:** This study demonstrates that EUS-PPG is a novel, safe, reproducible, and effective technique. Also, the fact that EUS-PPG, EUS-LB, variceal screening, and variceal banding could be performed in 1 session and on an outpatient basis speaks to the growing relevance and impact of the nascent field of endohepatology.

**Keywords:** EUS-PPG; EUS-LB; EUS; Portal pressure gradient; HVPG

## INTRODUCTION

Portal hypertension (PH) is a serious complication of cirrhosis that, among other metabolic derangements, results in resistance to hepatic blood flow. Portal hypertension is the root cause of many clinical manifestations of cirrhosis including ascites, spontaneous bacterial peritonitis, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome, hepatocellular carcinoma, and death.<sup>[1]</sup> The 1-year mortality rate of decompensated cirrhosis (defined by the presence of variceal bleeding or ascites) was significantly higher than that of compensated cirrhosis (20.2% vs. 5.4%).<sup>[2]</sup>

The severity of PH closely correlates with the measurement of the hepatic venous pressure gradient (HVPG), also known as the portal pressure gradient (PPG), which is the pressure difference between the portal and hepatic venous systems.<sup>[3]</sup> The HVPG provides valuable information regarding the prognosis of PH and serves as a risk-stratifying guideline that will influence the medical management of each patient with cirrhosis.<sup>[4]</sup>

The HVPG provides valuable information that predicts clinical outcomes of patients with cirrhosis. An HVPG >5 mm Hg defines PH. A clinically significant degree of PH is generally diagnosed when the HVPG exceeds 9 mm Hg. An HVPG >12 mm Hg predicts variceal hemorrhage, with a higher probability of rebleeding and longer intensive care unit stay with an increasing HVPG. An HVPG >15 mm Hg is associated with a significantly increased risk of hepatic decompensation and death; a recent retrospective study revealed that each increase of 1 mm Hg in HVPG increased the mortality rate by 3%.<sup>[5]</sup>

Interventional radiologists have traditionally measured the HVPG through a transjugular approach. Using a transjugular approach, a series of wedged-hepatic vein pressure, which indirectly measures portal vein pressure, and free hepatic vein pressure can be measured. The HVPG is calculated by subtracting the free hepatic vein pressure from the wedged-hepatic vein pressure, which serves as a surrogate measurement of the true PPG.<sup>[6]</sup> Reported adverse events with the Interventional Radiology approach include hematoma, arteriovenous fistula formation, neck pain, arrhythmia, and vagal reactions.<sup>[7,8]</sup>

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An alternative approach to transjugular HVPG measurement is EUS-guided PPG (EUS-PPG). EUS-PPG is a novel technique that permits a true, direct measure of portal vein pressure and hepatic vein pressure without the need for indirect pressure measurements as the IR approach mandates.<sup>[9]</sup> EUS-PPG involves the placement of a needle, attached to a pressure transducer, directly into the portal vein and a hepatic vein for pressure measurements under EUS guidance in real time. Huang et al.<sup>[10]</sup> published a comparison animal study that showed a strong correlation between EUS-PPG and transjugular approach–HVPG measurements ( $R = 0.985$ – $0.99$ ) across a wide range of pressures.

The first human pilot study of 28 patients successfully obtained EUS-PPG measurements without technical failures or adverse events. The EUS-PPG measured among these patients correlated with clinical parameters of PH including variceal bleeding or cirrhosis.<sup>[11]</sup> In this study, we retrospectively evaluated the effects of underlying liver diseases and other various patient-related factors on the clinical and technical success of EUS-PPG measurements. This manuscript details the authors' experience and lessons learned from 20 consecutive outpatient EUS-PPG procedures performed at a single center, along with simultaneous EUS-guided liver biopsy (EUS-LB), variceal screening, and variceal banding.

## METHODS

Data on the first 20 patients who underwent EUS-PPG at a single center were retrospectively viewed and analyzed. The total time frame to perform all 20 cases was 12 months. Medical records were analyzed for patient demographics, etiology of liver disease, Model for End-Stage Liver Disease (MELD) score, platelet counts, international normalized ratio (INR), identification of esophageal or gastric varices, EUS-PPG procedure characteristics and measurements, EUS-LB findings, and procedural-related adverse events, which were extracted and transferred to an Excel spreadsheet (Microsoft Excel, Redmond, WA). The effects of various liver diseases or other patient-related factors on the clinical and technical success of EUS-PPG measurements, as well as EUS-LB, were evaluated. The institutional review board approved this study.

Both advanced endoscopists (S.L. and D.G.A.) attended a single online, interactive training session that included a hands-on ex vivo model simulator station sponsored by the manufacturer of the EUS-PPG system.

### *EUS-PPG procedure*

An esophagogastroduodenoscopy (EGD) was performed to identify any evidence of PH, such as esophageal or gastric varices. An EUS examination was used to locate the optimal portal and hepatic vascular branches for the EUS-PPG measurements. Once the decision to collect EUS-PPG measurements was made, the Pressure Gradient Measurement System was prepared by attaching the fine-needle aspiration needle to noncompressible tubing flushed with heparinized saline. With the patient in the supine position, the pressure transducer was carefully held by the assistant on the left side of the patient at the level of the midaxillary line. The liver parenchyma was punctured with an EUS needle and directed to the center of the hepatic or portal venous branch as determined in the preliminary EUS examination. Heparinized saline was flushed through the noncompressible tube, and bubbles were observed within the lumen of vascular branches to confirm proper vascular access. When the pressure on the transducer stabilized, the pressure measurement was taken for 60 seconds. A series of 3 sequential

measurements were taken for the mean value. As the needle was withdrawn from vessels and liver parenchyma, color Doppler was used to exclude bleeding from the puncture. All EUS-PPG measurements were performed using the Cook EchoTip Insight 25-gauge EUS needle (Cook Endoscopy, Winston Salem, NC) with 5.2F sheaths, transducer, and 90-cm noncompressible tubing [Figure 1].

After the completion of EUS-PPG measurements, EUS-LB was performed. The left lobe of the liver was targeted through the transgastric approach, and the right lobe through the transduodenal approach as needed. All samples were obtained following the procedural protocols outlined by Diehl.<sup>[12]</sup> The liver core sample was collected with a 19-gauge fine-needle biopsy (Boston Scientific, Marlborough, MA) through a heparinized wet-suction technique; the sample was then expressed onto the filter paper and transferred to a formalin container. This sample was sent to the pathology department for histological evaluation.

During the procedure, if esophageal varices were encountered, they were assessed, and if felt to be clinically indicated, endoscopic variceal ligation was performed.

## RESULTS

### *Patient demographics*

The 20 patients included 10 male and 10 female patients. All patients were treated on an outpatient basis. The median age of the patients was 59 years (range, 26–76 years). With regard to etiology, 6 of 20 (30%) had alcoholic liver disease, 6 of 20 (30%) had nonalcoholic steatohepatitis, 1 of 20 (5%) had both alcoholic liver disease and nonalcoholic steatohepatitis, 4 of 20 (20%) had hereditary hemochromatosis, and in 3 of 20 (15%), the cause of their underlying liver disease/cirrhosis was unknown at the time of the procedure and was under investigation.

### *Preprocedural laboratory assessment*

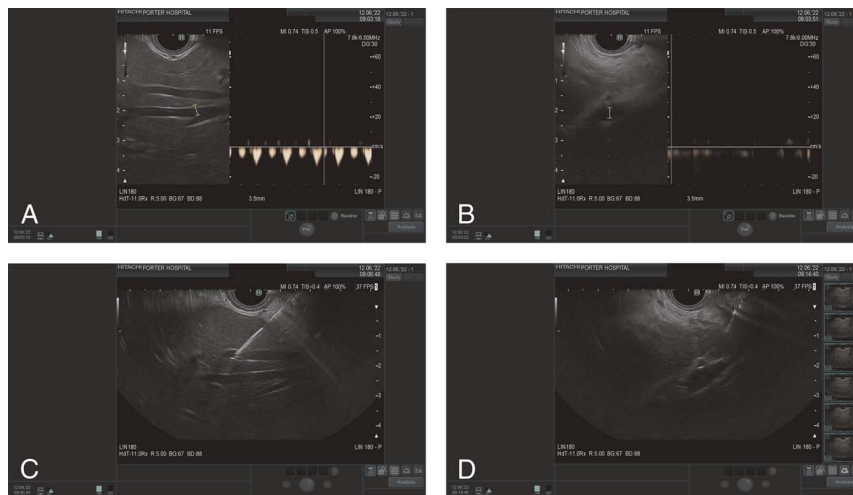
The MELD scores ranged from 6 to 23, with a median MELD score of 10. The platelet counts ranged from 44,000 to 334,000, with median platelet counts of 177,000 mcL. The INR ranged from 1.0 to 1.7, with a median INR value of 1.05. With regard to EGD findings, 3 of 20 patients (15%) had esophageal varices, 2 of 20 patients (10%) had gastric varices, and 2 of 20 patients (10%) had both esophageal and gastric varices simultaneously.

### *Procedure outcomes*

All procedures were technically successful. In all patients, the portal vein and hepatic veins could be easily identified. Mean procedure time, which was measured from scope-in time to scope-out time, for combined EGD, EUS analysis of vascular anatomy with all subsequent PPG measurements, and EUS-LB was  $42.5 \pm 13.8$  minutes. Average total procedure time became shorter as the endoscopists and staff became more familiar with the overall procedure. The first 5 procedures required an average of  $59 \pm 7.4$  minutes, the second 5 procedures required an average of  $40 \pm 13.1$  minutes, the third 5 procedures required an average of  $41 \pm 10.6$  minutes, and the fourth 5 procedures required an average of  $29 \pm 5.4$  minutes.

### *EUS-PPG and assessment of varices*

Among 5 patients with esophageal varices, 2 patients were found to have small varices without alarm features, and these vessels were



**Figure 1.** A, EUS identification of the hepatic veins. Note multiphasic waveform on pulse wave Doppler. B, EUS identification of the portal vein. Note monophasic waveform on pulse wave Doppler. C, Needle accessing a hepatic vein during the EUS-PPG measurement. D, Needle accessing the portal vein during the EUS-PPG measurement. PPG: portal pressure gradient.

not felt to warrant banding. Three patients had moderate size varices, and 2 of 3 underwent esophageal banding. One patient was noted to have moderate size varices, but these were not felt to warrant banding at the time of the examination [Table 1].

The mean EUS-PPG among 5 patients with esophageal varices was  $11.6 \pm 4.4$  mm Hg, compared with  $3.2 \pm 2.8$  mm Hg among 15 patients without esophageal varices.

*EUS-LB outcomes*

All 20 patients underwent EUS-LBs after EUS-PPG measurements. The heparinized wet suction method with 19-gauge core needle

(Boston Scientific) was implemented for EUS-LB. All 20 EUS-LBs were technically successful and yielded adequate samples for histological evaluations, with an average of 25 complete portal tracts per sample. There were no procedure-related adverse events due to EUS-LB.

*Adverse events*

One adverse event of bleeding occurred during the EUS-PPG measuring procedure. This incident happened during procedure number 6. The patient had a MELD score of 8, platelet counts of 178,000 mcL, and an INR value of 1.0. The patient underwent HV pressure measurement without difficulty, but when the PV

**Table 1**  
**Overview of EUS-PPG results and varices identification and treatment.**

Patients	Etiology of liver disease	EUS-PPG, mm Hg	Esophageal varices	Banded	Platelets	INR
1	Alcoholic liver disease	12	Small	No	52,000	1.3
2	Alcoholic liver disease	10	Medium	Yes	73,000	1.4
3	Alcoholic liver disease	3	None	No	179,000	1.7
4	Alcoholic liver disease	3	None	No	275,000	1.1
5	Alcoholic liver disease	6	None	No	334,000	1.0
6	Alcoholic liver disease	5	Small	No	178,000	1.0
7	Nonalcoholic steatohepatitis	5.67	None	No	130,000	1.1
8	Nonalcoholic steatohepatitis	1	None	No	182,000	1.0
9	Nonalcoholic steatohepatitis	1	None	No	210,000	1.0
10	Nonalcoholic steatohepatitis	2	None	No	122,000	1.0
11	Nonalcoholic steatohepatitis	1	None	No	50,000	1.0
12	Nonalcoholic steatohepatitis	2.3	None	No	174,000	1.0
13	Alcoholic liver disease and nonalcoholic steatohepatitis	15.33	Medium	Yes	123,000	1.3
14	Hereditary hemochromatosis	6.5	None	No	117,000	1.6
15	Hereditary hemochromatosis	10.66	None	No	176,000	1.0
16	Hereditary hemochromatosis	15.63	Medium	No	44,000	1.2
17	Hereditary hemochromatosis	2	None	No	230,000	1.3
18	Unknown	1	None	No	219,000	1.0
19	Unknown	1.9	None	No	229,000	1.1
20	Unknown	1	None	No	304,000	1.0

INR: international normalized ratio; PPG: portal pressure gradient.

pressure measurement was obtained, EUS visualized bleeding around the site of needle entry into the intrahepatic portal vein. This was confirmed with Doppler US. The bleeding stopped spontaneously over several minutes of observation. No intervention was performed. The patient could still undergo EUS-PPG, EUS-LB, and variceal screening despite this event without other difficulties. The patient presented with small esophageal varices, but these vessels were not felt to warrant banding at the time of the examination. The patient's vital signs did not change as a consequence of this bleeding episode. The bleeding was not felt to be clinically significant, and the patient did not require transfusion or hospitalization afterward. The patient was discharged home the same day without incident.

## DISCUSSION

IR physicians have traditionally indirectly measured the HVPG through a transjugular approach. Although many years of data support that this technique is safe, reliable, and reproducible, its highly invasive nature and significant procedural cost have limited physicians from acquiring PH in patients with cirrhosis.<sup>[13]</sup> In addition, a transjugular approach carries with it risks of procedure-related complications, such as bleeding or bile leakage when accessing vasculature, arteriovenous fistula formation, exposure to intravenous contrast agents, and arrhythmia.<sup>[14,15]</sup> In addition, not all interventional radiologists are trained in, or feel comfortable performing, this technique so access to this approach may be limited to large centers. Despite these limitations, HVPG provides valuable prognostic information for the medical and surgical management of patients with cirrhosis.<sup>[16]</sup>

EUS-PPG is a novel technique that permits a true, direct measure of the portal and hepatic vein pressures and their gradient without the need for indirect pressure measurements as the IR approach mandates. A recent prospective study of 9 patients revealed that direct, EUS-PPG measurement versus indirect, transjugular approach measurement of average HVPG was  $18.07 \pm 4.32$  mm Hg and  $18.82 \pm 3.43$  mm Hg, respectively (Pearson correlation coefficient of 0.923,  $P < 0.001$ ).<sup>[17]</sup> Both EUS-PPG and HVPG measurements, which were performed contemporaneously for the same individuals, yielded comparable pressure gradients in this study.

Huang et al.<sup>[11]</sup> published their first human pilot study of 28 patients and successfully obtained EUS-PPG measurements without technical difficulties or adverse events. The average EUS-PPG measured among patients with a high likelihood of cirrhosis was 10.33 mm Hg, compared with 3.81 mm Hg in patients with a low likelihood of cirrhosis ( $P = 0.005$ ). Also, the average EUS-PPG measured among patients with varices was 14.37 mm Hg, compared with 4.26 mm Hg in patients without varices ( $P = 0.0002$ ).<sup>[11]</sup> The authors of this study proposed that EUS-PPG measured among these patients correlated well with the standard clinical parameters. As previously discussed, HVPG  $>9$  mm Hg is considered a clinically significant PH, and HVPG  $>12$  mm Hg is associated with varices.<sup>[5]</sup>

In this study, 5 of 20 patients presented with esophageal varices. Mean EUS-PPG among patients with esophageal varices was  $11.6 \pm 4.4$  mm Hg, compared with  $3.2 \pm 2.8$  mm Hg among patients without esophageal varices. One patient with esophageal varices measured an outlier EUS-PPG of 5 mm Hg, which brought down the average pressure gradient to less than 12 mm Hg. If we exclude the outlier, the average EUS-PPG among patients with varices is  $13.24 \pm 2.72$  mm Hg. This retrospective study aligns well

with the conclusion made by Huang et al.<sup>[11]</sup>: EUS-PPG correlates well with other standard clinical parameters.

Along with HVPG measurements, IR traditionally obtained liver biopsies through the same transjugular route.<sup>[18]</sup> When the EUS-LB technique was first published in 2007, it became an appealing alternative for obtaining liver biopsies.<sup>[19]</sup> Some of the advantages of EUS-LB include procedural safety, excellent quality of core samples for histological evaluation, and easy access to bilobar liver biopsies, which can reduce sampling error.<sup>[20]</sup> Furthermore, patients are sedated throughout the procedure, which can reduce unnecessary anxiety and improve overall patient experience.<sup>[21]</sup> Critically, EUS-LB and EUS-PPG can be performed during the same intervention, likely reducing procedural costs and avoiding unnecessary multiple interventions for the patients. This retrospective study successfully obtained EUS-PPG measurements, as well as subsequent EUS-LB during the same procedure, in all 20 patients without technical difficulties.

Many major centers preferably perform liver biopsy through a transjugular route when platelet counts are low because the IR approach is a safe and feasible technique in patients with coagulopathy.<sup>[22]</sup> In our study, 3 patients had platelet counts between 50,000 and 100,000, and 1 patient had platelet counts less than 50,000 mcL at the time of the examination. Despite remarkably low platelet counts, all 4 patients successfully underwent EUS-PPG, EUS-LB, variceal screening, and variceal banding when necessary, with a 100% technical success rate. No adverse event was reported among these 4 patients. Thrombocytopenia did not seem to be a contraindication to the procedure.

One adverse event of bleeding occurred during the EUS-PPG measuring procedure. This patient had a MELD score of 8, platelet count of 178,000 mcL, and an INR value of 1.0. After several minutes of observation, the bleeding stopped spontaneously, and the vital signs remained reassuring. Despite the bleeding incident, we successfully completed the EUS-PPG, EUS-LB, and variceal screening. In the event of complications, we advise physicians not to advance with the procedure but to prioritize the patient's health and safety. If the bleeding eventually stops, vital signs remain hemodynamically stable, and there are no other clinical indications to terminate the procedure, they can resume their procedures.

Finally, it would be valuable to conduct cost analyses in future studies that demonstrate the actual cost savings incurred by performing EUS-PPG, EUS-LB, variceal screening, and variceal banding contemporaneously. It is reasonable to deduce that the total cost would be reduced, considering that all procedures can be performed with 1 sedation and on an outpatient basis. A cost analysis may objectively reveal the details of the true financial advantages of performing EUS-PPG, EUS-LB, variceal screening, and variceal banding in 1 session as opposed to multiple sessions or when compared with IR approaches.

## CONCLUSION

This study demonstrates that EUS-PPG is a novel, safe, reproducible, and effective technique. EUS-PPG successfully measured the pressure gradients in 20 patients with varying liver diseases, and EUS-LB obtained adequate liver biopsies in all cases. Furthermore, the technique permits screening for varices and banding if felt to be clinically warranted at the time of the examination. Specifically, 40% of patients with esophageal varices underwent banding in this

retrospective study. The fact that EUS-PPG, EUS-LB, variceal screening, and variceal banding could be performed in 1 session and on an outpatient basis speaks to the growing relevance and impact of the nascent field of endohepatology.

### Author Contributions

Sung Kim data collection and analysis, and drafting of article. Laura Meuller data collection. Scot Lewey data collection. Douglas Adler data collection and analysis, drafting of the article.

### Conflict of Interest

Douglas G. Adler is the Co-Editor-in-Chief of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of the editor and his research group.

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