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Endoscopic ultrasound portal pressure gradient measurement and its impact in managing portal hypertension

Lesmana CRA. EUS-PPG in PH

Abstract

Portal hypertension (PH) is still a challenging clinical condition due to its silent manifestations in the early stage and need to be measured accurately for early detection. Hepatic vein pressure gradient measurement has been considered as the gold standard measurement for PH, however, it would need special skill, experience, and high expertise. Recently, there has been an innovation development using endoscopic ultrasound (EUS) for diagnosis and managing liver diseases, including portal pressure measurement, which is commonly known as EUS-guided portal pressure gradient (EUS-PPG) measurement. EUS-PPG can be performed concomitantly with EUS evaluation for deep esophageal varices, EUS-guided liver biopsy, and EUS-guided cyanoacrylate injection. However, there are still major issues, such as different etiologies of liver disease, procedural training, expertise, availability, and cost-effectiveness in several situations with regard to the standard management.

Key Words: Portal hypertension; Hepatic vein; Endoscopic ultrasound; Portal pressure

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Core Tip: Portal hypertension (PH) is a challenging clinical condition due to its silent manifestations in the early stage. Hepatic vein pressure gradient measurement is still the gold standard for PH diagnosis; however, it is not recommended yet for a routine measurement in daily practice. Esophagogastroduodenoscopy is still the main procedure for variceal screening due to PH. Recently, there is a development using endoscopic ultrasound (EUS) for managing liver diseases. EUS-guided portal pressure gradient measurement seemed to be a promising method in the future for PH early detection and management.

INTRODUCTION

Portal hypertension (PH) is a challenging clinical condition due to its silent manifestations in the early stage and it needs to be measured accurately for early diagnosis. PH is defined when there is an increase of portal pressure above 5 mmHg. Clinically significant PH (CSPH) is defined when the portal pressure reaches 10 mmHg and above. CSPH is an important clinical condition because of its clinical consequences, such as the presence of esophageal and gastric varices, ascites, kidney dysfunction, as well as cardiopulmonary complications. These conditions are mostly observed in liver cirrhotic patients with liver disease progression, even though there is a non-cirrhotic condition with PH^[1,2]. Hepatic vein pressure gradient (HVPG) measurement has been considered as the gold standard measurement for PH, however, it would need special skill, experience, and high expertise. This procedure is also needs to be performed in a dedicated catheterization procedure room^[3]. Esophagogastroduodenoscopy (EGD) is a standard procedure for early detection of PH complication, *i.e.*, the presence of varices^[4,5]. A major drawback is that these two procedures might not be performed in the same session. Another issue in clinical practice is that not all cases might have accurate portal pressure measurement through this indirect measurement procedure due to the pathology of portal vein (PV), which does not include the liver architecture disturbance^[6,7]. Recently, there have been innovation for portal pressure measurement through endoscopic ultrasound (EUS) procedure. The liver images as well as the liver vascularity will be shown clearly for puncture location. However, it would need special skill and knowledge to perform the procedure^[8]. In our center, this procedure is also only performed by endoscopists with more than ten years of clinical experiences (Figures 1 and 2). This review will discuss more about the role of EUS in portal pressure measurement and its impact in clinical practice.

PH, portal pressure measurement, and issue in clinical practice

PH has been divided into prehepatic, intrahepatic, and post-hepatic. This condition happened due to increased portal blood flow resistance, where it is mostly caused by intrahepatic vascular resistance in chronic liver disturbances. Imbalance activation

between vasoconstrictors and vasodilators due to liver architectural disturbance is the main key to PH. In non-cirrhotic condition, or commonly known as non-cirrhotic PH (NCPH), PV fibrosis or thrombosis is the main issue^[9,10].

HVPG measurement is the gold standard for PH assessment. This measurement technique is considered safer than direct measurement *via* transhepatic or transvenous catheterization route because more advanced approach to the inferior vena cava will be required for portal pressure gradient (PPG). HVPG has been considered as a safe procedure. However, there are several patient's condition which needs special attention, such as cardiopulmonary disorders, hepatic encephalopathy, history of cardiac arrhythmias, and evidence of vena cava thrombosis. There are also some possible conditions which can happen during the procedure itself, such as allergic reaction to contrast agent, cardiac arrhythmia during catheter insertion in transjugular route, and bleeding in patient with very low platelet count or prolonged international normalized ratio^[11,12]. On the other hand, this procedure is preferable in patients with significant ascites^[3]. Based on HVPG measurement, the strategy of further management has been clearly defined with possible mortality rate. In the early stage, CSPH complications can be prevented with early medication. A randomized controlled trial of carvedilol *vs* endoscopic band ligation (EBL) by Tripathi *et al*^[4] has showed that carvedilol has the same efficacy with EBL primary prophylaxis in term of bleeding prevention. This study has also been supported by another more recent study by Shah *et al*^[13] in a multicentre randomized controlled trial. A recent systematic review and meta-analysis by Dwinata *et al*^[14] showed that carvedilol had similar efficacy with EBL for primary variceal bleeding prevention. Follow-up HVPG value can also be used to determine the response to the treatment and change to another strategy if needed. In late stage of the disease or decompensated condition, more advance complications prevention or advance management can be decided based on HVPG value^[2]. Moitinho *et al*^[15] showed the usefulness of early portal pressure measurement in acute variceal bleeding scenario. This prospective study concluded that higher HVPG value has been associated with longer interval between each hospital admission and lower mortality

rate. Another study conducted by Ripoll *et al*^[16] on 213 liver cirrhosis (LC) patients within 6 years period showed that HVPG value with 10 mmHg cut-off can be a good predictor for liver decompensation. The hazard ratio for liver decompensation of HVPG is higher than albumin level and model for end-stage liver disease score.

There has been development of non-invasive methods for PH assessment. A prospective study by Bureau *et al*^[17] on the use of transient elastography for PH prediction showed that there was a good correlation between liver stiffness and HVPG ($P < 0.001$). However, based on further analysis, the sensitivity and specificity are becoming higher in line with the increase of the liver stiffness. The main issues are the high value of liver stiffness due to the severity of liver fibrosis condition and varied etiologies of liver diseases^[17]. Another prospective study conducted by Palaniyappan *et al*^[18] on patients with advanced liver disease using magnetic resonance imaging (MRI) liver parameters, where patients also underwent liver stiffness measurement (LSM) before the MRI examination, showed that two MRI parameters, *i.e.*, liver T1 relaxation time and splenic artery velocity, are significantly associated with HVPG values ($r = 0.90$, $P < 0.001$). Even though the LSM was significantly correlated to HVPG ($r = 0.791$, $P < 0.001$), no significant correlation was found in the subgroup of patients and with HVPG more than 10 mmHg^[18]. Another innovation of non-invasive method for assessing PH in clinical practice has been showed in a study by Frankova *et al*^[19], where the use of ultrasound-based shear-wave elastography has been correlated well with HVPG values in all LC patients as well as in the subgroup of patients. The liver stiffness values of 16 and 20 mmHg are considered as the best predictors value associated with HVPG. In daily practice, non-invasive methods are still debatable due to its different study results and early detection for PH. MRI examination is also remaining a major issue at present as a routine follow-up examination due to its cost, availability, and patients' comfort^[20].

Metabolic condition, such as non-alcoholic fatty liver disease (NAFLD) or it is now well-known as metabolic dysfunction associated fatty liver disease, might be a new challenge in the field of hepatology. It has been postulated that this condition might not have liver fibrosis progression and PH condition in the same line^[21]. A prospective

study published by Hirooka *et al*^[22] revealed that there was a hemodynamic change in early course of the disease process in NAFLD patients, where patients were still at the early liver fibrosis condition based on the median hepatic arterioportal ratios together with splenic elasticity evaluation. Another database study conducted by Mendes *et al*^[23] on 354 NAFLD patients showed that 6% of NAFLD patients without evidence of LC had PH complications. NCPH is another issue, where HVPG measurement may not be as good as it is. The complexity of vascular system and liver pathology assessment for confirming diagnosis have been a challenging issue in clinical practice^[24].

EGD is still the main procedure in daily practice to diagnose PH condition based on the presence of esophageal or gastric varices^[25,26]. However, luminal evaluation does not always show a significant parameter for the presence of PH as well as in further management for PH^[27].

EUS-PPG measurement in PH

Recently, there has been an innovation development using EUS for diagnosis and management of liver diseases. It has been proposed as “endo-hepatology”, where endoscopic technique innovation can be used in the field of hepatology. It is started from EUS-guided liver biopsy, then followed by the use of EUS for abdominal fluid paracentesis, portal circulation, and EUS-guided intravascular injection for gastroesophageal varices^[28,29].

Initial animal study by Lai *et al*^[30] on feasibility of EUS-guided PV catheterization showed a good correlation between PV pressure (PVP) through EUS procedure and transhepatic route ($r = 0.91$). Giday *et al*^[31] conducted EUS-guided direct PVP measurement in pigs, and this study showed that there has been consistency in the pressure results, and no evidence of complications were recorded. Another pioneered animal study which used a novel device compact manometer was published by Huang *et al*^[32], where authors were able to show a good correlation between EUS approach with transjugular approach for right hepatic vein, PV, and aorta pressure measurements ($r = 0.985$). An innovative EUS-PPG-device animal study using a digital pressure wire

showed that this method was safe, and there were no complications such as thrombus or bleeding^[33]. A human pilot study was subsequently published by Huang *et al*^[34], where 28 patients underwent EUS-PPG without any complications. The technical success rate was 100% and the PPG had good correlation with varices ($P = 0.002$), low platelet count ($P = 0.036$), and gastropathy ($P = 0.007$). A recent study was conducted by Zhang *et al*^[35] on the role of EUS-PPG measurement in patients with acute or subacute PH. In this study, the technical success rate was achieved in 91.7% of the cases, where EUS-PPG measurement had a higher success rate than HVPG measurement. A good correlation was showed through the manometry result between EUS-PPG value with HVPG value ($r = 0.852$). No adverse events were observed during examination. Recently, a retrospective study conducted by Choi *et al*^[36] was looking at the correlation between portal pressure and clinical manifestations of PH. In this study, the PPG value was significantly higher in patients with LC (9.46 vs 3.61 mmHg; $P < 0.0001$), presence of gastroesophageal varices (13.88 vs 4.34 mmHg; $P < 0.0001$), and low platelet count (9.25 vs 4.71 mmHg; $P = 0.0022$). Seventy-one of 83 subjects underwent liver biopsy through EUS. No adverse events or complications were observed during and after the procedures. Lesmana^[37] has recently published a technique innovation where EUS-PPG was conducted by using standard manometer set in thirteen patients diagnosed with PH. In this case series, two LC patients with CP C score have been included. One patient has been diagnosed with NCPH. There were no adverse events or complications occurred during and after the procedure. Another more recent case report using standard pressure monitor was published just to show the procedural steps and the safety of its procedure^[38]. A systematic review and meta-analysis on EUS-PPG to diagnose cirrhosis showed that successful portal pressure measurement was achieved in 91.61% of the cases, with 0% of post-procedural complications, such as bleeding, perforation, and infection (95% confidence interval: 0-2.85). However, based on pool analysis, abdominal pain was 6.15%, emergency department visit was 3.11%, and sore throat was 2.82%^[39]. A very recent publication from Lei *et al*^[40] on EUS-PPG in fifty-two LC patients showed that this method has been successfully performed in 98% of the

cases. The authors showed the innovative puncture location, *i.e.*, transduodenal route, where it can be an alternative location if conventional puncture location was difficult. This study also showed that none of the patients experienced any adverse event (Table 1).

Future directions

EUS-PPG measurement is a better method in portal pressure measurement and diagnosing all PH condition, not limited to the chronic liver disease patients only. However, there are several issues that still need to be discussed before it will become a clinical recommendation in daily practice. First, EUS-PPG measurement can be performed concomitantly with EUS evaluation for the presence of deep esophageal varices or gastroesophageal varices. The clinical impact of EUS evaluation in the presence of deep esophageal varices in naïve patients as well as in patients with recurrence esophageal varices development have been reported in several studies^[41-43]. However, whether EUS evaluation is needed in the first setting in all patients with LC for deep varices evaluation is still debatable because there is no strong clinical evidence yet regarding its impact as the first-line examination, and there is a different course of liver disease progression based on each etiology. Second, EUS-PPG measurement can be performed together with EUS-guided liver biopsy, however, EUS-guided liver biopsy is not considered as a routine procedure yet in clinical practice due to unavailability of standard training, limited experience and availability, and the high cost when compared to percutaneous liver biopsy^[44,45]. Last but not least, EUS-PPG measurement can be performed and then followed by EUS-guided cyanoacrylate injection for large or deep gastroesophageal varices as well as isolated gastric varices^[37,46]. However, the need of EUS approach in acute variceal bleeding and impact of interventional radiology procedures, such as transjugular intrahepatic porto-systemic shunt or balloon-occluded retrograde transvenous obliteration, are still becoming a long way discussion for managing PH complications^[30,47].

CONCLUSION

EUS-PPG is a promising method in future clinical practice for managing PH condition and complications. However, it would need further studies and re-evaluation before it can be recommended as a routine clinical procedure.

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