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Journal

Gastrointestinal Endoscopy, 85(5)

ISSN

0016-5107

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Publication Date

2017-05-01

DOI

10.1016/j.gie.2016.09.026

Peer reviewed

HHS Public Access

Author manuscript

Gastrointest Endosc. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Gastrointest Endosc. 2017 May ; 85(5): 996–1001. doi:10.1016/j.gie.2016.09.026.

EUS-Guided Portal Pressure Gradient Measurement with a Simple Novel Device – A Human Pilot Study

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Abstract

Background & Aims—Portal hypertension (PH) is a serious complication of liver cirrhosis. The hepatic venous pressure gradient or portal pressure gradient (PPG) accurately reflects the degree of PH and is the single best prognostic indicator in liver disease. This is usually obtained by interventional radiology (IR) although it is not routinely performed.

Recently, we developed a simple novel technique for Endoscopic Ultrasound (EUS)-guided PPG measurement (PPGM). Our animal studies showed excellent correlation between EUS-PPGM and IR-PPGM. We now present the first human pilot study of EUS-PPGM in patients with liver disease.

Methods—EUS-PPGM was performed by experienced endosonographers using a linear echoendoscope, a 25G FNA-needle and a novel compact manometer. The portal vein and hepatic vein (or inferior vena cava) were targeted via a transgastric/transduodenal approach. Clinical parameters of PH were evaluated in each patient. Feasibility was defined as successful PPGM in each patient. Safety was based on complications captured via post-procedural interview.

Results—28 patients underwent EUS-PPGM with 100% technical success and no complications. PPG ranged from 1.5–19mmHg and had excellent correlation with clinical parameters of portal hypertension including the presence of varices (p=0.0002), PH gastropathy (p=0.007) and thrombocytopenia (p=0.036). PPG was increased in patients with high clinical evidence of cirrhosis (p=0.005).

Conclusion—This novel technique of EUS-PPGM using a 25G needle and compact manometer is feasible and appears safe. Given the availability of EUS and the simplicity of the manometry setup, EUS-guided PPG may represent a promising breakthrough for procuring indispensable information in the management of patients with liver disease

Introduction

Portal hypertension (PH) is a severe complication of liver cirrhosis. Clinical manifestations may include the formation of varices with associated gastrointestinal bleeding, ascites,

encephalopathy or hepatorenal syndrome.[1, 4] Therefore, the diagnosis and quantification of portal hypertension by measuring portal pressure holds tremendous therapeutic and prognostic implications[1–3]

The portal pressure gradient (PPG) is the difference between the portal vein pressure and the pressure within the hepatic vein (or inferior vena cava). It reflects the hepatic perfusion pressure. In patients with cirrhosis, portal pressure increases because of increased intrahepatic vascular resistance and increased portal blood flow[1].

PPG is derived from subtracting the hepatic venous (HV) pressure from the portal venous (PV) pressure. These pressures ideally should be obtained through direct venous puncture. However, currently, the PV pressure is not routinely measured and is indirectly estimated based on the wedged hepatic venous pressure (WHVP) and only the hepatic venous pressure is a true direct measure. In the cirrhotic liver, the WHVP is quite similar to the PV pressure. This gradient is termed the hepatic venous pressure gradient (HVPG) which accurately reflects the degree of PH in all forms of sinusoidal and post-sinusoidal causes of portal hypertension [4–6].

The definition of portal hypertension is a HVPG > 5mmHg. A HVPG of > 10mmHg represents clinically significant portal hypertension (CSPH) and it is usually a pre requisite to the development of ascites and variceal bleeding. Monitoring HVPG may be useful in guiding pharmacological prophylaxis of variceal bleeding. The risk of variceal bleeding is dramatically lowered if HVPG is reduced by 20% from baseline or an absolute value of <12mmHg is achieved [4, 7–9]. Furthermore, the severity of portal hypertension is an independent factor for survival in patients with liver cirrhosis [5].

The most common approach to quantifying portal hypertension in clinical practice is the transjugular route. This method is invasive, involves radiation exposure, requires the use of intravenous contrast, and provides only indirect measurements of the PV pressure. The technique involves placement of a radiopaque catheter into the right HV via the jugular vein under fluoroscopic guidance. A free HV pressure and a WHVP are obtained, and HVPG is calculated [5]. Other methods, such as surgical and transhepatic percutaneous approaches, can be used for obtaining direct measurements; however these are more invasive and are not performed in clinical practice.

We have recently presented Endoscopic Ultrasound (EUS) guided portal pressure gradient measurement using a 25 gauge needle and a novel compact manometer in an animal model [10] demonstrating excellent accuracy and strong correlation with pressure values obtained by the gold standard transjugular wedged and free hepatic venous pressure measurements by Interventional Radiology. Here we present the first pilot study in humans demonstrating safe and accurate direct portal pressure gradient measurements without the need for ionizing radiation, transhepatic catheter placement or surgery.

Methods

EUS-PPG was performed at a single tertiary academic center by experienced endosonographers. All cases were performed under moderate sedation or general anesthesia

in the supine position. Patients between the age of 18–75 with a history of liver disease or suspected cirrhosis were considered for PPG measurement. Exclusion criteria included pregnancy, significant bleeding risk (International Normalized Ratio (INR) > 1.5, platelet count < 50), active gastrointestinal bleeding and post sinusoidal portal hypertension. Feasibility was measured based on technical success, defined as a successful PPG measurement in each patient. Safety was assessed based on complications that were captured via post-procedural interview of all patients in person in recovery and by telephone within the subsequent 48 hours. Medical records including patient demographics, imaging studies, laboratory, EUS, and manometry results were retrospectively reviewed and analyzed. Full written informed consent was obtained from all patients. The study was approved by the Institutional Review Board for Human Research at the University of California, Irvine.

Endoscopic Procedure

Prior to EUS guided pressure measurement, a forward viewing endoscope (Olympus, Tokyo, Japan) was used to evaluate and document the endoscopic evidence of portal hypertension such as varices or portal hypertensive gastropathy (PHG). The apparatus for PPG measurement included a linear echoendoscope (GF-UC140P-AL5, Olympus, Tokyo, Japan), a 25G FNA-needle (Cook Medical, Winston-Salem, NC, USA), and a compact manometer (Figure 1) with non-compressible tubing (Cook Medical, Bloomington, IN, USA).

Prior to echoendoscope insertion, the manometer was zeroed at the mid axillary line. Measurements were conducted in the portal vein (PV) (Figure 2) and hepatic vein (HV) (Figure 3) where possible. If the HV was inaccessible due to anatomical limitations, the inferior vena cava (IVC) was targeted. When the PV was targeted, manometry was performed via a transgastric, and less often a transduodenal, transhepatic approach and only the intrahepatic portion near the PV bifurcation was accessed. Typically the scope was positioned in the vicinity of the gastroesophageal junction to first identify the IVC, followed by visualization of the HV ostia (opening of the HV as it junctions into the IVC). The needle tip was placed 2cm distal to the ostia where possible. Needle placement was meticulous to ensure consistency. A small amount (1ml) of heparinized saline was flushed through the primed FNA needle (no stylet) prior to each EUS reading. Following 30–60 seconds of pressure stabilization, the reading was recorded. Three separate readings per vessel were performed and a mean pressure was calculated. Upon withdrawal of the needle, just prior to leaving the liver capsule, color doppler was used to make sure there was no flow in the needle track. The needle was withdrawn from the liver capsule when no doppler signal was present within the needle track. Intraprocedural prophylactic antibiotics were given.

Definitions

The universal definition of portal hypertension (PH) of >5mmHg and clinically significant portal hypertension (CSPH) of >10mmHg were used [11].

Patients with liver disease were classified as high or low evidence for cirrhosis. A patient was deemed high evidence for cirrhosis if pre procedural clinical evaluation (e.g. clinical history, physical examination), laboratory, endoscopic or imaging demonstrated evidence was suggestive or consistent with portal hypertension.

Statistical analysis

Descriptive statistics including median, mean, standard deviation, minimum and maximum were calculated for continuous variable. For categorical variables, frequency counts within categories were obtained and reported. The Shapiro-Wilk test was utilized to examine the normality of the PPG distribution for four clinical outcomes. Due to violation of the normality assumption, for each clinical outcome the Wilcoxon Rank Sum test was then applied to compare the location shifts of PPG distributions between subgroups of patients. In order to maintain an experiment-wise significance level of 0.05, the Bonferroni-Holm method was applied to adjust for multiple comparisons.

Considering the non-normality of PPG, an alternative method of analysis also was utilized. The natural logarithm transformation was applied to PPG values. For the four clinical outcomes, pairs of means among patient subgroups were compared using two-sample *t*-tests with the Bonferroni-Holm method of multiple comparisons.

A binary variable was created by dichotomizing PPG values into two categories: > 5mmHg vs. ≤5mmHg. Logistic regression models were applied to estimate the odds of the presence of a clinical symptom with the PPG indicator as a predictor. All statistical analyses were performed with SAS v9.4.

Results

A total of 28 patients underwent portal pressure manometry in this study and pressures were successfully achieved in all 28 patients. Baseline patient data is outlined in Table 1. PPG values ranged from 1.5–19mmHg with a mean of 8.2mmHg. 15/28 (57.1%) had evidence of PH based on PPG of which 10/15 (66.7%) had CSPH. Eleven of 28 subjects had endoscopic evidence of either esophageal or gastric varices with all 11 (100%) having PH and 10 (90.9%) patients having CSPH based on EUS-PPG measurement.

Feasibility

EUS identification and access into all targeted vessels was achieved without any failures. However, in 9/28 (32.1%) access to the HV was unfavorable due to anatomical distortion from cirrhosis including caudate lobe hypertrophy. In these cases, accessing the IVC was felt to be a better alternative in obtaining the PPG. For portal vein access, a transgastric approach was used with the exception of 4 (14.3%) cases where a transduodenal approach was used.

Complications

There were no intra or post procedural complications such as bleeding, perforation or pain seen in any patient. There were no infectious complications in particular.

Clinical Correlation

There was excellent association between PPG and clinical parameters (Table 2). The relationship between PPG levels among patient subgroups for clinical outcomes is shown in Figure 4. PPG levels were increased in those with high clinical evidence of cirrhosis (Wilcoxon Rank Sum Test, nominal p=0.005), and in those with varices (nominal p=0.0002),

PHG (nominal p=0.007) and thrombocytopenia (nominal p=0.036), compared to those without these conditions. Similarly, natural log-transformed values of PPG reflected increased mean values in those with cirrhosis (t-test, nominal p=0.0015), varices (nominal p<0.0001), PHG (nominal p=0.0012), and thrombocytopenia (p=0.0359). The geometric means of natural log-transformed PPG were 8.5mmHg and 3.5mmHg with and without high evidence for cirrhosis, respectively, 13.8mmHg and 3.9mmHg with and without varices, respectively, and 11.9mmHg and 4.8mmHg with and without PHG, respectively.

Logistic regression models indicated that when a patient has PPG ≥ 5mmHg, the odds of high evidence of cirrhosis was 18.7 (95% confidence interval, 2.97, 180.66) times higher than a patient with a normal (< 5mmHg) measurement. In addition, when a patient has PPG ≥ 5mmHg, the odds of having thrombocytopenia was 6.1 (9%CI, 1.19, 38.38) times higher than a patient with PPG < 5 mmHg. Platelet count also had a moderate negative correlation with PPG (R = −0.473).

Discussion

This study demonstrates that EUS guided portal pressure measurement using a 25G needle and a novel compact manometer is feasible and appears safe in humans. There were no technical failures with PPG manometry and there were no complications in any patient.

The importance of knowing the portal pressure in the management of portal hypertension is well documented. This frequently alters management at every phase of medical treatment, namely, initiation, dose titration, cessation, escalation of therapy and prognostication [12–14]. It may also play a pivotal role in diagnosis and staging of advanced fibrosis or cirrhosis [14, 15]. Unfortunately, readily obtaining the portal pressure is hindered by many factors. EUS-PPG measurement using this novel approach may be an excellent modality to overcome many of these barriers. EUS is now widely available and the PPG manometry setup is simple and portable. This procedure requires no iodinated contrast or ionizing radiation and is well tolerated by patients, recovering in a similar manner to routine gastroscopy. Furthermore, direct portal pressure measurement is likely to be more accurate than the indirect WHVP, particularly in non-alcoholic cirrhosis or primary biliary cirrhosis [16–19].

There were no complications in this study even in the context of most of these patients suspected of having cirrhosis and some were also thrombocytopenic and coagulopathic. EUS-PPG measurement is likely a safe procedure as it is based on the well-established technique of EUS guided fine needle aspiration, which carries an excellent safety record [20, 21]. Furthermore, the use of a small gauge needle in concert with high-resolution real time Doppler imaging and liver parenchyma tamponade upon needle withdrawal likely all contribute to the relative safety of this novel technique.

There was excellent correlation between PPG measurement and clinical evidence of portal hypertension and clinical suspicion of liver cirrhosis. Patients with a high probability for cirrhosis, evidence of thrombocytopenia, portal hypertensive gastropathy or varices had

significantly elevated PPG measurements compared to those without. All patients with varices had portal hypertension based on EUS PPG.

The limitations of this study include the retrospective study design, a single center study with a relatively small cohort of patients. Patients did not have simultaneous transjugular HVPG measurements. Patients with suspected cirrhosis did not have a percutaneous liver biopsy.

In conclusion, this study showed that EUS-guided portal pressure measurement using a 25G needle and compact manometer is feasible and appears safe in humans. This technique represents a promising breakthrough for procuring indispensable information in the management of patients with liver disease. This work sets the stage for larger clinical trials to establish its role in a wider spectrum of liver disease and portal hypertension.

Acknowledgments

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number P30CA062203. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Figure 1.
Compact manometer

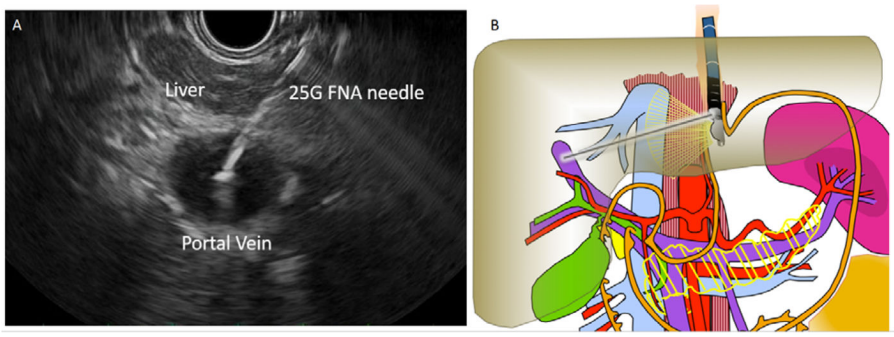

Figure 2.

A)Endoscopic Ultrasound Image of transgastric transhepatic needle puncture into the portal vein with a 25G FNA needle B) Diagram representing EUS guided transgastric portal vein puncture.

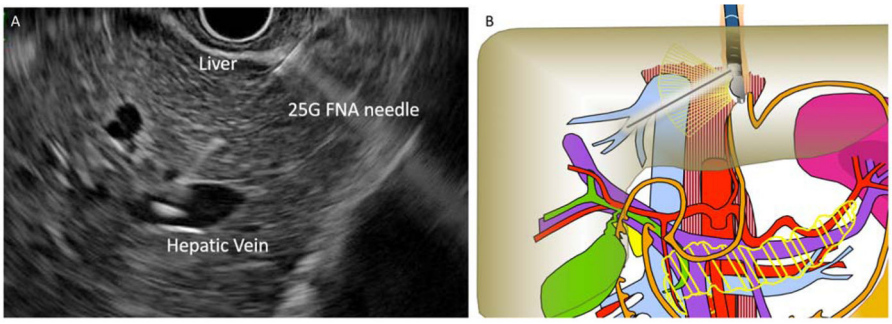

Figure 3.

A) Endoscopic Ultrasound Image of transgastric transhepatic needle puncture into the hepatic vein with a 25G FNA needle. B) Diagram representing EUS guided transgastric hepatic vein puncture.

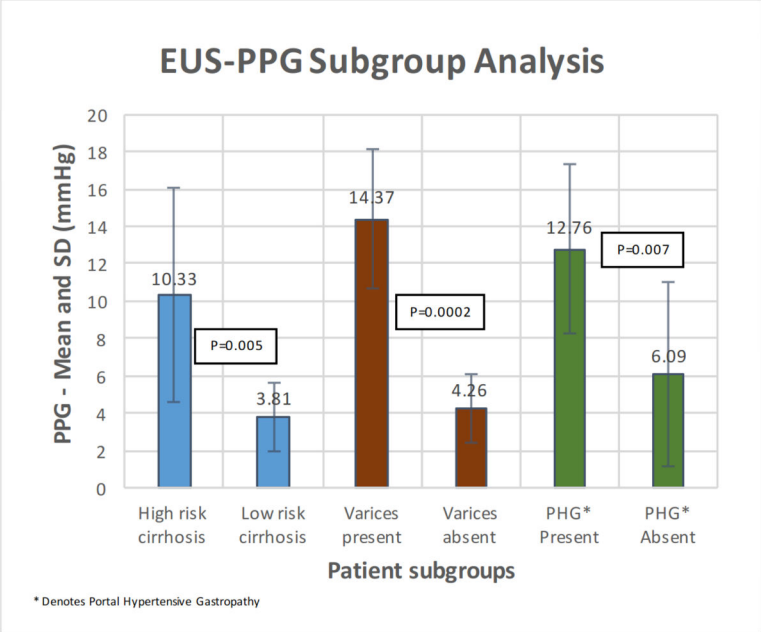

Figure 4.

PPG levels according to presence or absence of clinical condition. Error bars denote standard deviation. p values of Wilcoxon rank sum test.

Table 1

Baseline Patient Characteristics

	n	%
Patient Demographics		
Total	28	
Male subjects	18	64%
Age (y), mean (range)	63, (30–80)	
Etiology/Indication		
Viral hepatitis	15/28	53.6%
EtOH	6/28	21.4%
Increased LFTs	5/28	17.9%
NAFLD	2/28	7.1%
Bleeding risk		
Coagulopathic (INR > 1.2)	4/26 *	15.4%
Thrombocytopenic (<150k)	16/28	57.1%
Urea > 30	3/28	12.5%
Cirrhosis †		
High clinical evidence for cirrhosis	19/28	67.9%
Varices present	11/28	39.3%
Portal hypertensive gastropathy	9/28	32.1%

* 2 patients had incomplete data on INR,

† suspected based on clinical parameters

Table 2

EUS-PPG Measurement Clinical Subgroup analysis

	Cirrhosis			Varices			Gastropathy			Thrombocytopenia		
	High Clinical Evidence of Cirrhosis	**Low Clinical Evidence of Cirrhosis**	**p-value***	**Present**	**Absent**	**p-value***	**Present**	**Absent**	**p-value***	**Present**	**Absent**	**p-value***
N	19	9		11	17		9	19		16	12	
Mean PPG	10.33	3.81	0.005	14.37	4.26	0.0002	12.76	6.09	0.007	10.30	5.48	0.036
Median PPG	10.70	3.60		14.70	4.00		12.30	4.00		9.50	4.00	
Standard Deviation	5.73	1.87		3.75	1.85		4.52	4.96		6.13	3.76	
Minimum	1.70	1.50		6.50	1.50		6.00	1.50		1.70	1.50	
Maximum	19.00	8.00		19.00	8.00		18.00	19.00		19.00	14.30	

* P –value of Wilcoxon Rank Sum test