Review Article

Portal pressure monitoring—state-of-the-art and future perspective

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Abstract: Portal hypertension is a serious symptom of chronic liver diseases, which can lead to many critical complications, such as the formation of varices related to upper digestive bleeding, ascites, infection, hepatic encephalopathy, renal failure, and even death. As a result, portal pressure monitoring has important prognostic and clinical implications. The hepatic venous pressure gradient measurement, a gold-standard method applied to monitor portal pressure, is invasive and only available in experienced centers. Over the past decade, noninvasive methods aimed at monitoring the portal pressure have been increasingly investigated, including serum markers, radiological features, ultrasound elastography, doppler and contrast-enhanced ultrasonography. In this study, we focused on both invasive and noninvasive methods for portal pressure monitoring and explored their roles in clinical setting. The advantages and limitations of various techniques for future research are also discussed.

Keywords: Portal pressure monitoring; portal pressure; hepatic venous pressure gradient (HVPG); invasive; noninvasive

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Introduction

Portal hypertension (PH), a severe symptom of chronic liver diseases, is defined as a pathologically increased portal pressure gradient (PPG) greater than 5 mmHg (1). Measuring the hepatic perfusion pressure, PPG is the difference between the portal vein pressure (PVP) and hepatic vein pressure or inferior vena cava (IVC) pressures. It is caused by the interaction of the portal blood flow with the vascular resistance against the flow (2). The relationship can be given by Ohm's law as follows:

$$\Delta P\ (PPG) = Q\ (\text{blood flow}) \times R\ (\text{vascular resistance}) \quad [1]$$

Based on Ohm's law, the increased PVP is attributed to an increased portal vein blood flow, an increased vascular resistance, or a combination of both (3). Based on the anatomical location of the increased resistance to blood flow within liver circulation, PH can be classified into three types: pre-hepatic PH, intra-hepatic PH, and post-hepatic PH (*Table 1*). Among the aforementioned diseases related to PH liver cirrhosis is the leading cause of PH worldwide. Other less common causes of PH account for less than 10% of cases, mostly due to vascular liver diseases such as extrahepatic portal vein occlusion (Budd-Chiari Syndrome) and idiopathic PH (4,5).

Table 1 Classification of portal hypertension

Type	Etiologies	Hepatic vein pressure measurement		
		WHVP	FHVP	HVPG
Pre-hepatic	Splenic vein thrombosis	Normal	Normal	Normal
	Portal vein thrombosis			
	Congenital stenosis of the portal vein			
	Extrinsic compression of the portal vein (neoplasia, lymph node, granuloma, abscess)			
	Arteriovenous fistulae			
Intra-hepatic (liver)	Pre-sinusoidal	Normal	Normal	Normal
	Idiopathic portal hypertension			
	Schistosomiasis			
	Tuberculosis			
	Primary biliary cholangitis			
	Sinusoidal	↑	Normal	↑
	Cirrhosis			
	Alcoholic hepatitis			
	Amyloidosis			
	Acute fatty liver of pregnancy			
	Post-sinusoidal	↑	Normal	↑
	Veno-occlusive disease (sinusoidal obstruction syndrome)			
Post-hepatic	Hepatic veins thrombosis (Budd-Chiari syndrome)	Unable to catheterize hepatic vein		
	Constrictive pericarditis	↑	↑	Normal
	Right heart failure			

WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient.

The normal range of PPG is 1–5 mmHg. When the value of PPG is in the range of 5–9 mmHg, it represents subclinical PH (6). However, when PPG increases to ≥10 mmHg, PH complications are more likely to occur, such as the formation of varices related to upper digestive bleeding, ascites, infection, hepatic encephalopathy, or renal failure (7,8). As the most common cause of PH, liver cirrhosis is a significant cause of global health burden. It is the eleventh-leading cause of adult deaths worldwide, and it results in 1.16 million deaths per year (9). PH complication may result in the need for liver transplantation, and it may also lead to death in patients with cirrhosis (10,11). Approximately 80–90% of asymptomatic PH patients already have an increased PPG [assessed clinically as an alternative indicator easy to obtain, namely the hepatic venous pressure gradient (HVPG)], and endoscopy has shown that 40% of patients already have gastroesophageal varices (6). According to the HVPG threshold, patients with PH could be classified into two levels: mild PH (HVPG >5 but <10 mmHg) and clinically significant PH (CSPH) (HVPG ≥10 mmHg) (1). For cirrhosis patients, CSPH further predicts the development of the decompensation of cirrhosis (12), higher risk of postsurgical decompensation, and increased risk of liver cancer (13,14). Based on the evidence, HVPG >12 mmHg indicates bleeding risk among CSPH patients with gastroesophageal varices (15). For, HVPG >16 mmHg, a higher risk of death is predicted (16). HVPG >20 mmHg is an independent prognostic factor of treatment failure and mortality (17,18). For cirrhosis patients waiting for liver transplantation, each 1-mmHg elevation in HVPG increases the risk of death by 3% during a median follow-up of 19 months (19). Therefore, measuring and

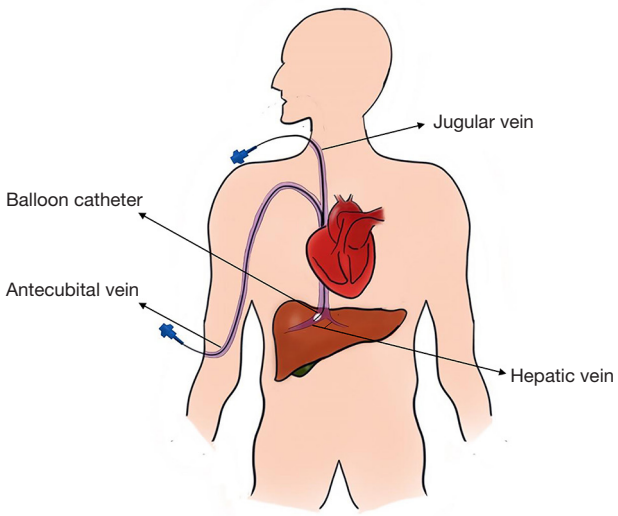

Figure 1 Venous access of hepatic venous catheter. As shown, HVPG can be acquired by catheterizing the right jugular vein or the cubital vein and shifting the catheter tip into the hepatic veins. It allows clinicians to measure the free hepatic venous pressure, which indicates caudal vena cava pressure. The wedged hepatic venous pressure can be obtained by occluding the hepatic vein through inflating the catheter balloon. HVPG, hepatic venous pressure gradient.

monitoring the portal pressure (PPG or its approximate value HVPG) in PH patients is important to guide the clinical treatment and evaluate the treatment efficacy.

The absolute portal pressure can be affected by intraabdominal pressure, which can be risen by obesity and ascites. However, increased intraabdominal pressure can increase both the portal vein and IVC pressures, without altering the value of PPG (20). As a result, compared with absolute portal pressure, it is clinically more meaningful to represent hepatic perfusion pressure in terms of PPG. The portal pressure can be directly acquired from transhepatic or transvenous catheterization of hepatic portal vein. However, the IVC pressure is also required to catheterize to determine the PPG. Considering the high risk of intraperitoneal bleeding and the requirement of significant procedural experience, HVPG measurement, a gold-standard technique to assess PH, has replaced other invasive methods of measuring PPG in cirrhosis since 1951 (1,21). In spite of its safety and reproducibility, it was still invasive, relatively expensive, and only available in experienced constitutions. As a result, over the past decade, noninvasive methods for assessing PH have been increasingly investigated (22).

In this study, we focus on both invasive and noninvasive methods to monitor the portal pressure and explored their roles in clinical setting. The advantages and limitations of various techniques for future research are also inquired.

Invasive methods for assessing portal pressure—measurement of HVPG

The catheterization of hepatic vein with the measurement of HVPG is the gold-standard method of monitoring the portal pressure in cirrhosis (sinusoidal PH) (1). HVPG is defined as the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP) (23).

$$HVPG = WHVP - FHVP \quad [2]$$

In 1951, Myers and Taylor first reported WHVP, the pressure of the hepatic sinusoid, an indirect measure of PVP (21). The WHVP is obtained by blocking the hepatic vein to form a static column of blood, which represents the pressure of hepatic sinusoids. This has been demonstrated for cirrhosis attributed to alcohol, viral infection (hepatitis B virus and hepatitis C virus), and nonalcoholic steatohepatitis (1,24). As in cirrhosis, the connections between sinusoids are lost owing to fibrosis and nodule and septa formation; the sinusoidal pressure equals to the portal pressure (25). The FHVP, as its name suggests, is measured by the pressure of the nonoccluded hepatic vein.

HVPG is measured by catheterizing the right jugular vein or femoral vein under local anesthesia. Then, a balloon-tipped catheter is inserted under fluoroscopic guidance into a hepatic vein to acquire the FHVP and WHVP (*Figure 1*). The FHVP is obtained by keeping the tip of the catheter floating freely in the hepatic vein, 2–4 cm from its opening into the IVC. Inflating the balloon, the WHVP is measured by occluding the hepatic vein (26). The doctors connect the pressure sensor to the catheter and read the pressure value from the detector. The WHVP and FHVP should be measured until a stable value is obtained. All measurements should be taken minimally twice. The final value is calculated as the mean of these measurements. Although the technique of acquiring the HVPG values is relatively straightforward, specialist training is still required to achieve accurate measurements.

The value of HVPG is widely applied for the diagnosis of chronic liver disease, monitoring the development of PH, guiding clinical treatment, assessing new therapeutic agents, and survival prediction of cirrhosis patients (1).

Table 2 Prognostic value of HVPG in patients with chronic liver disease

HVPG thresholds	PH grades	Prognostic value	Ref.
<5 mmHg	Normal	–	–
5–10 mmHg	Mild portal hypertension		
>6 mmHg		Progression of chronic viral hepatitis	(27)
		High risk of viral hepatitis recurrence after liver transplantation	(28)
>10 mmHg	Clinically significant portal hypertension		
>10 mmHg		Development of gastroesophageal varices	(7,29)
		Ascites development	(12)
		High risk of hepatocellular carcinoma occurrence	(14)
		High risk of decompensation after hepatic resection	(13)
>12 mmHg		High risk of gastroesophageal variceal hemorrhage	(15)
>16 mmHg		High mortality	(30)
>20 mmHg		High risk of treatment failure	(18)
>22 mmHg		High mortality in severe alcoholic hepatitis	(31)

HVPG, hepatic venous pressure gradient; PH, portal hypertension.

Based on the evidence from clinical trials, the HVPG is likely the most validated tool for assessing PH and cirrhosis prognosis (*Table 2*) (7,12-15,18,27-31). Compared with direct PPG measurement, the HVPG is easy, safe, and less invasive. However, it should be noted that the WHVP (and, consequently, the HVPG) represents liver sinusoidal pressure. Therefore, hardly does it provide useful data in prehepatic or presinusoidal PH (*Table 1*). Additionally, although the measurement of HVPG is less invasive, some complications such as hematoma, bleeding, bile leakage, arteriovenous fistulae, or Horner syndrome still occur in a small number of patients (26). In addition, this invasive method requires specific expertise and setting, which limit its applicability in nonteaching centers. As stated in the Baveno consensus conferences, noninvasive methods for assessing the PH are required (22). Patients would benefit from noninvasive methods that can provide similar information.

Noninvasive methods for assessing portal pressure

Although the measurement of HVPG is less invasive, some complications such as hematoma, bleeding, bile leakage, arteriovenous fistulae, or Horner syndrome still occur in a small number of patients (26). In addition, this invasive method requires specific expertise and setting, which limit its applicability in nonteaching centers. As stated in the Baveno consensus conferences, noninvasive methods for assessing the PH are required (22). Patients would benefit from noninvasive methods that provide similar information.

Serum markers

In recent years, several laboratory tests and serum markers have been able to evaluate the PH (32,33). Hayashi *et al.* directly measured PVPs in 40 patients and evaluated the association of PVP with the level of serum bile acid and the splenic volume. The equation for estimating PVP was given as follows: PVP = serum bile acid (μmol/L) ×2.593+ splenic volume (cm^3) ×0.416+65.929 (r^2=0.698) (33). Hsieh *et al.* investigated the correlations between noninvasive models (*Table 3*) and HVPG, including fibrosis-4 (FIB-4), aspartate aminotransferase to platelet ratio index, cirrhosis discriminant score, Lok index, Goteborg University Cirrhosis Index, and albumin-bilirubin (ALBI) score (34). They found that there was a weak correlation between all noninvasive markers and HVPG; the ALBI score had the best correlation (r=0.307, P<0.001) (34). Lim *et al.* evaluated the clinical implications of serum apelin (s-apelin), an endogenous ligand for angiotensin-like receptor 1, as a noninvasive prognostic role of chronic liver disease (35). The results showed that s-apelin was correlated with the

Table 3 The noninvasive serum-test models

Noninvasive models	Components
FIB-4	Platelet count, AST, ALT, age
AST-to-platelet ratio index (APRI)	AST, platelet count
Albumin-bilirubin (ALBI) score	Bilirubin, albumin
Lok index	Platelet count, AST, ALT, INR
Cirrhosis discriminant score (CDS)	Platelet count, ALT/AST ratio, INR
Goteborg university cirrhosis index (GUCI)	AST, INR

AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio of prothrombin time.

measurement of HVPG (r^2=0.356, P<0.001) (35). Procopet *et al.* assessed the diagnostic accuracy of six serum scores (*Table 3*) for diagnosing CSPH and found that the Lok score was the best with area under the receiver operating curve (AUROC) =0.84 (95% CI: 0.76–0.91, P<0.0001) (32). Thus, laboratory tests and serum markers show acceptable clinical utility, and many of them are not sufficiently accurate to diagnose PH and are not yet ready to be used in clinics.

Radiological features—computed tomography (CT) and magnetic resonance imaging (MRI)

In a retrospective study, the score of liver surface nodularity quantified based on CT images was correlated with HVPG (r=0.75, P<0.001) (36). Based on a 385 patients-enrolled multi-institutional prospective diagnostic clinical trial (ClinicalTrials.gov identifier: NCT03138915), Liu *et al.* developed a radiomics-based model, and the results showed that HVPG exhibited good performance in detecting CSPH (C-index =0.849, 95% CI: 0.786–0.911). The sensitivity and specificity were 78.7% and 76.9%, respectively (37). Recently, the advances in the fields of three-dimensional modeling based on imaging and computational fluid dynamics analysis allow the noninvasive measurement of blood pressure (38,39). In a prospective multi-institutional study (ClinicalTrials.gov identifier: NCT02842697), Qi *et al.* developed a model to estimate the HVPG through CT angiographic images, termed virtual HVPG. The results showed that virtual HVPG correlated with invasive HVPG (r=0.61, P=0.001) (40). However, the interpretation of the virtual HVPG was relatively time consuming (about 2.5 hours for each case) in their study, and the number of patients without CSPH was small in their study. Therefore, the clinical usability of the virtual HVPG should be studied further.

Although some studies have shown that CT can predict HVPG, this technique has the disadvantage of requiring ionizing radiation. In a prospective study, MRI characteristics associated with both hepatic architecture and splanchnic hemodynamics were observed to be significantly correlated with HVPG. The liver T1 relaxation time and the velocity of splenic artery were also significantly correlated to HVPG (r=0.90, P<0.001) (41). Zhang *et al.* established a linear model to assess PVP based on the MR characteristics as follows: PVP (mmHg) =2.529+1.572× splenic venous diameter (mm) +0.231× splenic volume/body mass index (×10^4 cm^5/kg) +3.44× aspartate aminotransferase-to-platelet ratio index (42). The model indicated accuracy in detecting PH with AUROC =0.945 (95% CI: 0.867–1.000), with sensitivity and specificity of 91.7% and 93.7% respectively (42). Chouhan *et al.* revealed that caval subtraction hepatic arterial fraction had a significant positive relationship with HVPG (r=0.780, P=0.014), based on the caval subtraction phase-contrast magnetic resonance imaging (PCMRI) procedure (43). However, the caval subtraction PCMRI is likely to be less successful in patients with abnormal hepatic venous outflows, such as the Budd-Chiari syndrome. In addition, a larger patient cohort is needed to further investigate whether this technique can be successfully used as a clinically practical alternative.

MR elastography (MRE) is a type of MRI technique that is based on quantitatively evaluating the mechanical characteristics of tissues through the propagation of shear waves (44). In a prospective cohort including 15 patients, the investigations showed that MRE was associated with HVPG (r^2=0.377, P=0.02) (45). However, the size of the study was too small to draw reliable conclusions. Moreover, the MRE technique is only available at very few medical centers, and it is expensive compared to transient elastography (TE). The aforementioned limitation may therefore restrict its dissemination and application in clinical practice.

Ultrasound elastography (USE)

In the 1990s, Ophir *et al.* first described USE as an imaging technique, which is sensitive to tissue stiffness (46). In recent years, further studies have enabled quantitative assessments of liver, breast and spleen stiffness (47-50). Although the USE technique was originally applied to assess the hepatic fibrosis grade, some recent researches have expanded its use to assess potential liver function, such as PH, and risk of liver cancer development or liver failure (51-54). Based on the physical quantity measured, the USE technique can be classified into two types: strain imaging and shear wave imaging (SWI) (47). The SWI technique for measuring the Young's modulus of tissue is mostly used in liver, breast and spleen stiffness examination. Currently, there are three technical methods for SWI: (I) TE, (II) two-dimensional shear wave elastography (2D SWE), and (III) point SWE (pSWE). Current studies in this field have revealed that USE may be a reliable noninvasive alternative to evaluate PH by measuring the liver stiffness (LSM) and/or spleen stiffness (SSM).

You *et al.* performed a meta-analysis included 11 studies to determine the relationship between liver stiffness measured using TE (TE-LSM) and HVPG. The results showed that TE-LSM significantly correlated with HVPG (r=0.783, 95% CI: 0.737–0.823) and represented good diagnostic performance for assessment of CSPH, with a sensitivity of 87.5% and specificity of 85.3% (55). However, the measurement results from TE can be affected by factors such as obesity and ascites, which may limit the application of the technique in advanced liver diseases (56). Compared with TE, measurement sites with the pSWE technique can be visualized with B-mode ultrasound. This advantage not only ensures LSM in the correct tissue site by avoiding ligament and vascular structures but also improves the accuracy of diagnosis (57). The results from a prospective cohort including 88 patients showed that pSWE values were correlated well with HVPG (r=0.646, P<0.001), and the sensitivity and specificity for pSWE were respectively 71.4% and 87.5% at the optimal cut-off (2.58 m/s). In the study, the TE performance was inaccurate in 22 patients (25%), whereas only one failure was noted for pSWE (0.9%) (58). The detection field of 2D SWE is larger than pSWE. It can show the measurement of elastography on a color display. Some studies have shown that, compared to TE, LSM by 2D SWE is a promising parameter to diagnose PH with higher success rate and better diagnostic value (59-61). The Baveno VI consensus meeting confirmed the role of TE-LSM in determining CSPH and PH (22). Moreover, SSM measured by USE has also been proven to be useful for assessing PH (57,62,63). The hemodynamic changes in PH can cause splenic congestion, which might induce splenic fibrosis and increased SSM. A meta-analysis including nine studies showed that SSM is strongly correlated with HVPG (r=0.72, 95% CI: 0.63–0.80) (64).

Some research studies have indicated that LSM is superior to SSM for diagnosing CSPH (61,65); however, the results of other studies provide contrary views (66,67). According to current literature, it is difficult to determine which one is the superior metric. Jansen *et al.* developed an algorithm to rule-in and rule-out CSPH based on LSM and SSM measured by 2D SWE (68). The accuracy of this algorithm was validated in a large cohort comprising 191 patients by Elkrief *et al.* (52). However, the results showed that these algorithms were not good enough to replace HVPG measurements or for use as the basis of clinical decision making.

Doppler ultrasonography (DUS)

DUS is a mainstay in the assessment of portal vein blood flow and hemodynamic changes (69,70). A prospective pilot study of 76 cirrhosis patients used DUS to assess the correlations between damping index (DI) of the hepatic vein waveforms and HVPG, and showed a relation between DI and HVPG (r^2=0.468, P<0.001) (71). However, in another study including 138 cirrhosis patients, the investigators found that none of the DUS characteristics (such as the velocity of portal vein and the splenic vein, pulsatility, and resistive indices of the hepatic and splenic arteries) correlated with HVPG (72). The patient-related factors were observed to influence the DUS measurement values, such as respiration, timing of meals, and equipment; this might have contributed to the inconsistent results among the different studies (73). Considered together, the available data do not provide convincing results to recommend DUS measurements as a reliable alternative to HVPG (74).

Contrast-enhanced ultrasound (CEUS)

In recent years, the advancement of microbubble ultrasound contrast agents (UCAs), consisting of encapsulated microbubbles, and improvement of imaging technology have led to the possibility of using CEUS to evaluate hemodynamics and anatomical structures in real time (75). The microbubble is encapsulated with a stable shell of a lipid, albumin, or other material (76). High molecular weight and low solubility gases

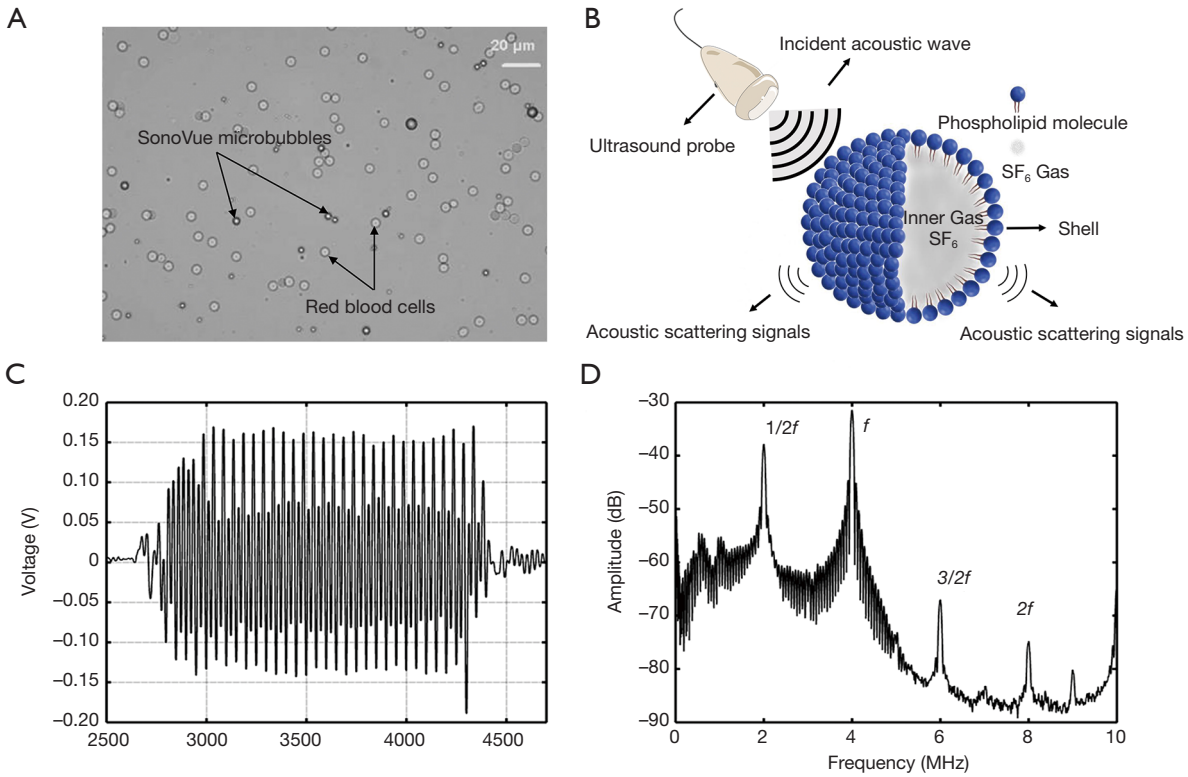

Figure 2 The structure and acoustic characteristics of the SonoVue microbubble. (A) Microscopic picture of SonoVue microbubbles and red blood cells by Petelska *et al.* (77); (B) the SonoVue microbubble is composed of a phospholipid shell and a core of sulfur hexafluoride (SF6) gas. The microbubbles act as nonlinear scatters of the incident acoustic wave and lead to acoustic scattering signals; (C) the measured scattering signals from microbubbles (a single received signal) (78); (D) the averaged power spectrum of 50 received signals. The acoustic scattering signals are consisted of fundamental (*f*), subharmonic (1/2*f*), second harmonic (2*f*), and ultraharmonic (3/2*f*) components. The driving frequency was 4 MHz, the acoustic pressure was 350 kPa, and the overpressure was 8 mmHg (78).

Table 4 Second generation microbubble UCAs in clinical use

Microbubble UCAs	Structure			Company	Country
	Shell material	Gas core	Mean diameter (μm)		
Definity	Lipid	Octafluoropropane	1.1–3.3	Lantheus Medical Imaging	USA
Optison	Sonicated albumin	Octafluoropropane	3.0–4.5	GE Healthcare	UK
SonoVue	Phospholipid	Sulfur hexafluoride	1.5–2.5	Bracco SpA	Italy
Sonazoid	Phospholipid	Perfluorobutane	2.1	GE Healthcare	UK

UCAs, ultrasound contrast agents.

such as octafluoropropane or sulfur hexafluoride are filled in the core of the microbubble (*Figure 2A,B*). The microbubble UCAs act as nonlinear scatters of the incident ultrasound pulse, which can be distinguished from the linear response of the tissue, thus significant improving the contrast to tissue ratio by using nonlinear scattering signals from microbubbles. Since the UCAs were approved for imaging outside the heart by the Food and Drug Administration (FDA) in 2016 (76) (*Table 4*), the CEUS has been used in many applications, such as detecting liver tumors and evaluating the treatment response of chemotherapy (79,80). Currently, some studies have expanded the utility of CEUS to the assessment of PH (81-85).

Table 5 Comparison of diagnostic abilities of studies used transit time to assess portal hypertension

Study	Patients	UCAs	Parameters	Reference standard	Cut-off	Correlation	Grade of PH	AUROC	Se/Sp/PPV/NPV/Ac/PLR/NLR	Ref.
Zhang *et al.*	31	SonoVue	HVHAT	FPP	NR	r=−0.90, P<0.001	NR	NR	NR	(82)
			PVHAT	FPP	NR	r=0.81, P<0.001	NR	NR	NR	
Kim *et al.*	71	SonoVue	HVAT	HVPG	14 s	r^2=0.55, P<0.001	CSPH	0.973	93/87/91/90/NR/6.95/0.08	(83)
Shimada *et al.*	91	Sonazoid	PET	HVPG	13.5 s	r=0.46, P=0.001	CSPH	0.76	71/68/69/70/NR/NR/NR	(87)
			PET	HVPG	14.5 s	r=0.46, P=0.001	SPH	0.76	60/80/75/67/NR/NR/NR	
Jeong *et al.*	53	SonoVue	HVAT	HVPG	19 s	r=−0.34	SPH	0.72	56/89/95/35/63/NR/NR	(84)
			ITT	HVPG	6 s	r=−0.61	SPH	0.94	91/89/97/73/91/NR/NR	

The four studies show the diagnostic abilities of transit time based on microbubble ultrasound contrast agents (UCAs). HVHAT, hepatic-vein-hepatic-artery interval time; PVHAT, portal-vein-hepatic-artery interval time; HVAT, hepatic vein arrival time; PET, peak enhancement time; ITT, intrahepatic transit time; FPP, free portal pressure; HVPG, hepatic venous pressure gradient; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; Ac, accuracy; PLR, positive likelihood ratio; NLR, negative likelihood ratio; CSPH, clinically significant portal hypertension; SPH, severe portal hypertension; AUROC, area under the receiver operating curve; NR, no report.

Transit time

Transit time, defined as the average time interval required for the bubbles to move from one vessel to another, is a representative parameter for microbubble hemodynamics (86). A study by Zhang *et al.* including 31 patients reported that the free portal pressure significantly correlated with hepatic-vein–hepatic-artery interval time (r=−0.900, P<0.001) and the portal-vein-hepatic-artery interval time (r=0.808, P<0.001) (*Table 5*) (82). However, the investigators applied the free portal pressure as standard reference. As mentioned previously, the free portal pressure is affected by intraabdominal pressure, surgery, and anesthesia. The hepatic vein arrival time (HVAT) is the average time taken for the UCA microbubbles to reach the hepatic vein after injection. Two studies revealed that HVAT had a significant correlation with HVPG and was accurate for detection of CSPH and severe PH (*Table 5*) (83,84). The splenic circulation measured by CEUS is also a promising predictor of PH. The peak enhancement time (PET), defined as the average time of the microbubble UCA from arriving at the splenic artery to reaching maximum intensity level in the splenic vein, was correlated with HVPG in a cohort of 91 patients (r=0.4573, P<0.0001) and provided a good rate of prediction of CSPH and severe PH (*Table 5*) (87). However, the transit time can be influenced by a poor echo window related to obesity, respiration, or changes to hepatic anatomy in patients with severe liver cirrhosis (83). Despite these promising data, in our opinion, transit time measurement with CEUS is more suitable for use as a supplementary or screening tool, rather than as a surrogate of HVPG.

Subharmonic imaging—microbubble-based pressure sensors

Based on the compressible properties of gas-filled microbubble UCAs, their acoustic characteristics can change with the variations of blood pressure. Currently, three techniques are available to estimate the local blood pressure using microbubbles as sensors: based on the shift in resonance frequency of microbubbles (88-90), using the time of free bubbles disappearance as a measure of local blood pressure (91,92), and using the amplitude variations of the scattered echo of microbubbles (78,93-97). However, the first two approaches have high error rates, which prevent their preclinical or clinical applications. According to previous studies, the technique based on amplitude variation of the scattered echo is therefore the most promising option for clinical application (78,81,97,98).

The microbubbles act as nonlinear scatters of the incident ultrasound pulse and lead to echo response emissions consisting of fundamental (*f*), subharmonic (1/2*f*), second harmonic (2*f*), and ultraharmonic (3/2*f*) components (78) (*Figure 2C,D*). A study showed he subharmonic amplitude significantly correlated with ambient pressure (94). Moreover, the subharmonic signal generation can be classified into three stages—occurrence, growth, and saturation (*Figure 3A*) (96). The subharmonic amplitude decreased linearly with increasing hydrostatic pressure in the growth stage (78,93) (*Figure 3B,C*). As

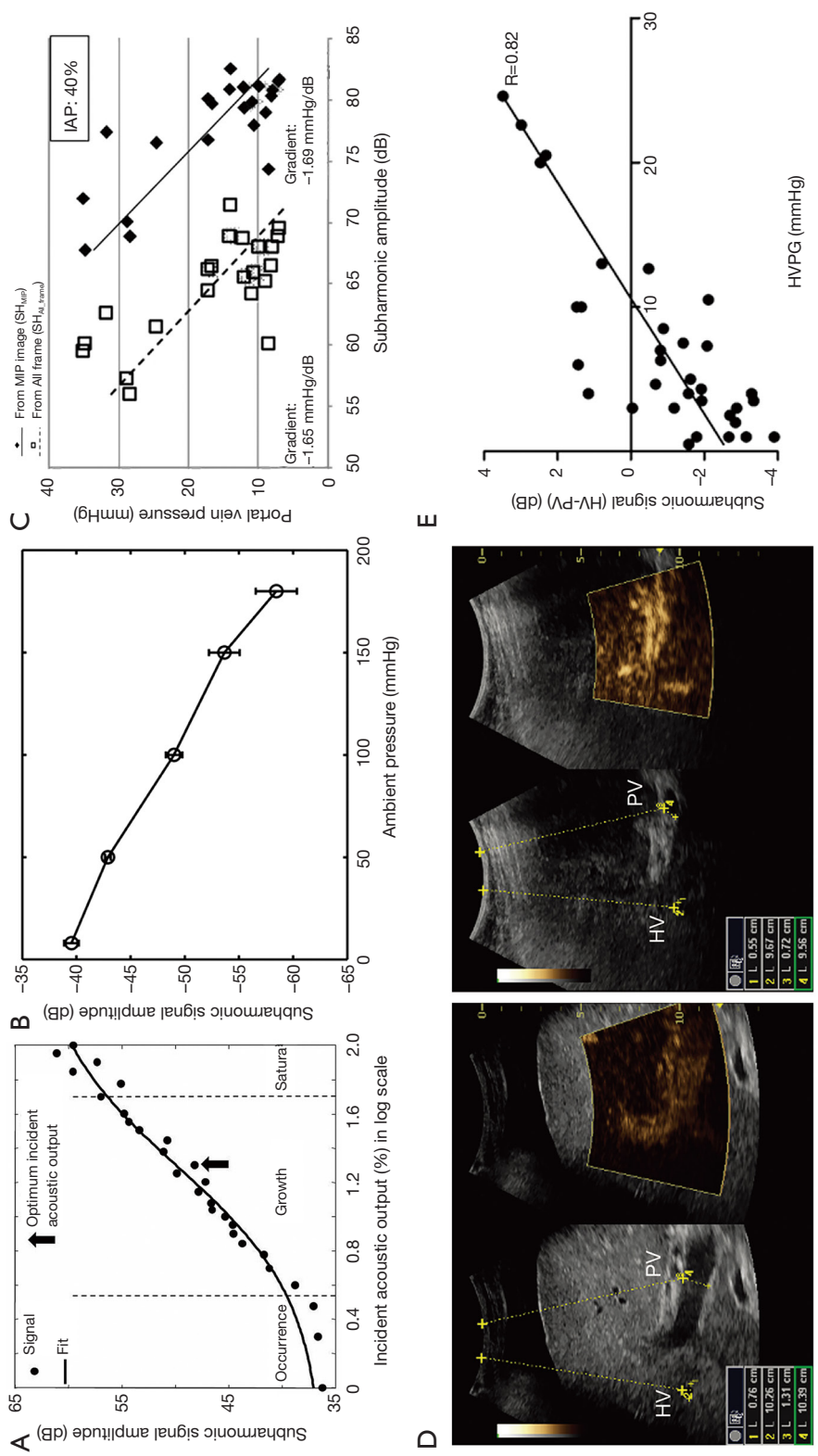

Figure 3 The relation between subharmonic amplitude and ambient pressure. (A) The subharmonic signal generation consists of three stages: occurrence, growth, and saturation. Reproduced with permission; (B) Li *et al.* (78) used SonoVue microbubbles as pressure sensors to detect the ambient pressure. The result revealed that subharmonic amplitude significantly correlated with the ambient pressure (r=0.9919) and ambient pressure sensitivity was −9.1 mmHg/dB; (C) Dave *et al.* (93) reported the correlation between subharmonic signal amplitudes and absolute portal vein pressures *in vivo*; (D) a study by Eisenbrey *et al.* (81) showed ultrasound images in two patients, with the region of interest (ROI) of subharmonic (marker with yellow box) located within the portal vein (PV) to calibrate acoustic output; (E) the results of the correlation between the noninvasive subharmonic gradient—the average subharmonic amplitude difference between hepatic vein (HV) and PV—and the corresponding HVPG in the study of Eisenbrey *et al.* (81). MIP, maximum intensity projection; IAP, incident acoustic power; ROI, region of interest; HVPG, hepatic venous pressure gradient.

a consequence, Shi *et al.* proposed a technique using microbubbles as sensors to assess the changes of ambient pressure, called subharmonic-aided pressure estimation (SHAPE) (94). A pilot study measured the SHAPE image in both hepatic vein and portal vein (*Figure 3D*), and the results showed that SHAPE values correlated well with HVPG measurements in 45 patients (r=0.82) but had poor technical success rate (73%) (*Figure 3E*). In addition, SHAPE gradient strongly correlated with the HVPG in patients with severe PH (r=0.97); however, the sample size of their study was only six patients (81). Although SHAPE may be a useful clinical tool for monitoring PVPs in the future, there are still many difficulties to be addressed, including those on a case-by-case basis, depending on the physiological environment of the body and the differences that caused by attenuation, reverberation, and aberration through the abdominal wall. While this technique estimated local blood pressure using microbubbles as sensors, it still requires validation in larger cohorts.

Conclusions

Liver disease account for a significant burden of disease and costs worldwide. As shown in the present review, although HVPG measurement is an invasive method to assess portal pressure and to evaluate the treatment response, it is still irreplaceable in clinical practice. In the past few decades, numerous noninvasive methods have shown promising results for monitoring portal pressure and assessing PH; however, challenges still remain in accurate evaluation. The cause of PH varies considerably: in Western and developed countries, alcoholic and nonalcoholic fatty liver disease related to cirrhosis is the major causes, whereas in Asian countries, viral hepatitis continues to be the primary cause. As a result, more prospective studies focused on different populations and disease etiologies are needed in the future. In addition, new evaluation techniques, such as 2D SWE, pSWE, and SHAPE can be used for consensus or guidelines, which are needed for investigators to interpret test results consistently. In recent years, some new technologies have emerged, such as radiomics and artificial intelligence. They are more likely to bring precision medicine closer to PH patients. Although the road to noninvasive measurement of portal pressure is still long, noninvasive methods hold great potential for a great variety of clinical applications, and further development may lead to their widespread clinical adoption in the future.

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Footnote

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