THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

Endoscopic Ultrasound Guided Portal Pressure Gradient Measurement

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A thesis submitted for the degree of Master of Philosophy at

The University of Queensland in 2018

Faculty of Medicine

Abstract

Portal hypertension is most commonly associated as a complication related to liver cirrhosis. Portal hypertension increases morbidity and mortality usually through gastrointestinal bleeding however other complications such as ascites formation and subsequent spontaneous bacterial peritonitis may occur. The degree of portal hypertension is already well established as a useful predictor of prognosis. Knowing this information will also help guide management. Currently treatment of portal hypertension is almost empirical without an easily accessible and safe method of monitoring portal pressure response and often it is unclear whether treatment targets have been attained. It is akin to treating arterial hypertension without a sphygmomanometer.

Currently the gold standard and most frequently employed method of measuring portal hypertension is via the transjugular method at interventional radiology. This provides a measure of the free and wedged (or occluded) hepatic venous pressure from which the hepatic venous pressure gradient is derived. This gradient is currently the key value to determining risk of morbidity, mortality and guide management, in particular, when to provide active intervention or to help identify non responders to medical therapy. However this is not readily available (only in select expert centres) as this is a long and very technically demanding procedure to produce reliable and consistent clinical data. Therefore the need for an equally safe yet simpler procedure is needed.

Endoscopic ultrasound guided portal pressure measurement is a novel technique whereby patients have their portal pressure gradient or hepatic venous pressure gradient measured with direct access into the portal vein and hepatic vein to calculate the hepatic venous pressure gradient. This procedure can be integrated into a session of diagnostic gastroscopy which is already a necessary component of the current management algorithm of portal hypertension. The gastroscopy can identify subjective endoscopic evidence of portal hypertension such as oesophageal varices and the endoscopic ultrasound guided portal pressure measurement can objectively quantify the degree of portal hypertension. In this thesis the author presents the novel technique and results in animal as well as the first human pilot study which has shown great promise and has paved the way for a larger international multicentre trial to be commenced in the near future.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

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Publications during candidature

1. **Huang JY**, Samarasena JB, Tsujino T, et al. EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study. Gastrointest Endosc 2017;85:996-1001.

2. **Huang JY**, Samarasena JB, Tsujino T, et al. EUS-guided portal pressure gradient measurement with a novel 25-gauge needle device versus standard transjugular approach: a comparison animal study. Gastrointest Endosc 2016;84:358-62.

3. Samarasena J, **Huang JY**, Tsujino T, et al. Endoscopic ultrasound guided portal pressure gradient measurement with a simple novel device – First human pilot study. Journal of Gastroenterology and Hepatology 2016;31:357.

4. Tsujino T, **Huang JY**, Samarasena J, et al. Safety and Feasibility of Combination EUS-Guided Portal Pressure Gradient Measurement and Liver Biopsy: The Realization of Endo-Hepatology. Gastrointest Endosc 2016;83:AB415-416.

5. Samarasena JB, **Huang JY**, Tsujino T, et al. Endoscopic Ultrasound Guided Portal Pressure Gradient Measurement with a Simple Novel Device. Gastrointest Endosc 2016;83:AB186.

6. Samarasena JB, **Huang JY**, Tsujino T, et al. Endoscopic Ultrasound Guided Portal Pressure Gradient Measurement With a Simple Novel Device – First Human Pilot Study. Gastrointest Endosc 2016;83:AB169-170.

7. **Huang JY**, Tsujino T, Samarasena J, et al. Endoscopic Ultrasound (EUS)-Guided Liver Biopsy: A Comparison Between 19 Gauge Straight Standard (SSN) Versus Core Histology Needle (CHN) in Benign Hepatic Parenchymal Disease. Am J Gastroenterol 2015;110:S653.

8. **Huang JY**, Tsujino T, Samarasena J, et al. Endoscopic Ultrasound-Guided Portal Pressure Gradient (PPG) measurement: A simplified novel technique using 25 gauge FNA needle with compact transducer vs standard transjugular approach: A comparative animal study. Am J Gastroenterol 2015;110:S636.

9. **Huang JY**, Chang KJ. Improvements and innovations in endoscopic ultrasound guided fine needle aspiration. J Hepatobiliary Pancreat Sci 2015;22:E37-46.

10. **Huang JY**, Samarasena j, Tsujino T, et al. Late-breaking abstracts. United European Gastroenterology Journal 2015;3:561-571.

11. **Huang JY,** Ghani H, Samarasena JB, et al. A pilot study regarding safety and histological yield of endoscopic ultrasound (EUS) guided liver biopsy with a 19 gauge core histology needle (CHN) for the diagnosis and staging of benign hepatic parenchymal disease. Am J Gastroenterol 2014;109:S592.

12. United European Gastroenterology Week 2015, Barcelona, Spain – Late breaking oral presentation

13. American College of Gastroenterology 2015, Hawaii, United States – The Presidential Award for poster presentation

14. Digestive Disease Week 2016, San Diego, United States – Presidential Plenary oral presentation

15. Asian Pacific Digestive Week 2016, Kobe, Japan – Oral presentation

16. Australian Endoscopic Ultrasound symposium 2015 and 2018 – Invited Speaker

Publications included in this thesis

Publication 1

Incorporated as Chapter 3.

Huang JY, Samarasena JB, Tsujino T, et al. EUS-guided portal pressure gradient measurement with a novel 25-gauge needle device versus standard transjugular approach: a comparison animal study. Gastrointest Endosc 2016;84:358-62.

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	Drafting and production (10%)

Publication 2

Incorporated as Chapter 4.

Huang JY, Samarasena JB, Tsujino T, et al. EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study. Gastrointest Endosc 2017;85:996-1001.

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Contributions by others to the thesis

Professor Kenneth Chang

Senior mentor and author of the included published manuscripts as well as critical revision of the manuscript for important intellectual content. Approval and fine tuning of study concept and design; acquisition of data; analysis and interpretation of data.

Professor John Lee

Possessing one of the highest interventional endoscopic volume in the world, Professor Lee had provided invaluable technical and procedural advice in development of this novel technique.

Professor Barbara Leggett

Overall management within the school of medicine as well as providing a pre-eminent specialist hepatologist perspective on this novel technique and its potential future implications on management of portal hypertension in cirrhotic patients whilst providing invaluable advice regarding the research higher degree process.

Associate Professor Benedict Devereaux

Overall management within the school of medicine as a supervisor to ensure consistent progress with thesis and facilitating milestone meetings

Statement of parts of the thesis submitted to qualify for the award of another degree

None

<u>Research Involving Human or Animal Subjects</u>

This thesis involved human and animal subjects. The research approvals are as follows

1. University of California Irvine institutional review board (IRB FWA#0004071)
2. University of California Irvine institutional Animal Care and Use Committee (IACUC number 1999-1712)

The approval letter is included in the appendix

Acknowledgements

Financial support

<u>Keywords</u>

Portal hypertension, portal pressure gradient, hepatic venous pressure gradient, portal vein, endoscopic ultrasound, fine needle aspiration, liver cirrhosis.

<u>Australian and New Zealand Standard Research Classifications (ANZSRC)</u>

ANZSRC code: 119999, Medical and Health Sciences not elsewhere classified, 100%

<u>Fields of Research (FoR) Classification</u>

FoR code: 1199, Medical and Health Sciences not elsewhere classified, 100%

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List of abbreviations

CSPH   Clinically significant portal hypertension

EUS   Endoscopic ultrasound

EUS-PPG   Endoscopic ultrasound guided portal pressure gradient

HV   Hepatic vein

HVPG   Hepatic venous pressure gradient

IR   Interventional radiology

IVC   Inferior vena cava

PH   Portal hypertension

PPG   Portal pressure gradient

PPGM   Portal pressure gradient measurement

PV   Portal vein

PVP   Portal vein pressure

RHV   Right hepatic vein

Chapter 1 – Background and literature review

1.1 Background

Portal hypertension (PH) can be a complication related to liver cirrhosis[1] or a vascular disorder[2] such as Budd Chiari or extrahepatic portal venous obstruction. Majority of the non-cirrhotic causes of PH are positioned in the pre or post hepatic zones. Given PH is more commonly related to liver cirrhosis, this thesis is focused specifically on liver cirrhosis (or sinusoidal) induced PH as opposed to PH related to primary vascular disorders.

Liver cirrhosis

Liver cirrhosis is a consequence of chronic liver injury secondary to a variety of aetiologies including but not limited to viral (e.g. hepatitis B or C), metabolic (e.g. haemochromatosis, Wilson's disease, fatty liver disease), toxin mediated (e.g. alcoholic liver disease) or autoimmune processes (e.g. Autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis). Given that liver cirrhosis is the leading cause of PH in the western world,[3] an overview of the concurrent mechanisms and changes within the liver parenchyma, regulatory mechanisms and impact on the vasculature are outlined below.

1. Architecturally, chronic liver injury invariably leads to necroinflammatory reaction, diffuse nodular regeneration, dense fibrous tissue deposition and finally the collapse of liver architecture and ultimately distortion of liver parenchyma which also results in vascular distortion and altered flow resistance. Functionally this impairs blood flow though the liver parenchyma leading to progressive elevation portal flow resistance manifesting as PH as the progressive elevation in pressure is redistributed throughout the venous network.

2. During progression to cirrhosis endogenous vasoconstricting factors are upregulated through increased activity of vasoconstrictive mediators such as endothelin, noradrenaline, angiotensin 2, vasopressin, leukotrienes and thromboxane A2. The heightened response to these vasoconstrictors by the vascular smooth muscle cells ultimately results in elevated hepatic vascular resistance therefore contributing to the degree or severity of PH.[4]

3. Vasodilating effects are also down regulated due to inhibition of nitric oxide release largely due to low endothelial nitric oxide synthetase activity[5] hence further compounding this issue of PH.

The prevalence of liver cirrhosis is estimated to be 0.27% in the United States.[6] Cirrhotic patients are known to carry a higher risk for development of PH, most commonly manifesting as oesophageal varices. A cirrhotic patient has a risk of up to 8% per year for developing varices and 10% risk per year of these varices enlarging.[7] Unfortunately, most cirrhotic patients will develop varices at some stage throughout the course of their disease therefore early identification and treatment is ideal, as severity of cirrhosis progress, the risk of developing varices increase. For example, a Child's Pugh Class A patient may have up to 40% chance of developing oesophageal varices compared to a more advanced decompensated Child's Pugh Class C cirrhotic whom may have up to an 85% risk.[7] Generally the risk of bleeding from varices is up to 15% per year. If left untreated, the rebleeding risk within 2 years is up to 60%.[8] The mortality rate at 6 weeks post an index variceal bleed is up to 26%.[9-11]

Portal hypertension

The blood flow through the portal vein in healthy volunteers is estimated to be approximately 13.5ml/min/kg[12] as it receives blood flow from the small and large intestine as well as from intra-abdominal organs such as spleen and pancreas via the mesenteric veins (both superior and inferior) and the splenic vein. The portal vein also receives venous blood flow from the oesophagus and stomach via the left gastric vein. Obstruction to this flow cascade at the level of the portal vein or downstream sinusoids can result in PH and consequent engorgement or enlargement of other intra-abdominal veins which communicate with the systemic circulation such as the umbilical vein and epigastric venous plexus of the abdominal wall, superior haemorrhoidal veins and the middle/inferior haemorrhoidal veins and the short or left gastric with the azygos vein which in turn can result in complications at those particular anatomical sites.[13, 14] The negative sequelae of PH are not only confined to variceal formation and consequent gastrointestinal bleeding, however, it also includes development of abdominal ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary or portopulmonary syndrome and ultimately death[14]. Therefore, being able

to quantify the degree of PH is of paramount importance in establishing a diagnosis, guiding treatment and monitoring of PH.

PH is quantified by the portal pressure gradient (PPG), which derived from the difference between the portal venous (PV) pressure and the pressure within the hepatic vein (or inferior vena cava)[1]. It reflects the hepatic perfusion pressure. In patients with cirrhosis, portal pressure increases due to increased intrahepatic vascular resistance and increased portal blood flow overall.

Portal pressure gradient measurement (PPGM) may be performed directly through PV puncture, and hepatic vein (HV) pressure may also be measured directly, allowing for calculation of PPG. However, portal pressure is usually determined indirectly by subtracting the free hepatic venous pressure (FHVP) from the wedged hepatic venous pressure (WHVP). In cirrhotic patients, the WHVP equals portal (sinusoidal) pressure, as the catheter in the occluded position forms a continuous column of fluid between the catheter itself, the blood in the HV, the sinusoids and the PV. 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.[15, 16]

Overall, the severity of PH is an independent factor for survival in patients with liver cirrhosis [15] and can be associated with common sequelae such as variceal bleeding and formation of ascites and less common syndromes such as portopulmonary, hepatopulmonary or hepatorenal syndrome. In certain circumstances, when the primary cause of liver cirrhosis is treated, the degree of PH can improve significantly. For example, anti-viral therapy for chronic hepatitis B infection,[17] reduced mean portal pressure from 14.4mmHg to 12.4mmHg and 77% of patients experienced a significant reduction to below the 12mmHg, which is a major treatment target in order to significantly reduce the risk of gastrointestinal bleeding or the subsequent associated mortality.

The definition of PH is a HVPG > 5mmHg. HVPG of 6mmHg or more correlates well with liver cirrhosis[18] and cirrhotic patients with HVPG of ≤10mmHg are very likely to remain in a compensated state at a median follow up of 4 years.[19] 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 and re-bleeding as well as predicting development of jaundice, encephalopathy[20] and hepatocellular carcinoma (HCC).[21, 22] The risk of developing HCC in patients with HVPG of > 10mmHg vs < 10mmHg is 6 times greater.[21] The presence of PH also predicts risk of decompensation in post liver transplant patients.[23] HVPG is also an important predictor for surgical mortality post HCC resection in cirrhotic patients[24-26]. There was a significant difference in post-operative 90 day mortality between patients with HVPG of 12mmHg vs 8mmHg. Thus the diagnosis and quantification of PH has relevant diagnostic, prognostic and therapeutic implications.[27-29]

Monitoring HVPG has been increasingly used to assess target reductions of portal pressure during secondary, and less commonly, primary pharmacological prophylaxis of variceal bleeding. It is well established that the risk of variceal bleeding is dramatically lowered if HVPG is reduced by 20% from baseline or an absolute value of <12mmHg is achieved.[30-33] Not all patients are responders (between 36%[33] to 64%[34]) hence it would be useful to identify the non-responders and discontinue pharmacotherapy (propranolol or carvedilol) as appropriate and consider alternatives. Development of ascites may also be preventable if the HVPG is lowered by ≥ 10%.[35] Without ascites, spontaneous bacterial peritonitis, a complication of cirrhosis which carries up to a 75% 2 year mortality rate,[36] is unlikely to develop.

The procedure most often used to diagnose PH in clinical practice is the transjugular portosystemic pressure gradient. This percutaneous method is invasive, requires ionizing radiation, intravenous contrast, provides only indirect measurements and is rarely available as the service is confined to expert centers due to technical requirements of the procedure to ensure reliable and consistent outcomes. The procedure is performed by placing a radiopaque catheter (either an occlusion balloon or a wedge catheter) into the right jugular vein and advancing it into the HV tributaries under fluoroscopic guidance. A FHVP and WHVP are obtained, providing an indirect measurement of the PV pressure, and the HVPG is estimated by subtracting the former from the latter. This can be inaccurate in cases of pre-hepatic PH, such as PV thrombosis, and duplex ultrasonography is often also required.

Other methods, such as the surgical and transhepatic approaches, can be used for obtaining direct measurements; however these are more invasive and are seldom employed.

Given the importance of quantifying severity of PH, a less invasive, adjunctive modality and more direct method would be ideal. A simpler and widely accessible approach available outside of expert centres which can be combined with a routine test is needed given the prevalence of liver cirrhosis, PH and the likely need for subsequent repeated examinations or pressure measurements during the monitoring phase.

Portal pressure measurement

The first animal experiment to measure mesenteric vascular pressure was reported in 1896.[37] In humans, the first portal circulatory manometry was performed surgically and directly into the splenic vein in 1937[38] and subsequently the portal venous pressure (PVP) was measured by direct cannulation at surgery in 1950.[39] Shortly after, the WHVP was measured[40] via the cubital fossa guided by fluoroscopy. This produced accurate results even compared to this day whereby 12 healthy individuals displayed a mean WHVP of 4.8mmHg and 7 cirrhotic patients exhibited a mean pressure of 20mmHg (11.5-32mmHg). The technique was further refined by introduction of the balloon occlusion (as opposed to catheter wedge) in 1979[41] which improved technical ease of the procedure and allowed wider sampling of the venous tributaries draining towards the IVC as a previous study demonstrated different wedge locations could produce different results.[34] Although WHVP is a close estimate of the PVP (excluding pre-sinusoidal conditions such as schistosomiasis and early primary biliary cirrhosis[42]), this is affected by intra-abdominal pressure. Therefore, in order to neutralise this variable, subtracting the FHVP from WHVP will yield the HVPG which is unaffected by intra-abdominal pressure variations, as it is a gradient and both FHVP and WHVP are equally affected. HVPG is currently the preferred[43] method for measuring PH to determine diagnosis, prognosis and treatment targets to lower morbidity and mortality related to liver cirrhosis. Despite this, transcutaneous (often transjugular) approach as a well established technique and the current gold standard,[43] the degree of unacceptable variability in results or tracings can be up to 30%[44] hence rendering this technique only exclusively useful in high volume expert centers.

Other potential drawbacks to this approach include inadvertent damage to the structures surrounding the internal jugular vein, use of ionising radiation, the need for injection of intravenous contrast and failure to negotiate tortuous venous anatomy for HV cannulation.

EUS guided direct PV manometry was first reported in animal models in 2004.[45] 22G Fine needle aspiration (FNA) needles were used in 21 pigs to study feasibility of this novel approach. There were technical failures in 38% of pigs and periduodenal bleeding which prevented the authors from pursuing human studies (information obtained via private communications). 4 years later, the Johns Hopkins group, with the same objective, utilised a 5.5fr ERCP catheter for direct PV manometry after gaining access to the PV via EUS FNA and wire guidance. PV measurements were obtained continuously for an hour and 2 of 5 pigs were survived to demonstrate no complications.[46] These two studies employed complex set-ups using fluid filled manometers and neither measured PPG which is the key pressure differential between the portal vein (PV) and inferior vena cava (IVC) or hepatic vein (HV). The results were somewhat inconsistent with the direct portal pressure varying between 11 to 41mmHg, non of which were cirrhotic models. Since then, although no further studies described EUS guided PPG, there have been many studies showing safety in EUS facilitated direct access into the PV for various indications including multiple animal studies support safety[45-50] of this procedure with bleeding adverse events only occurring with larger needles (19 and 22G) or anticoagulated swine undergoing transduodenal FNA [45, 50] and human studies demonstrating uneventful EUS-FNA of the PV with a 25G needle in thrombocytopenic liver patients.[51, 52] and 19G needle for PV sampling[53, 54] for pancreatic cancer cells.

In this thesis, the author presents the first animal and human study of EUS-guided PPG measurement with a novel simplified technique using a fine 25-gauge needle and compact digital manometer with simultaneous correlation to the current gold standard, transjugular free and wedged hepatic venous pressure (WHVP).

1.2 Objective

The key objectives were to develop a simple endoscopic approach which complements the already necessary routine screening gastroscopy for oesophageal or gastric varices which can also measure direct PPGM with high levels of safety, consistency, accuracy and accessibility, to ensure this technique can be widely disseminated. Therefore, in this thesis, a novel yet simple method of endoscopic ultrasound (EUS) guided PPG was developed and examined for its feasibility, accuracy (by comparison with current gold standard of the transjugular method) and safety.

1.3 Thesis Structure

The structure of this thesis is developed around the core two papers which have already been published in Gastrointestinal Endoscopy. I begin with a background and literature review (Chapter 1) which then lead into the design and methods (Chapter 2) section followed by two core papers (Chapters 3 and 4) where the author had introduced a new method for direct PPGM first developed in an animal model (Chapter 3), with and without PH, and subsequently progressing to a human pilot study (Chapter 4).

Chapter 2: Design and methods

2.1 Animal study

2.1.1 Animal model

The initial approach was to establish feasibility in an animal model and with dextran induced PH rather than producing a cirrhotic model. This also allowed real time tracking of dynamic pressure increases and decrease as the PV compensate for the fluid overload. 3 yorkshire pigs (approximately 50kgs) were used for EUS-PPG. All swine were placed under general anaesthetic and euthanised immediately upon completion of the procedures. Necropsy and survival were not performed.

2.1.2 EUS procedure

A linear echoendoscope (GF-UC140P-AL5, Olympus,Tokyo,Japan), 25G FNA-needle (Cook Medical,Winston-Salem,NC), manometer and non-compressible tubing (Cook Medical, Bloomington, IN) were used.

Measurements were conducted in the right hepatic vein (RHV), PV, IVC and aorta. All venous measurements were performed via the transgastric transhepatic approach (Figure 2). When evaluating RHV pressure, FNA needle placement was targeted at 2cm distal to the ostia. When targeting the left main PV, only the intrahepatic portion near the PV bifurcation was accessed. IVC was accessed at the level of the RHV ostia and aorta was accessed just above the coeliac takeoff. Up to 1ml of heparinized saline was flushed through the FNA needle prior to each EUS reading. Following 30-60 seconds of stabilization, the pressure was recorded and generally ≥3 separate readings per vessel per FNA were performed. Transjugular and EUS pressure transducers were zeroed at an identical level (mid axillary line).

2.1.3 Interventional radiology (IR) procedure.

Manometric data was obtained from the RHV (both free and wedged), IVC and aorta. External jugular venous cut down facilitated venous access while aortic pressure (at the level just above coeliac takeoff) was obtained via the femoral artery. A 5Fr 11mm balloon occlusion catheter connected to a pressure transducer and recorder was used. Calibration

was performed at 6.8cm (5mmHg), 13.6cm (10mmHg) and 20.4cm (15mmHg) of water. This procedure was performed by a radiologist.

2.2 Human pilot study

2.2.1 Human pilot study

EUS-PPG was performed at a single tertiary academic center by 2 experienced endosonographers (KC and JH). All cases were performed under moderate sedation or general anaesthesia in the supine position. Patients must be between the age of 18-75 with a history of liver disease or suspected cirrhosis. 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, which was defined as successful PPG manometry in each case. Complications that were documented 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 captured prospectively then 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.

2.2.2 Endoscopic Procedure

Prior to EUS PPG measurement, a forward viewing endoscope (Olympus, Tokyo, Japan) was used to evaluate and document the endoscopic evidence of PH such as varices or portal hypertensive gastropathy (PHG). The apparatus for PPGM included a linear echoendoscope (GF-UC140P-AL5, Olympus, Tokyo, Japan), a 25G FNA-needle (Cook Medical, Winston-Salem, NC, USA), and a compact manometer with non-compressible tubing (Cook Medical, Bloomington, IN, USA). The manometer was zeroed at the mid axillary line then the EUS scope was inserted. Measurements were conducted in the PV and HV 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 transhepatic, 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 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. One ml 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. The FNA needle was withdrawal from the PV to the level of the liver capsule, color doppler was used to make sure there was no flow in the needle track before complete withdrawal of the needle into the scope channel. Intraprocedural prophylactic antibiotics were given.

2.2.3 Definitions

The universal definition of portal hypertension (PH) of >5mmHg and clinically significant portal hypertension (CSPH) of >10mmHg were used [19].

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.

2.2.4 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.

Chapter 3: Endoscopic ultrasound guided portal pressure gradient (PPG) measurement with a novel 25 gauge needle device versus standard transjugular approach – A comparison animal study.

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Citation

Huang JY, Samarasena JB, Tsujino T, et al. EUS-guided portal pressure gradient measurement with a novel 25-gauge needle device versus standard transjugular approach: a comparison animal study. Gastrointest Endosc 2016;84:358-62.

3.1 Abstract

Background and Aims: Portal hypertension (PH) is a serious adverse event of liver cirrhosis. The hepatic venous pressure gradient (HVPG) accurately reflects the degree of PH and is the single best prognostic factor in liver disease. Currently, PPG measurement is performed at interventional radiology (IR) with a standard transjugular approach requiring radiation and IV contrast. The aim of this study was to develop a novel EUS-guided system using a 25G FNA needle and compact manometer to directly measure PPG and to evaluate its performance and clinical feasibility.

Methods: Experiments were performed in 3 swine under general anesthesia by 3 proceduralists (KC, JS and JH). Manometry was performed in venous (Baseline and PH) and arterial (aorta) systems.. The PH model was created by rapid Dextran-40 infusion peripherally. Under EUS guidance, a 25G FNA needle with attached manometer was used to puncture (transgastric-transhepatic approach) and measure pressures in the portal vein (PV), right hepatic vein (RHV), inferior vena cava (IVC), and aorta. With the IR approach, RHV (free and wedged), IVC, and aorta pressure were measured with an occlusion balloon. Pressure correlation was divided into three groups; low pressure (baseline), medium pressure (non-cirrhotic portal hypertensive model) and high pressure (arterial). Correlation between the two methods of measurement was charted in scatter plots and the Pearson's correlation co-efficient (R) was calculated.

Results: EUS identification, access and manometry was successful in all targeted vessels. There was excellent correlation (R=0.985 to 0.99) between EUS and IR methods in all pressure ranges. No adverse event occurred.

Conclusion: This novel technique of EUS-PPG measurement using a 25G needle and novel manometer was feasible and demonstrated excellent correlation with the standard transjugular method throughout low, medium and high pressure ranges.

3.2 Introduction

Portal hypertension (PH) is a serious adverse event of liver cirrhosis.[14] Patients with portal hypertension are at risk of developing gastro-esophageal varices and related bleeding, ascites, hepatorenal syndrome and hepatic encephalopathy.[27] The hepatic venous pressure gradient (HVPG) accurately reflects the degree of PH in all forms of sinusoidal and post-sinusoidal causes. Knowing the HVPG can guide medical therapy, assess degree of liver fibrosis[56], predict risk of decompensation and developing hepatocellular carcinoma. [43, 46] However, the transjugular procedure to obtain the HVPG is invasive and not readily available, therefore, most patients with suspected PH do not undergo this procedure.

Older studies have been conducted studying the feasibility of EUS guided Portal vein pressure (PVP) measurements. These studies have employed 5.5Fr catheters.[46] and 22-gauge (G) FNA needles[45] and have been based on direct PVP measurement. These studies employed complex set-ups using fluid filled manometers and no studies measured the portal pressure gradient (PPG), that is, the pressure differential between the portal vein (PV) and inferior vena cava (IVC) or hepatic vein (HV).

Here we present the first study of EUS-guided PPG measurement with a novel simplified technique using a 25G needle and compact manometer (figure 1) with simultaneous correlation to the current gold standard, transjugular free and wedged hepatic venous pressure (WHVP). Feasibility and accuracy of this novel technique and setup was evaluated in a porcine model with and without PH.

3.3 Methods

Animal model

Three Yorkshire swine weighing 43.5-48 kg were sedated with Telazol/Xylazine followed by intubation and maintained in supine position with Isoflurane. Continuous monitoring for heart rate, respiratory rate, end-tidal CO2 and oxygen saturation was carried out throughout the experiment until euthanasia with pentobarbital/phenytoin. Pressure measurements were carried out at baseline hemodynamics and then post induction of non-cirrhotic portal hypertension by rapid peripheral infusion of Dextran-40 (≤1.5 liters). This study protocol was approved by the hospital's Institutional Animal Care and Use Committee.

EUS Procedure

A linear echoendoscope (GF-UC140P-AL5, Olympus,Tokyo,Japan), 25G FNA-needle (Cook Medical,Winston-Salem,NC), manometer and non-compressible tubing (Cook Medical, Bloomington, IN) were used.

Measurements were conducted in the right hepatic vein (RHV), PV, IVC and aorta. All venous measurements were performed via the transgastric transhepatic approach (Figure 2). When evaluating RHV pressure, FNA needle placement was targeted at 2cm distal to the ostia. When targeting the left main PV, only the intrahepatic portion near the PV bifurcation was accessed. IVC was accessed at the level of the RHV ostia and aorta was accessed just above the coeliac takeoff. Up to 1ml of heparinized saline was flushed through the FNA needle prior to each EUS reading. Following 30-60 seconds of stabilization, the pressure was recorded and generally ≥3 separate readings per vessel per FNA were performed. Transjugular and EUS pressure transducers were zeroed at an identical level (mid axillary line). The procedure was conducted by 3 experienced endosonographers (KC, JS and JH).

Interventional Radiology (IR) Procedure

Manometric data was obtained from the RHV (both free and wedged), IVC and aorta. External jugular venous cut down facilitated venous access while aortic pressure (at the level just above coeliac takeoff) was obtained via the femoral artery. A 5Fr 11mm balloon occlusion catheter connected to a pressure transducer and recorder was used. Calibration was performed at 6.8cm (5mmHg), 13.6cm (10mmHg) and 20.4cm (15mmHg) of water.

Correlation

In the RHV, IVC and aorta, the transjugular balloon catheter tip and FNA-needle tip were
targeted at the exact same location within the vessel as confirmed on fluoroscopic venogram
and EUS (figure 3) and paired manometric datasets were recorded simultaneously. Needle
placement was very specific to maximize consistency and to establish a standardized venous
manometry protocol. Pressure correlation was divided into three groups; low pressure
(baseline), medium pressure (non-cirrhotic portal hypertensive model) and high pressure
(arterial).

Statistical Analysis

Descriptive statistics including median, mean, standard deviation, minimum and maximum
were calculated for continuous variables. Correlation between the two methods of
measurement was charted in scatter plots and the Pearson's correlation co-efficient (R) was
calculated.

3.4 Results

Feasibility

EUS identification and access into all targeted vessels was achieved without any failures. All desired pressure readings were able to be obtained in each of the vessels in all pigs.

Data and Correlation

Using EUS there were a total of 17 independent manometry measurements made in the portal vein, 17 in the hepatic vein, 9 in the IVC and 4 in the aorta. Using the IR approach there were 17 wedged hepatic vein measurements, 17 free hepatic vein measurements, 9 IVC measurements and 4 aortic measurements (See Table 1). There was excellent correlation between the EUS and IR approach at all pressure ranges. Pearson's correlation co-efficient was 0.999 (all vessels, Figure 4A), 0.985 (all veins, Figure 4B), 0.988 (PV and WHVP, Figure 4C) and 0.986 (FHVP, Figure 4D).

Hemodynamic Monitoring

Every swine was hemodynamically stable (blood pressure, heart rate, oxygen saturation and end tidal carbon dioxide) throughout all procedures despite multiple punctures into a variety of blood vessels. Furthermore, there was no evidence of bleeding seen at EUS or contrast extravasation on fluoroscopy; including during induced portal hypertension. Necropsy, however, was not performed.

3.5 Discussion

HVPG is the single most important predictor of variceal bleeding risk.[43, 57, 58] The current transjugular techniques to obtain HVPG are invasive and not readily performed. Our novel EUS-guided technique using a 25G needle and compact manometer demonstrated no technical failures related to vascular access or manometry, and demonstrated excellent correlation with the standard transjugular method that were maintained throughout low, medium and high pressure ranges indicating that this novel EUS method is highly accurate. An EUS guided approach is an attractive option for several reasons. EUS has the advantage of minimizing bleeding risk as real-time Doppler facilitates avoidance of intervening vessels and provides confirmation of hemostasis within the needle tract prior to needle withdrawal. This novel technique uses a small 25G needle via a transhepatic approach, allowing the surrounding liver parenchyma to tamponade the needle path. Unlike WHVP obtained via the transjugular approach, the accuracy of direct PV manometry is not influenced by liver tissue compliance. Lastly, EUS is widely available and with our novel method of attaching a pocket-sized battery-operated manometer, HVPG can be readily obtained in a rapid, convenient manner. We propose calling this procedure EUS-guided portal pressure gradient (PPG) measurement, as it reflects the true gradient between direct portal vein and direct hepatic vein pressure measurements.

Standardization of technique to ensure consistency is of paramount importance, as previously highlighted in the radiology literature.[44] We measured the RHV no further than 2cm from the ostia. The transducer was leveled and fixed at the mid axillary line in the supine position. It was important to perform both PV and HV manometry as this would neutralize confounding factors such as respiratory motion or variation in the device zeroing level. Limitations of this study include that it was a non-survival study without necropsy which would preclude definitive diagnosis of potential adverse events related to EUS-PPG measurement such as subacute bleeding, infection or thrombosis. However, there was no EUS evidence of bleeding or haematoma at the completion of the pressure measurements, despite multiple punctures into the same target areas. There have been several uncomplicated human and animal studies involving EUS-FNA of the PV for various indications. One study included 10 patients who uneventfully underwent EUS-FNA of the PV with 19G needle for cancer diagnosis.[53] Two human cases reported uneventful EUS-FNA of the PV with a 25G needle in

thrombocytopenic liver patients.[51, 52] Multiple animal studies also support safety[45-50] of this procedure with bleeding adverse events only occurring with larger needles (19 and 22G) or anticoagulated swine undergoing transduodenal FNA.[45, 50] Lastly, our portal hypertension model did not incorporate coagulopathy related to synthetic dysfunction and the lack of a cirrhosis model therefore does not truly reflect the physiology of a cirrhotic liver and assessment of the impact of anatomical distortion on technical feasibility was not possible.

3.6 Conclusion

This novel technique of EUS-PPG measurement using a 25G needle and compact manometer was shown to be feasible in a porcine model and demonstrated excellent correlation with the standard transjugular method in a wide range of vascular pressures. Early human clinical trials are currently underway to further evaluate this promising concept.

3.7 Figures and tables

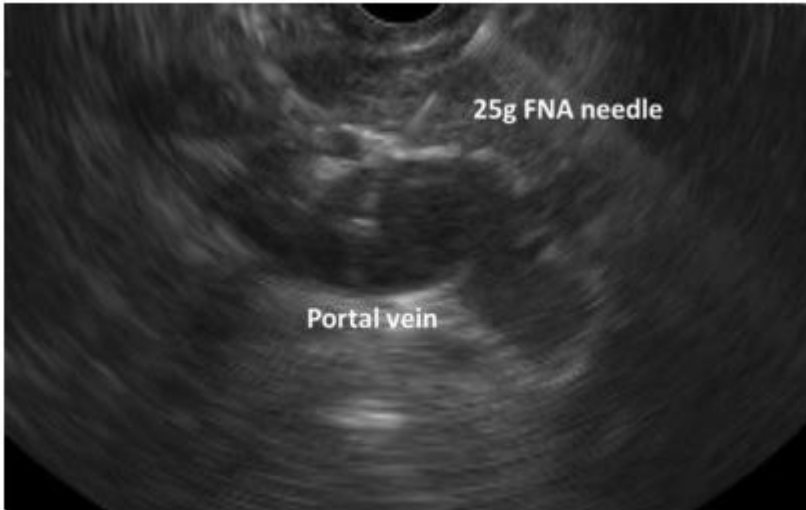Figure 1. Compact pocket sized battery operated manometer.

Figure 2. Transgastric transhepatic EUS placement of 25G needle into the left main portal vein.
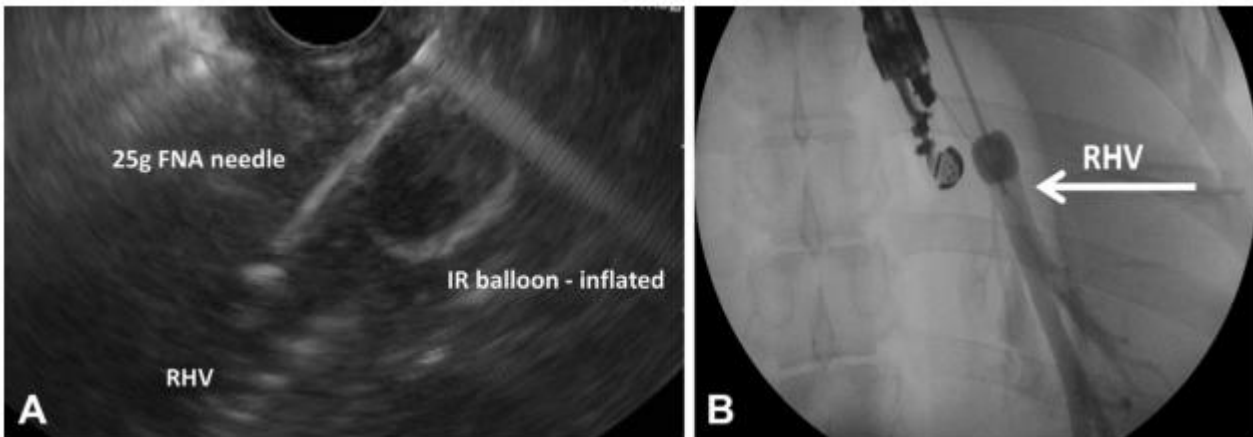

Figure 3. Simultaneous placement of transjugular (IR) balloon (inflated) and 25G EUS needle in the right hepatic vein. A. EUS and B. Fluoroscopy.

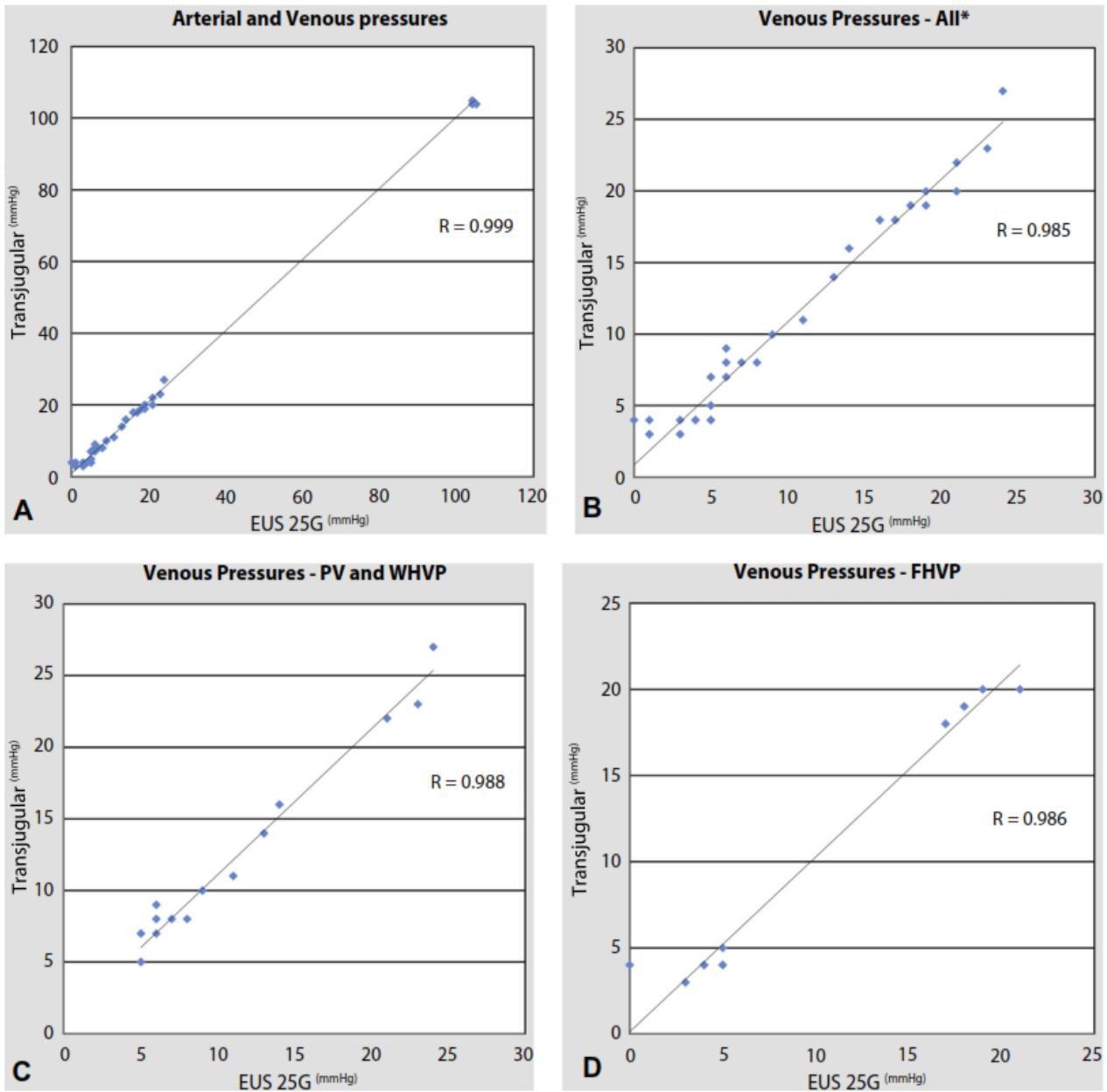Figure 4. Correlation between transjugular and EUS 25G methods - (A) Correlation of 47 paired manometric data points from all vessels (arterial and venous) (B) Correlation of 43 paired manometric data points from all venous structures * denotes inferior vena cava, portal and hepatic vein. (C) Correlation of 17 paired manometric data points from WHVP and PV (D) Correlation of 17 paired manometric data points from FHVP/RHV.

Table 1. Manometric data from PV, FHVP/RHV, aorta by EUS and IR methods.

		PV	WHVP	FHVP		IVC		Aorta	
		EUS	IR	EUS	IR	EUS	IR	EUS	IR
Baseline	Number	10	10	11	11	6	6	4	4
	Mean (mmHg)	5.8	6.9	4	4	1.7	3.3	104.3	104.3
	(S.D) (mmHg)	1.03	1.45	1.48	0.45	1.03	0.52	0.5	0.58
	Median (mmHg)	5.5	7	4	4	1	3	104	104.5
	Range (mmHg)	5-8	5-9	0-5	3-5	1-3	3-4	104-105	104-105
Portal hypertensive model	Number	7	7	6	6	3	3		
	Mean (mmHg)	16.4	17.6	18.3	19	17	18.3		
	(S.D) (mmHg)	6.1	6.5	1.51	0.89	1.73	0.58		
	Median (mmHg)	14	16	18	19	16	18		
	Range (mmHg)	9-24	10-27	17-21	18-20	16-19	18-19		
Combined Baseline and Portal hypertensive model	Number	17	17	17	17	9	9		
	Mean (mmHg)	10.2	11.3	9.3	9.1	7.5	9		
	(S.D) (mmHg)	6.6	6.8	7.2	7.4	7.76	7.52		
	Median (mmHg)	7	8	5	4	3	4		
	Range (mmHg)	5-24	5-27	0-20	3-21	1-19	3-19		

Chapter 4: Endoscopic Ultrasound Guided Portal Pressure Gradient Measurement with a Simple Novel Device – A Human Pilot Study

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4.1 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 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

4.2 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.[27, 30] Therefore, the diagnosis and quantification of portal hypertension by measuring portal pressure holds tremendous therapeutic and prognostic implications[27-29]

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[27].

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 [15, 16, 30].

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 [30-33]. Furthermore, the severity of portal hypertension is an independent factor for survival in patients with liver cirrhosis [15].

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 [15]. 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 [59] 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.

4.3 Methods

EUS-PPG was performed at a single tertiary academic center by 2 experienced endosonographers (KC and JH). 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 [19].

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.

4.4 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).

4.5 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 [20, 43, 60]. It may also play a pivotal role in diagnosis and staging of advanced fibrosis or cirrhosis [56, 60]. Unfortunately, readily obtaining the portal pressure is hindered by many factors and establishing a gradient (rather than PVP only) is necessary as discussed previously to minimise factors which could adversely affect the accuracy of portal pressure manometry. 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 [61-64].

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 [65, 66]. 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.

4.6 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.

Acknowledgements

4.7 Figures and tables

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.
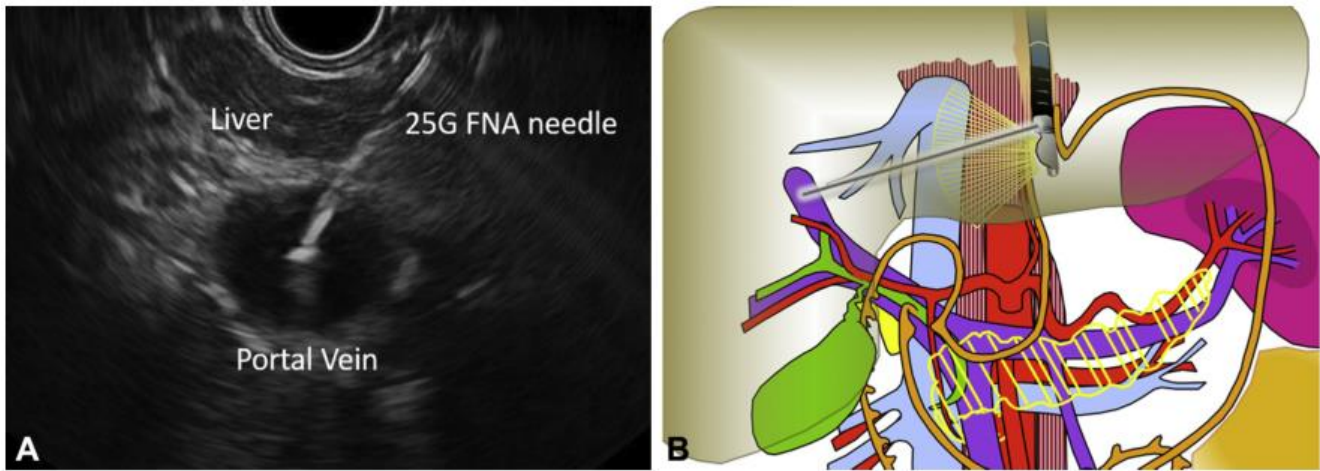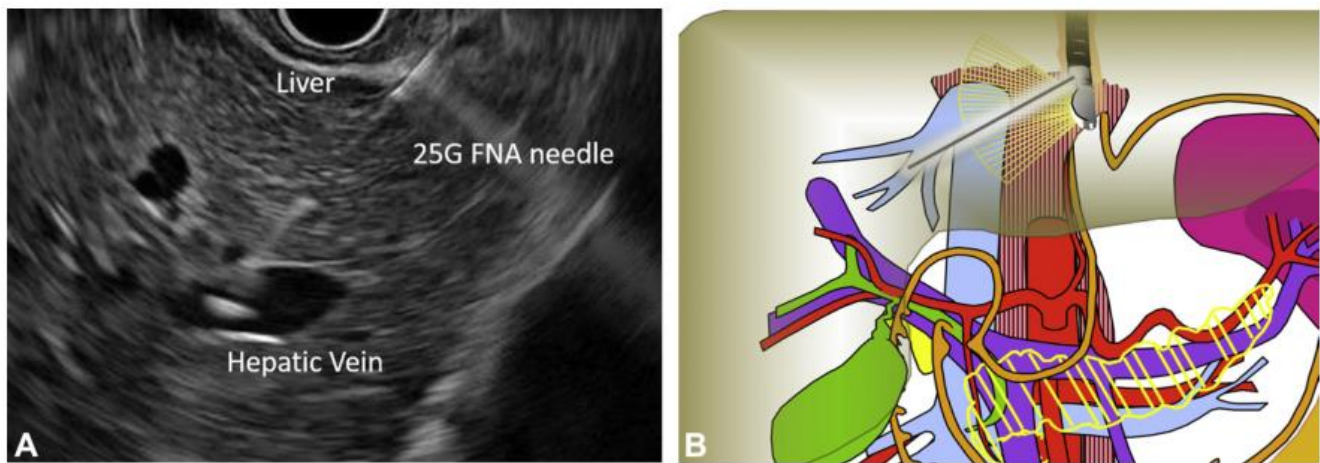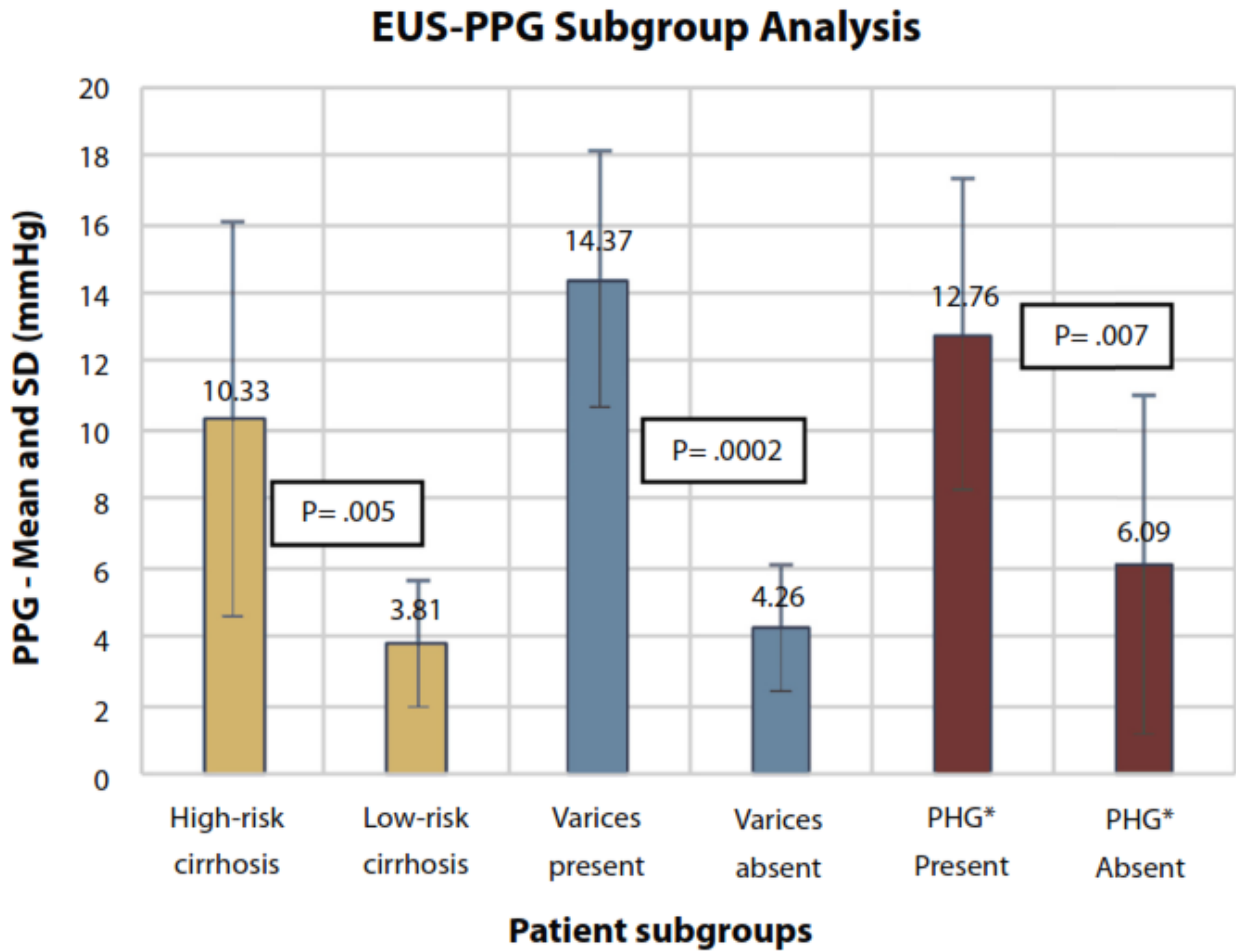

Figure 3. A) Endoscopic Ultrasound Image of transgastric transhepatic needle puncture into the hepatic vein with a 25G FNA needle. B) Diagram representing EUS guided transgastric hepatic vein puncture.

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

Chapter 5 - Discussion

5.1. Implications of this study

Knowing the HVPG has significant impact on clinical management of patients and future research related to liver cirrhosis or PH hypertension, however, it is not commonly done due to difficulties with access to this information. Most importantly, HVPG can predict risk of decompensation, in particular, variceal bleeding and/or re-bleeding. It is well known that variceal bleeding risk related to portal hypertension is much lower below 12mmHg and essentially zero when HVPG is < 10mmHg as varices are absent.[67] This can also potentially guide management both in the acute setting whereby a higher HVPG predicts increased risk of rebleeding [68] therefore early TIPS may be considered as a more aggressive intervention over conventional endoscopic variceal band ligation. In the elective setting, it may impact on decision to band varices seen at screening endoscopy. It is also helpful in determining response to pharmacotherapy for PH. This will facilitate determination of the optimal medication dose to achieve the key pressure reduction targets hence optimising the clinical outcome particularly with regards to bleeding risk. In those who fail to achieve any meaningful response, the medication can be confidently discontinued. The effective end points could include HVPG reduction; by ≥ 20%, into the < 12mmHg range or even 10% reduction whilst the HVPG is less than 12mmHg. Other potential indications could include assessment of peri-operative mortality prior to liver resection and predicting risk of developing HCC or facilitate studies on anti-fibrotic drugs[69] by providing a clear and accessible outcomes parameter.

With EUS being widely accessible, EUS-PPG can be performed at the same session as the routine screening gastroscopy for endoscopic evidence of PH in patients with known risk factors. Unlike the transjugular approach, EUS-PPG requires no iodinated contrast or ionizing radiation and is well tolerated by patients (no pain), 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 early primary biliary cirrhosis. This simple yet innovative method has been shown in Chapter 4 which correlated extremely well (R=0.986) with the current gold standard of transjugular method for procuring HVPG in the animal model through a wide range of pressures from low pressure (baseline/normal), medium pressure (non-cirrhotic portal hypertensive model) and high pressure (arterial). Subsequent human pilot study demonstrated feasibility and tight correlation with presence of portal hypertension in patients with clinical, endoscopic and/or biochemical evidence suggestive of liver cirrhosis. There were no complications in this

study despite majority of patients were suspected of having cirrhosis and some were also thrombocytopenic and coagulopathic as this technique is based on a well-established technique of EUS guided FNA, which carries an excellent safety record. The use of a small 25G gauge needle in conjunction with high-resolution real time doppler imaging and liver parenchyma tamponade prior to needle withdrawal likely all contribute to the safety of this novel technique. The most feared complications, including bleeding and infection, did not occur. Prophylactic antibiotics were given however it may be the case in the future where this is proven to be unnecessary as we had adopted a very conservative approach and are proceeding with extreme caution. This technique was 100% successful in acquiring a PPG.

Lastly, clinical implications aside, this novel method of acquiring HVPG can also be useful tool in many aspects of PH related research.

5.2. Limitations

The animal study (chapter 4) was a non-survival model therefore no specific safety data was generated other than lack of immediate complications as seen on real time doppler study. Although a wide pressure range was measured and correlated with a very high Pearson's correlation co-efficient, the portal hypertensive model was non cirrhotic.

The human study (chapter 5) was a single center pilot study consistent of only a small cohort of patients (28). Although the results are favourable, a larger multicentre study is needed to confirm safety and accuracy of this novel method for measuring HVPG. Further correlation with transjugular method can be considered if achievable.

5.3. Future direction

An multicentre study with transjugular HVPG correlation is in the planning phase to assess the safety and accuracy of EUS-PPG. If this technique is accepted as a main stream diagnostic tool, it will facilitate further research on the natural history, treatment and prognosis of portal hypertension. In the clinical setting, this technique could be used to help define which patients require endoscopic intervention and/or modification of medications to treat portal hypertension. The training requires in-depth knowledge of liver anatomy in order to identify the key vascular targets for manometry. No additional support personnel are required in an existing unit capable of EUS-FNA.

5.4. Conclusion

EUS-PPG is a promising technique which improve the easy of access to the HVPG which is likely to induce a paradigm shift in the management algorithm for PH in a diagnostic, therapeutic and prognostic fashion, whether it is in an elective or emergency situation.

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Appendices

1. Institutional Review Board and Institiutional Animal Care and Use Committee Letter

UC Irvine Health

February 22nd, 2018

To Whom It May Concern:

The work completed by Dr. Jason Huang for the manuscripts listed below received University of California, Irvine (UCI) Institutional Review Board (IRB, FWA# FWA00004071) and Institutional Animal Care and Use Committee (IACUC) approval for the duration of the project.

- Huang JY, Samarasean JB, Tsujino T, Lee JG, Hu KQ, McLaren CE, Chen WP, Chang KJ. EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study. Gastrointestinal Endoscopy. 2016, Vol. 85 (5): 1002-1004.
- Huang JY, Samarasean JB, Tsujino T, Chang KJ. EUS-guided portal pressure gradient measurement with a novel 25-gauge needle device versus standard transjugular approach: a comparison animal study. Gastrointestinal Endoscopy. 2016, Vol. 84 (2): 358-362.

UCI IRB number: HS# 2008-6258

IACUC number: 1999-1712

Please let me know if you have any questions about the above information.

Sincerely,

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